UNIVERSITAT DE BARCELONA

Enolates Go Radical. Stereoselective Radical Alkylation Reactions of Titanium Enolates from *N*-Acyl Oxazolidinones with Carboxylic Acid Derivatives. Synthesis of Umuravumbolide

Marina Pérez Palau

Programa de Doctorat de Química Orgànica

Enolates Go Radical

Stereoselective Radical Alkylation Reactions of Titanium Enolates from *N*-Acyl Oxazolidinones with Carboxylic Acid Derivatives. Synthesis of Umuravumbolide

Marina Pérez Palau

Supervised by

Prof. Pedro Romea García

Prof. Fèlix Urpí Tubella

Secció de Química Orgànica

Departament de Química Inorgànica i Química Orgànica

Facultat de Química

Universitat de Barcelona

UNIVERSITAT DE BARCELONA

This thesis was performed from October 2017 until June 2022 in the section of Organic Chemistry of the Department of Inorganic Chemistry and Organic Chemistry of the University of Barcelona. The work has been carried out with the financial support of the “Ministerio de Ciencia e Innovación” (Projects CTQ2015-65759-P and PGC2018-094311-B-I00) and with the support of “ajuts per a la contractació de personal investigador predoctoral en formació” (FI 2018) fellowship and “ayudas para la formación de profesorado Universitario” (FPU2017-00679) fellowship.

Acknowledgments

Aquestes línies són per totes aquelles persones que m'han acompanyat al llarg d'aquesta gran aventura que és la tesi, i que entre totes han fet possible que aquest llibre sigui aquí, i que també l'obrireu, però per veure què hi he posat aquí.

Primerament agrair-vos Pere i Fèlix per donar-me l'oportunitat d'embarcar-me en aquest doctorat. Gràcies per confiar en mi i donant-me la llibertat que m'ha permès madurar com a científica i alhora guiar-me i acompanyar-me quan ho he necessitat. También quiero darte las gracias a ti Alejandro, mi mentor, que me diste una base sólida para empezar esta tesis, a la vez que dabas un toque de humor a los radicales y los días de laboratorio. També donar les gràcies a tots els que heu treballat amb mi i heu ajudat a tirar aquest gran projecte endavant, ja sigui breument, Sonja i Timo, o compartint una etapa important també per vosaltres i que a part de la feina heu donat el vostre toc personal a aquells mesos al laboratori. Marc, gràcies per aquesta actitud teva que aconsegueix que fins i tot una columna sigui *sassy*, he passat molt bons moments al teu costat. Nil, tu em vas fer costat durant les setmanes més dures d'aquesta tesi, i potser sense tu saber-ho la teva naturalitat i simplicitat es van convertir en un flotador per sortir d'aquell entrellat. No les perdis mai, m'encanten i converteixen tots moments amb tu en records genials i divertits. Ja estic esperant la propera retrobada Miquel-Nil-Marina! I Eduard, que m'has animat tot el que calia durant aquesta última etapa, sé que deixo el projecte en bones mans. Y a Stuart y a Saj, gracias por las correcciones exprés del inglés de esta tesis.

No em podria oblidar de tots els companys de laboratori amb qui no he compartit projecte però que heu estat al meu costat, ja sigui discutint sobre la química com alegrant el dia a dia. Javi, empezamos con mal pie, pero entre peinados y canciones creo que me gané un buen sitio en tu corazón, igual que tú en el mío. Saul, siempre con una sonrisa puesta y, por supuesto, con un tequila debajo del brazo. I les últimes incorporacions, Oriol amb els teus debats sobre química i Elias, amb les teves riallades diàries heu fet del laboratori un lloc nou. Stuart, Marina i Miquel, vosaltres aneu més tard.

I vosaltres, els "companys de departament", amb qui he passat de compartir les hores de dinar a formar un grup d'amics molt variable però indispensable. Recordo grans moments i anècdotes (encara tinc la llista!) que han fet que els anys de tesi siguin especials. Gràcies: Ari i les teves bogeries. Roser, la meva Caracola. Roberto, crec que no

n'ets conscient de la pau que em dona saber que tinc un amic que té un pensament de vida molt semblant al meu. Héctor, per ser tant atent i donar-me serenitat. Anna, per tots els moments de tonteria compartida. Marta, por estar siempre pendiente de cómo me siento. Sergi, per recolzar-me i confiar en mi, més que no pas jo. Júlia, per calmar-me amb la teva innocència quan més em fa falta. Davor, perquè segueixo esperant els bon dies amb la teva salutació (..!..). Saj, por estar ahí aun y cuando lo haga difícil. Sencher, per mi també ets d'aquest grup, gràcies per la teva autenticitat. I també Mariona, Fernanda, Manel i Víctor. Macarena i Marina, heu de llegir més endavant.

Una gran part de les millors estones al llarg d'aquesta tesi han estat possible gràcies a La Colla. Héctor, Stuart, Macarena, Tomeu, Cristian i Anna, gràcies per fer que aquell projecte fos possible, sempre en guardaré un molt bon record i n'estaré orgullosa de tot el que vam aconseguir.

And also thank you to all the people that I met during my stay in Mülheim and made the town a happier place. Julia, Uri, Rakan, Sílvia, Mire, Jan, Diane, Feng, Ektoras. And especially: Pep, per ensenyar-me una altra manera de fer química. Franck for our goûter times, without you my time there would had been much more difficult. And Daniel, for all the encouraging talks, the entertaining ones and the "fixing the academia" ones.

També vull agrair-vos als químics que heu estat la meu costat durant aquests anys i que heu vist pacientment com evolucionava aquesta tesi. Guille, Rai, Imma, Aina, Eva, Roger i Eli, sempre disposats a fer una cerveseta per posar-nos al dia i desconnectar de la rutina.

I també als amics dels clàssics, Wiwi, Eli, Marc, Judit, Berta i Laia, que m'heu recolzat durant aquesta etapa que semblava que mai acabava.

Gràcies família pel vostre suport incondicional. Sobre todo: Papa, por tus incansables intentos de entender esta tesis y consejos para seguir con ella. Mama, per posar-li tota l'emoció i empenta quan jo no en tenia gaire. Jordi, per ensenyar-me a donar-li el *carinyo* que també necessitava. Germanets Dani i Pol, que no us quedava altra opció que aguantar-me, gràcies per la paciència, Dani per ensenyar-me de la teva experiència i Pol per escoltar i entendre tots els meus drames. I Tata, por tu constante atención y motivación con viajes pasados y futuros.

I la família de Numància, que aquest any i mig us heu convertit en una base essencial per a mi, no hi ha sentiment tan càlid com el saber que quan torno a casa sou allà i podem

parlar de TOT el que hagi passat durant el dia. Això sí que no té marge de millora. Carla, gràcies per entendre tant com en sento en determinades situacions, fas que siguin molt més fàcils de superar. Poques vegades he agafat tan ràpid tanta confiança i m'he sentit tan còmode amb algú com ho he fet amb tu. Macarena, gràcies per haver-te convertit en una amiga tant gegant, des de que vam començar que cada cop m'he anat sentint més propera a tu, fins a arribar al punt en què sé que sempre ets i seràs allà quan més ho necessiti. I també dir-te que adoro i no vull que marxin mai els nostres moments de rialles descontrolades sense que estiguin gaire justificades.

Stuart, empezar dándote las gracias por todo lo que me has enseñado y ayudado en el lab y con la tesis. Pero lo que agradezco más es que siempre estés dispuesto a regalarme un momento para que *la Karma*, o yo, nos podamos reír de ti. No home, és broma! Gracias por haberte convertido en el gran amigo que eres ahora, y por haber dejado claro que siempre estás aquí. Sé que esta es una amistad de las que ya no se desvanecen.

Marina, mi "enantiómero favorito". Qui m'havia de dir que d'aquells mesos compartint vitrina en sortiria una amistat tant maca. Gràcies per fer tan fàcil parlar amb tu de qualsevol tema, per compartir angoixes i normalitzar sentiments, i per totes les estones de diversió al llarg d'aquests anys.

Miquel, tu que vas entrar al lab de manera discreta, quina dolça sorpresa quan vaig entendre que t'havies convertit en un amic tan important. Gràcies per ensenyar-me que puc dir les coses (vaja, ja veus que encara n'estic aprenent) i ensenyar-me que tot es pot parlar. I no et preocupis perquè potser no et portaré gaire més l'esmorzar, però ni de bon tros ens deixaré allunyar.

Marina, com explicar-te lo difícil que hauria estat arribar fins aquí si no fos per tu, t'ho dic una altra vegada perquè sàpigues com n'és de tranquil·litzant saber que aquests sentiments nostres no són únics i que no estic boja. De ben segur que les barquetes inflables arriben molt lluny i els esperen mil i una odissees juntes.

I per últims, per a tots, no us feu els badocs, ho sento molt però heu perdut el joc.

“Imagination is the only weapon in the war against reality”

Lewis Carroll, in Alice’s adventures in Wonderland

“We especially need imagination in science. It is not all mathematics, nor all logic, but it is somewhat beauty and poetry”

Maria Mitchell

Table of Contents

GENERAL INTRODUCTION

"The synthesis of a complicated molecule is, however, a very difficult task; every group, every atom must be placed in its proper position and this should be taken in its most literal sense. It is sometimes said that organic synthesis is at the same time an exact science and a fine art. Here nature is the uncontested master..."

These lines belong to the speech given by Professor ARNE FREDGA to introduce the Chemistry Nobel Prize in 1965, Professor ROBERT B. WOODWARD, who was awarded the honor for his achievements in organic synthesis.[1] In fact, a vast number of molecules have been prepared to this day since the origins of organic synthesis in 1828 with WÖHLER's synthesis of urea. Hence, total synthesis has become one of the main fields in natural sciences.[2] Some will pursue a target molecule for its unique properties, either in the pharmaceutical, cosmetics or nutritional industry,[3] while others will seek the answer to a natural's product structure, or to gain insight of important biochemical pathways, and a few might do it just for fun. Regardless of the objective, organic chemists have been challenged to overcome the hurdles of total synthesis, and consequently, new and improved transformations are constantly being developed. One could say that total synthesis is the driving force of organic methodology while, simultaneously, the latter empowers the synthesis of molecules of greater complexity. That is why the frame of this thesis is to develop new methods which would then also be applied to the total synthesis of target compounds (Figure 1).

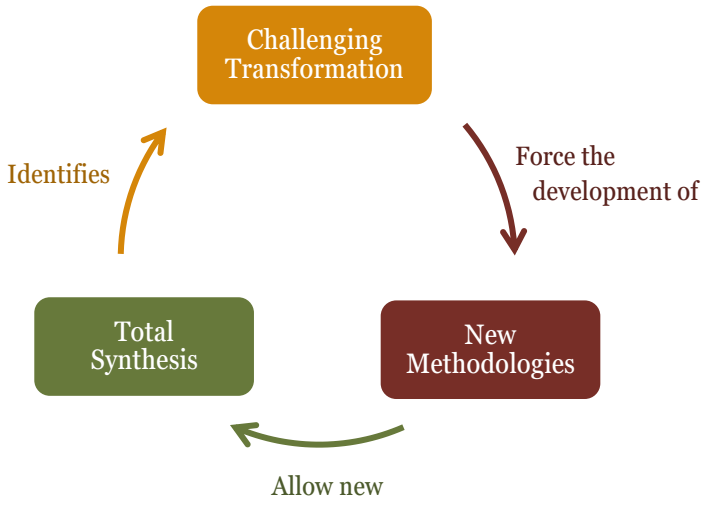


Figure 1. Relationship between total synthesis and the development of new methodologies

1. Radical chemistry

For many years, organic chemists had focused their efforts on transformations based on heterolytic mechanisms leaving radical methodologies in the background. However, radical reactions have been rationally studied since 1900, when GOMBERG reported the synthesis of the trityl radical.[4] Notwithstanding the initial mistrust in the existence of such species, several experiments kept proving the formation of radicals and through to the mid-20th century, physical chemists conducted kinetic and stability studies establishing the fundamental basis of organic radical chemistry.[5–8] These investigations allowed the development of practical radical procedures such as: the Minisci reaction, Giese radical addition, or tin hydride chemistry.[9] Despite that important radical synthetic methods have been described over the years, poor attention has been paid to these processes in organic textbooks, in which full-headed arrows are the main staple. Consequently, the belief that radicals are difficult to control and exhibit tumultuous reactivity is still shared among chemists. Conversely, ignoring all the possibilities that radical chemistry can offer would be akin to the chemist community progressing by using just half of its total power. On the good side, a better knowledge of open-shell species, stability and reactivity-wise, has recently entailed a great development of elegant radical intermolecular reactions. Fields such as photoredox catalysis or electrochemistry have largely expanded during this last decade, converting radical species, specifically alkyl radicals, into important intermediates in modern organic synthesis.[9,10]

Generation of alkyl radicals

The generation of alkyl radical intermediates using mild conditions to enable these species to be used in a controlled and selective manner has been a challenge for chemists for years. Main alkyl radical reactivity was born when VAN DER KERK reported the formation of alkyl radicals from alkyl halides by a halogen abstraction process using stannanes (*Figure 2*).[11] However, radical reactivity remained quite unnoticed until BARTON and MCCOMBIE developed xanthate chemistry, which allowed the generation of alkyl radicals from secondary alcohols as raw materials, and yet again, using organotin species to induce the homolytic scission of the aforementioned xanthates (*Figure 2*).[12] In fact, despite their toxicity, organotin reagents were so established that some authors refer to that time as “the tyranny of tin”.[13,14]

Radical chemistry took a turn when UV photoinduced homolysis of the O-N bond in Barton esters proved the potential of photochemistry to generate alkyl radicals (*Figure 2*).[15] "Light" is, as a matter of fact, an ideal reagent since it interacts in the reaction without leaving any trace, which constitutes a greener alternative that does not require heat or aggressive reagents. Another important milestone was the development of *N*-hydroxyphthalimide esters by ODA and OKADA (*Figure 2*). Homolytic cleavage of these species, which are prepared from carboxylic acids, was achieved by a single electron reduction promoted by a ruthenium photocatalyst and visible light.[16] However, it was not until a decade ago, when MACMILLAN,[17] YOON[18] and STEPHENSON[19] separately reported examples of new visible-light photoredox chemistry promoted by ruthenium complexes (*Figure 2*). Since then, radical generation has experienced tremendous growth within the field of photochemistry.

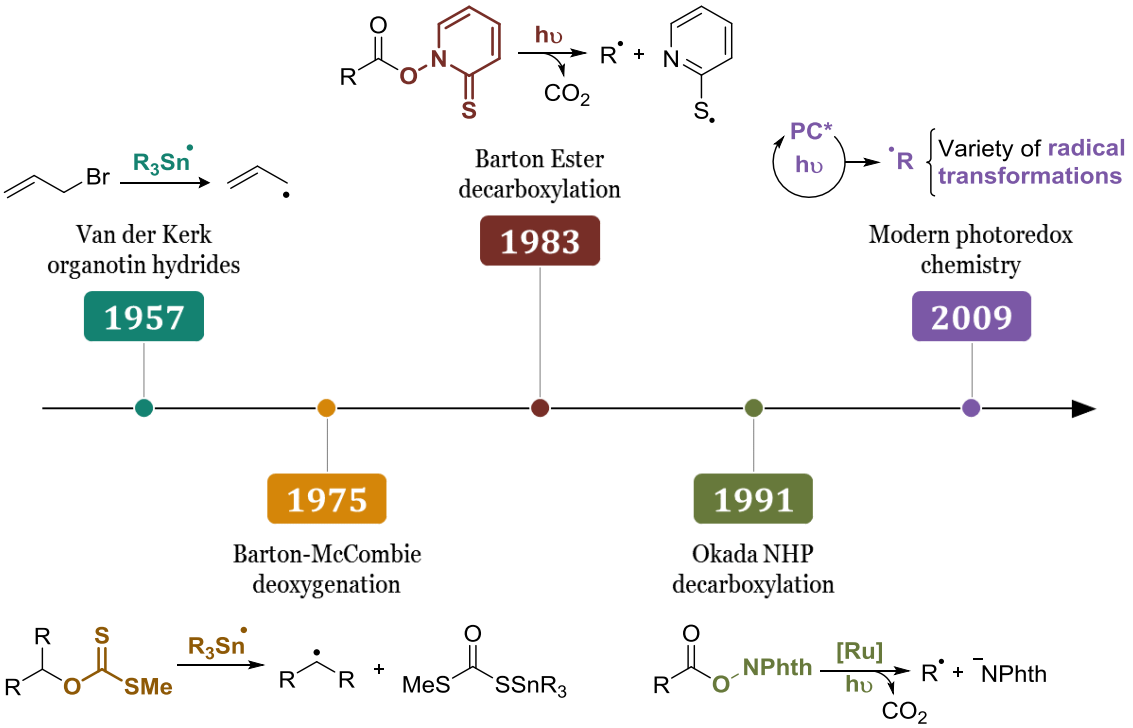
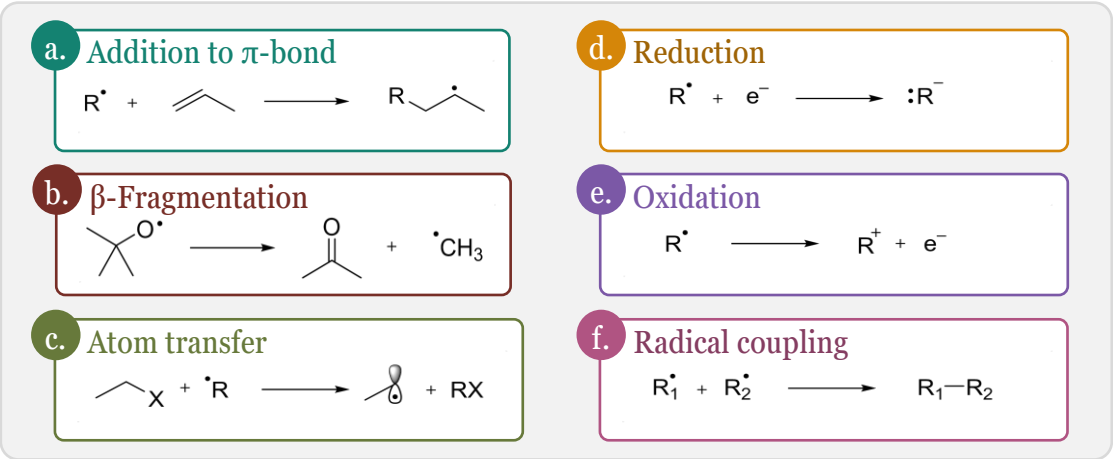


Figure 2. Alkyl radical generation milestones

Reactivity of radicals

Once formed, a radical species can react in different ways to either give another radical, a new ion, or a neutral molecule (*Scheme 1*). Indeed, radicals easily add to π-bonds (*a, Scheme 1*). In this type of reaction nucleophilic radicals (bearing alkyl substituents) react much faster with electron-poor olefins; on the contrary, electrophilic radicals (bearing electron-withdrawing substituents) react preferably with electron-rich

double bonds. In addition, radicals can effect the reverse reaction, a β-fragmentation that generates a π-bond and a new radical species (*b, Scheme 1*). Radicals can also perform atom (or group) transfers to abstract an atom (or group) and produce a new radical (*c, Scheme 1*). The radical species can also be reduced or oxidized leading to ionic species (*d and e, Scheme 1*). And finally, they can also react with other radical species, forming a neutral molecule (*f, Scheme 1*). Most importantly, radicals are highly reactive intermediates that react with each other in a very exothermic manner, which makes selectivity difficult to control.[20]



Scheme 1. Main radical reactivity

In most practical transformations, radical species react with a neutral molecule or an ion, creating a radical chain reaction. In this type of reaction, the radical-radical coupling is prevented because of the low concentration of such species. Thus, the main reactivity observed is between a radical and a molecule (or ion). Alternatively, some cases of cross-coupling between two radical species have been uncovered. The cross-selectivity of this phenomenon is explained by the persistent radical effect in which a *persistent* radical reacts with a *transient* radical. The *persistent* and *transient* terms were defined by GRILLER and INGOLD and refer to kinetic features of radical species.[5] A *persistent* radical is that with a lifetime significantly greater than the methyl radical, while a *transient* radical has a lifetime shorter than 10^{-3} seconds. These terms should not be confused with stabilized and destabilized radicals, which are thermodynamic concepts that are related to the strength of the R-H bond which is broken to form an R radical. Usually, resonance effects are responsible for stabilized radicals, for instance allyl radicals; while steric hindrance is responsible for persistent radicals, for example the trityl radical (*Figure 3*). For radical cross-selective reactions, the two radical species should be generated at the

same rate. Thus, at the beginning of the reaction the concentration of both radical species is the same. However, the transient radical reacts much faster, by either homocoupling or reacting with other species, even the solvent. On the other hand, the persistent radical does not react due to its significantly longer lifetime. Therefore, the transient radical concentration becomes lower than that of the persistent radical, favoring the cross-coupling between the transient and persistent radicals.[21]

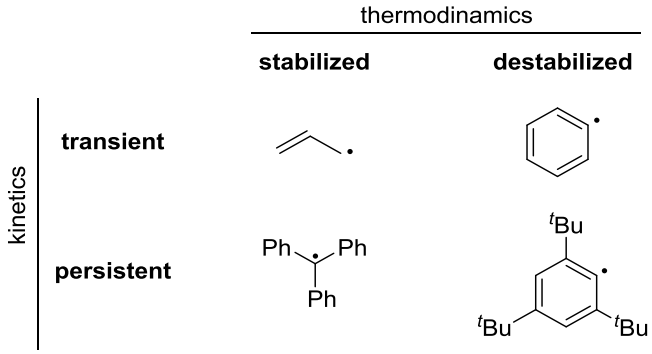


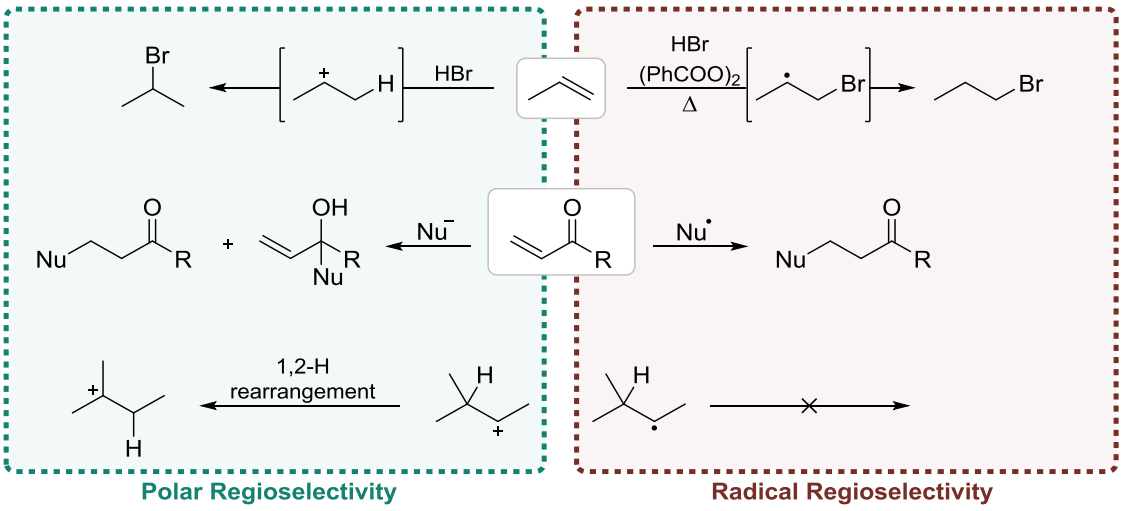
Figure 3. Kinetic and thermodynamic definitions of radicals

Importantly, radicals exhibit different reactivity patterns than those from closed-shell species, and they thus display chemoselective and regioselective features that offer valuable alternatives.

Chemoselectivity of radical processes can be rationalized by means of bond dissociation energy (BDE) of the bonds engaged in the transformation. For instance, the homolysis of bonds such as O-H or N-H, which are stronger than C-H bonds, is not usually observed in radical reactions, as well as the addition of radical species to a carbonyl group, which is usually prevented. Therefore, tedious protection and deprotection steps can be avoided due to the high functional group tolerance of radical processes.

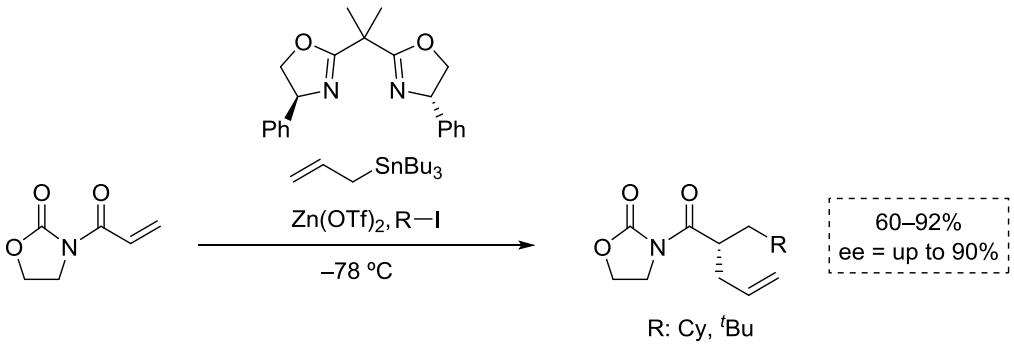
Regioselectivity of radical transformations also differs from ionic pathways (*Scheme 2*). For instance, the ionic addition of HBr to olefins renders Markovnikov selective halogenated products due to the formation of the most stable carbocationic intermediate after the protonation of the double bond. On the contrary, the analogous radical reaction affords the anti-Markovnikov isomer, since the first step involves the radical bromination of the double bond, which produces a radical intermediate. Another example is the exclusive nucleophilic radical addition to the double bond of α,β-unsaturated carbonyl compounds, while nucleophilic carbanions may offer a mixture of 1,2- and 1,4 addition

products. Furthermore, the use of free-radicals is also advantageous to avoid 1,2-alkyl or hydrogen rearrangements.



Scheme 2. Polar versus radical regioselectivity

In turn, stereoselectivity of radical reactions has been traditionally less studied given that methods to generate such species under mild conditions were scarce and made controlling the configuration of the new stereocenter rather difficult. Moreover, the classical perception of radical processes as chaotic and difficult to control did not ease the emergence of stereoselective procedures. However, as the field grew and more radical-generation approaches were developed, diastereoselective methods based on chiral auxiliaries emerged. Indeed, pioneering studies by SIBI and PORTER proved that radical processes could also be highly stereoselective (*Scheme 3*)[22] and paved the way for recent enantioselective radical-based processes grounded in the use of chiral Lewis acids, organocatalysts, transition metal complexes bearing chiral ligands and, lately, non-covalent avenues that rely on hydrogen bonding or ion pairing interactions.[23]

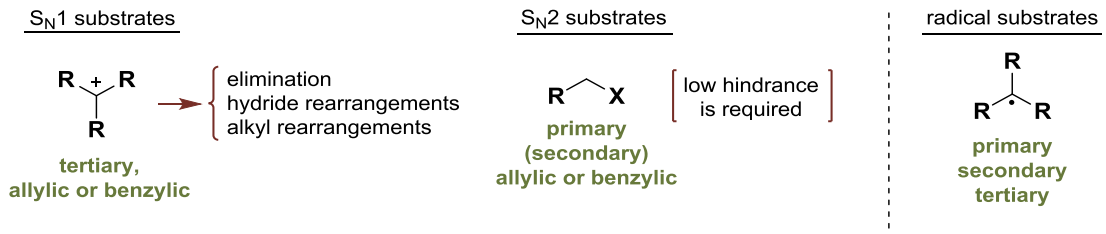


Scheme 3. Preliminary reports of enantioselective radical transformations

Radicals as an alternative

As a result of the mastering of radical generation in a controlled fashion and the broad knowledge of their reactivity, a wide array of stereoselective radical-based methods has recently blossomed. Actually, radical procedures usually complement polar transformations and offer solutions to overcome the hurdles found in heterolytic approaches.

A clear example is the radical alternative for substitution processes (S_N1 and S_N2) that Fu describes.[24] He first highlights the limited scope of such substitutions given that alkyl halides must satisfy some demanding requirements (*Scheme 4*). Specifically, the alkyl halide for S_N1 pathways must be prone to form a carbocation, which limits the options to tertiary, benzylic or allylic substrates. Furthermore, the formed alkyl carbocations may then undergo elimination to form a double bond or hydride and alkyl rearrangements, which seriously restrict the scope of such processes. Parallelly, electrophiles suitable for S_N2 substitutions are mostly restricted to non-hindered primary alkyl halides, allyl or benzyl halides, which are a small group of privileged substrates. More generally, hindered primary or secondary alkyl halides often suffer from serious difficulties to participate in such transformations.



Scheme 4. Issues in S_N1 and S_N2 processes

On the contrary, a wide scope of primary, secondary or tertiary alkyl radicals can be prepared from alkyl halides under mild conditions. Additionally, such species do not suffer undesired transformations such as hydride or alkyl rearrangements. Hence, halide substitution via radical pathways using transition metal catalysis is presented by Fu as an attractive alternative to classic substitution reactions.

More specifically, a restricted scope of electrophiles is also observed in the α-alkylation of carbonyl compounds, which is mainly achieved by heterolytic approaches that rely on S_N2 substitution reactions that use enolates as nucleophilic species.

Consequently, as FU states, the scope of the alkylation reactions is therefore also limited to privileged electrophiles.

2. α-Alkylation of Carbonyl Compounds

A fundamental piece of organic synthesis is the construction of the molecular framework. In this context, carbon-carbon bond formation is probably one of the most important tools for an organic chemist. Transformations such as nucleophilic addition to carbonyls, α-alkylation of carbonyls, aldol, transition metal-catalyzed coupling reactions (Heck, Suzuki-Miyaura, Sonogashira...) or pericyclic reactions are essential to the formation of the skeleton of the target molecules. Particularly, the asymmetric α-alkylation of carbonyl compounds is a useful transformation that involves the construction of a new carbon-carbon bond and, very often, the installation of a new stereocenter. This is the reason why it has been a key step in many total syntheses. For example, EVANS reported the total synthesis of Ionomycin A, an antibiotic that contains 14 stereocenters, four of which were installed through alkylation of chiral lithium or sodium enolates with alkyl bromides or alkyl iodides (*Figure 4*).[25]

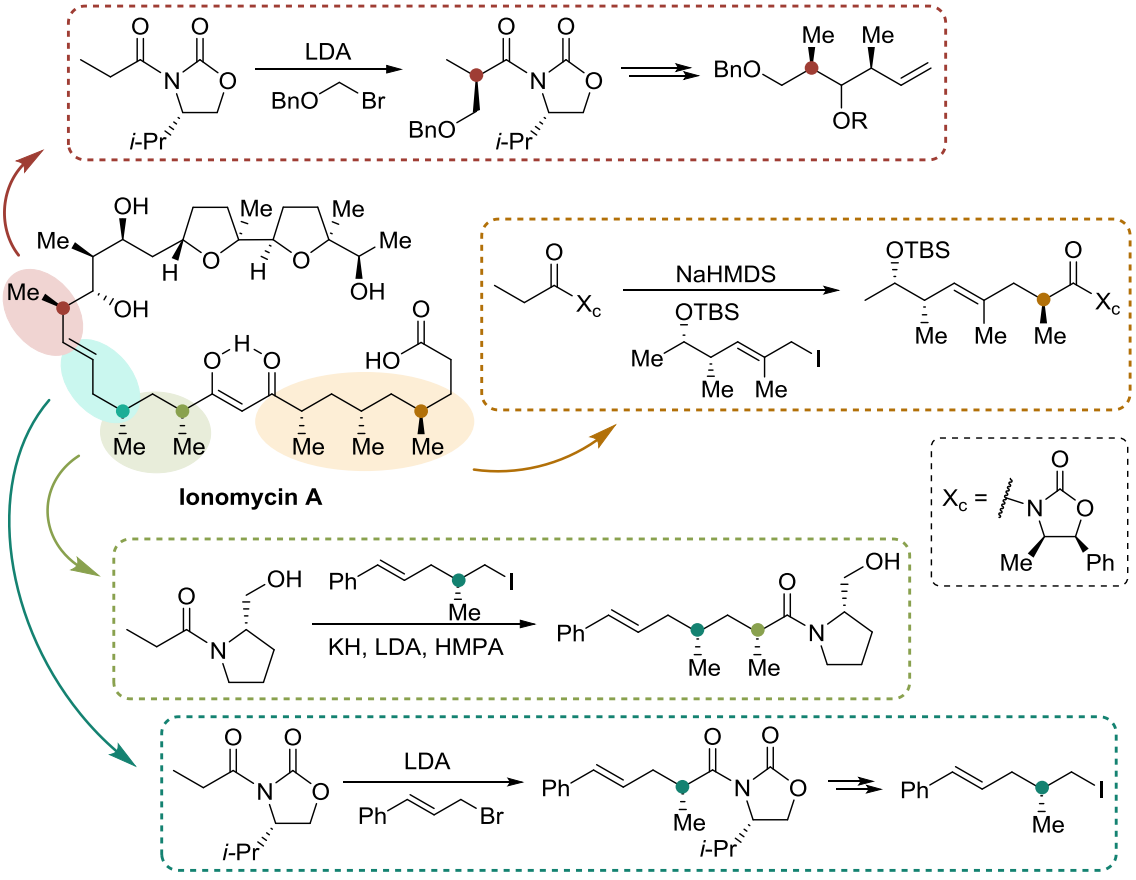


Figure 4. Asymmetric α-alkylation steps in the total synthesis of Ionomycin A

An asymmetric alkylation was also a key step in the synthesis of the diuretic drug Indacrinone, which was obtained through enolate formation in a biphasic medium with NaOH and a cinchoninium catalyst (*Figure 5*).[26] Although the α-alkylation reaction has been broadly studied for years, the development of new methodologies with a wider scope or higher functional group tolerance still generates interest among organic chemists.

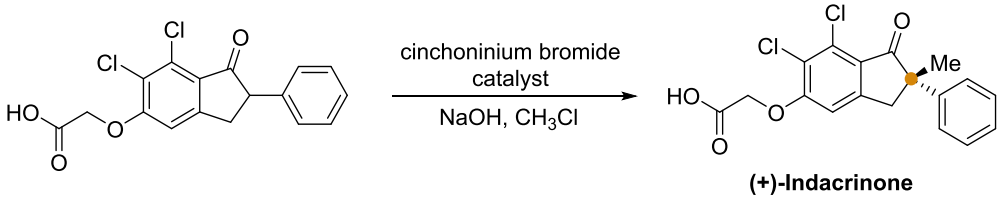
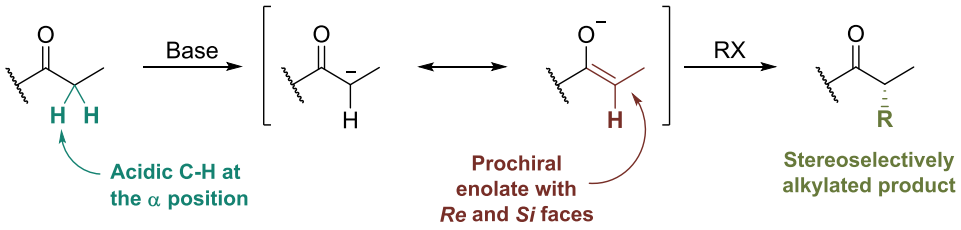


Figure 5. Asymmetric α-alkylation steps in the synthesis of Indacrinone

2.1 Heterolytic Approaches

As in many other fields, the α-alkylation of carbonyl compounds is mainly achieved by heterolytic methods. These leverage the acidity of the α position of a carbonyl compound to easily form an enolate. Enolates are commonly used in organic synthesis as nucleophilic species since they can react with a large range of electrophiles, for instance, with alkyl halides to yield α-alkylated products (*Scheme 5*).



Scheme 5. Asymmetric electrophilic addition to enolates

In terms of stereoselectivity, enolates can be defined as prochiral entities which can react *via* two different π-faces. An accurate differentiation of these faces will provide highly stereoselective alkylations. Additionally, the *Z*/*E* geometry of the enolate will have an impact on the final stereochemical outcome of the reaction. To solve such differentiation between the π-faces, different asymmetric methodologies have been developed over the past decades.[27–30]

Regarding the electrophile used, different alkylation pathways can be considered. For most approaches, the alkylation proceeds *via* S_N2 mechanisms, but some S_N1-like alkylations have also been reported.

α-Alkylations *via* S_N2 pathway

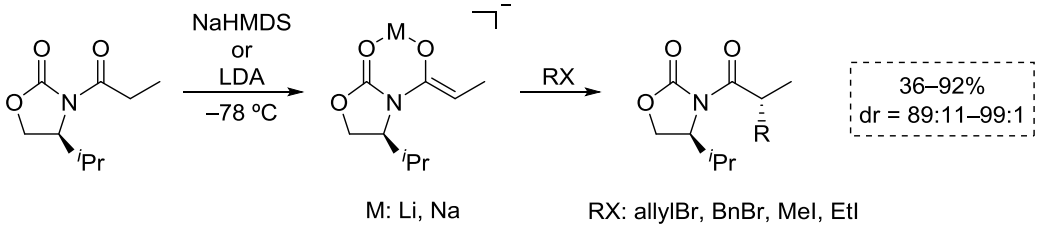
S_N2 based alkylations are, by far, the most employed in organic synthesis. In such reactions, electrophiles such as primary and unhindered alkyl halides are mainly used since they easily undergo S_N2 substitutions. A vast number of methods have been developed in which different approaches to control the stereochemistry can be found.

Use of chiral auxiliaries

With the use of prolinol as an early milestone,[31,32] several chiral auxiliaries have been developed since the eighties. Indeed, they have been established as the basis of α-alkylation of carbonyls due to their robustness, excellent stereocontrol and high yields. For the alkylation of carboxylic acids, imide-based auxiliaries were developed, as they can be easily attached to the substrate through amide-bond formation. In parallel, auxiliaries containing a hydrazine moiety were developed for the asymmetric alkylation of ketones or aldehydes.

EVANS' Oxazolidinones

They were first reported for aldol addition purposes[33] but soon after, Evans used oxazolidinones in diastereoselective alkylation reactions,[34] and since then, different analogues have been developed. Attachment of the chiral auxiliary to the acyl group gives the corresponding *N*-acyl oxazolidinone, which can be deprotonated with strong bases such as NaHMDS or LDA to form the enolate. In this case, *Z*-geometry of the enolate is conveniently forced due to $A_{1,3}$ steric interactions. In addition, the chelate formed between the *N*-acyl oxazolidinone and the metal center provides rigidity to the enolate structure. Both structural features favor a highly stereocontrolled alkylation (*Scheme 6*).

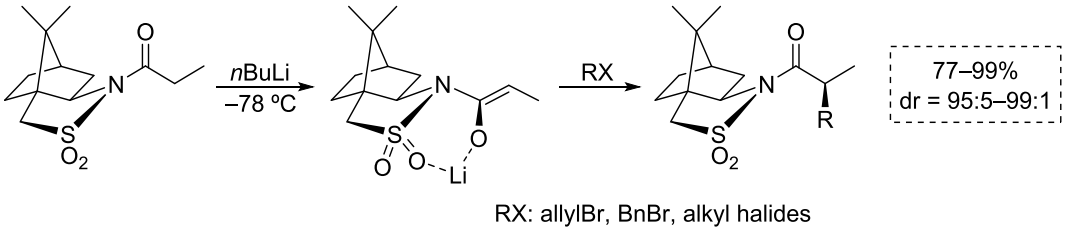


Scheme 6. Evan's alkylation of *N*-acyl oxazolidinones

Lithium enolates are only alkylated by highly activated electrophiles such as allyl or benzyl bromides through a S_N2 mechanism. Instead, more nucleophilic sodium enolates can react with other unhindered alkyl halides. Nevertheless, the scope of suitable alkyl halides is narrow and confined to small alkyl iodides, allyl and benzyl bromides.

OPPOLZER's Sultam

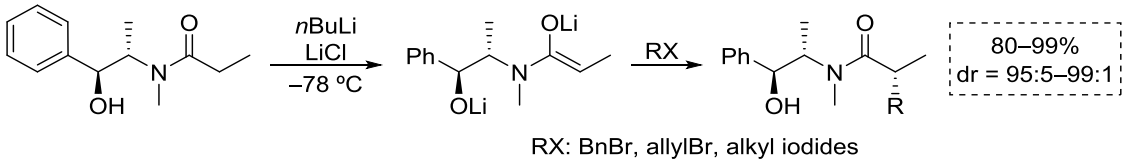
This camphor-based auxiliary[35] operates closely aligned to oxazolidinones. The *N*-acyl sultams can be deprotonated using *n*-BuLi or NaHMDS to form *Z*-enolates that undergo alkylation with a variety of primary alkyl, allyl or benzyl halides with excellent diastereoselectivities and good yields through a S_N2 mechanism (*Scheme 7*). As an advantage, the alkylated products are usually crystalline so can be easily purified *via* recrystallization.



Scheme 7. Oppolzer's alkylation of *N*-acyl camphor sultams

MYERS' Pseudoephedrine

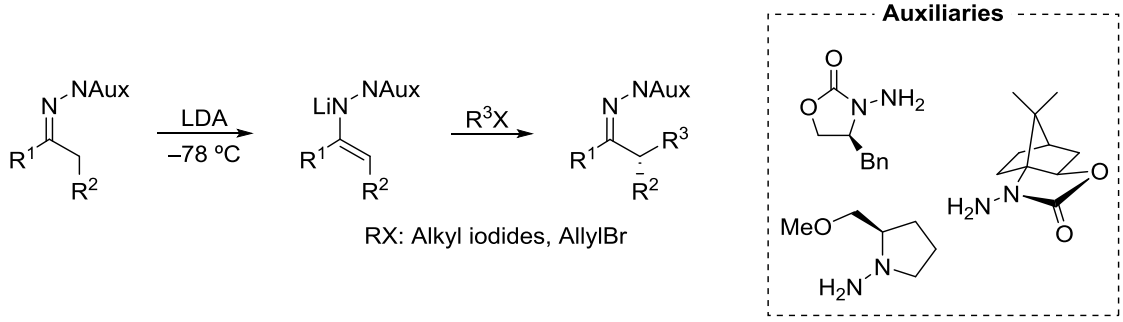
Inspired by LARCHEVEQUE's use of ephedrine,[36] MYERS described the alkylation of enolates using pseudoephedrine as the chiral auxiliary.[37] While other auxiliaries are used to form standard enolates, pseudoephedrine contains a hydroxyl group that is firstly deprotonated. Thus, a second equivalent of the base is required to form the desired enolate as a dianionic species, which is more reactive than monoanionic enolates. A broad range of branched primary alkyl halides engaging S_N2 substitutions can be used due to the high reactivity of the dianion (*Scheme 8*).



Scheme 8. Myers' alkylation of dianionic acylated pseudoephedrine

Auxiliaries for the alkylation of ketones

On the other hand, hydrazine-based auxiliaries have been described for the asymmetric alkylation of ketones. Attachment of these auxiliaries proceeds through formation of a hydrazone. Thus, the alkylation takes place through an aza-enolate species which presents higher nucleophilicity than the enolate analogue (*Scheme 9*). Again, these enolates can be alkylated just with primary alkyl and allyl halides.[38,39]

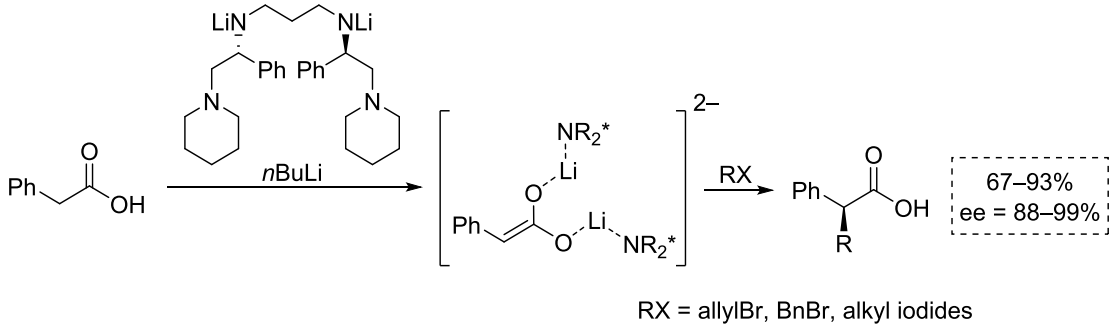


Scheme 9. Asymmetric alkylation of ketones and auxiliaries

Use of chiral reagents

Although chiral auxiliaries are a reliable solution for the asymmetric Cα-alkylation of carbonyl compounds, the need for both an attachment and a removal step entails a disadvantage, considering that it extends the total synthesis by two steps. Therefore, other approaches have emerged.

For instance, ZAKARIAN[40] developed a methodology in which the base, a lithium diamide, is the source of chirality. Therefore, the straightforward asymmetric alkylation of enolates can be achieved directly from carboxylic acids. Indeed, the double deprotonation of aryl carboxylic acids generates endiolate species that form aggregates with the chiral lithium amide. Subsequently, these aggregates are alkylated following a S_N2 pathway with great enantioselectivities using alkyl halides (*Scheme 10*). Given that endiolates have superior nucleophilicity than conventional enolates, the alkylation functioned with less activated alkyl halides. However, this method can only be applied to phenylacetic derivatives or α,β-unsaturated carboxylic acids.



Scheme 10. Asymmetric alkylation using Zakarian's chiral amide

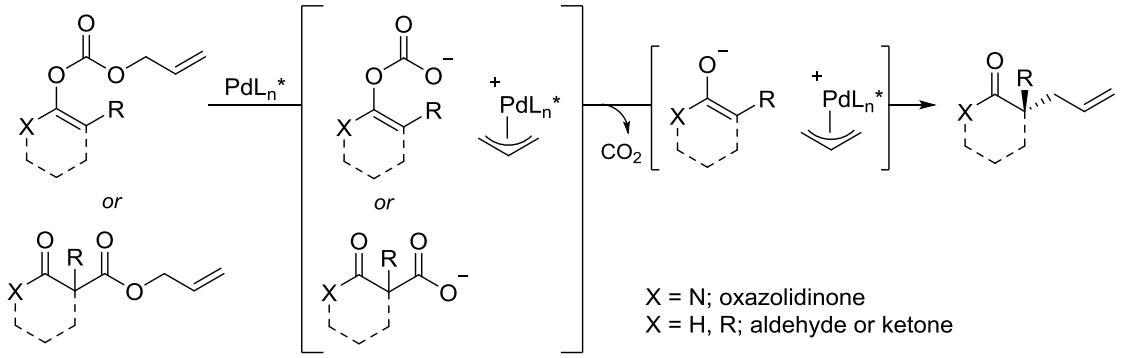
Chiral catalysis

While the use of chiral amines allows the asymmetric α-alkylation of carbonyl compounds in one step, the source of stereocontrol is still employed in stoichiometric

amounts. Alternatively, the development of asymmetric alkylations using chiral catalysts has become a growing area in both facets; transition-metal catalysis and organocatalysis.

Enantioselective TSUJI-TROST Allylation

Inspired by TSUJI-TROST allylation, where a β-allyl ketoester or an allyl enol carbonate is allylated through a decarboxylative process by means of Pd(0) catalysis, STOLTZ[41] and TROST[42] independently described the enantioselective version using a chiral ligand. In this transformation, an electrophilic π-allyl palladium complex is formed, and the resultant anion counterpart undergoes decarboxylation which gives way to an enolate that, upon recombination with the chiral π-allyl palladium, produces an asymmetric α-allylated product (*Scheme 11*). However, the alkylation is limited to symmetric cyclic ketones. Later, this approach had been further studied and there are now plenty of improved variations including the use of external allyl donors or the allylation of ester derivatives.[29,43] Even so, this catalytic method has a very narrow scope in terms of alkylating agents since just allyl groups can be attached following this procedure.



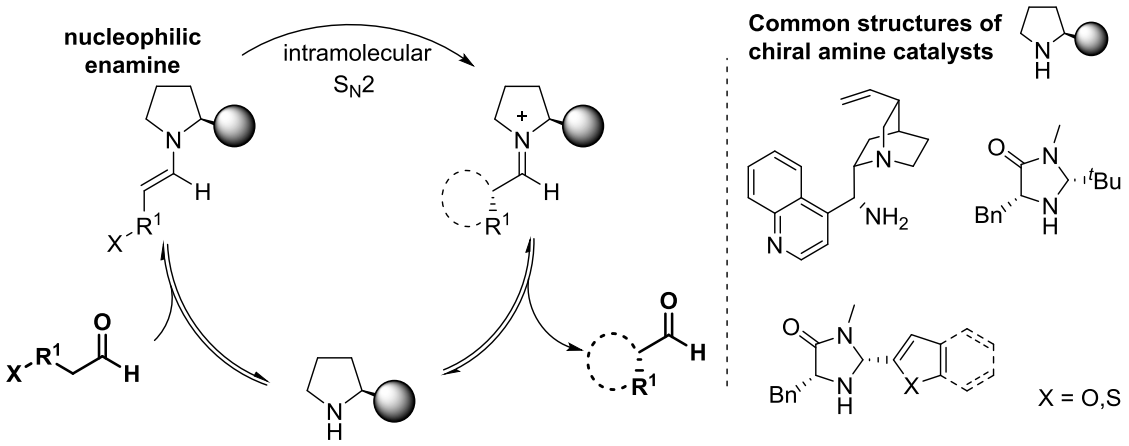
Scheme 11. Enantioselective and catalytic allylation

Enamine catalysis

Formation of an enamine is a common strategy to activate carbonyl compounds in an organocatalytic fashion. The use of a chiral amine in substoichiometric quantities to form such enamines was driven by LIST as he described an asymmetric aldol reaction catalyzed by proline.[44] Since then, other chiral amines have been developed that permit the catalysis of addition reactions at the α-position of carbonyls to a range of electrophiles such as Michael acceptors, aldehydes or imines.[45]

However, the use of alkyl halides as electrophiles has not been fully successful. The low nucleophilicity of enamines compared to the enolate partner hampers the substitution reaction of an alkyl halide *via* S_N2. Unfortunately, most of the examples

reported so far are intramolecular, so the intermolecular alkylation still remains a challenge (*Scheme 12*).

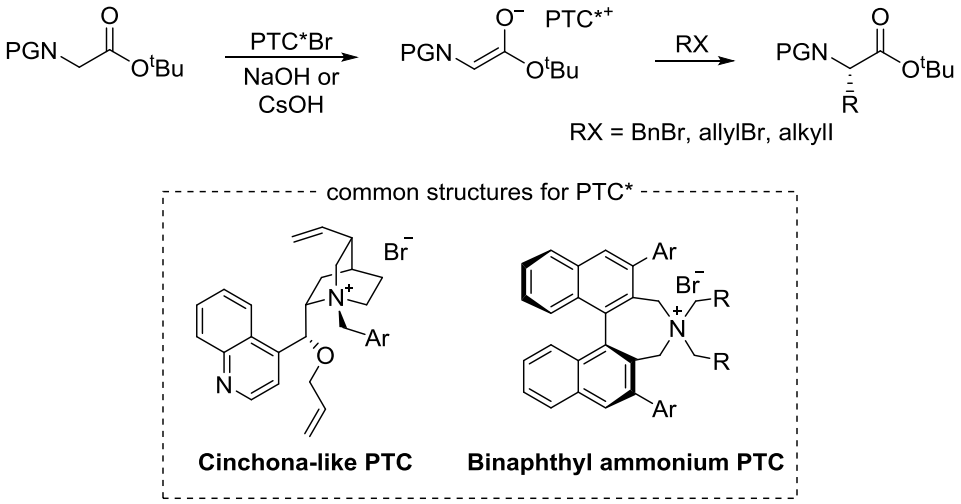


Scheme 12. α-Alkylation of carbonyl compounds using enamine catalysis

Phase-Transfer Catalysis

The fact that phase-transfer catalysis offers mild reaction conditions together with the use of inexpensive and environmentally friendly reagents has triggered intense research in this field for a wide range of transformations.[46,47] The enantioselective alkylation of enolates is no exception.

Nowadays, there are different chiral phase-transfer catalysts (PTC), such as those developed by COREY[48] or MARUOKA[49], that allow the alkylation of protected glycines with benzyl or allyl bromides or sterically unhindered alkyl iodides in a biphasic solvent system (*Scheme 13*). The key to obtain high enantioselectivities is the exchange of the counterion of the enolate species with the chiral quaternary ammonium cation that forms the PTC. Other catalysts have also been applied to the asymmetric alkylation of ketones, esters or other amino acid derivatives.[29,30]

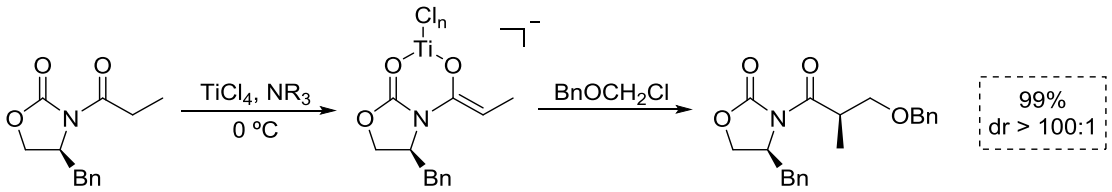


Scheme 13. Phase-transfer catalyst alkylation approach

α-Alkylations via S_N1 pathway

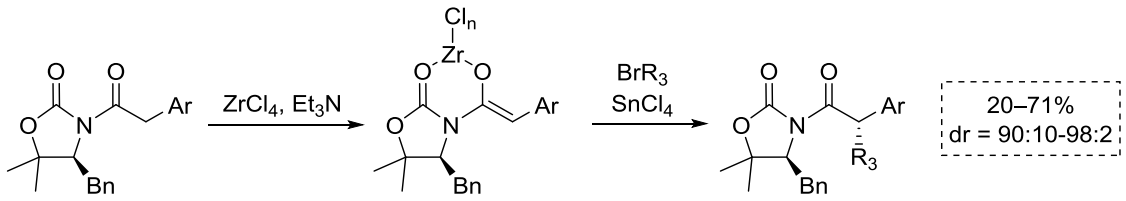
In most of the methodologies described in the previous section the enolate is alkylated with an alkyl halide through a S_N2 pathway. Due to mechanistic requirements, these examples have a limited scope in terms of alkylating agents, which mainly encompass activated primary alkyl iodides, allyl and benzyl bromides. In contrast, few alternatives that use alkyl halides prone to undergo S_N1 substitutions have been developed.[50]

For example, EVANS reported the *soft-enolization* of *N*-acyl oxazolidinones to form titanium enolates, which do not react *via* S_N2 but through S_N1-like processes with electrophiles predisposed to form carbocations (*Scheme 14*).[51]



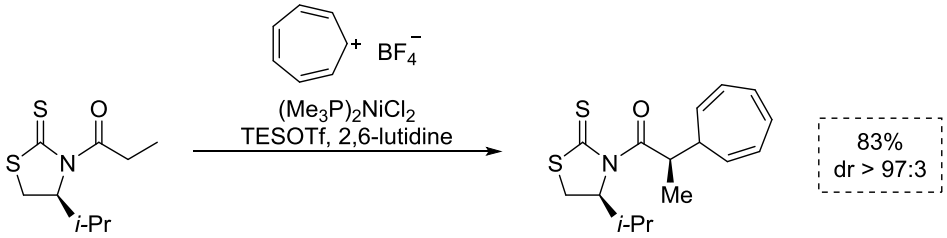
Scheme 14. Evans' soft enolization and S_N1-like alkylation

A rare example of the tertiary alkylation of zirconium enolates was described by ZAKARIAN.[52] In this work, oxazolidinone α-arylacetic derivatives are alkylated with tertiary alkyl bromides, which are activated with tin chloride (*Scheme 15*). Although the scope for this alkylation is quite narrow, tertiary alkylation has otherwise been accomplished on just a few occasions, usually in a non-stereoselective manner.



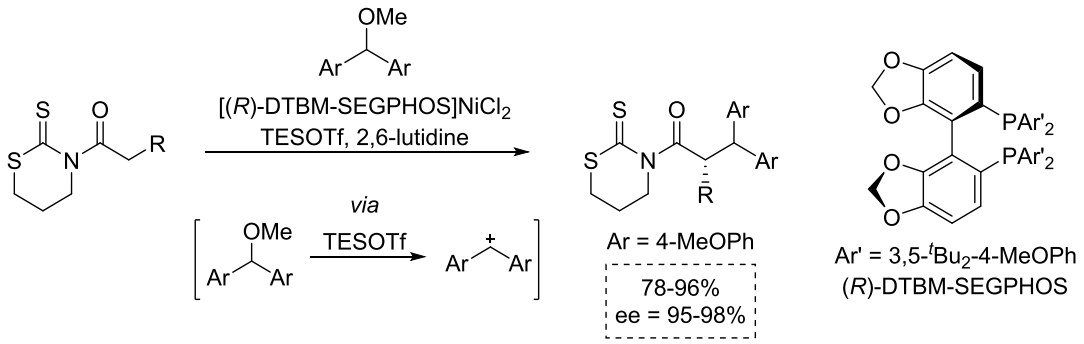
Scheme 15. Tertiary alkylation of zirconium enolates

Interestingly, S$_N$1 alkylations that proceed through catalytic metal enolate formation have been reported. For instance, insertion of carbenium cations was achieved by our group in a nickel catalyzed S$_N$1-like alkylation.[53] In that work, tropylium salts were used to alkylate the chiral enolates in a highly diastereoselective and high yielding direct reaction (*Scheme 16*).



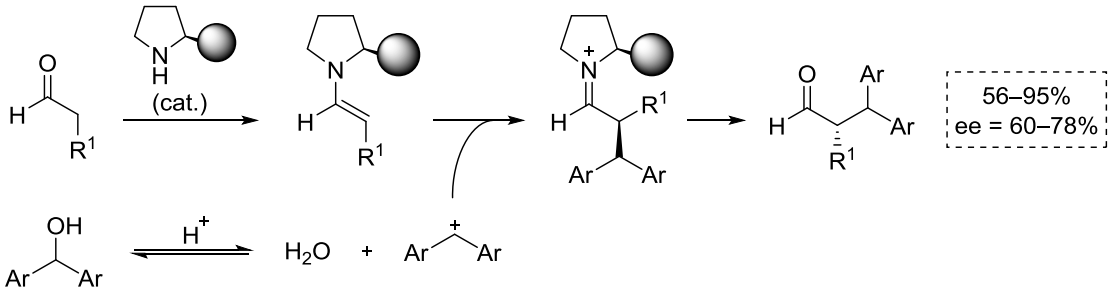
Scheme 16. Direct alkylation of nickel enolates with carbenium ions

Later, the group also described the enantioselective alkylation of *N*-acyl thiazinanethiones with activated benzhydryl ethers catalyzed by chiral nickel(II) complexes.[54] In this work, the electrophile is activated with TESOTf to produce a carbenium intermediate that reacts with the enolate through a S$_N$1 mechanism. The enantioselective formation of the new bond is achieved due to the chiral ligands of the nickel complex without the need of a chiral auxiliary. High yields and excellent enantioselectivities were attained for a variety of aryl groups (*Scheme 17*).



Scheme 17. Direct catalytic alkylation of nickel enolates with benzhydryl derivatives

On the other hand, while enamine catalysis was not successful for SN2-predisposed alkyl halides, formation of carbocation species to undergo SN1 reactions has been more prosperous.[55] For instance, COZZI developed the organocatalyzed alkylation of aldehydes with diaryl alcohols that proceeds through carbenium intermediates (*Scheme 18*).[56]

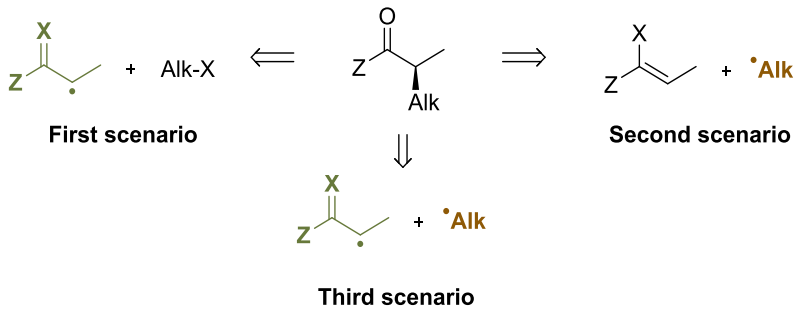


Scheme 18. Cozzi's alkylation of aldehydes

Even though these examples provide a broader scope of alkylating agents, species able to form stabilized carbocations that do not suffer side reactions such as elimination, especially in the basic conditions of enolate formation, are limited.

2.2 Radical Approaches

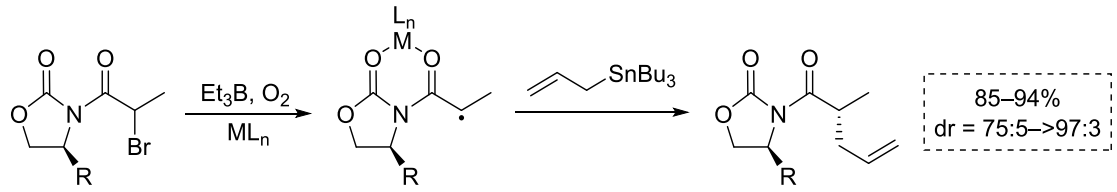
Up to this point, the alkylations described rely on polar mechanisms. To expand the asymmetric alkylation methods, the chemical community has also attempted this transformation from the opposed point of view: the homolytic pathway. The involvement of radicals has enabled α-alkylations of carbonyl compounds that were not possible using polar mechanisms. With that in mind, three main scenarios can be considered. Firstly, the generation of a Cα-carbonyl derived radical species that reacts with a neutral alkylating agent. Secondly, the opposite approach in which an enolate species reacts with a radical alkylating agent. Finally, a third approach consists in the generation of two types of radical species; one derived from the carbonyl and the other as alkylating agent.



Scheme 19. Approaches to radical alkylation

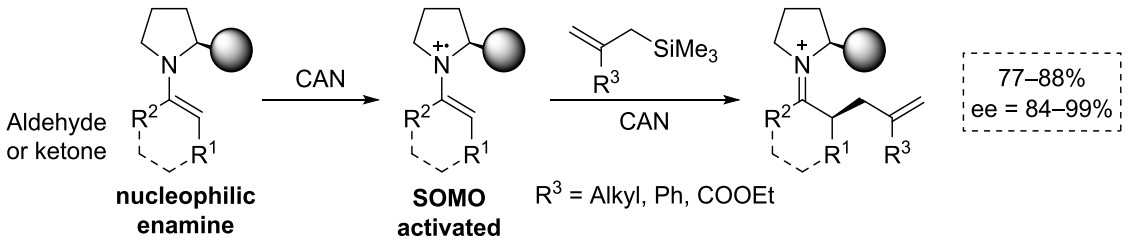
First scenario: Radical carbonylic counterpart

An early example of radical alkylation based on the first scenario was described by SIBI in 1996.[57] In his work, α-carbonyl radicals are obtained from their α-bromo counterparts using Et_3B and oxygen as initiators. These intermediates then react with allyltributyl stannanes affording allylated products. Diastereoselectivity is achieved with oxazolidinones as chiral auxiliaries and a Lewis acid to form a chelate to ensure rigidity (*Scheme 20*).



Scheme 20. Sibi's radical allylation

In 2007 MACMILLAN coined the concept of Single Occupied Molecular Orbital (SOMO) activation adapted to the frame of the first scenario. In this approach, a chiral enamine is oxidized *via* single electron transfer (SET) so that a 3π electron radical cationic intermediate (SOMO) is formed. In a pioneering report, enamines derived from aldehydes are activated using cerium(IV) ammonium nitrate (CAN) as a single electron oxidant. The resultant radical intermediate reacts with allyl trimethyl silanes to give asymmetrically allylated products (*Scheme 21*).[58] Subsequently, the methodology was expanded to the allylation of ketones[59] and other transformations including α-vinylation, α-enolation, α-nitroalkylation or α-arylation.[55]



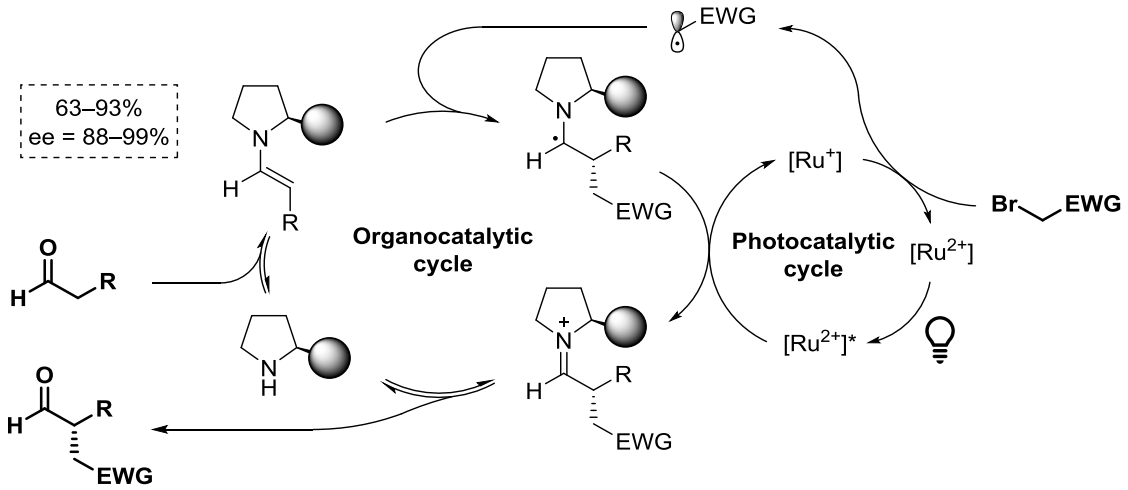
Scheme 21. Key steps for SOMO activation of carbonyl compounds

In both methodologies, the formation of a Cα-radical carbonyl derivative allows the introduction of electron-rich alkyl chains. However, the scope is limited in terms of the alkylating agent since it is restricted to allylation transformations.

Second scenario: Radical alkylating agent

While in the previous example the use of electron-rich allyl silanes as alkylating agents accounts for the formation of a radical cation, the second scenario permits the alkylation of chiral enamine nucleophiles with radicals derived from electron-poor alkyl halides.

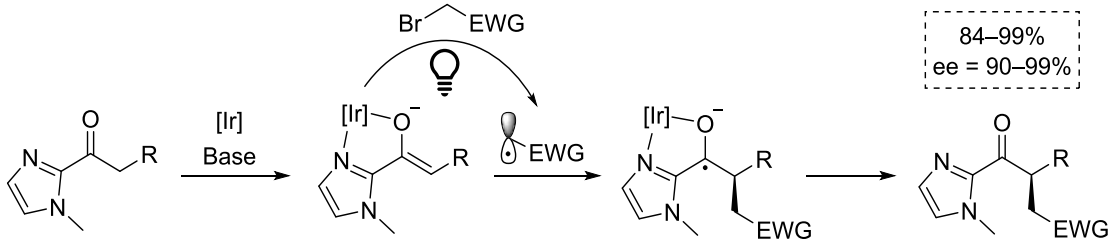
This scope-expansion of alkylating substrates firstly reported by MACMILLAN combines chiral enamine catalysis to activate an aldehyde with photoredox catalysis to generate electron-deficient radicals from α-bromocarbonyl species and a ruthenium photocatalyst (*Scheme 22*).[17] Later on, iridium and organo-photocatalysts have been used to perform such transformations.[55]



Scheme 22. Alkylation combining organo- and photoredox catalysis

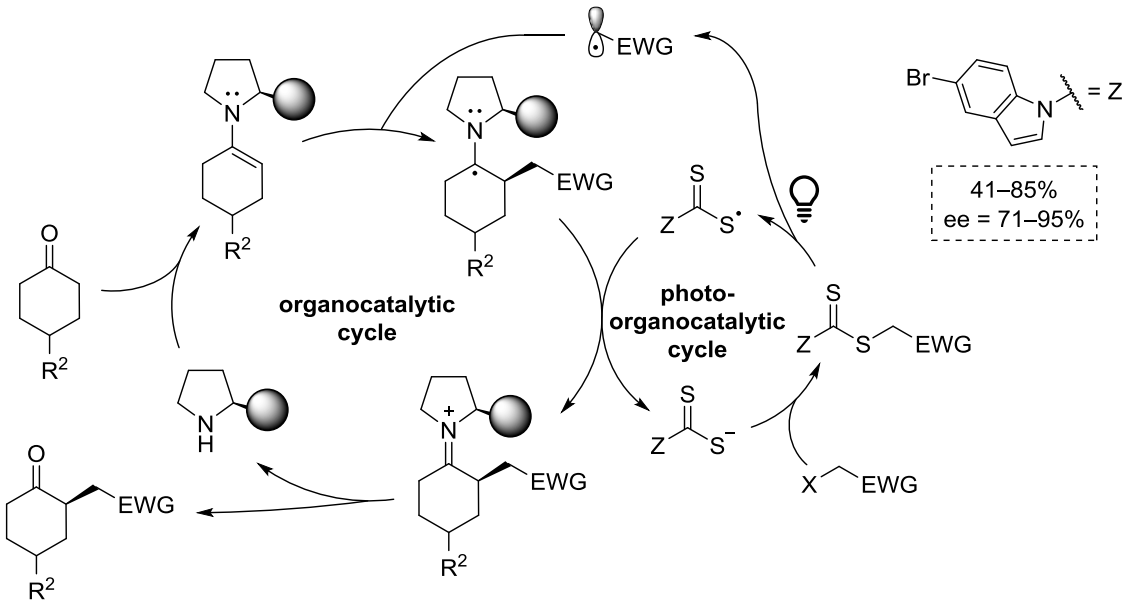
Interestingly, MEGGERS developed the alkylation of 2-acyl imidazoles with electron-deficient alkyl bromides and an iridium chiral catalyst that acts as both chiral-at-metal Lewis acid and photosensitizer (*Scheme 23*).[60] Formation of a chelate between the chiral photocatalyst and the 2-acyl imidazole allows a favored deprotonation of the acyl group to form the enolate with a soft base and remarkable stereocontrol. On the other hand, the excited iridium photocatalyst prompts the scission of the C–Br bond of the alkyl halide creating an alkyl radical that combines with the one-face hindered enolate to furnish the α-alkylated product. Similarly to the previous example, the photocatalytic cycle is closed by the resultant radical intermediate. The method was proved to work with high enantioselectivities and yields for a wide range of acyl imidazoles as well as alkyl bromides, which always bear an electron-withdrawing group. Post functionalization of

the product by removal of the imidazole leads to functional groups such as carboxylic acids, esters or amides.[61]



Scheme 23. Megger's α-alkylation of acyl imidazoles using photoredox transition-metal catalysis

Moving away from transition metal catalysis, MELCHIORRE developed an organocatalyst to generate radical species, which was crucial to establish an experimentally mild alkylation of ketones.[62] Indeed, light does not excite the catalyst itself. Instead, the anionic catalyst reacts *via* S_N2 with primary (and even secondary) electrophiles to generate an alkyl dithiocarbamate species, which absorbs light and consequently breaks homolytically through the C–S bond to generate the alkyl radical species, which are easily trapped by the chiral enamine. Finally, the organo-photocatalyst is regenerated by oxidation of the radical intermediate formed in the alkylation step (*Scheme 24*).



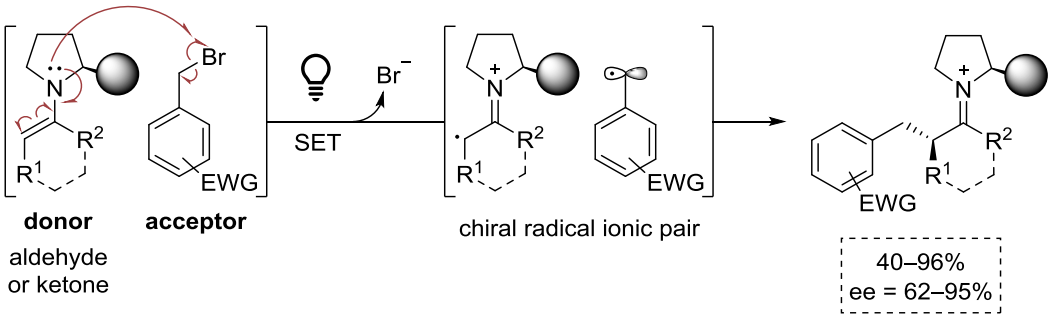
Scheme 24. Melchiorre's photochemical organocatalytic α-alkylation of carbonyl compounds

In this second scenario, the nucleophilic species, either enamines or metal enolates, react with alkyl radicals to furnish the alkylated products. Unfortunately, these examples

require activated alkyl halides that possess an electron-withdrawing group to facilitate radical generation, which once again restricts the scope of such alkylations.

Third scenario: Radical carbonylic counterpart and alkylating agent

Finally, a two radical species approach has been reported by MELCHIORRE. As shown in *Scheme 25*, formation of an electron donor-acceptor complex (EDA) avoids the use of a photocatalyst and still generates two different radicals. In this strategy, a chiral enamine behaves as a donor species, while an alkyl bromide bearing an aromatic ring acts as an acceptor counterpart. When this EDA complex is irradiated, a SET process takes place from the enamine to the alkyl halide, which undergoes homolysis of the C-Br bond to produce an alkyl radical, leading to a chiral radical ionic pair. Recombination of the alkyl radical with the chiral radical cation furnishes a new carbon-carbon bond in a stereocontrolled manner.[63] Such a procedure was later applied to the alkylation of ketones with a quinine derived catalyst.[64]



Scheme 25. Key step for the alkylation of carbonyl compounds through an EDA complex

In fact, it was also described that when irradiated, enamines themselves, could act as a photosensitizer and initiate the homolytic cleavage of the C–Br bond of some electron-poor alkyl halides without the need to form an EDA complex. Then, the alkyl radical formed reacts with another neutral enamine compound, starting a radical chain reaction.[60,65]

All these examples prove that the involvement of electronically open shell species in alkylation reactions has permitted the problem to be addressed through new perspectives. For instance, enamine catalysis was not a feasible solution for the alkylation of carbonyls with alkyl halides through classic S_N2 nucleophilic substitution due to the low nucleophilicity of enamines. However, the generation of alkyl radicals has allowed chemists to exploit this type of organo-catalysis in such transformations, thus expanding

their scope and providing novel advantageous alternatives. All the same, in these examples, an electron-withdrawing group attached to the primary alkyl halide is usually required to generate the radical species, which restricts the scope of alkyl groups that can be attached utilizing these procedures.

2.3 Scope overview

In summary, the available scope of the alkyl group that can be asymmetrically attached to the α position of a carbonyl compound is not broad at all (*Figure 6*). Firstly, there are numerous methodologies to insert activated allylic or benzylic groups *via* heterolytic or radical mechanisms. Instead, the alkylation with primary alkyl moieties, which can also be performed through many diverse heterolytic or radical procedures, is mainly restricted to non-hindered or activated alkyl bromides and few other alkyl iodides. Much fewer methodologies allow the insertion of secondary substrates, for which it is very difficult to undergo S_N2 substitutions. Alternatively, some S_N1 alkylations have been achieved with very particular substrates, robust enough to avoid undesired rearrangements of the carbenium intermediates. Finally, alkylation with tertiary alkyl groups is very rare; it can't be achieved through S_N2 procedures, and again there is a limited scope of suitable substrates composed by those prone to S_N1 mechanisms.

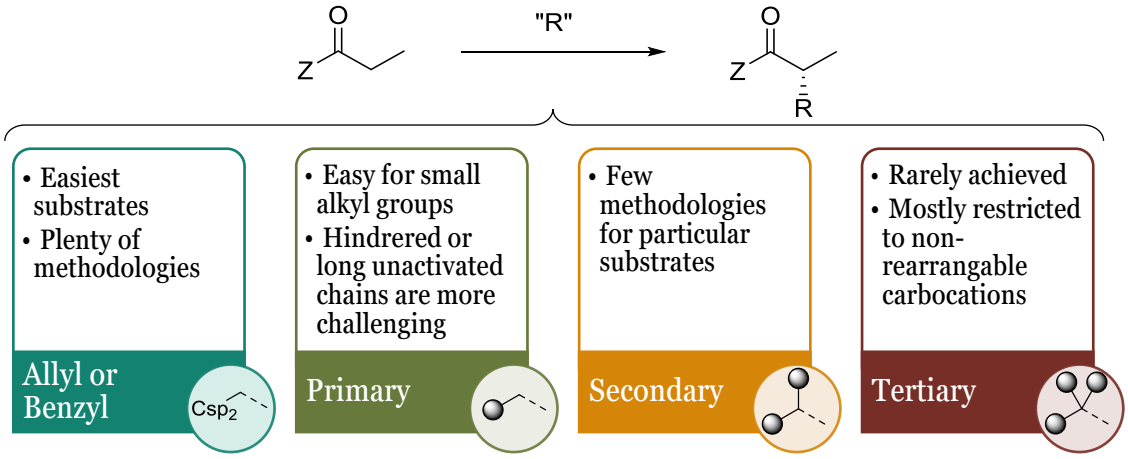


Figure 6. Scope of alkylation reactions – alkylating agents

On the other hand, for the nucleophilic component there are abundant reports for performing alkylations of either carboxylic acid derivatives, aldehydes or ketones through heterolytic methods. However, there are far less radical methods available to perform such transformations and, while some work has been done in the field of radical ketone alkylation, mainly through enamine catalysis, there are limited examples that allow the

radical alkylation of carboxylic acid derivatives through metal enolate formation (*Figure 7*).

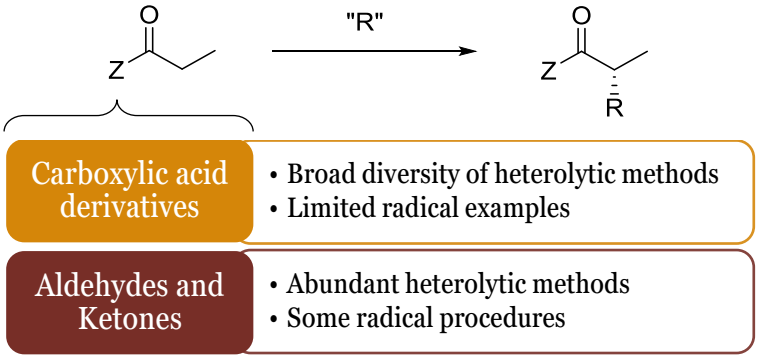


Figure 7. Scope of alkylation reaction – carbonyl derivative

3. Titanium Enolates

Enolates are one of the most common and useful types of carbon nucleophiles. Indeed, they easily react with carbon electrophiles to form new carbon-carbon bonds, which is one of the bases to construct the backbone of a target molecule. As shown in the previous section, formation of an enolate is the main strategy to achieve the α-alkylation of carbonyl compounds. It is important to highlight that enolates are not isolated due to their high reactivity, and because they are moisture, air, and sometimes temperature sensitive. Consequently, a wide range of reaction conditions can be used for their preparation *in situ*, leading to different structures and reactivities of these nucleophilic species. Variables such as the base, the solvent, the addition of chelating compounds, the temperature or the enolization procedure are certainly crucial to understand the changes in reactivity.[66] Although sodium or lithium enolates are the most popular and have been extensively studied for many decades, other metal enolates exhibit different features and allow new transformations. For some years now, the group has been studying the special radical reactivity of titanium enolates, and how it can contribute to improve some already established methodologies.

3.1 Preparation and Structure

Titanium enolates can be prepared by transmetallation from lithium enolates, replacement of the silyl group from silyl enol ethers, or direct enolization from a carbonyl compound.[67] The last method employs titanium Lewis acids that coordinate to the carbonyl, and a soft base to deprotonate the α-carbon.[68,69] This technique is known as

soft-enolization since it does not require a strong base to form the enolate, uses mild conditions and is compatible with sensitive functional groups. The direct enolization of *N*-acyl oxazolidinones was described in 1990 by EVANS.[51] It was specified that first, titanium species (either $TiCl_4$ or Ti(*i*-PrO)Cl_3) form a complex with the substrate, and then, after a trialkylamine is added, the enolization takes place, affording a deep-dark purple solution (*Figure 8*).

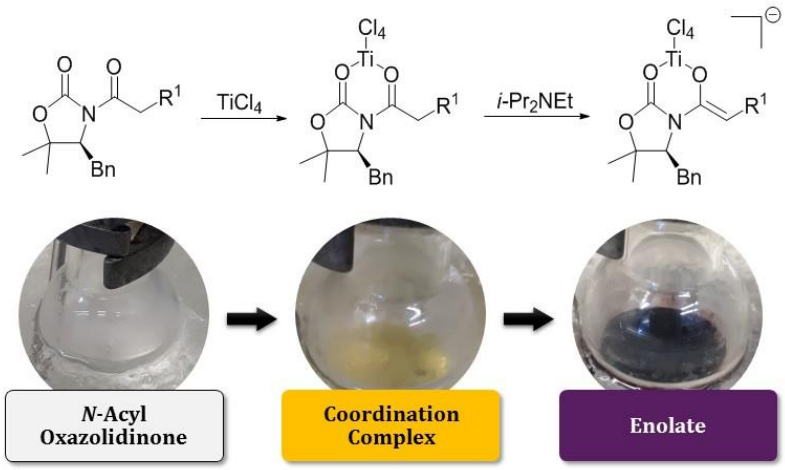


Figure 8. Soft enolization of titanium enolates

The metal in titanium enolates from *N*-acyl oxazolidinones is coordinated to both the carbonyl oxygen of the oxazolidinone and that of the acyl moiety. Therefore, the whole system acquires rigidity, which leads to higher π-face differentiation (*Figure 9*). For these species, the *Z* geometry of the enolate is preferred due to allylic strain in the *E*-enolate.

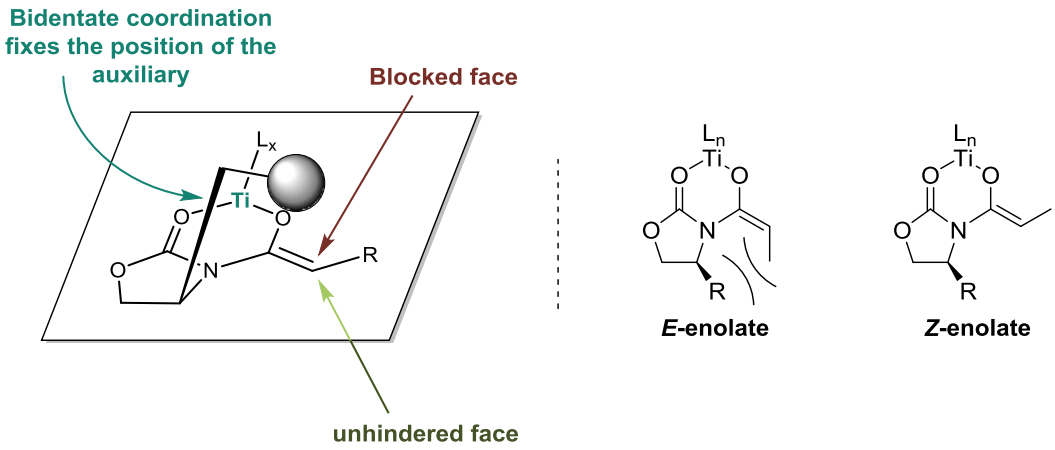
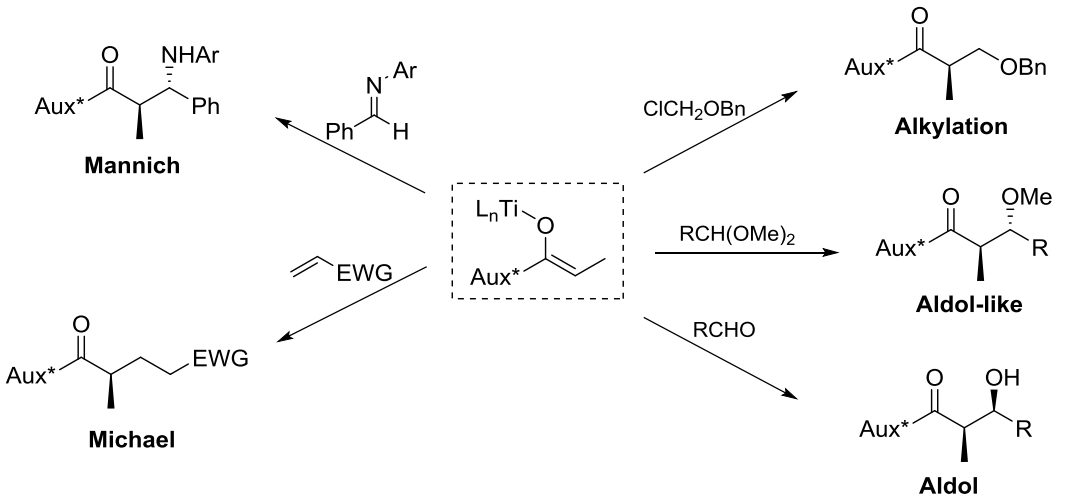


Figure 9. Structure of titanium enolates

3.2 Reactivity and Applications

Titanium enolates have been used as nucleophilic species in a broad variety of reactions, most of which, include an EVANS-like chiral auxiliary for the induction of asymmetry (*Scheme 26*).[66,67] Contrary to other metal enolates, they only react with electrophiles with a predisposition for S_N1 reactivity.[51] Moreover, the addition of titanium enolates to acetals has also been reported as an aldol-like reaction that generates two stereocenters. Additionally, a vast amount of work has been published regarding aldol reactions with titanium enolates, and conditions to access either the *syn*- or the *anti*-adducts have been reported. Besides, aldol additions to titanium enolates from chiral ketones have also been studied. Alternatively, imines derived from aromatic aldehydes are also suitable electrophiles to perform MANNICH-type reactions. And finally, some work in conjugate additions with Michael acceptors has also been completed.[66]

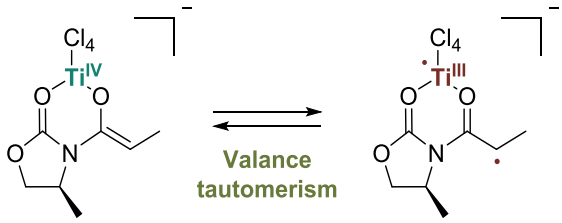


Scheme 26. Reactivity of titanium enolates

3.3 Biradical Character

Interestingly, titanium enolates exhibit an extraordinary character that remained hidden for many years. Quantum chemical studies of titanium enolates from chiral α-benzyloxy ketones indicated that these species are found in equilibrium between a nucleophilic titanium(IV) enolate and a biradical titanium(III) enolate.[70,71] Later, this character was further studied in titanium enolates from *N*-acyl oxazolidinones (*Scheme 27*).[71] This equilibrium, known as *valence tautomerism*, arises from a single electron transfer (SET) between the organic ligand (the enolate) and the titanium metal. This process should not be mistaken for resonance structures, in which two drawings represent the same structure. In this valence tautomerism, changes in the structure of the

enolate, particularly the Ti-O distance, are responsible for the equilibrium between the two different species.



Scheme 27. Model substrates used in the computational studies of the valance tautomerism

According to computational studies, this process entails a change in the electronic distribution of the ligand; the titanium(IV) enolate corresponds to a closed shell configuration, while titanium(III) species have an open shell configuration in which one electron is localized in the titanium and the other in the acyl moiety. As a matter of fact, the species with an open shell configuration can be found in two different electronic states: *singlet* and *triplet*, which correspond to nearly identical geometries and electronic features of the enolate. *Figure 10* describes the energies of the main electronic configurations; it shows that the singlet and triplet biradical states have very similar energy curves (red and orange respectively), which are not far from the closed shell curve (blue). The low difference between the energies of the two configurations causes the low energy barrier of the equilibrium between the two species, which makes it impossible to isolate them.

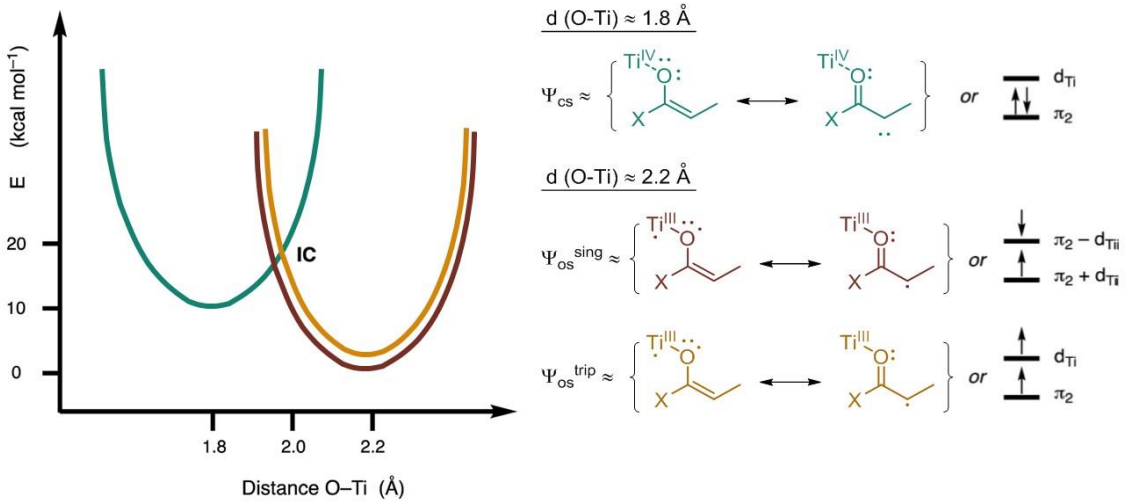
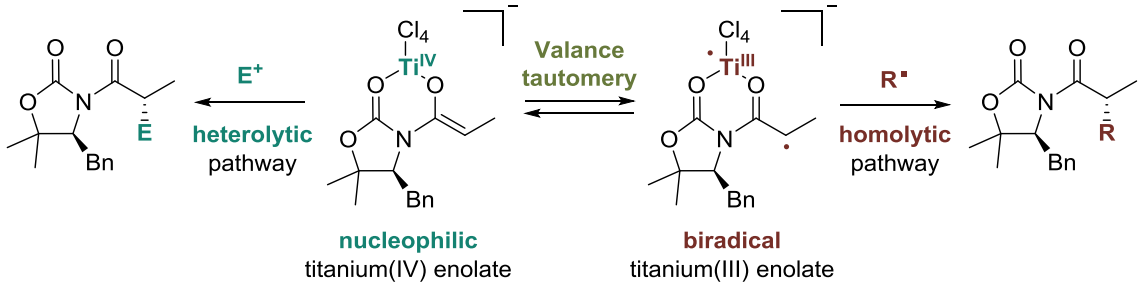


Figure 10. Description of the electronic states involved in the valence tautomerism[71]

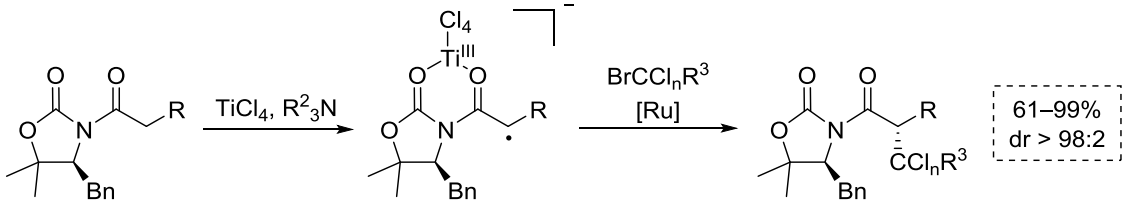
Additionally, EPR studies of the titanium enolate from 4-benzyl-5,5-dimethyl-*N*-propanoyl-1,3-oxazolidin-2-one were conducted and identified the triplet electronic state; proving the existence of a titanium(III) biradical enolate.

This valance tautomerism provides titanium enolates with a dual behavior. The closed shell configuration is responsible for their polar reactivity in the presence of electrophiles (*Scheme 28, left*), as seen in the previous section, whereas the open shell configuration grants titanium enolates a biradical character that allows them to react with other radicals, opening the opportunity to explore new transformations that may overcome the limitations of the heterolytic world (*Scheme 28, right*).



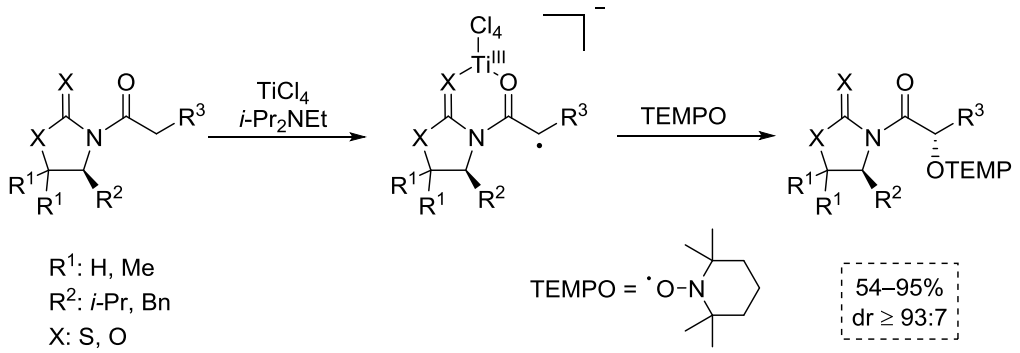
Scheme 28. Dual character of titanium enolates

Some examples of this reactivity have already been published, which give support to the hypothesis of the biradical enolate. ZAKARIAN reported the haloalkylation of the titanium(IV) enolates from chiral *N*-acyl oxazolidinone species using a ruthenium catalyst to generate *in situ* a chloroalkyl radical that recombines with the titanium enolate (*Scheme 29*).[72,73]



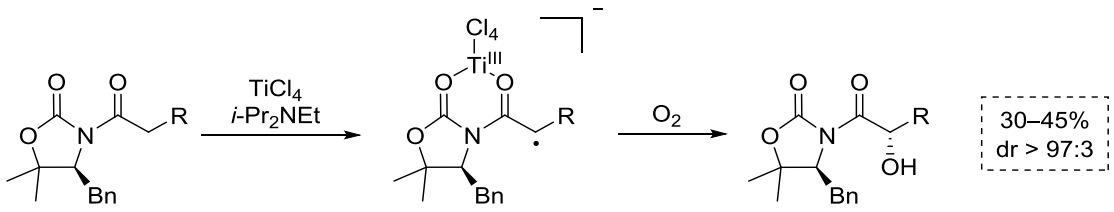
Scheme 29. Radical trichloromethylation of titanium enolates

More recently, ZAKARIAN and URPÍ and ROMEA independently described the radical reaction of titanium enolates with TEMPO, a stable oxygen radical. The corresponding aminoxylated products were then obtained in high yields and diastereoselectivities (*Scheme 30*).[74–76]



Scheme 30. Radical aminoxylation of titanium enolates

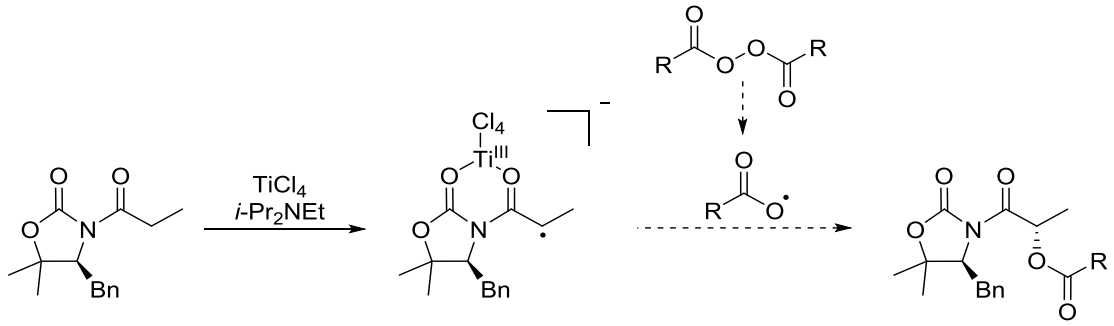
Finally, the simple oxidation of biradical titanium enolates with oxygen, a paramagnetic molecule, was reported by URPÍ and ROMEA. α-Hydroxy adducts were obtained in low yields and high diastereoselectivities (*Scheme 31*).[77]



Scheme 31. Radical oxidation of titanium enolates

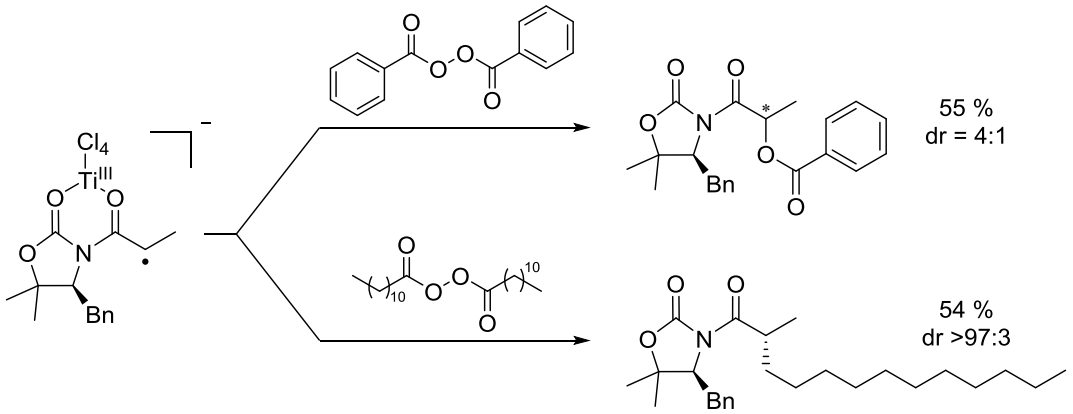
3.4 Background of this thesis

The stereoselective oxidation of titanium enolates provided experimental evidence of their biradical character, which encouraged the group to keep studying radical precursors to react with titanium enolates. For that reason, diacyl peroxides were thought to be good candidates since they possess a labile O-O bond, whose homolytic cleavage might render two acyloxy radicals (*Scheme 32*).



Scheme 32. Expected oxidation of titanium enolates with diacyl peroxides

Therefore, Alejandro Gómez-Palomino tested titanium enolates from *N*-acyl oxazolidinones with commercially available dibenzoyl peroxide (**BPO**) and dilauroyl peroxide (**LPO**) during his thesis.[78] As seen in *Scheme 33*, different results were obtained with the two peroxides. After the addition of dibenzoyl peroxide, the expected aroyloxidized adduct was obtained with a moderate yield and a moderate diastereoselectivity. On the contrary, dilauroyl peroxide afforded an alkylated product as a result of a radical decarboxylative process in a moderate yield and excellent diastereoselectivity. A lot of attention was drawn to such an unexpected result because it meant the introduction of a long and deactivated alkyl chain, which is a rare accomplishment.



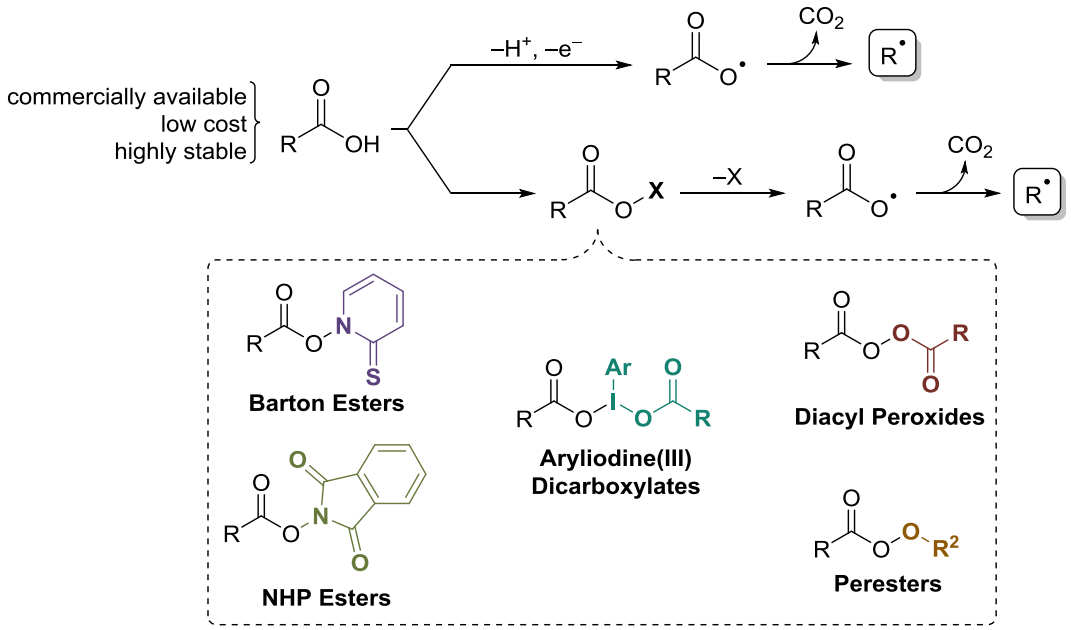
Scheme 33. Preliminary results of the reaction between titanium enolates and diacyl peroxides

After these results, Alejandro Gómez-Palomino started the study of this decarboxylative radical alkylation reaction with diacyl peroxides, which set the starting point of this thesis. In a broader sense, this thesis revolves around the development of radical alkylations of titanium enolates using different alkyl radical sources obtained from carboxylic acids.

Carboxylic acids are abundantly found in nature and are also produced on a large scale by chemical industries, which makes them commercially available at low costs. These considerations, together with their high stability, are the reasons why carboxylic acids are frequently used as an organic stock in synthesis.

Among many other applications, carboxylic acids can be used as a source of alkyl radicals by means of their radical decarboxylation. One option to achieve this is the direct decarboxylation of the anionic carboxylate, which can be achieved by a single oxidative process (*Scheme 34, top*).

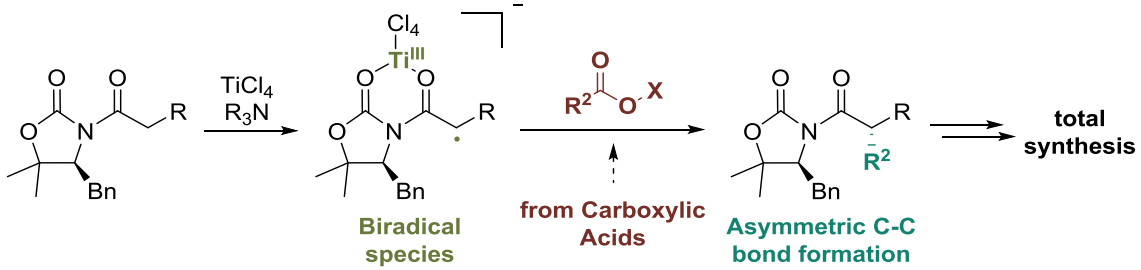
In a differing process, carboxylic acids can be turned into another alkyl radical source by the attachment of an appropriate moiety that creates a labile bond (O–X). The carboxylic acid derivative is sensitive to being homolyzed under different conditions to render the corresponding acyloxy radical, which decomposes into carbon dioxide and an alkyl radical (*Scheme 34, bottom*). Examples of activated carboxylic acids are Barton esters, *N*-hydroxyphthalimide (NHP) esters, aryliodine(III) dicarboxylates, diacyl peroxides, and peresters.



Scheme 34. Radical decarboxylation of carboxylic acids

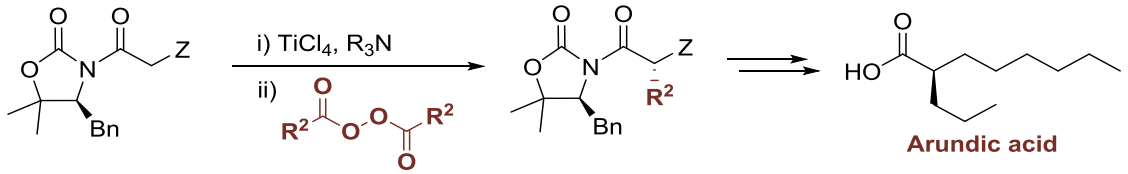
OBJECTIVES

Keeping in mind the ideas presented in the preceding introduction, the main purpose of this thesis is to exploit the biradical character of titanium(IV) enolates by using carboxylic acid derivatives to perform asymmetric α-alkylations of carbonyl compounds (*Scheme 35*). Once the feasibility of such a new approach is proven, the total synthesis of small molecules, in which a crucial step involved the developed methods, would be envisaged.



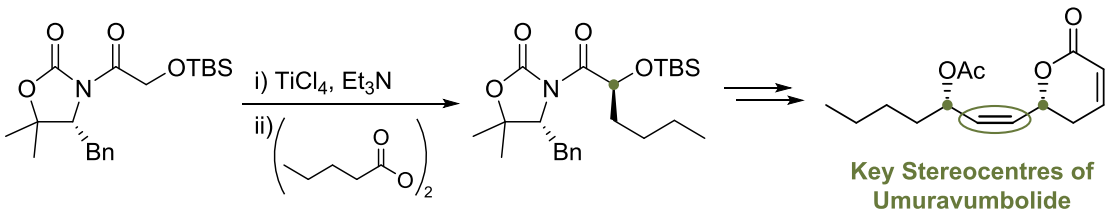
Scheme 35. Radical alkylation of titanium enolates

In **Chapter I**, the objective is to study the asymmetric α-alkylation of titanium enolates using diacyl peroxides (*Scheme 36*). Preliminary studies on these reactions had been performed prior to this thesis. Therefore, the starting point will be the assessment of the scope of enolates capable of undergoing such transformation. During this evaluation, by-products will be isolated, and their structure elucidated for a better understanding of the mechanism of the reaction as well as an improvement of the alkylation conditions. Finally, the synthesis of Arundic Acid, a simple small molecule, will be attempted using this methodology.



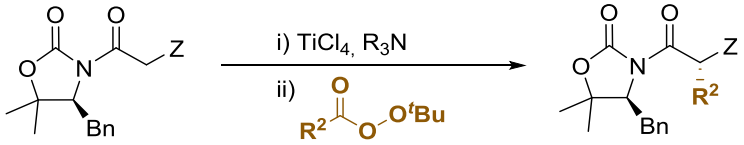
Scheme 36. Objectives of Chapter I

Chapter II will focus on the synthesis of Umuravumbolide, a chiral α-pyrone with interesting biological properties (*Scheme 37*). Concretely, the alkylation of titanium enolates with diacyl peroxides will be used to generate the stereocenter of the side chain of the target. Further studies to generate the *Z*-double bond and the stereocenter of the ring will be carried out using already described procedures.



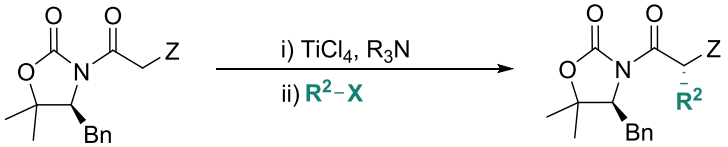
Scheme 37. Objectives of Chapter II

In **Chapter III**, turning back to methodology studies, the goal will be to develop an alkylation of titanium enolates with secondary and tertiary alkyl groups. In this case, *tert*-butyl peresters will be employed (*Scheme 38*). Similarly to the first chapter, an optimization of the reaction conditions will be required, followed by identification of by-products and a full assessment of the scope of the reaction. Eventually, chiral auxiliary removal will be assessed to gain access to enantiomerically pure derivatives.



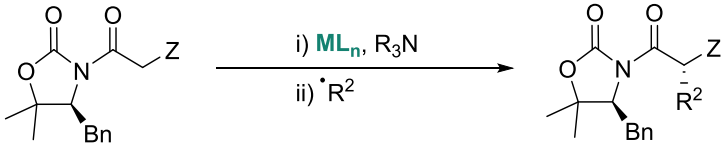
Scheme 38. Objectives of Chapter III

Finally, **Chapter IV** will report efforts to push the project ahead and will be divided into two main sections. The aim of the first part will be to find radical sources other than peroxides or peresters to achieve an alternative alkylating procedure that enables us to overcome the difficulties found in previous chapters (*Scheme 39*). Examples of these sources are *N*-hydroxyphthalimide esters or thiocarbonyl compounds.



Scheme 39. Objectives of Chapter IV.I

In the second and most challenging part, we will focus our attention on the substitution of titanium by another transition-metal. The objective is to find a replacement for titanium that can feature the same biradical character but at the same time under catalytic premises (*Scheme 40*).



Scheme 40. Objectives of Chapter IV.II

CHAPTER I

Alkylation of Titanium Enolates with Diacyl Peroxides

1. Introduction

For some years now, the group has been studying the radical reactivity of titanium(IV) enolates derived from *N*-acyl oxazolidinones. For instance, their oxidation with radical species such as TEMPO or oxygen has been fully reported. From this experience and considering that the radical reactivity of titanium(IV) enolates might positively contribute to well established methodologies, the current thesis was oriented to further explore this radical field. To that aim, an inquiry of other reagents that could produce radical species and combine with titanium enolates started. As seen in the general introduction, Alejandro Gómez-Palomino observed that diacyl peroxides react with titanium enolates to afford alkylated products, which is an appealing reactivity to be fully studied.

1.1 Preliminary results

In most of the studies of titanium(IV) enolates derived from *N*-acyl chiral oxazolidinones, the EVANS like-chiral auxiliary 4-benzyl-5,5-dimethyl-*N*-propanoyl-1,3-oxazolidin-2-one, also known as *SuperQuat*, turned out to be especially advantageous in our group. This auxiliary was reported by DAVIES to bypass the shortcomings of the already established oxazolidinones.[79] Indeed, introduction of two geminal methyl groups at the C5 position of the oxazolidinone lent it two advantages. Firstly, the presence of the new methyls compels the bulky substituent (the benzyl) into a position towards the acyl group, where the reaction takes place, thus, assuring better diastereoselectivity. Secondly, the methyl groups shield the oxazolidinone ring from a nucleophilic attack to the endocyclic carbonyl, which improves the selectivity of the auxiliary removal (*Figure 11*). The good results obtained with this auxiliary in the past led the group to work with this type of chiral auxiliary.

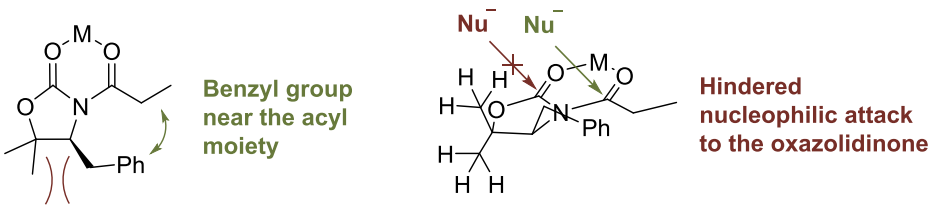
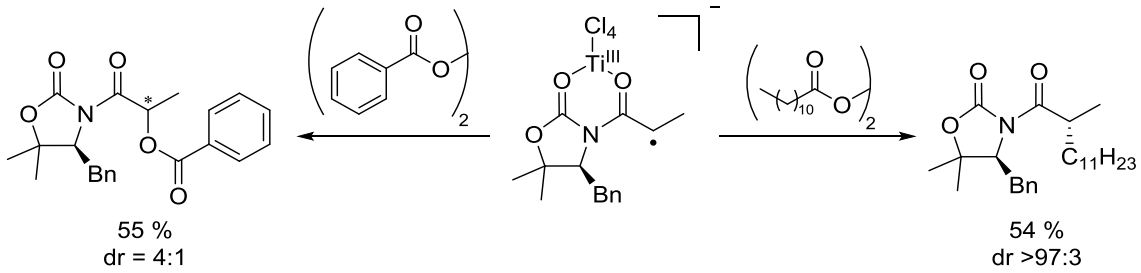


Figure 11. *SuperQuat* features

In connection with the former comments, Alejandro Gómez-Palomino explored the reaction of diacyl peroxides mentioned in the introduction with titanium(IV) enolates

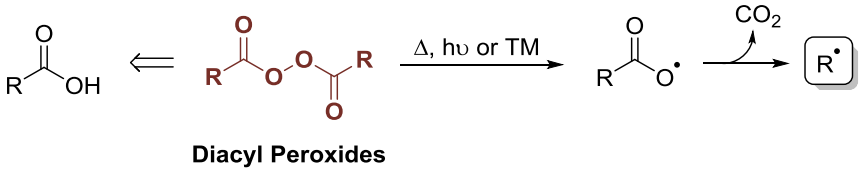
from *N*-propionyl oxazolidinone.[78] As a reminder, the treatment of the corresponding titanium enolate with dibenzoyl peroxide (**BPO**) afforded the aroyloxydized adduct while the use of dilauroyl peroxide (**LPO**) rendered the alkylated product through a decarboxylative process (*Scheme 41*). Such a result highlights the importance of diacyl peroxides as a source for alkyl radicals.



Scheme 41. Preliminary results obtained by Alejandro Gómez-Palomino

1.2 Diacyl peroxides

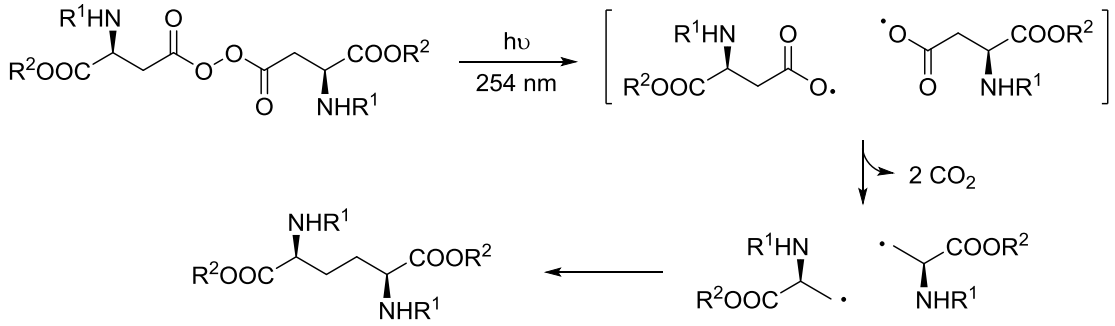
Diacyl peroxides can be easily prepared from carboxylic acids and hydrogen peroxide, from acyl halides and sodium peroxide, or from acyl halides and peroxyacids. They are mainly employed as radical initiators, especially in polymer chemistry, or as one-electron oxidants. However, although they are not as known as Barton esters or NHP esters, diacyl peroxides are also redox active compounds that can be used as a source of alkyl or aryl radicals after their homolytic scission and consequent β-fragmentation to release CO_2 (*Scheme 42*). This lack of popularity is probably due to their perception as being thermally unstable and potentially hazardous. On the contrary, their resistance to nucleophilic cleavage or reductant species is quite unexpected. Therefore, it should come as no surprise that a remarkable expansion of the use of diacyl peroxides has been experienced in the last 5 years.[80,81]



Scheme 42. Diacyl peroxides decomposition

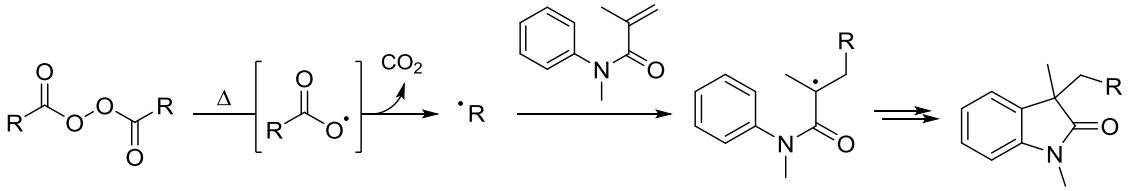
Recently, it has been firmly established that alkyl acyl peroxides are valid alkylating agents. Indeed, their decomposition to render alkyl radicals can be achieved under heat, light irradiation or reduction with a transition metal (TM).

VEDERAS described the controlled photolysis of alkyl diacyl peroxides of α-amino acid derivatives under UV irradiation at low temperatures. Decarboxylation of the two acyloxy radicals obtained after the scission renders two alkyl radicals that recombine to form a new Csp^3–Csp^3 bond (*Scheme 43*).[82]



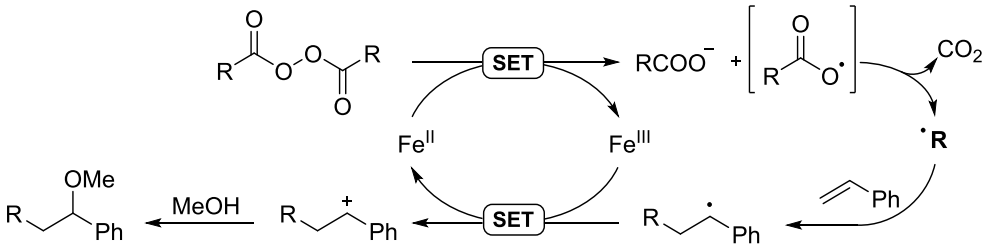
Scheme 43. Photolysis of alkyl diacyl peroxides

Alternatively, thermolysis of diacyl peroxides has also been applied to obtain alkyl radicals through the homolytic scission and resulting decarboxylation of these species. For instance, YU applied this strategy to the radical annulation of aromatic acrylamides (*Scheme 44*).[83]



Scheme 44. Thermolysis of alkyl diacyl peroxides

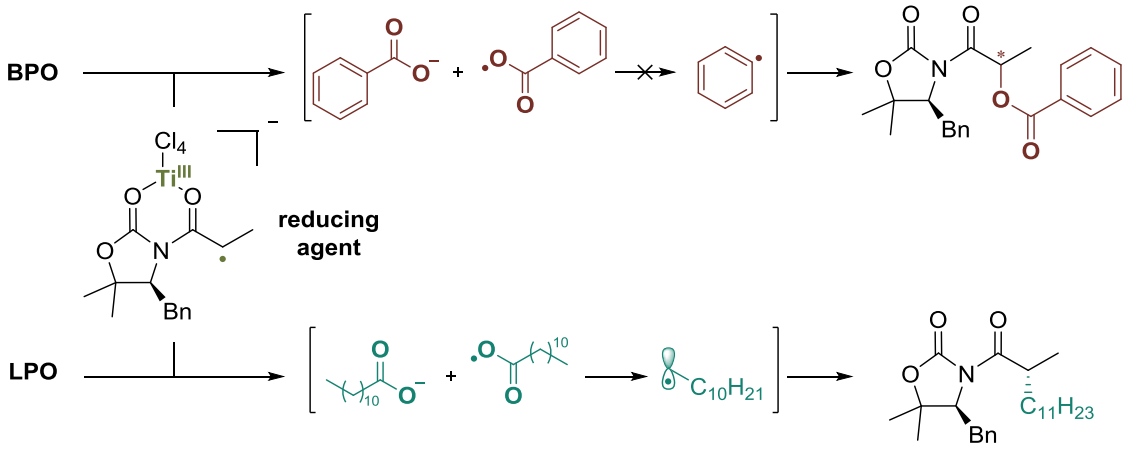
Finally, a different avenue has been utilized by BAO. Diacyl peroxides split after a single electron reduction promoted by either a transition-metal catalyst[84–88] (copper(I) or iron(II)) or a photocatalyst[89] (*ruthenium(II)). Instead of obtaining two acyloxy radicals, the cleavage produces a carboxylate anion and an acyloxy radical, which rapidly decarboxylates to give an alkyl radical that can be trapped by a range of substrates, for example, styrene derivatives (*Scheme 45*).[87]



Scheme 45. Decomposition of diacyl peroxides using transition metal catalysts

To sum up, there are three main modes to trigger the scission of the O-O bonds in diacyl peroxides: UV irradiation, heat, or reduction with a transition metal. If the reaction of these species with titanium enolates is considered, the observed splitting of both peroxides could not be explained by thermal homolysis since these tests were performed at room temperature, which should not be enough to prompt the homolysis. Photolysis was also discarded since the reaction mixture was not irradiated. Therefore, some species in the reaction mixture might act as a reducing agent. Presumably the radical titanium enolates are not innocent species, and instead, they could trigger the decomposition of diacyl peroxides. To confirm this hypothesis, Alejandro Gómez-Palomino ran several tests with the boron and lithium enolate analogues, neither of which reacted with dilauroyl peroxide. Once again, titanium enolates had shown a unique reactivity in contrast to other metal enolates.

In turn, the different behavior of diaryl acyl peroxide (**BPO**) or a dialkyl acyl peroxide (**LPO**) hinges on their stability. Indeed, decarboxylation of the alkyl acyloxy radicals formed can take place at room temperature to give an alkyl radical. If an aryl diacyl peroxide is used instead, decarboxylation to give a destabilized aryl radical will only take place if high temperatures are applied. This difference may explain the fact that dilauroyl peroxide grants an alkylated adduct while dibenzoyl peroxide delivers the aryloxidized product (*Scheme 46*).

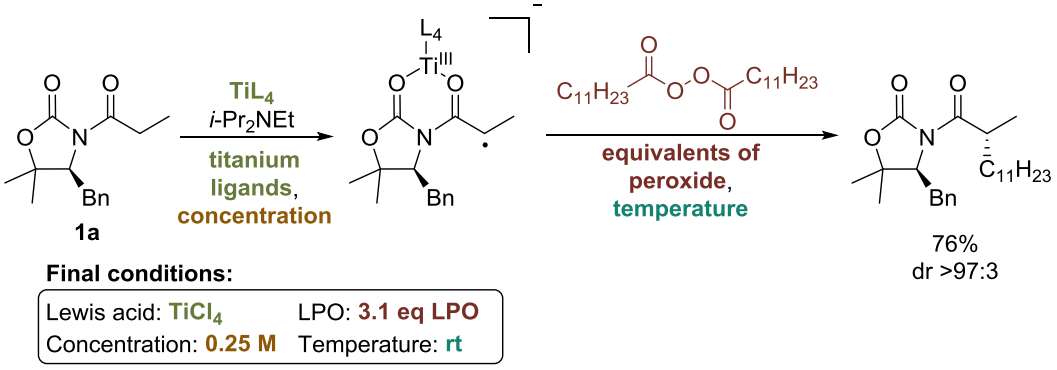


Scheme 46. Preliminary results of the reaction between titanium enolates and diacyl peroxides

1.3 Prior work

The preliminary results obtained with dilauroyl peroxide (**LPO**) encouraged the group to study the stereoselective alkylation of titanium enolates. Hence, Alejandro Gómez-Palomino optimized the reaction conditions using **1a** and **LPO** as model

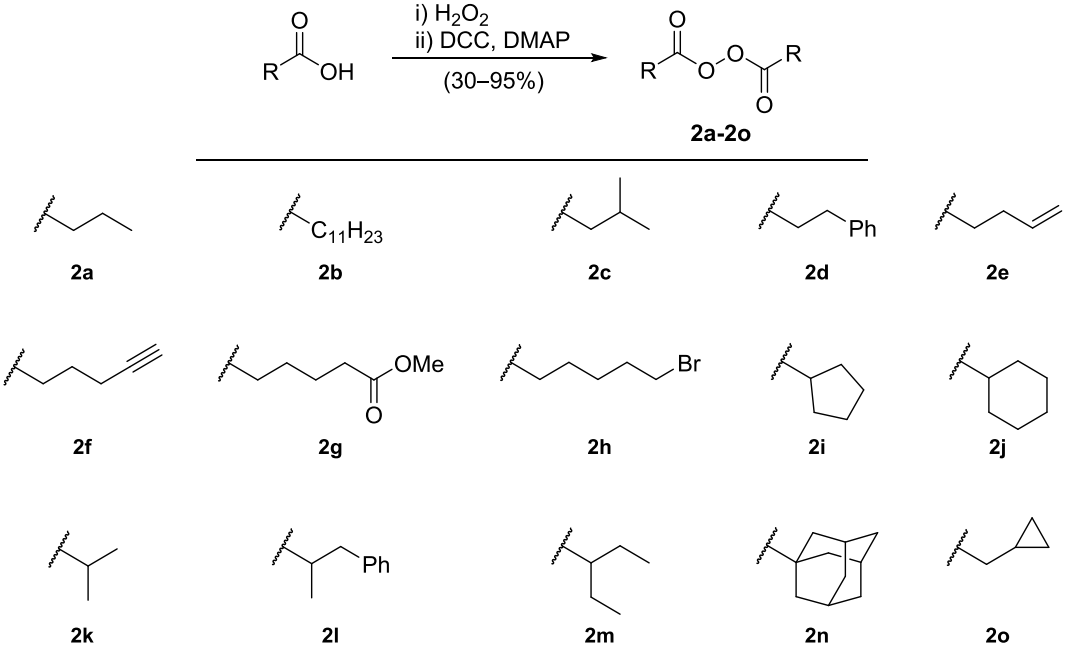
substrates; which involved: the screening of ligands for titanium, the temperature, the amount of peroxide and concentration. Nevertheless, just an increase of the equivalents of peroxide led to an improvement of the yield from 54% to 76% while maintaining an excellent diastereoselectivity (*Scheme 47*).[78]



Scheme 47. Optimization of reaction conditions by Alejandro Gómez-Palomino

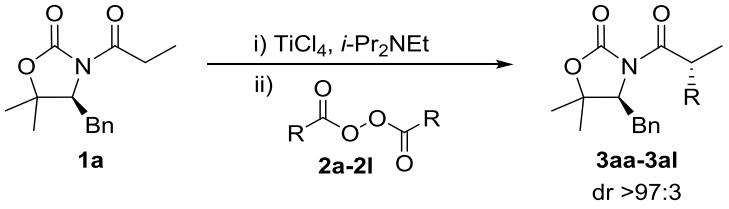
Scope of diacyl peroxides for the alkylation

With these conditions in hand, Alejandro Gómez-Palomino assessed the diacyl peroxides suitable for this alkylation. For that, a battery of diacyl peroxides (**2**) was prepared from commercially available carboxylic acids by oxidation with hydrogen peroxide and coupling with carbodiimides catalyzed by DMAP (*Scheme 48*).[87] Diacyl peroxides are stable enough to be purified by a short flash column chromatography, and they were obtained in pure batches that assured the reproducibility of the reaction.



Scheme 48. Preparation of diacyl peroxides

Once prepared, the peroxides were tested with the titanium enolate from *N*-propionyl oxazolidinone (**1a**). Primary diacyl peroxides, saturated (**2a**-**2c**) or containing a variety of functional groups such as aromatic rings or unsaturated carbon-carbon bonds (**2d**-**2f**), furnished the corresponding alkylated product with good to excellent yields (*entries 1-6, Table 1*). Primary diacyl peroxides bearing an ester group (**2g**) however, gave a moderate yield (*entry 7, Table 1*). It was also possible to introduce a bromo-containing alkyl chain that would allow further functionalization (*entry 8, Table 1*). Additionally, peroxides that generate a secondary alkyl radical (**2i**-**2k**) were also suitable for the alkylation and afforded the products with good yields (*entries 9-11, Table 1*). Importantly, the stereocontrol on the configuration of the new stereocenters was excellent in all the examples, given that just one diastereomer was observed. On the contrary, there was no control on the formation of a second stereocenter in β position (*entry 12, Table 1*).



i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (1.1 eq), DCM, 0 ºC, 40 min; ii) peroxide (3.1 eq), rt

Entry	Peroxide	R	Product	Isolated Yield
1	**2a**	Pr	**3aa**	87%
2	**2b (LPO)**	$C_{11}H_{23}$	**3ab**	76%
3	**2c**	*i*-Bu	**3ac**	71%
4	**2d**	CH_2CH_2Ph	**3ad**	85%
5	**2e**	$(CH_2)_2CH{=}CH_2$	**3ae**	87%
6	**2f**	$(CH_2)_2C{\equiv}CH$	**3af**	72%
7	**2g**	$(CH_2)_4COOMe$	**3ag**	54%
8	**2h**	$(CH_2)_4CH_2Br$	**3ah**	84%
9	**2i**	C_5H_9	**3ai**	64%
10	**2j**	C_6H_{11}	**3aj**	60%
11	**2k**	*i*-Pr	**3ak**	78%
12	**2l**	CH(Me)Bn	**3al**	70%[a]

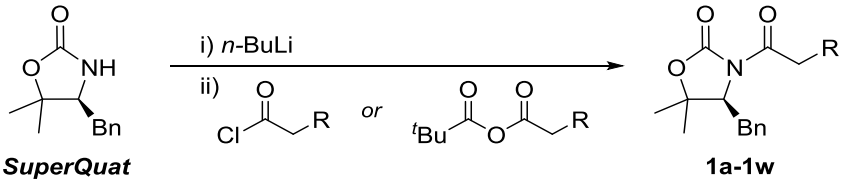
[a]dr 2:1

Table 1. Scope of diacyl peroxides

2. Scope of enolates suitable for the alkylation

The outstanding results obtained after the survey of diacyl peroxides led to the starting point of this thesis. To keep studying the scope of the reaction, different enolates

were investigated. With that in mind, *N*-acyl oxazolidinones (**1**) bearing more or less hindered acyl chains and containing a variety of functional groups were synthesized according to standard procedures in high yields (*Scheme 49*).

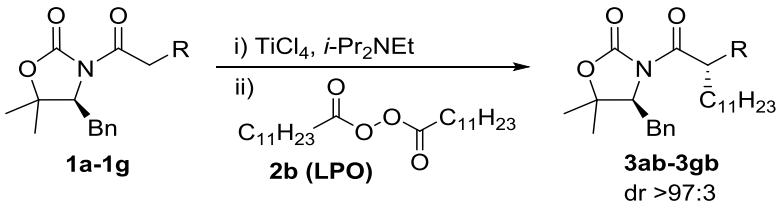


i) *n*-BuLi (1.3 eq), THF, –78 ºC, 15 min; ii) $XCOCH_2R$ (1.3 eq), –78 ºC to rt, 2 h

Scheme 49. Acylation of SuperQuat chiral auxiliary

2.1 Alkyl side chains

N-Acyl oxazolidinones containing saturated acyl groups (**1a**-**1c**) were alkylated with **LPO** following the conditions described by Alejandro Gómez-Palomino. Unfortunately, the yield of the alkylation was dramatically affected by the increase of steric hindrance of the R group (*entries 1–3, Table 2*). In turn, the enolate showed good tolerance towards unsaturated carbon-carbon bonds (*entries 4–6, Table 2*) as well as esters (*entry 7, Table 2*), and produced the corresponding α-alkylated compounds in moderate yields.



i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (1.1 eq), DCM, 0 ºC, 40 min; ii) LPO (3.1 eq), rt

Entry	*N*-acyl ox.	R	Product	Isolated Yield
1	**1a**	Me	**3ab**	76%
2	**1b**	Et	**3bb**	63%
3	**1c**	*i*-Pr	**3cb**	37%
4	**1d**	Bn	**3db**	44%
5	**1e**	$(CH_2)_2CH{=}CH_2$	**3eb**	53%
6	**1f**	$(CH_2)_2C{\equiv}CH$	**3fb**	48%
7	**1g**	$(CH_2)_2COOMe$	**3gb**	51%

Table 2. Scope of enolates, alkyl groups

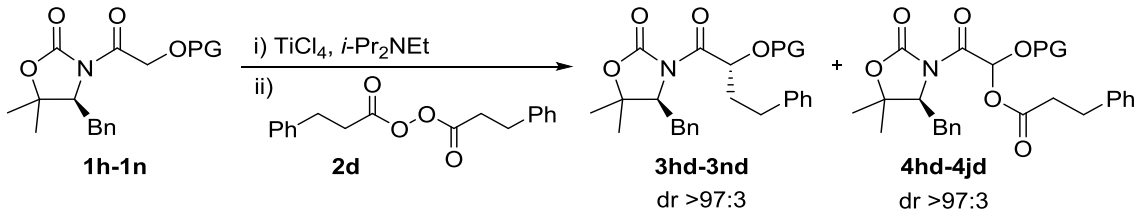
2.2 α-Heteroatom side chain

Although the results from the evaluation of a range of enolates did not give as good results as the differing peroxides, we were able to perform alkylations with a large deactivated alkyl group (from **LPO**) in a highly stereoselective and easy manner, which

encouraged us to further explore the scope of such a transformation. Particularly, we were interested in assessing the outcome of parallel reactions from acyl groups containing a heteroatom at the α position. It should be noted that the alkylation had already proven to be highly sensitive to steric effects, so dihydrocinnamoyl peroxide (**2d**) was used instead of **LPO** since it had already showed better results during the peroxide screening (*entries 2 and 4, Table 2)*.

The introduction of an unprotected hydroxyl group would not be compatible with the formation of the enolate, therefore, a screening of protecting groups was performed starting with α-silyloxy groups. Unexpectedly, aside from the alkylated product, a single diastereomer of the acyloxidized adduct (**4**) was observed. This result indicated that occasionally the acyloxy radical did not undergo decarboxylation before recombining with the enolate. Formation of this by-product resulted in lower alkylation yields, so the suppression of its formation was attempted by a small screening of temperatures using the TBS protected starting material. During the screening it was discovered that, surprisingly, at lower temperatures the proportion of acyloxidized product (**4hd**) was minor (*entries 1–3, Table 3*), which allowed **3hd** to be obtained in a good yield. However, at temperatures lower than –20 °C no reaction was observed at all (*entry 4, Table 3*), probably due to the inhibition of the biradical character of the titanium enolate. In another attempt to minimize the by-product, TBDPS and TIPS protecting groups were assessed. Unfortunately, lower conversions were noted and complex reaction mixtures difficult to purify were obtained (*entries 5 and 6, Table 3*).

Moving on, the benzyl protecting group was also examined. The reaction at room temperature was considerably faster than usual (15 minutes) but several unknown by-products were formed, none of which corresponded to the acyloxidized adduct **4**. The same reaction was repeated at lower temperatures, which delivered a clearer crude resulting in a higher yield (*entries 7-9, Table 3*). Even though they are not standard protecting groups, the alkylation was also studied with other common ethers such as methoxy and phenyloxy groups. The first gave **3ld** in a clean reaction crude and a good yield (*entry 10, Table 3*), but the phenyl ether gave a messy reaction mixture that was difficult to purify and a poor diastereoselectivity of the alkylated product was observed (*entry 11, Table 3*). Finally, the pivalic ester was investigated; in this case, the alkylated product was isolated with a moderate yield, but with poor diastereoselectivity, so the use of esters as a protecting group was discarded (*entry 12, Table 3*).



1h-1n **2d** **3hd-3nd** dr >97:3 **4hd-4jd** dr >97:3

i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (1.1 eq), DCM, T, 40 min; ii) **2d** (3.1 eq), T

Entry	*N*-acyl ox.	OPG	Product	T	Isolated Yield (3)	Isolated Yield (4)
1	**1h**	OTBS	**3hd**	rt	40%	22%
2	**1h**	OTBS	**3hd**	0 °C	49%	21%
3	**1h**	OTBS	**3hd**	–20 °C	62%	14%
4	**1h**	OTBS	**3hd**	–40 °C	-	-
5	**1i**	OTBDPS	**3id**	0 °C	(37%)[a]	(11%)[a]
6	**1j**	OTIPS	**3jd**	0 °C	(23%)[a]	(7%)[a]
7	**1k**	OBn	**3kd**	rt	(47%)[a]	-
8	**1k**	OBn	**3kd**	0 °C	61%	-
9	**1k**	OBn	**3kd**	–20 °C	55%	-
10	**1l**	OMe	**3ld**	0 °C	61%	-
11	**1m**	OPh	**3md**	0 °C	50%[b]	-
12	**1n**	OPiv	**3nd**	0 °C	49%[c]	-

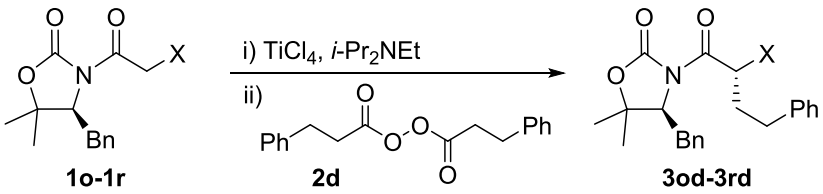
[a]slightly impure fractions; [b]dr 70:30; [c]dr 77:23

Table 3. Scope of enolates, α-hydroxy protected groups

Overall, the best options for the alkylation of α-hydroxy enolates were the TBS silyl ether, as well as the benzyl and methyl ether. All these protecting groups gave good yields and excellent diastereoselectivities.

Instead, the placing of nitrogen in the α position was not successful. First, the alkylation of the enolate using phthalimide as protecting group did not proceed, probably due to the large volume of the phthalimide (*entry 1, Table 4*). In turn, the use of the smaller azido group did not withstand the formation of the enolate, which decomposed even at low temperatures (–78 °C, *entry 2, Table 4*).

Finally, the introduction of a halogen was also investigated. Moderate yields were obtained for chlorine, with a slight erosion of diastereoselectivity (*entry 3, Table 4*). The use of larger bromine, however, gave very poor conversion as well as a worse diastereoselectivity (*entry 4, Table 4*).



i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (1.1 eq), DCM, T, 40 min; ii) **2d** (3.1 eq), rt

Entry	*N*-acyl ox.	X	Product	Isolated Yield	dr
1	**1o**	NPhth	**3od**	-	-
2	**1p**	N_3	**3pd**	-	-
3	**1q**	Cl	**3qd**	45%	85:15
4	**1r**	Br	**3rd**	<20%	85:15

Table 4. Scope of enolates, α-amino protected groups and α-halogens

In summary, the study of the impact of the enolate on the alkylation with diacyl peroxides revealed that the reaction is highly sensitive to steric effects of the side chain. Despite this, functionalities such as double, triple bonds or esters were well tolerated. In addition, alkylation of titanium enolates bearing an α-oxygen or α-chlorine were also successful, although the latter showed lower stereoselectivity.

3. Identification of by-products

In the introduction, it was indicated that the soft enolization of *N*-acyl oxazolidinones with $TiCl_4$ produces a deep purple solution. Following the addition of the peroxides, the mixture's color changed slightly to dark red, and it lost the characteristic darkness of the enolate, which turned bright orange as the reaction proceeded. Indeed, it was noted that at this point, the reaction would not advance any further, what was referred to as a "*self-quenched*" reaction.

Figure 12. Colors during the alkylation of titanium enolates

Analysis of the "*self-quenched*" crude mixture by ^{1}H NMR revealed that there was still unreacted starting material and also two minor by-products were identified. The most characteristic peaks of ^{1}H NMR spectra of the crude mixture of the reaction between **1a** and **LPO** are shown in *Figure 13*. Almost at the same shift (~4.5 ppm) two pairs of doublets of doublets were easily assigned as the oxazolidinone's proton belonging each to the alkylated product (**3ab**) and the starting material (**1a**) (blue and orange respectively). The quartet at ~5.7 ppm (green) belonged to one of the by-products; prior experience within the group using titanium enolates allowed the identification of this signal as the αH of the α-chlorinated adduct of the *N*-acyl oxazolidinone (**5a**). Finally, a doublet at ~6.1 ppm corresponded to the other by-product (**6a**, red), which had not been previously identified because it was formed in small amounts and hence was considered that it would not compromise the yield of the reaction.

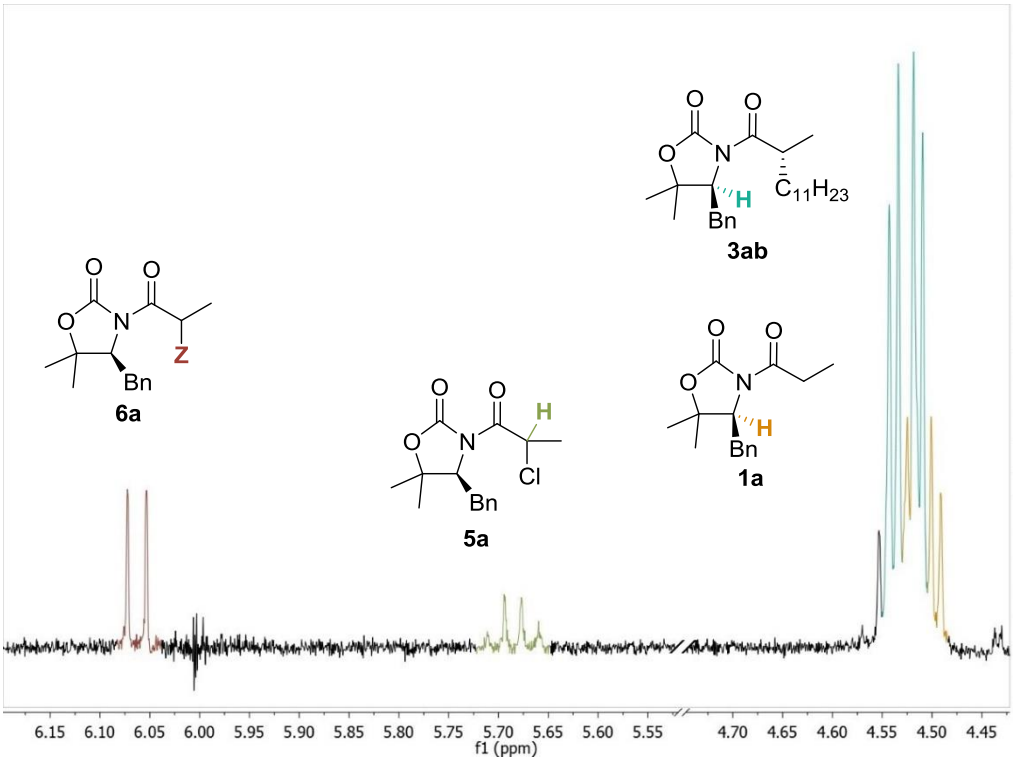
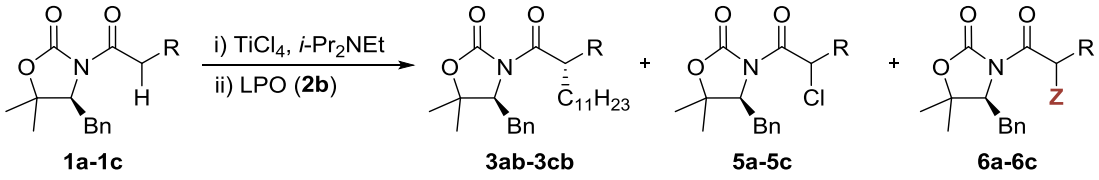


Figure 13. Main products observed by ^{1}H NMR of the crude mixture of the alkylation reaction

However, the formation of this unknown by-product (**6**) was also observed during the assessment of the enolate scope. Interestingly, its characteristic NMR signal did not change much from one enolate to another. Furthermore, it was much more abundant when the reaction gave low yields, for example, the simple lengthening of the side chain by one carbon doubled the amount of by-product (*entries 1 and 2, Table 5*). What is more, when the enolate's steric hindrance was increased by using a branched alkyl chain

the amount of **6c** formed was almost comparable to that of the alkylated product (*entry 3, Table 5*). Thus, the formation of **6c** could account for the low yield obtained for **3cb**. Moreover, from an experimental point of view, the presence of significant amounts of **6** seriously hindered the chromatographic purification of the alkylated product.

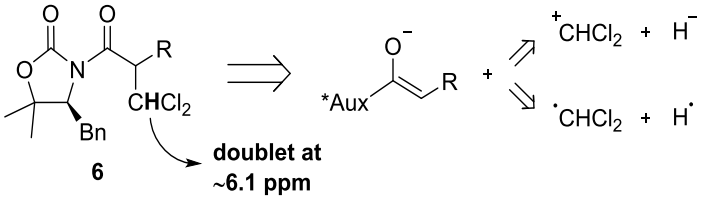


i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (1.1 eq), DCM, 0 °C, 40 min; ii) **LPO** (3.1 eq), rt

Entry	*N*-acyl ox.	R	^{1}H NMR crude				Isolated Yield (3)
			1	3	5	6	
1	**1a**	Me	13	78	3	6	76%
2	**1b**	Et	10	74	4	12	63%
3	**1c**	*i*-Pr	29	41	5	25	37%

Table 5. By-products found in the crude mixture analyzed by ^{1}H NMR

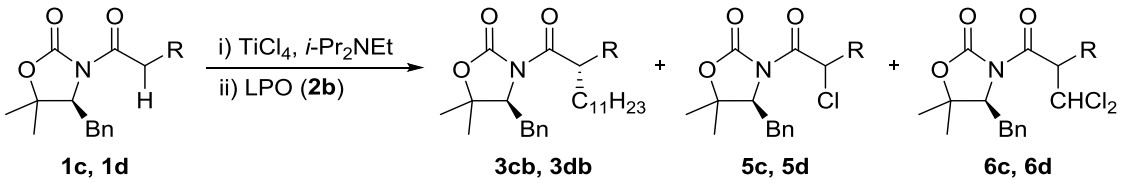
This problem had a dramatic impact on the alkylation of the branched enolate of **1c** with **LPO**, however this also produced enough by-product (**6c**) to be easily isolated and its structure elucidated. The doublet at ~6.1 ppm was finally assigned to the proton of a dichloromethyl group attached to the enolate, thus giving a comparatively highly shifted signal due to the two chlorine atoms (*Scheme 50*).



Scheme 50. Retrosynthesis of dichloromethylated product

Identification of this by-product gave valuable mechanistic information. Clearly, its formation stemmed from a molecule of solvent: dichloromethane. In order to react with a nucleophilic enolate, one possibility is that dichloromethane might have been split into a hydride and an electrophilic dichloromethyl cation, which is highly unlikely. Alternatively, a dichloromethyl radical could have been formed after hydrogen abstraction from the solvent. The second option suggested that a radical process came into play during the alkylation reaction, proving once again, that titanium enolates are involved in radical reactivity.

In this context, aiming for higher yields, the alkylation of *N*-acyl oxazolidinones **1c** and **1d** was repeated using 6 equivalents of **LPO**. Surprisingly, even lower yields of **3cb** were obtained due to a greater formation of dichloromethylated by-product (**6c**), while the chlorinated adduct (**5c**) was formed in the same quantities (*entries 1 and 2, Table 6*). This trend was even more pronounced for the alkylation of **1d** (*entries 3 and 4, Table 6*). These results hint that the diacyl peroxide was involved in the formation of by-product **6**; probably after the homolytic cleavage of the peroxide, the radical species formed were responsible for the hydrogen abstraction of dichloromethane. Further mechanistic details will be discussed in *section 6.1*.



1c, 1d **3cb, 3db** **5c, 5d** **6c, 6d**

i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (1.1 eq), DCM, 0 ºC, 40 min; ii) **LPO** (**X** eq), rt

Entry	*N*-acyl ox.	R	LPO	^{1}H NMR crude				Isolated Yield (3)
				1	3	5	6	
1	**1c**	*i*-Pr	3 eq	29	41	5	25	37%
2	**1c**	*i*-Pr	6 eq	34	33	5	29	29%
3	**1d**	CH_2Ph	3 eq	27	49	7	16	44%
4	**1d**	CH_2Ph	6 eq	29	41	6	24	37%

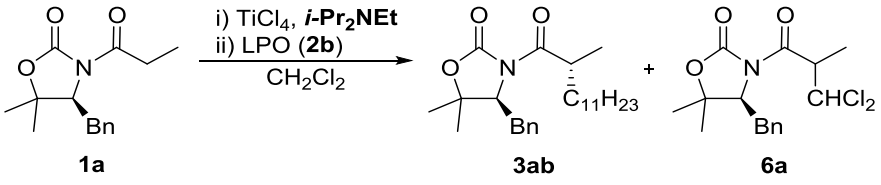
Table 6. By-product formation using 6 equivalents of LPO

4. Further optimization

Apart from the mechanistic information, the elucidation of the structure of by-product **6** permitted the identification of the crucial role played by the solvent as a parallel source of radicals. Therefore, the solvent and other reaction conditions were reassessed. To match the previous optimization, **1a** and **LPO** were used as model substrates, using just two equivalents of diacyl peroxide for a better appreciation of changes in the results. Also, from now on the chlorinated by-product (**5**) will not be considered due to its low formation amounts.

4.1 "Self-quench" of the enolate

As explained in the previous section, the "*self-quenched*" reaction still had unreacted *N*-acyl oxazolidinone, which was a hint that a portion of the enolate had been protonated. To overcome this problem, the amount of base was increased; although the difference was subtle, it seemed that the change led to crude mixtures with less starting material (**1a**) (*Table 7*). Interestingly, the increase of base lead to a darker end color of the reaction mixture, which was no longer considered as "*self-quenched*". However, the yield of alkylated product remained the same because more proportion of dichloromethylated adduct (**6a**) was formed.

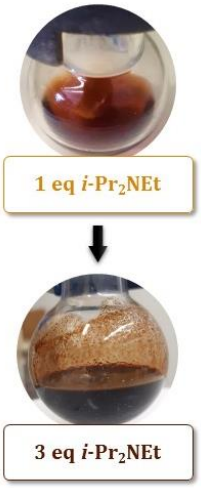


1a **3ab** **6a**

i) $TiCl_4$ (1.1 eq), ***i*-Pr$_2$NEt** (**X** eq), DCM, 0 °C, 40 min; ii) **LPO** (2 eq), rt

Entry	*i*-Pr$_2$NEt	^{1}H NMR crude			Isolated Yield (3ab)
		1a	3ab	6a	
1	1 eq	18	67	15	66%
2	2 eq	16	67	17	66%
3	3 eq	11	67	22	67%

Table 7. Optimization of the amount of base

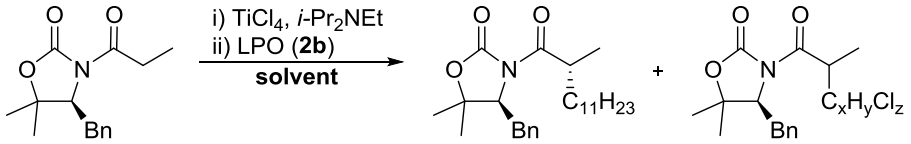


4.2 Solvent

Clearly, the solvent was a key component that should be changed in order to improve the alkylation yields. Nevertheless, titanium tetrachloride easily coordinates to solvents such as tetrahydrofuran or acetonitrile, meaning that the room for change regarding the solvent was limited. Chlorinated alkanes are suitable solvents for the formation of titanium enolates, so a screening of these was performed.

Results summarized in *Table 8* are organized starting from solvents with less chlorine atoms to fully chlorinated alkanes. Fortunately, the use of 1,2-dichloroethane (DCE) did not form any sort of chloroalkylated adduct, which notably increased the yield of **3ab** (*entries 1 and 2, Table 8*). However, the use of 1,1,2,2-tetrachloroethane (TCE) led to similar quantities of the corresponding chloroalkylated adduct (**7a**) than DCM, but a lot of remaining starting material was observed in the crude mixture (*entry 3, Table 8*). An even worse scenario was presented by chloroform, which yielded the trichloromethylated adduct (**8a**) as the main product (*entry 4, Table 8*). Finally, carbon tetrachloride was not

polar enough to fully dissolve the enolate and no alkylated product was formed. The starting *N*-acyl oxazolidinone **1a** was the main component in the crude mixture and additionally, trichloromethylated by-product (**8a**) as well as dimerized **1a** were found in significant quantities.



i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (3 eq), **solvent**, 0 °C, 40 min; ii) **LPO** (2 eq), rt

Entry	solvent	byprod.	$C_xH_yCl_z$	^{1}H NMR crude			Isolated Yield
				1a	3ab	byprod.	
1	DCE	-	-	-	100	-	76%
2	DCM	**6a**	$CHCl_2$	18	67	15	66%
3	TCE	**7a**	CCl_2CHCl_2	60	20	20	-
4	$CHCl_3$	**8a**	CCl_3	22	19	59	-
5[a]	CCl_4	**8a**	CCl_3	54	-	27	-

[a]The rest of material was found as dimer of the starting material.

Table 8. Solvent screening

Considering that the corresponding chloroalkyl radical species derived from the solvent were formed, results shown in *Table 8* are not surprising. Carbon centred radicals are stabilized when substituted with atoms bearing a lone pair of electrons, such as chlorine. This effect is cumulative, the more chlorine substituted an alkyl radical is therefore, the more stabilized it becomes. Such a stabilization can also be measured by C–H bond dissociation energies (BDE) of the solvents or by radical stabilization energies (RSE), that is, the C–H BDE of the solvent compared to methane's BDE. RSE of some chlorinated solvents are represented in *Figure 14*, where it can be appreciated that trichloromethyl radical, being the most substituted, is the most stable.[90] Therefore, it is plausible that chloroform yields greater amounts of chloroalkylated adduct due to the higher stabilization of the trichloromethyl radical compared to a dichloroalkyl radical, which is the case for DCM or TCE. Following this argument, DCE would generate a monochloro-substituted alkyl radical, which is the least stable of the analogues and accounts for the absence of chloroalkylated by-product when using this solvent.

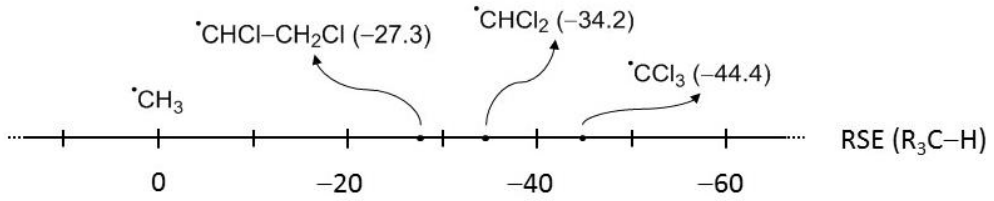


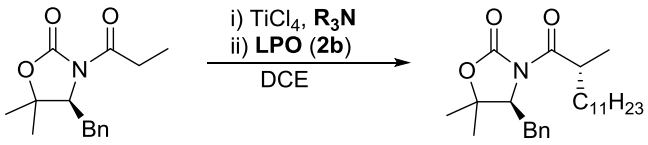
Figure 14. Radical stabilization energies (in kJ/mol)

After this screening, the solvent of the alkylation was switched from dichloromethane to 1,2-dichloroethane, which inhibits the formation of chloroalkyl adducts and thus resulting in higher yields.

4.3 New base and final details

Although conversions were improved by addition of greater amounts of base and the chloroalkylated by-product was eliminated by changing the solvent, the isolated yield of alkylated product was still not excellent. Hence, as reported in the literature,[51] triethylamine was used instead of Hünig's base in a hopeful attempt to improve the results. Indeed, this change produced clearer reaction crudes that resulted in higher isolated yields (*entries 1 and 2, Table 9*).

At this point, some other conditions were also tested to see if the atom economy of the alkylation could be improved. Firstly, it was thought that maybe titanium tetrachloride could be used in sub-stoichiometric amounts. Unfortunately, this proved to be a non-feasible option (*entry 3, Table 9*). Next, the equivalents of peroxide were reduced to 1.5 which nicely replicated the excellent results obtained (*entry 4, Table 9*). What is more, with these new conditions, the reaction time could be lowered from 2 h to 15 min (*entry 5, Table 9*). Finally, a decrease of the amount of the new base did not render the same results (*entry 6, Table 9*).



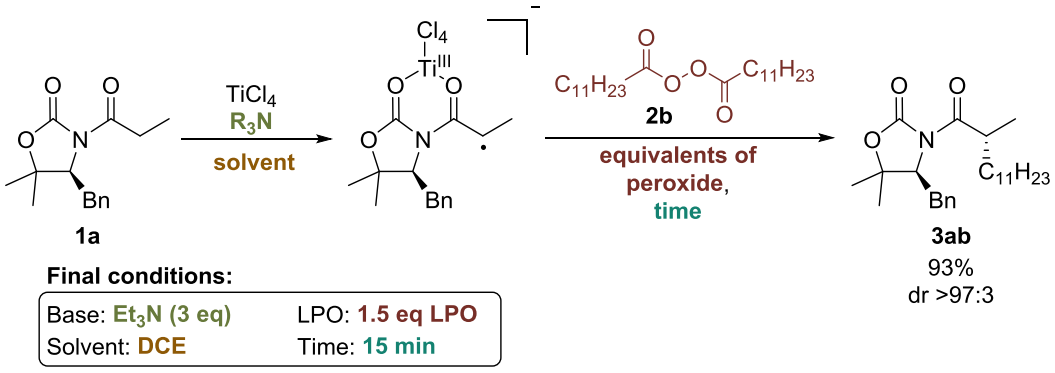
i) $TiCl_4$ (**X** eq), $\mathbf{R_3N}$ (3 eq), DCE, 0 °C, 40 min; ii) **LPO** (**X** eq), rt

Entry	base	$TiCl_4$	LPO	^{1}H NMR crude conversion	Isolated Yield
1	*i*-Pr_2NEt	1.1 eq	2 eq	quantitative	76%
2	Et_3N	1.1 eq	2 eq	quantitative	90%
3	Et_3N	0.5 eq	2 eq	50%	-
4	Et_3N	1.1 eq	1.5 eq	quantitative	87%
5[a]	Et_3N	1.1 eq	1.5 eq	quantitative	93%
6[a]	Et_3N (2 eq)	1.1 eq	1.5 eq	quantitative	84%

[a]reaction time: 15 min

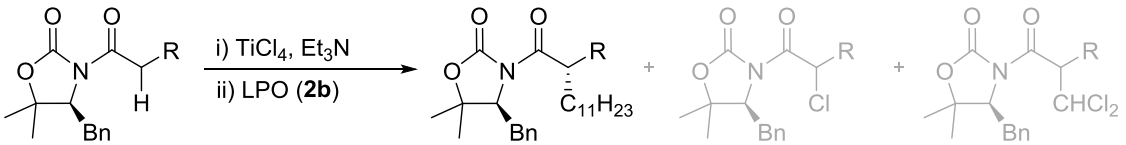
Table 9. New base and final changes

With this re-optimization, which involved the solvent change, and the modification and increase of the base, the alkylated product **3ab** was isolated in a higher 93% yield with a lower amount of peroxide and shorter reaction time while maintaining the excellent diastereoselectivity.



Scheme 51. Re-optimization of the reaction conditions

To challenge the new conditions, the three substrates that were studied in detail for the formation of by-products (*Table 5*) were reevaluated. Delightfully, the yield for **3bb** was also improved to an excellent level, and the hindered **1c** was alkylated in good yield, which almost doubled the previous result. As expected, none of the examples showed formation of the dichloromethyl adduct, but surprisingly, the chlorinated by-product was not observed either. Additionally, flash column purifications of the products became much easier and faster due to the absence of said by-products.



i) $TiCl_4$ (1.1 eq), Et_3N (3 eq), DCE, 0 ºC, 40 min; ii) **LPO** (1.5 eq), rt

Entry	*N*-acyl ox.	R	^{1}H NMR crude				Isolated Yield (3)	Previous Yield
			1	3	5	6		
1	**1a**	Me	1	99	-	-	93%	76%
2	**1b**	Et	5	95	-	-	88%	63%
3	**1c**	*i*-Pr	26	74	-	-	65%	37%

Table 10. Application of reoptimized conditions to other substrates

5. Scope reassessment

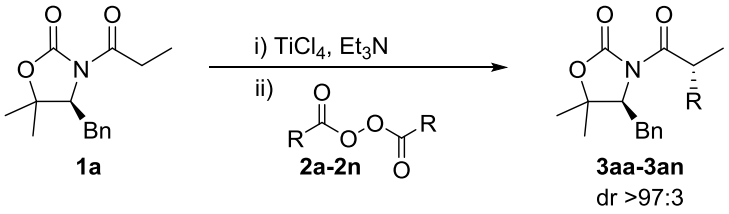
With new enhanced conditions in hand and preliminary examples showing an even greater improvement than the model substrates, it was believed that the scope should be reassessed. Therefore, the former evaluation was repeated and, occasionally, new examples were also explored.

5.1 Peroxide scope

During his master thesis, Marc del Olmo worked on the study of the impact of primary diacyl peroxides in the alkylation reaction.[91] Despite the very good yields already obtained by Alejandro Gómez-Palomino, a general improvement was observed in all cases, this time only using half the equivalents of peroxide. Aliphatic alkyl peroxides including branched examples behaved greatly (*entries 1-3, Table 11*), as well as peroxides bearing a phenyl, a double, or a triple bond (*entries 4-6, Table 11*). The most challenging peroxide was the methyl ester (**2g**), which required two equivalents of peroxide to perform the alkylation in a good yield (*entry 7, Table 11*). Finally, a bromine in the alkyl chain afforded the alkylated product in outstanding yield (*entry 8, Table 11*), lending the possibility for further functionalization of the product (**3ah**).

Secondary diacyl peroxides were more challenging. Their preparation was not reproducible due to purification issues, which forced a change. From then on, EDC was used as coupling agent since it could be removed *via* aqueous work-up and the residue was purified with a short pad of alumina. This allowed for an easier preparation of secondary peroxides, yet they were used during the same day to perform the alkylation because of their low trustable stability. Regardless, the new yields for cyclic and linear

secondary peroxides were slightly better than in the previous section even when, again, half of the peroxide equivalents was used for the alkylation (*entries 9–11, Table 11*). Eventually, the scope was extended to a larger branched peroxide (**2m**), which gave slightly lower yields than the rest of the examples (*entry 12, Table 11*). The same previous results were obtained with an asymmetric secondary peroxide that rendered two chiral centers (**2l**); full control of the α stereocenter was achieved, but the β stereocenter was obtained with only a 2:1 diastereomeric ratio (*entry 13, Table 11*). Finally, in an attempt to push the limits of the alkylation, the preparation of a tertiary alkyl diacyl peroxide was tried using 1-adamantane carboxylic acid as a model. Unfortunately, the peroxide could not be prepared (*entry 14, Table 11*).



i) $TiCl_4$ (1.1 eq), Et_3N (3 eq), DCE, 0 ºC, 40 min; ii) peroxide (1.5 eq), rt

Entry	peroxide	R	Product	Isolated Yield	Previous Yield[a]
1	**2a**	Pr	**3aa**	87%	87%
2	**2b**	$C_{11}H_{23}$	**3ab**	93%	76%
3	**2c**	*i*-Bu	**3ac**	84%	71%
4	**2d**	CH_2CH_2Ph	**3ad**	95%	85%
5	**2e**	$(CH_2)_2CH{=}CH_2$	**3ae**	93%	87%
6	**2f**	$(CH_2)_3C{\equiv}CH$	**3af**	91%	72%
7[b]	**2g**	$(CH_2)_4COOMe$	**3ag**	77%	54%
8	**2h**	$(CH_2)_4CH_2Br$	**3ah**	91%	84%
9	**2i**	C_5H_9	**3ai**	70%	64%
10	**2j**	C_6H_{11}	**3aj**	74%	60%
11	**2k**	*i*-Pr	**3ak**	77%	78%
12	**2m**	$CH(CH_2CH_3)_2$	**3am**	57%	not performed
13	**2l**	CH(Me)Bn	**2al**	75% (dr 2:1)	70% (dr 2:1)
14[c]	**2n**	Adamantyl	**3an**	-	not performed

[a]Yields form Alejandro-Gómez-Palomino thesis; [b]2 eq of peroxide were used: [c]Diacyl peroxide could not be obtained

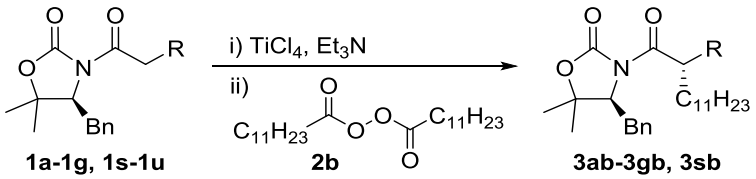
Table 11. Second scope of diacyl peroxides

Encouraged by such good results, the preparation of a new kind of peroxide was attempted. This time, the objective was to synthesize peroxides derived from protected glycolic acid. Unfortunately, the synthesis of such substrates was also unfeasible, and this subproject was then abandoned.

Scheme 52. Failed preparation of glycolyl-derived peroxides

5.2 Enolate scope

Having reassessed the peroxides that undergo the desired reaction, the project moved to analyze the scope of enolates using the new conditions. The first three examples have already been discussed, which were greatly improved upon using the new reaction conditions (*entries 1–3, Table 12*). Despite that slightly better results being expected a good yield was still obtained for an enolate with a sensitive benzylic position (*entry 4, Table 12*). However, the example with a double bond in the acyl moiety did not show a great improvement (*entry 5, Table 12*); it was believed that intramolecular side reactions could lead to cyclization of the enolate. To rule out this option, a shorter alkenyl enolate was prepared and alkylated, however, similar results were obtained (*entry 6, Table 12*). Instead, when a triple bond was incorporated the yield was boosted again (*entry 7, Table 12*). A similar increase was observed for the methyl ester functional group (*entry 8, Table 12*). An additional enolate with an α-CF_3 group was studied this time, but it did not afford any alkylated product, even if the enolate was prepared at low temperatures (–78 °C, *entry 9, Table 12*).



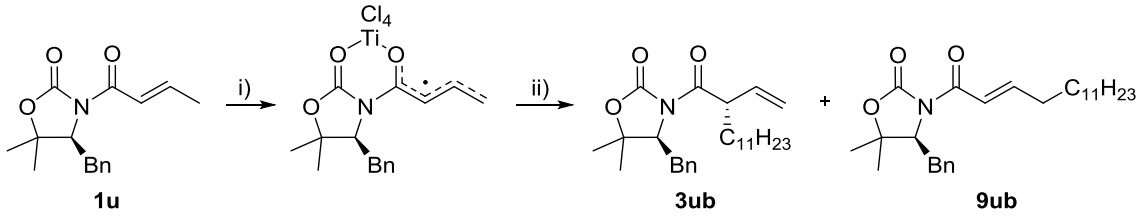
1a-1g, 1s-1u **2b** **3ab-3gb, 3sb**
dr >97:3

i) $TiCl_4$ (1.1 eq), Et_3N (3 eq), DCE, 0 °C, 40 min; ii) LPO (1.5 eq), rt

Entry	*N*-acyl ox.	R	Product	Isolated Yield	Previous Yield
1	**1a**	Me	**3ab**	93%	76%
2	**1b**	Et	**3bb**	88%	63%
3	**1c**	*i*-Pr	**3cb**	65%	37%
4	**1d**	Bn	**3db**	67%	44%
5	**1e**	$(CH_2)_2CH=CH_2$	**3eb**	60%	53%
6	**1s**	$CH_2CH=CH_2$	**3sb**	55%	not performed
7	**1f**	$(CH_2)_2C\equiv CH$	**3fb**	81%	48%
8	**1g**	$(CH_2)_2COOMe$	**3gb**	83%	51%
9	**1t**	CF_3	-	-	not performed
10	**1u**	(*E*) $CH=CHCH_3$	-	-	not performed

Table 12. Second scope of enolates, alkyl groups

Also, a β-unsaturated enolate was prepared to see if the alkylation was regioselective in the α or the γ-carbon (*Scheme 53*). Sadly, a complex mixture of products was obtained (*entry 10, Table 12*).

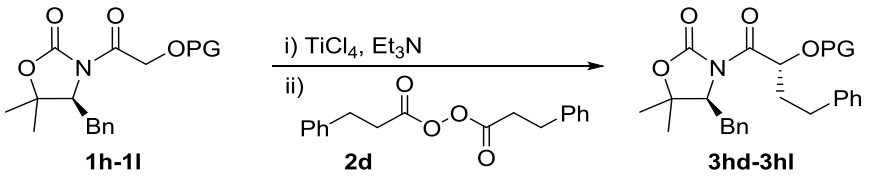


i) $TiCl_4$ (1.1 eq), Et_3N (3 eq), DCE, 0 ºC, 40 min; ii) LPO (1.5 eq), rt

Scheme 53. Regioselectivity of the alkylation

Having improved the results of the alkylation, it was worth determining how enolates with α-heteroatoms behaved. Since they were considered more challenging enolates, two equivalents of peroxide **2d** were used in the analysis of the scope.

For glycolic derived enolates it should be emphasized that the acyloxidized adduct (**4**) became a minor by-product (*see Section 2.2*). Indeed, it was just observed in tiny amounts in the crude ^{1}H NMR, a fact that entailed better isolated yields for silyl ethers protecting groups. Specifically, not only TBS showed a great improvement, but TBDPS and TIPS rendered excellent yields, where previously they had performed poorly (*entries 1–3, Table 13*). On the other hand, benzylic ether went from good to excellent yield, while methyl ether gave similar results (*entries 4 and 5, Table 13*).



i) $TiCl_4$ (1.1 eq), Et_3N (3 eq), DCE, T, 40 min; ii) **2d** (2 eq), T

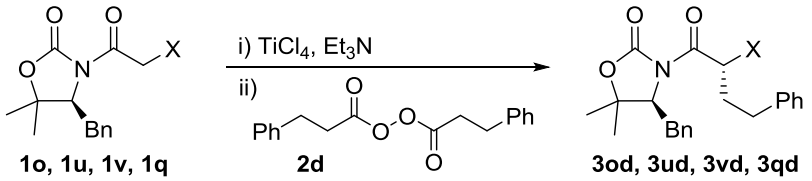
Entry	*N*-acyl ox.	OPG	Product	T	Isolated Yield	Previous Yield
1	**1h**	OTBS	**3hd**	–10 °C	85%	62%
2	**1i**	OTBDPS	**3id**	–20 °C	84%	(37%)[a,b]
3	**1j**	OTIPS	**3jd**	–20 °C	78%	(23%)[a,b]
4	**1k**	OBn	**3kd**	0 °C	82%	61%
5	**1l**	OMe	**3ld**	0 °C	(60%)[b]	61%

[a]At 0 °C; [b]not completely pure fractions

Table 13. Scope of enolates, α-hydroxy protected groups

To finish with the second scope assessment, other heteroatoms were also studied. Delightfully, in this occasion the alkylation of a nitrogen containing enolate was achieved

for the first time by its protection with phthalimide, which afforded the alkylated product (**3od**) in a 30% yield (*entry 1, Table 14*). Encouraged by this result, we considered the use of other nitrogen protecting groups. Particularly, we paid attention to pyrrole as a less hindered protecting group. On this occasion, the reaction worked nicely, and the alkylation yield rose up to 66% (*entry 2, Table 14*). More common nitrogen-protecting group Fmoc was also studied, but without success. Finally, alkylation of **1q,** which contained an α-chlorine, was largely improved in terms of yield, yet the diastereomeric ratio stayed the same as previously observed (*entry 4, Table 14*).



i) $TiCl_4$ (1.1 eq), Et_3N (3 eq), DCE, T, 40 min; ii) **2d** (2 eq), rt

Entry	*N*-acyl ox.	X	Product	Isolated Yield	dr	Previous Yield
1	**1o**	NPhth	**3od**	30%	>97:3	-
2	**1v**	1-pyrrole	**3ud**	66%	>97:3	not performed
3	**1w**	NHFmoc	**3vd**	-	-	not performed
4	**1q**	Cl	**3qd**	93%	85:15	45%

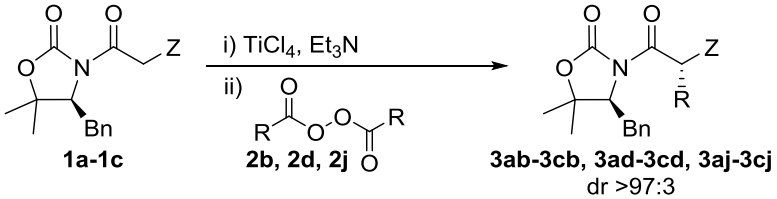
Table 14. Scope of enolates, α-amino protected groups and α-chlorine

In summary, really nice improvements of the enolate scope were accomplished after the reevaluation of the reaction conditions. The general enhancement for alkyl side chains, especially those presenting more steric hindrance, the great improvement of silyl protected glycol enolates and the new possibility to alkylate glycine derivatives should also be highlighted.

5.3 Crossed examples

Up to this point, just **1a** was used to study the scope of peroxides, while peroxides **LPO** (**2b**) or **2d** were used to study the scope of enolates. Nevertheless, to provide a wider representation of the scope, some examples crossing other *N*-acyl oxazolidinones and peroxides were performed. As seen before, an increase of the steric hindrance of the enolate resulted in lower yields of alkylation with **LPO** (*first column, Table 15*). However, the drop in yield is not that pronounced as it used to be with the initial conditions (previous yields in brackets). The same erosion was observed for **2d**, which gave similar results as **LPO** for all the *N*-acyl oxazolidinones (*second column, Table 15*). On the contrary, this tendency was even more pronounced when a bulkier, secondary

peroxide **2j** was used (*third column, Table 15*). These examples show clearly that the alkylation reaction is highly sensitive to steric hindrance, either from the enolate or the peroxide. However, good yields were still obtained for large substituents, except for **3cj**, which is a truly challenging alkylation to perform due to the formation of a highly sterically crowded product.



i) $TiCl_4$ (1.1 eq), Et_3N (3 eq), DCE, 0 ºC, 40 min; ii) Peroxide (1.5–2 eq), rt

Z \ R	(2b) $C_{11}H_{23}$	(2d) CH_2CH_2Ph	(2j) C_6H_{11}
(1a) Me	93% (76)	95% (87)	74% (60)
(1b) Et	88% (63)	73% (70)	51% (-)
(1c) *i*-Pr	65% (37)	67% (39)	20% (-)

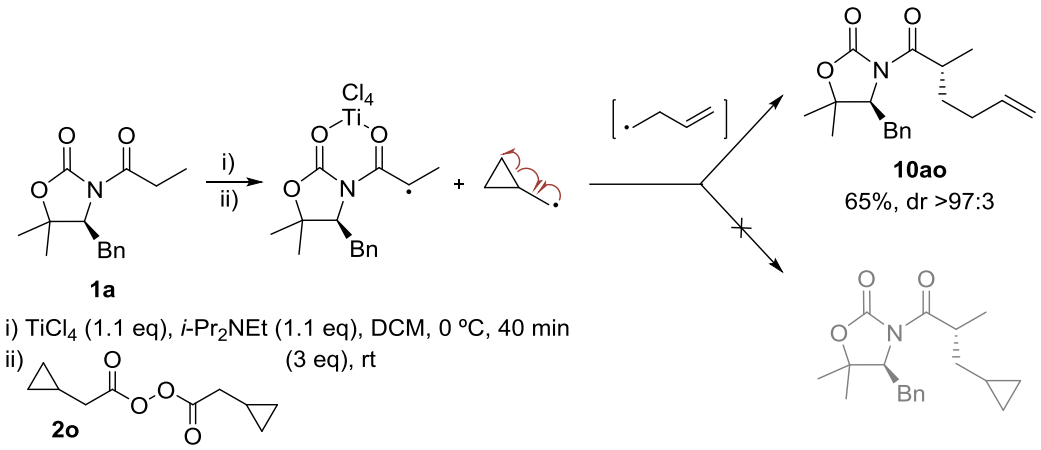
Table 15. Scope, isolated yields of crossed examples (previous yields in brackets)

6. Other studies

6.1 Mechanistic studies

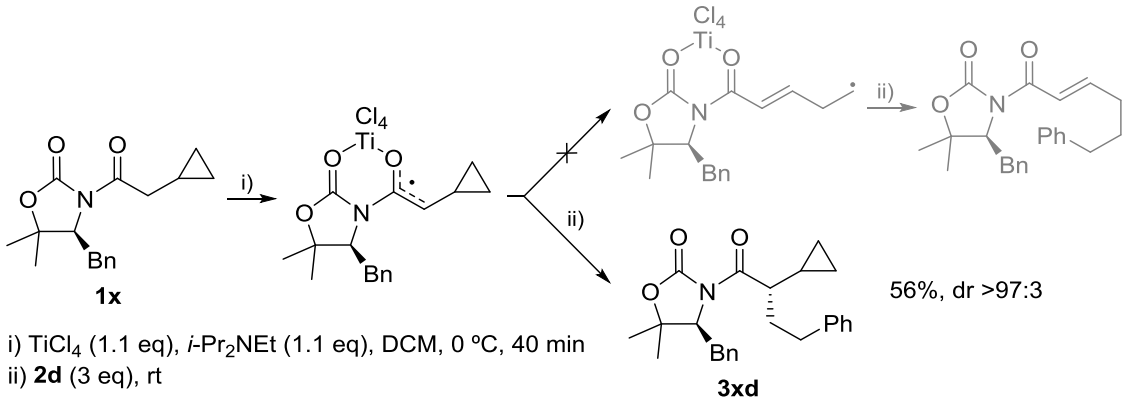
Parallel to the former studies, alkylation tests to learn about the mechanism of the reaction were also conducted. The cyclopropyl group is a commonly used radical clock to determine if a radical species is being formed during a reaction. If a radical is placed in the α-position of a cyclopropyl group, the ring can be opened homolytically through a β-fragmentation to release ring strain, giving way to another radical species with a terminal double bond.

During his thesis, Alejandro Gómez-Palomino performed the alkylation of **1a** with **2o**, which contained an α-cyclopropyl group. The opening of the cycle during the alkylation to yield **10ao** indicated that this transformation was most probably going through a radical mechanism (*Scheme 54*).



Scheme 54. Radical clock in the peroxide, results from Alejandro Gómez-Palomino

Similarly, the same radical clock experiment was performed on the enolate, for that, **1x** was prepared and alkylated with **2d**. However, the ring remained stable and the potential open chain was not observed, so **3xd** was obtained in a moderate yield (*Scheme 55*). This may be explained because the radical in the enolate is delocalized in the acyl moiety instead of being centered on the α-carbon, thus, the ring-opening is less favored since a non-delocalized primary radical would be formed.



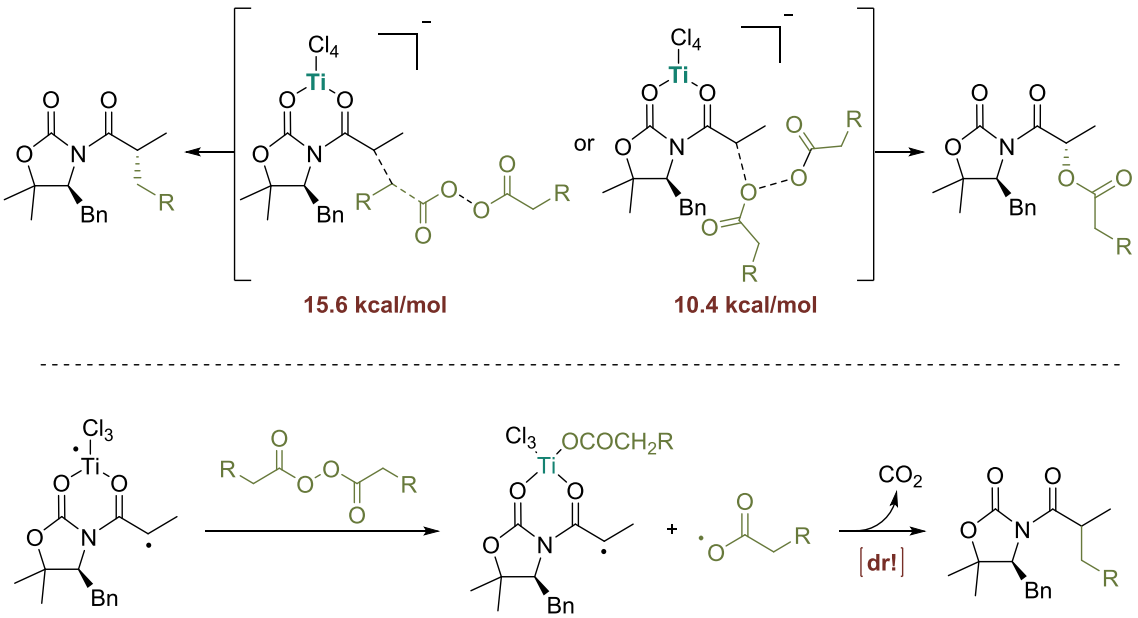
Scheme 55. Radical clock in the enolate

Along the discussion, several experimental details have suggested that the mechanism of the alkylation reaction goes through a radical pathway. Firstly, the formation of chloroalkyl adducts derived from chlorinated solvents that are only formed when a diacyl peroxide is added to the enolate solution suggests that radical species are formed during the mechanism. Then, the ring-opening of the peroxide derived from cyclopropylacetic acid during the alkylation reaction indicates that an alkyl radical derived from the peroxide is generated during the transformation. However, these alone

are not enough evidence to propose a mechanism. This is the reason why computational studies were carried out by GÓMEZ-BENGOA's group.

As in the experimental studies, *N*-acyl oxazolidinone **1a** and **LPO** were used as model substrates to perform such calculations. The objective was to find a plausible mechanism that was compatible with the experimental data. Firstly, the alkylation reaction must have a low activation energy since it is performed at room temperature and occurs in less than one hour. Also, the mechanism should explain the high levels of diastereoselectivity observed in most examples. And finally, it should involve radical species to explain the formation of a chloroalkylated by-product **6** (*see Section 3*) and the product resulting from the opening of a radical clock **10ao**.

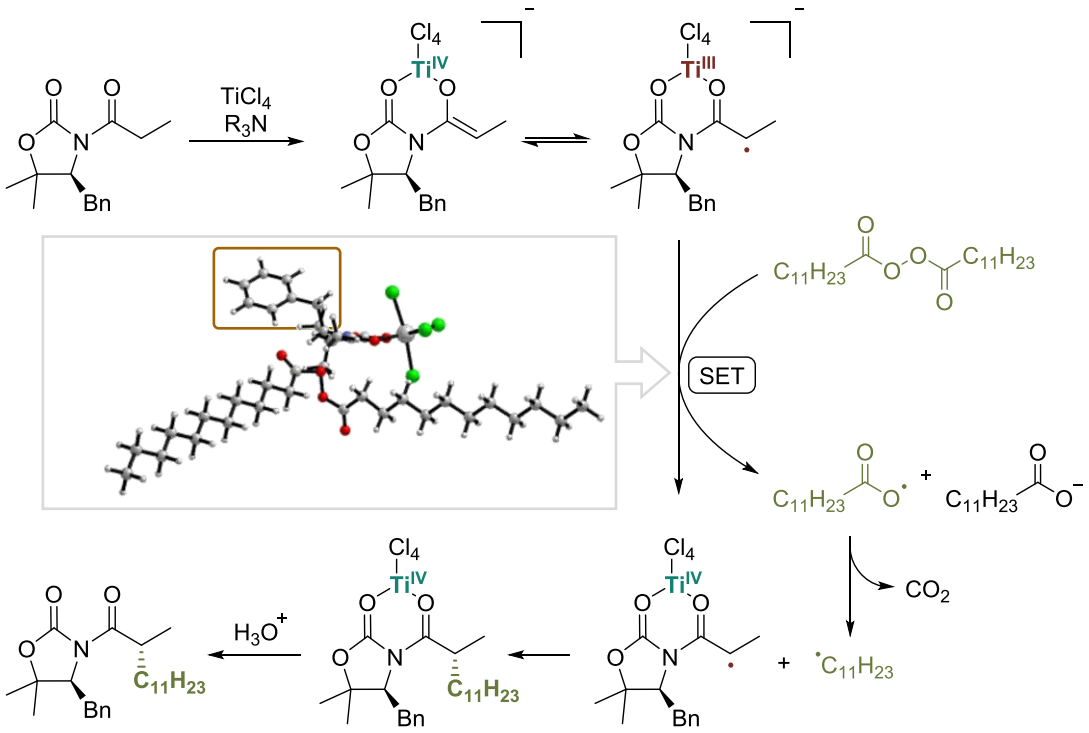
Mechanisms based on two electron nucleophilic attack from the enolate to the peroxide were discarded since they indicated a much lower activation energy for the C–O bond formation, which would correspond to the delivery of an acyloxidized product instead of the experimentally isolated alkylated adduct (*top, Scheme 56*). However, other radical mechanisms studied, in which titanium would react with diacyl peroxide leading to the coordination of a carboxylate moiety to titanium and an alkyl radical, did not explain the great stereoselectivity obtained experimentally because of the low sterically demanding characteristics of the alkyl radical (*bottom, Scheme 56*).



Scheme 56. Refused mechanisms

Alternatively, a redox process between the enolate, with reducing character, and the peroxide would meet all the criteria. In this proposal (*Scheme 57*), a single electron

transfer would occur from the titanium enolate to the diacyl peroxide, which would lead to an unstable radical anion that would decompose homolytically through the O–O bond. As a result, a carboxylate anion would be formed as well as an acyloxy radical that would spontaneously decarboxylate to generate a carbon centered radical. Recombination of the alkyl radical with the titanium enolate would render a new C–C bond, furnishing an alkylated product. Regarding the stereoselectivity, the enolate and diacyl peroxide should be found at short distances in order for the SET process to be feasible. Then, the hindrance of one of the faces of the enolate and the bulkiness of the peroxide would assure good diastereoselectivity for the whole transformation. Actually, it was calculated that the energy difference between the approach from both π-faces is around 3.5 kcal/mol, which corresponds to a diastereomeric ratio of 99:1, that matches the experimental diastereoselectivity.



Scheme 57. Mechanistic hypothesis

6.2 X-ray analysis

Besides the study of the reaction mechanism, the configuration of the new stereocenter needed to be confirmed. For that, one of the solid products, **3cd**, was recrystallized to perform X-ray diffraction analysis to firmly establish its absolute configuration. As predicted, the chiral auxiliary hindered the *Re* face of the enolate, thus, affording the *S* configuration of the new stereocenter (*Figure 15*).

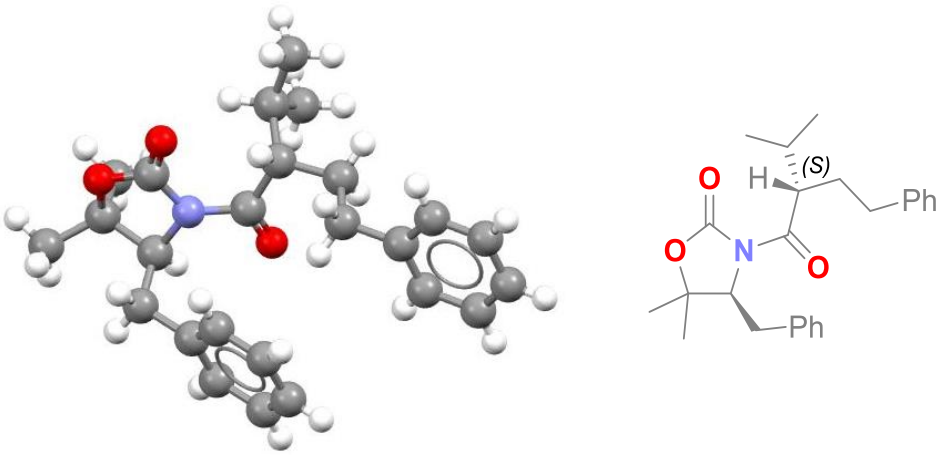


Figure 15. Structure from X-ray analysis of **3cd**

7. Synthesis of Arundic Acid

To complete the development of the alkylation of titanium enolates with diacyl peroxides, a short synthesis of a small molecule to prove the application of the methodology was accomplished.

Arundic acid is an alkyl branched carboxylic acid that was discovered during a screening process by Minase Research Institute of Ono Pharmaceutical Co. Ltd. (Japan). This non-natural compound prevents the expansion of cerebral infarction by improving the astrocyte function.[92] Therefore, it could be used as a drug against neurodegenerative diseases. At the moment, it has completed phase II of clinical trials for Alzheimer's disease, amyotrophic lateral sclerosis and Parkinson's disease.

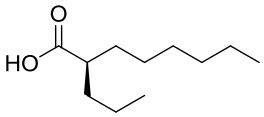
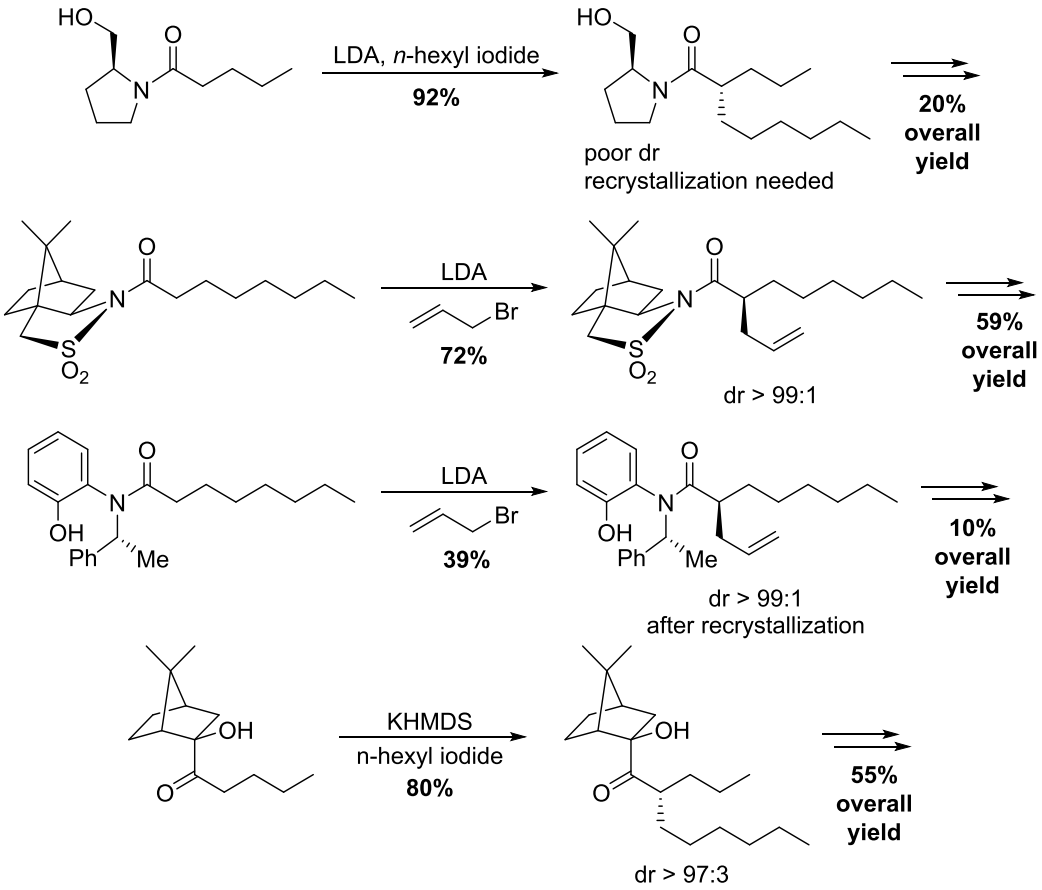


Figure 16. Arundic acid

Due to its simple structure, arundic acid has been synthesized on many occasions. The first synthesis reported by NAKAI hinged on a chiral resolution by recrystallization of an alkyne carboxylate with (*R*)-α-methylbenzylamine.[93]

Following this first approach, other asymmetric syntheses have been published. These include the aldehyde enantioselective alkylation with a carbenium ion,[94] a palladium-amine co-catalyzed allylation of aldehydes[95] and the asymmetric allylation of ethers with organolithium compounds.[96] A miscellaneous array of techniques have also

been described: diastereoselective photodeconjugation,[97] opening of an epoxide that was chirally enriched by hydrolytic kinetic resolution,[98] asymmetric crotylation of an aldehyde,[99] Johnson-Claisen orthoester rearrangement,[100] proline catalyzed asymmetric aminoxylation[101] or zirconium catalyzed carboalumination followed by copper cross coupling.[102] Finally, a few syntheses of this branched acid are based on the stereoselective alkylation of an enolate with an alkyl halide utilizing a chiral auxiliary.[103–107] Regarding such an enolate alkylation approach, different chiral auxiliaries have been used such as (L)-prolinol or Oppolzer camphorsultam among others (*Scheme 58*). However, the insufficient nucleophilicity of enolates to react with deactivated alkyl halides forced some of the approaches to use allyl halides in order to obtain good alkylation yields. Consequently, a reducing step to obtain the saturated target was added to the overall route. In addition, the alkylation diastereoselectivity was often not good enough and recrystallizations were necessary to obtain the desired enantiopurity levels of the target.



Scheme 58. α-Alkylation approaches to the synthesis of arundic acid

Herein, the alkylation of titanium enolates with saturated diacyl peroxides allowed the direct synthesis of arundic acid *via* two different pathways on the grounds that this alkylation permits the introduction of long deactivated alkyl chains (*Figure 17*). During

their Erasmus studies, Timo Hesse and Sonja Fleckenstein collaborated in the three-step synthesis of arundic acid through both approaches and in the scale up of one of them.[108,109]

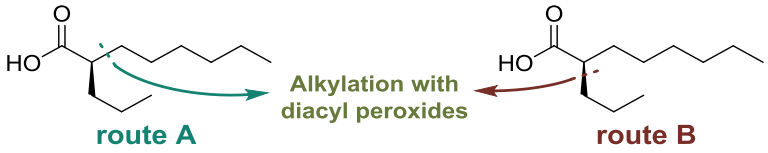
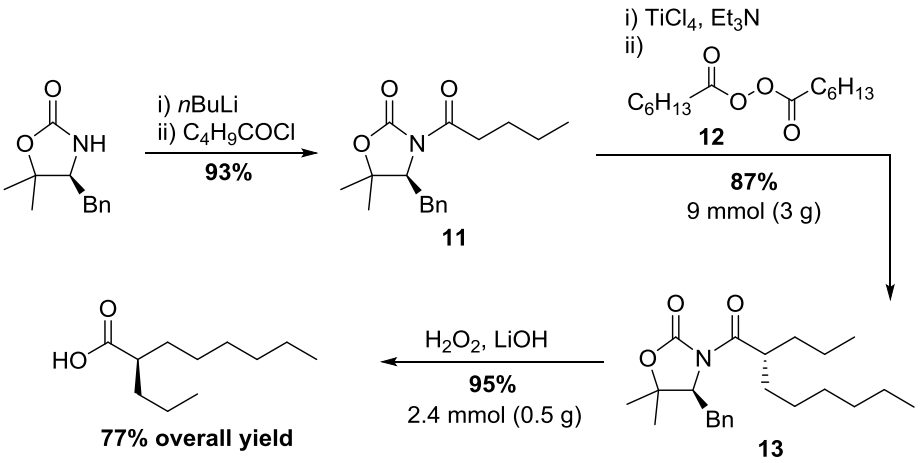


Figure 17. Synthesis of arundic acid through two different paths

7.1 Route A

Initially, arundic acid was synthesized using the chiral auxiliary derived from the natural aminoacid phenylalanine. First, it was acylated with pentanoyl chloride affording **11** in an excellent yield (93%). Then, alkylation of the corresponding titanium enolate with diheptanoyl peroxide (**12**) furnished **13** with outstanding diastereoselectivity and yield (87%). Moreover, the alkylation could be scaled up to 9 mmol (~3 g) while maintaining such features. Finally, removal of the chiral auxiliary with lithium peroxide afforded arundic acid in a 77% overall yield and a recovery of the chiral oxazolidinone of 98% (*Scheme 59*).

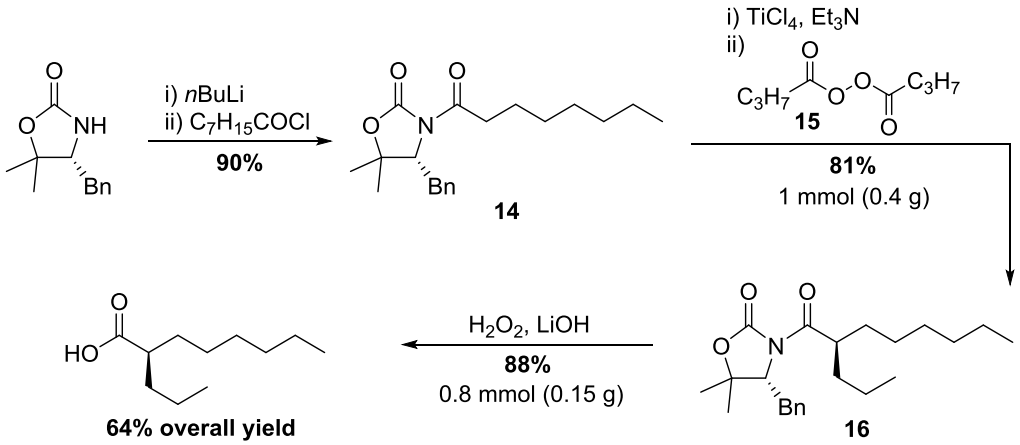


Scheme 59. Route A to arundic acid

7.2 Route B

On the other hand, arundic acid was also synthesized following an alternative route based on the opposite alkylation as indicated above (*Figure 17*). In order to obtain the same stereocenter, since the alkylation was reversed, the enantiomer of the previously used chiral auxiliary was required. Its acylation with octanoyl chloride afforded **14** with

a great yield (90%). Then, the alkylation with dibutyryl peroxide (**15**) proceeded smoothly to give a single diastereomer of **16** in an excellent 81% yield. Final removal of the chiral auxiliary led to arundic acid in an 88% yield and with 91% of recovered auxiliary. The overall yield for this route was 64% (*Scheme 60*), although better yields might be achieved at a higher scale.

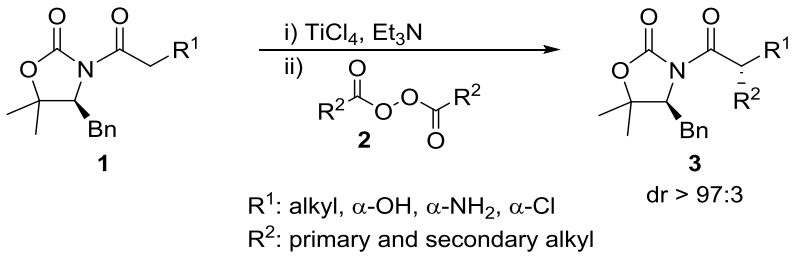


Scheme 60. Route B to arundic acid

In contrast to the previous synthesis, our approach based on the alkylation of the corresponding titanium enolates with saturated diacyl peroxides provides high yields and diastereoselectivities and permits the straightforward synthesis of arundic acid *via* two complementary pathways.

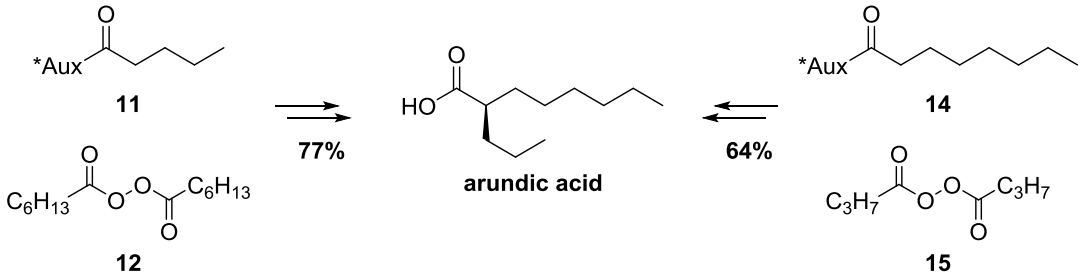
8. Outline

Overall, Chapter I describes a new alkylation approach with diacyl peroxides that relies on the biradical character of titanium enolates and uses carboxylic acids as an alkyl source, which are abundant and inexpensive organic materials (*Scheme 61*). This enables the highly stereocontrolled addition of deactivated primary and secondary alkyl groups, which cannot be introduced using most of the current methodologies. Furthermore, it was proved that the alkylating agent can also include a variety of functional groups. A broad range of enolates containing different functionalities are also suitable for such transformations. It is worth mentioning that the alkylation described is an experimentally easy procedure that proceeds under mild temperature conditions and short reaction times.



Scheme 61. Alkylation of titanium enolates with diacyl peroxides

Finally, this alkylation procedure has been applied to the synthesis of arundic acid *via* two complementary pathways, both of which have rendered the target acid with great overall yields (*Scheme 62*).



Scheme 62. Synthesis of arundic acid

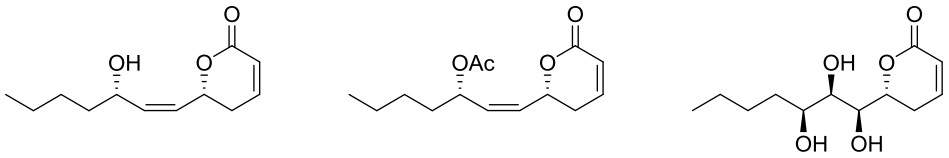
CHAPTER II

Total Synthesis of Umuravumbolide

1. Introduction

As described at the beginning of the introduction, the total synthesis of organic molecules is a lingering testing ground for well-established methodologies as well as that it may offer excellent opportunities to unveil the lack of appropriate procedures and examine the synthetic efficiency of new ones. Following that statement, we considered it would be worth examining the radical alkylation of titanium enolates with diacyl peroxides described in the previous chapter in the synthesis of umuravumbolide, a small substituted pyrone extracted from a medicinal plant.

In central Africa, *Iboza Riparia* (known as Umuravumba) is broadly used as a natural remedy for several sicknesses such as fever, aches, diarrhea or even malaria. In the hunt for new bioactive molecules, the extracts of this plant's leaves were found to show a remarkable chemotherapeutic activity. Back in 1979, VAN PUYVELDE isolated three α-pyrones from *Iboza Riparia* (*Figure 18*), one of them being umuravumbolide, for which he proposed a close but not accurate structure.[110] Its structure was totally elucidated years after by DAVIES-COLEMAN, who disclosed the *Z* geometry of the olefin and the absolute configuration of both chiral centers.[111]



Deacetylumuravumbolide Umuravumbolide Deacetylboronolide

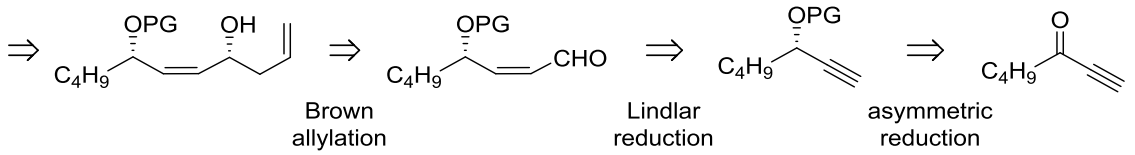
Figure 18. α-Pyrones isolated from *Iboza Riparia*

1.1 Previous syntheses

Following those studies and considering that natural products containing the moiety of 6-substituted 5,6-dihydro-α-pyrone exhibit interesting activities such as plant growth inhibition, insect antifeedant, antifungal or antitumoral, umuravumbolide has attracted much attention.[112] In fact, umuravumbolide was first synthesized in 2001 by RAMACHANDRAN[113] and since then, other routes have been described.

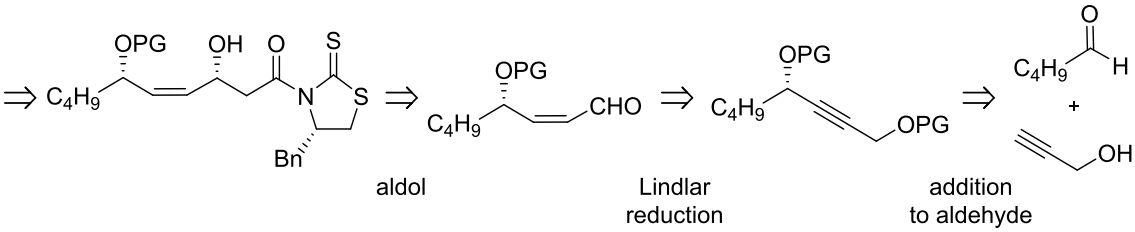
In the first synthesis (*Scheme 63*), RAMACHANDRAN created the first stereocenter by asymmetric reduction of an acetylenic ketone.[113] Unfortunately, low levels of enantiocontrol forced the recrystallization of a benzoate derivative to obtain the optically

pure alcohol. Then, the selective reduction of the triple bond to form the *Z*-olefin followed by a Brown allylation of the corresponding α,β-unsaturated aldehyde provided the main features of the target. This first route is still one of the shortest reported (11 steps), but the overall yield, being less than 10%, was negatively impacted by the low stereoselectivity of the first step, the ketone reduction.



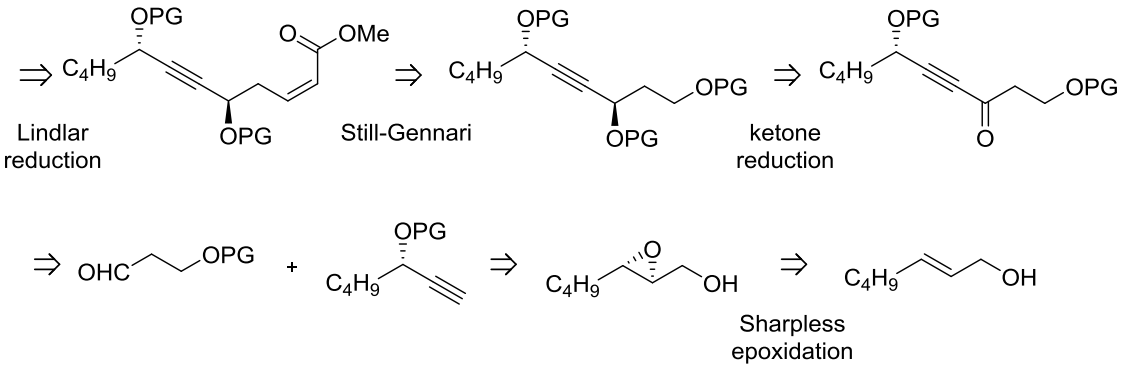
Scheme 63. RAMACHANDRAN synthesis of umuravumbolide

In 2011, VENKATESWARLU devised another approach to the synthesis of umuravumbolide (*Scheme 64*).[114] He performed a BINOL-mediated enantioselective addition of a propargylic alcohol to an aldehyde to create the first stereocenter. Once again, selective triple bond reduction generated the *Z* double bond but, this time, the second chiral center was installed *via* an asymmetric acetate aldol reaction assisted by a chiral auxiliary. This second synthesis achieved a 22% overall yield over 11 steps.



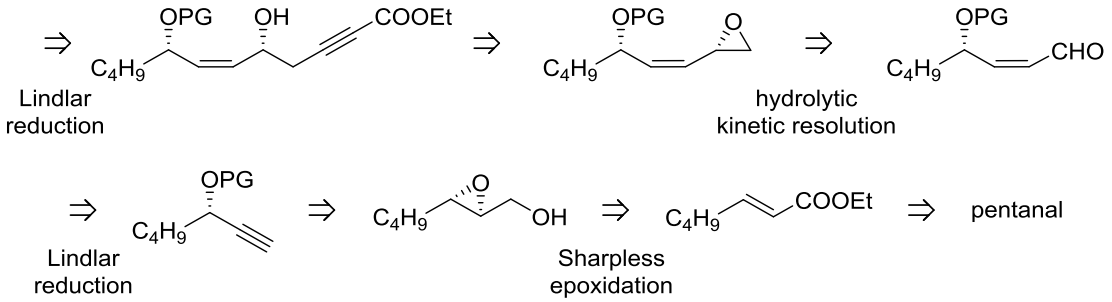
Scheme 64. VENKATESWARLU synthesis of umuravumbolide

Shortly after, SABITHA described a new route in which a Sharpless epoxidation was crucial to install the stereocenter of the side chain (*Scheme 65*).[115] Whereas the second one was introduced by enantioselective reduction of the corresponding ketone derivative. Then, a Still-Gennari olefination was used to furnish the *Z* double bond in the pyrone. Finally, the olefin in the lateral chain was obtained again, through a Lindlar reduction of the triple bond. This was a 16-step synthesis with many protection/deprotection and reduction/oxidation steps and a poor overall yield (< 5%).



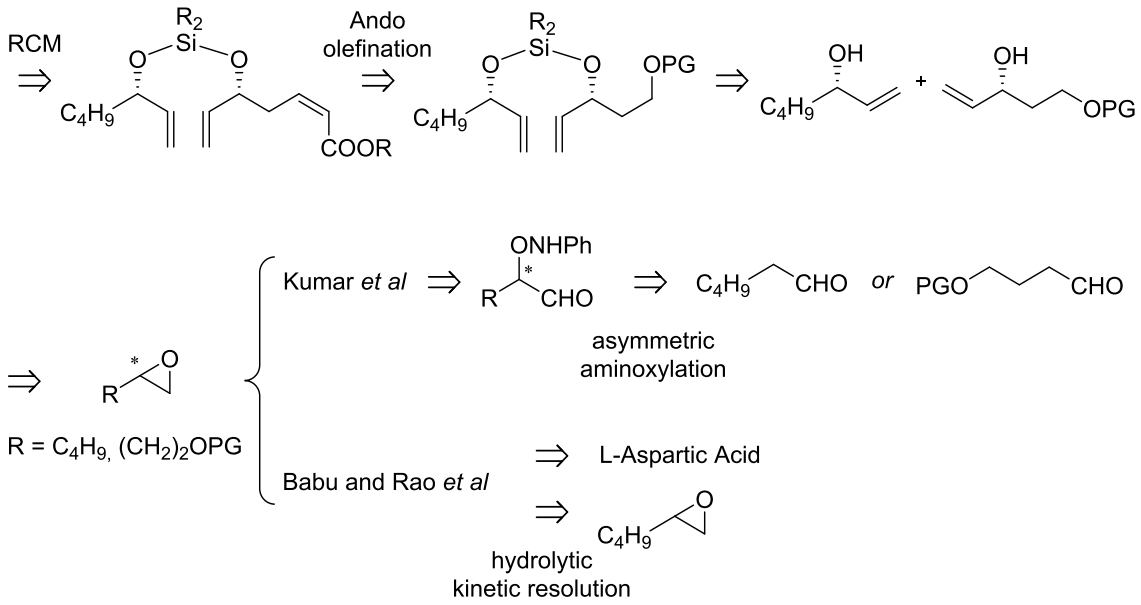
Scheme 65. SABITHA synthesis of umuravumbolide

VENKATESWARLU also developed a new approach that hinged on the use of epoxides to create the chiral centers (*Scheme 66*).[116] Firstly, a Sharpless epoxidation allowed the introduction of the first stereocenter, while the second one was obtained through a kinetic resolution of a mixture of diastereomers. In this case, both the cyclic and the side chain *Z* olefins were also formed through Lindlar reduction of a triple bond. Again, this was another long synthesis that furnished umuravumbolide in 15 steps and an overall yield lower than 5%.



Scheme 66. VENKATESWARLU synthesis of umuravumbolide

Finally, BABU and RAO, and separately KUMAR described two similar convergent approaches (*Scheme 67*). Different routes were followed to synthesize the corresponding epoxides leading to the two key allylic alcohols; KUMAR[117] used an asymmetric aminoxylation while BABU and RAO[118] employed a kinetic resolution. In both routes the allylic alcohols were then tethered through a silicon bridge and subsequent RCM on the resulting molecule forced the formation of the *Z* olefin of the side chain. The double bond of the pyrone was installed through a *Z*-selective Ando olefination.



Scheme 67. KUMAR and BABU and RAO syntheses of umuravumbolide

In summary, the main challenge in the total synthesis of umuravumbolide stands in the formation of the two oxygen-containing stereocenters (*Figure 19*). To recapitulate, some strategies relied on epoxides to induce the chirality of the target either by hydrolytic kinetic resolution (HKR)[118] or Sharpless epoxidation[115,116]. Alternatively, the stereochemical control was obtained from carbonyl compounds, either by enantioselective reduction of a ketone[113,115] or asymmetric nucleophilic additions to aldehydes[113,114]. Lastly, KUMAR used an α-aminoxylation of an aldehyde to get the desired stereocenters.[117]

Despite the abovementioned variety of approaches, none of the syntheses described to date have reported the alkylation of a metal enolate to install the stereocenter of the exocyclic unsaturated fragment, which implies a new retrosynthetic fragmentation (*in green, Figure 19*). This was the strategy followed in our synthesis of umuravumbolide, aiming to challenge the alkylation methodology described in the previous chapter.

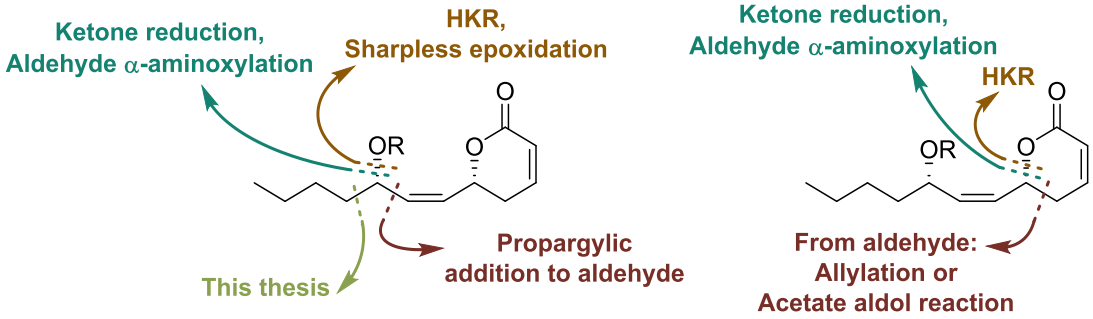


Figure 19. Different strategies to form the stereocenters in umuravumbolide

The key steps of our synthetic plan were the diastereoselective alkylation of a titanium enolate derived from glycolic acid with dipentanoyl peroxide to furnish the stereocenter in the side chain, a Wittig olefination to form the *Z*-double bond, and an asymmetric allylation to gain access to the pyrone stereocenter. The rest of the pyrone would be constructed through acylation with acryloyl chloride and RCM.

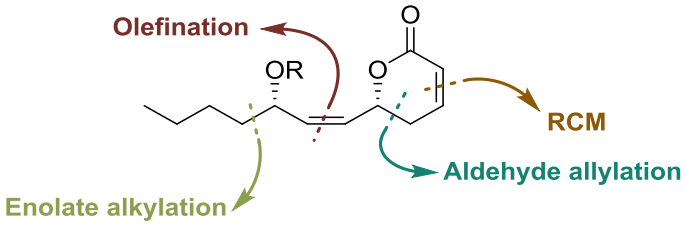
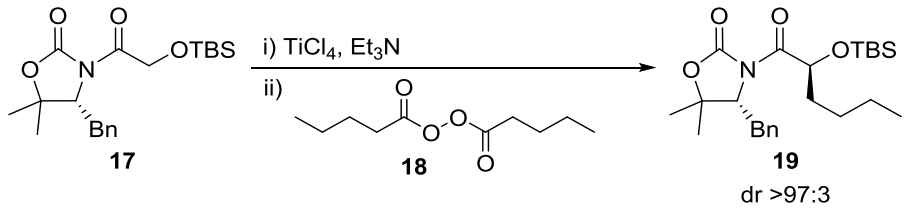


Figure 20. Main steps of the synthesis of umuravumbolide

2. Side chain chiral center

The synthesis of umuravumbolide started with the radical alkylation of the titanium enolate of a glycolate derivative (**17**) with dipentanoyl peroxide (**18**) under the conditions described in the previous chapter. The yield of the preliminary experiments was notably lower than that of the analogous examples previously described (*entry 1, Table 16*). To our pleasure, a simple change of temperature, from –20 °C to room temperature, boosted the yield of the reaction to give excellent results (*entry 2, Table 16*). Moreover, the alkylation could be performed with just 1.5 equivalents of diacyl peroxide, which represents a remarkable advance in terms of atom economy (*entry 3, Table 16*). With optimized conditions in hand, the alkylation step was scaled up to three and then six mmol, with reproducible results (*entries 4 and 5, Table 16*). It is worth adding that gas release was observed at large scale, which was due to the carbon dioxide formed in the decarboxylation step. Importantly, reaction crudes were clean and a second diastereomer was never observed, what resulted in an easy purification of the product that consisted of a filtration through a short pad of silica.

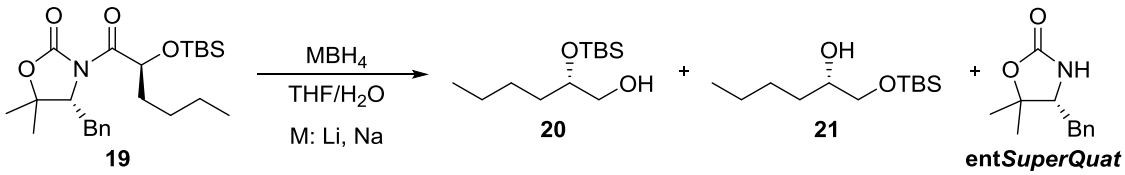


i) $TiCl_4$ (1.1 eq), Et_3N (3 eq), DCE, T, 40 min; ii) **18** (X eq), T

Entry	Scale	Temperature	Peroxide	Isolated Yield
1	0.5 mmol	–20 °C	2 eq	48%
2	0.5 mmol	rt	2 eq	92%
3	1 mmol	rt	1.5 eq	88%
4	3 mmol	rt	1.5 eq	88%
5	6 mmol	rt	1.5 eq	87%

Table 16. Alkylation of the titanium enolate with dipentanoyl peroxide

Once the stereocenter was installed, removal of the chiral auxiliary was attempted. First, reduction with sodium borohydride to give the corresponding alcohol was attempted, but low conversions were achieved after long reaction times and high amounts hydride employed (*entry 1, Table 17*). To accelerate the reaction, the reducing agent was swapped to lithium borohydride, which rendered much better results, especially at room temperature (*entries 2 and 3, Table 17*). Unfortunately, migration of the silyl protecting group to the primary alcohol was sometimes observed (*entry 4, Table 17).* This was partially suppressed at lower temperatures (*entries 5 and 6, Table 17*). Furthermore, it was finally found that freshly opened lithium borohydride gave better results, and the use of six equivalents of the reducing agent allowed the isolation of enantiomerically pure alcohol **20** with a 79% yield when the reaction was performed at a larger scale (*entry 7, Table 17*).



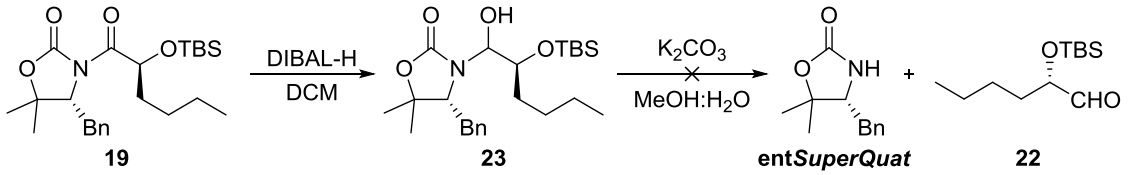
Entry	MBH_4	T	time	Isolated Yield (20)	Isolated Yield (ent*SuperQuat*)
1	12 eq $NaBH_4$	0 °C to rt	24 h	59%	73%
2	6 eq $LiBH_4$	0 °C	8.5 h	80%	quantitative
3	6 eq $LiBH_4$	rt	6 h	98%	94%
4	5 eq $LiBH_4$	rt	1 h	72% (18%)[a]	95%
5	5 eq $LiBH_4$	0 °C	1 h	87%	92%
6	4 eq $LiBH_4$	–10 °C	3 h	91%	97%
7[b]	6 eq $LiBH_4$	–10 °C	1.5 h	79%	92%

[a]silyl migration by-product (**21**); [b]4.6 mmol scale

Table 17. Cleavage of the chiral auxiliary with metal borohydrides

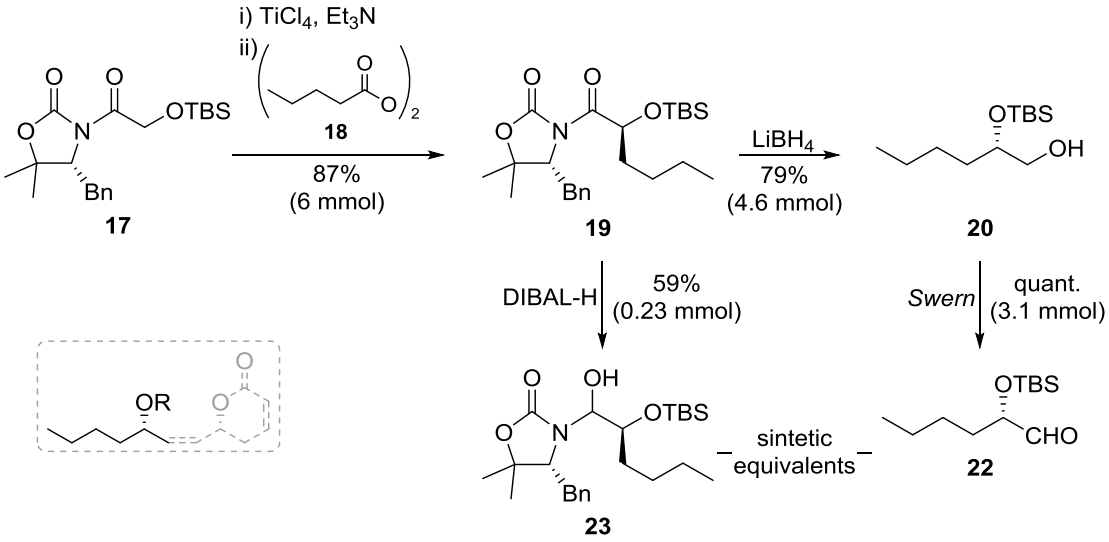
An aldehyde was required for the next step (olefination reaction). Therefore, alcohol **20** was oxidized under Swern conditions, which rendered the corresponding aldehyde **22** quantitatively without need for further purification (*Scheme 69*).

Alternatively, the cleavage of the chiral auxiliary to directly obtain aldehyde **22** and minimize the number of steps was attempted with DIBAL-H. Reduction of **19** generated a single diastereomer of the carbinol species **23** together with minor quantities of chiral auxiliary and aldehyde **22** (*Scheme 68*). As reported in the literature, similar hemiaminal species can be further reduced to remove the chiral auxiliary and yield the aldehyde.[119] Unfortunately, the described conditions led to an unclean crude mixture in which characteristic signals of the chiral auxiliary moiety were not found by ^{1}H NMR.



Scheme 68. Cleavage of the chiral auxiliary with DIBAL-H

Despite the unsuccessful obtention of aldehyde **22**, reduction with DIBAL-H was not discarded since species such as **23** can be used as an aldehyde analogue in olefination reactions (see further discussion in *section 3.1*).[120] Therefore, after the radical alkylation of the titanium enolate with dipentanoyl peroxide, two different paths to form olefination precursors could be followed: complete reduction with $LiBH_4$ to produce the corresponding alcohol and its subsequent oxidation, or partial reduction with DIBAL-H, although worse yields are achieved with the latter option (*Scheme 69*).



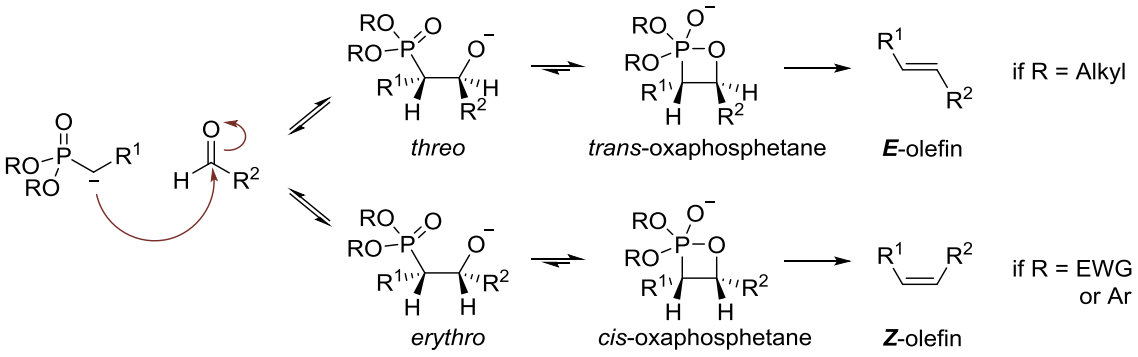
Scheme 69. Summary of the formation of the fragment of the side chain containing the stereocenter

3. Side chain olefin

Double bonds are commonly found in natural products so, as would be expected, numerous approaches have been developed for their synthesis. Wittig unlocked a whole new avenue when he described the olefination through the nucleophilic addition of phosphonium ylides to carbonyl compounds. Further studies in this field led to the known Horner-Wadsworth-Emmons (HWE) reaction, which instead of phosphonium salts, uses phosphonate stabilized carbanions. HWE was initially described as an *E*-olefin yielding reaction, but many variations have been developed to selectively access the *Z* isomer.[121]

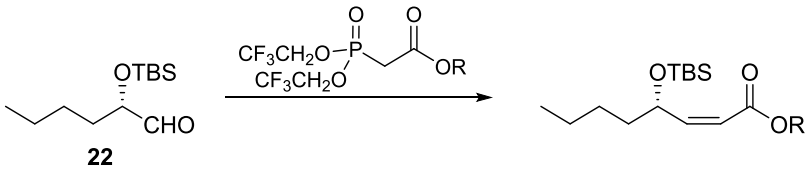
Differences in the selectivity of the geometry of the double bound for this type of reaction are explained through the mechanism,[122] which consists of the attack of the phosphonate carbanion to the aldehyde followed by a ring closure to form an oxaphosphetane species. Subsequent phosphate elimination finally leads to the carbon-carbon double bond (*Scheme 70*). Since just the final elimination of the phosphate group is irreversible, all the other species may be found in equilibrium. The attack of the phosphonate carbanion to the aldehyde can occur through either of the two faces of the aldehyde providing a *threo* and an *erythro* adduct. Computational studies seem to indicate that the *anti*-attack forming the *erythro* adduct is favored. However, the *trans*-oxaphosphetane arising from the ring closure of the *threo* isomer is more stable than the *cis*. Hence, due to the equilibrium of all these species, the *E* selectivity of the HWE olefination can be rationalized.

In contrast, when the alkoxy groups of the phosphonate are substituted by electron-withdrawing substituents, the resultant oxaphosphetane intermediates are stabilized and the equilibrium is shifted towards the *cis*-oxaphosphetane after the favored formation of the *erythro* adduct. As a result, these changes in the structure of the phosphonate invert the selectivity to the *Z* diastereomer.[122]



Scheme 70. HWE mechanism

Such stereoselective capability of HWE-like reactions to produce *E* as well as *Z* olefins has made of them an essential tool that has been largely exploited in the total synthesis of natural products.[121] From our experience, the Still-Gennari modification to generate *Z* double bonds seemed a suitable choice for the olefin formation in the side chain of umuravumbolide (*Scheme 71*).



Scheme 71. Still-Gennari *Z*-olefination from aldehyde **22**

3.1 Still-Gennari olefination

STILL and GENNARI described a new phosphonate with 3,3,3-trifluoroethoxy substituents to perform such olefination. They reported the use of a combination of KHMDS and 18-crown-6 ether to deprotonate the phosphonate to attain the desired control on the *Z*-geometry of the olefin,[123] however, individual cases may need screening of bases, solvents, and temperature conditions to find the most suitable combination.[122] Preliminary tests at low scale were thus performed to identify the base/solvent system that would render the best *Z*-selectivity. For that, the *Z*:*E* diastereomeric ratio was directly measured by ^{1}H NMR of the crude mixture (*Figure 21*).

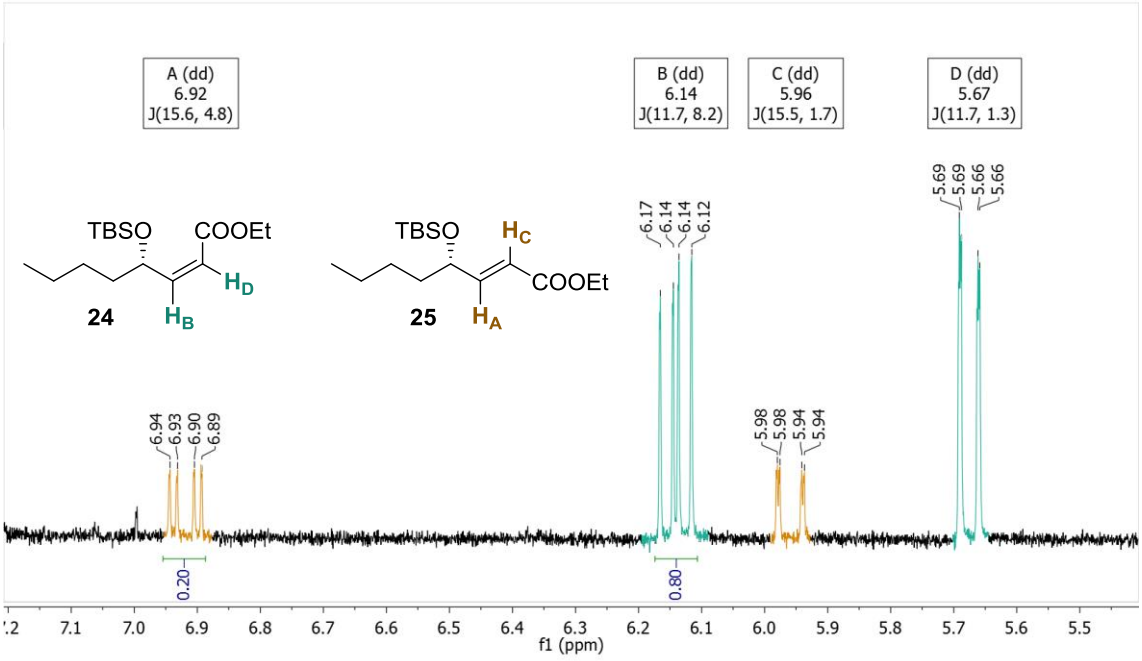
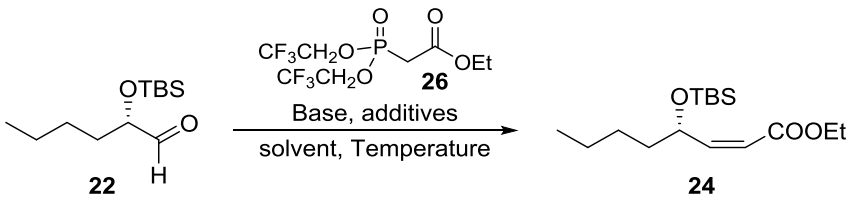


Figure 21. Diagnostic peaks to establish the *Z*/*E* diastereomeric ratio by ^{1}H NMR of the crude

Initially, olefination with commercially available phosphonate **26** was carried out as originally described, using KHMDS and 18-crown-6 in THF at –78 °C.[123] However, a poor selectivity was obtained (*entry 1, Table 18*). Then, softer potassium carbonate together with 18-crown-6 in toluene at 0 °C were employed since these conditions were successfully used by the group in previous studies.[124] Unfortunately, a poorer selectivity was observed in this case (*entry 2, Table 18*). Seeing that the *Z* isomer is preferred under kinetic control, the reaction was repeated at lower temperature, which showed slightly better, though insufficient, results (*entry 3, Table 18*). Sodium hydride in THF at –60 °C gave much better results (*entry 4, Table 18)*. The temperature was then lowered to –78 °C to achieve an even better *Z*-selectivity; this was indeed improved, but the conversion dropped dramatically (*entry 5, Table 18)*. An acceptable selectivity/conversion balance was achieved with temperatures between –60 °C to –50 °C. Finally, the reaction was scaled up to 1.4 mmol and the *Z* isomer was isolated in a 77% yield (*entry 6, Table 18)*.

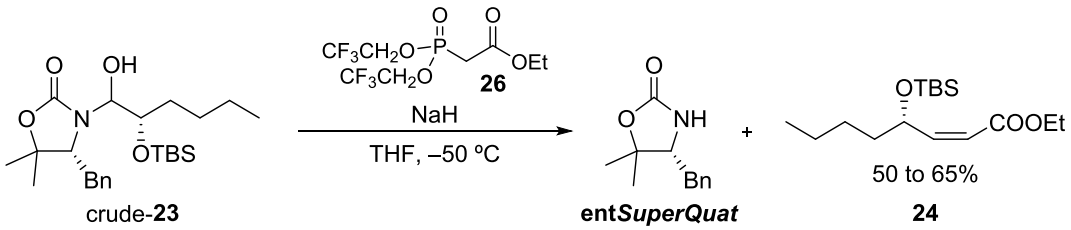


Entry	Base/additives	Solvent	Temperature	time	*Z* : *E*[a]
1	KHMDS/18-crown-6	THF	–78 °C	2 h	80:20
2	K_2CO_3/18-crown-6	PhMe	0 °C	16 h	70:30
3	K_2CO_3/18-crown-6	PhMe	–20 °C	16 h	75:25
4	NaH	THF	–60 °C	1 h	91:9
5[b]	NaH	THF	–78 °C	1 h	96:4
6[c]	NaH	THF	–50 °C	1 h	89:11 (77%)[d]

[a]Calculated by ^{1}H NMR of the crude mixture; [b]not complete conversion; [c]1.44 mmol scale; [d]isolated yield of pure *Z* diastereomer.

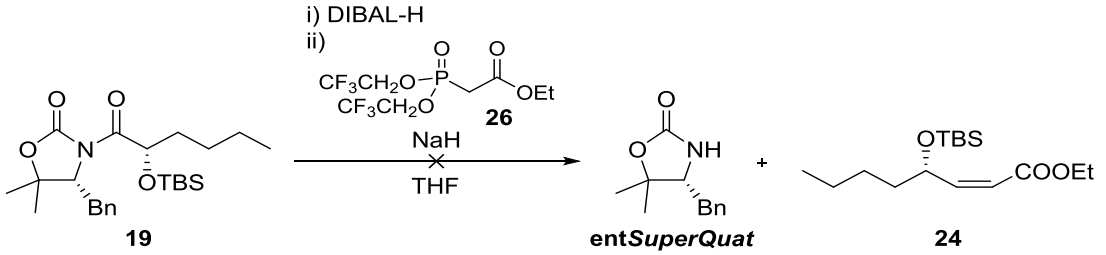
Table 18. Condition screening for Still-Gennari olefination

With optimized conditions in hand, the Still-Gennari olefination was attempted from carbinol species **23** as an aldehyde analogue. As shown in *Scheme 69*, such a species was obtained together with significant quantities of aldehyde. Therefore, crude **23** was used for the olefination. Full conversion was achieved and the stereoselectivity was maintained, however, unclean reduction of the alkylation product with DIBAL-H led to unreproducible overall yields ranging from 50% to 65% (*Scheme 72*).



Scheme 72. Still-Gennari olefination from **23**

Given the success of the olefination and aiming to reduce the steps of the whole synthesis, we explored the one-pot elimination of the chiral auxiliary and Still-Gennari olefination as described in the literature.[120] However, reduction of the alkylated product **19** had to be performed in the same solvent as the olefination (THF), which sadly did not succeed (*Scheme 73*), so we abandoned this advantageous one-pot process.



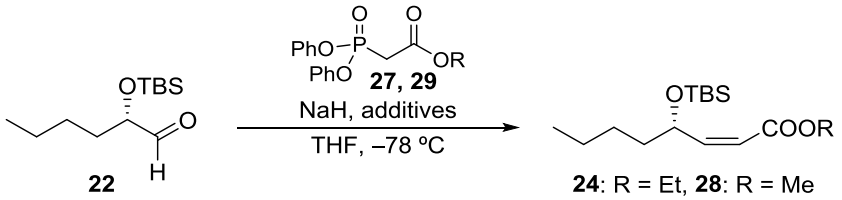
Scheme 73. One-pot cleavage of the auxiliary and Still-Gennari olefination

3.2 Ando olefination

During his master's thesis, Eduard Balaguer focused on a last scale-up of the alkylation and auxiliary removal, and the improvement of the olefination's selectivity.[125] In that light, he studied the Ando modification of HWE, in which the phosphonate used contains phenoxy groups as suitable substituents to render *Z* geometries of the olefin.[126] Hence, the methyl ester of Ando phosphonate reagent **27** was prepared according to literature from diphenyl phosphite and methyl bromoacetate.[127]

The best conditions found for the *Z*-selectivity of the Still-Gennari olefination were initially used. Indeed, phosphonate **27** was deprotonated with NaH in THF at –78 °C, and addition of aldehyde **22** rendered alkene **28** with an excellent diastereomeric ratio of 96:4, from which pure *Z*-olefin was isolated after flash column purification in a 79% yield (*entry 1, Table 19*). Although high levels of selectivity were achieved, further studies were conducted to reach even better results. As described by PIHKO,[128] NaI was added to generate an excess of counter-cation in order to improve the *Z*-selectivity, but no remarkable differences were noticed (*entry 2, Table 19*). Another factor described by

ANDO that could improve the selectivity was the bulkiness of the phosphonate's ester moiety.[129] Therefore, the ethyl ester analogue of the phosphonate reagent **29** was prepared, but no significant changes were observed although the diastereoselectivity achieved an outstanding value (dr 97:3) when NaI was employed (*entries 3 and 4, Table 19*). Despite that similar results being obtained for all the conditions screened, phosphonate **29** and the addition of NaI were chosen for the scale-up of the olefination, in which the diastereoselectivity was maintained, moreover, a higher isolated yield was obtained for **24** (*entry 5, Table 19).*

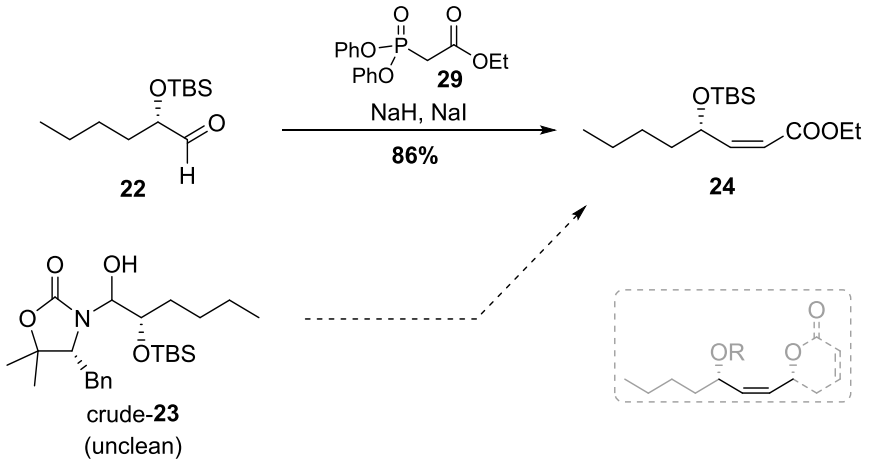


Entry	Phosphonate	R	additives	*Z* : *E*[a]	Isolated Yield
1	**27**	Me	-	96:4	79%
2	**27**	Me	NaI	96:4	73%
3	**29**	Et	-	96:4	81%
4	**29**	Et	NaI	97:3	79%
5[b]	**29**	Et	NaI	96:4	86%

[a]Calculated by ^{1}H NMR of the crude mixture; [b]3 mmol scale

Table 19. Condition screening for Ando olefination

To sum up, olefination from carbinol species **23** was discarded due to unclean reduction crudes (*Scheme 74*). Then, for the studied α-OTBS aldehyde **22**, the Ando olefination proved to be much more selective towards the *Z*-alkene than the Still-Gennari variation, which translated to higher yields for the *Z*-α,β-unsaturated ester **24**.



Scheme 74. Construction of the side chain carbon-carbon double bond

4. The pyrone stereocenter

Once the side chain of umuravumbolide was already obtained, the next step of the synthesis was to incorporate the second stereocenter, the one found in the pyrone ring. To achieve this, we envisaged that an allyl group might be added to the previously incorporated ester moiety after the required derivatization to the aldehyde. Allylation of carbonyl compounds is a useful transformation that not only forms a new carbon-carbon bond, but it also generates a new hydroxyl group and incorporates a double bond. Both functional groups can be used in further steps of a total synthesis; in this route, the alcohol and double bond obtained will be used to complete the pyrone ring (*Figure 22*).

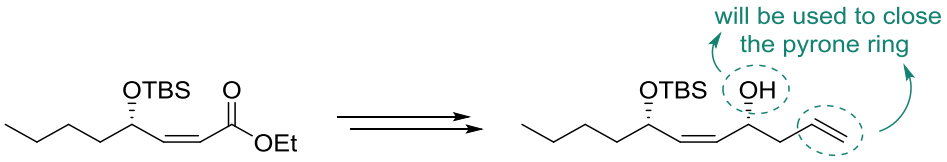
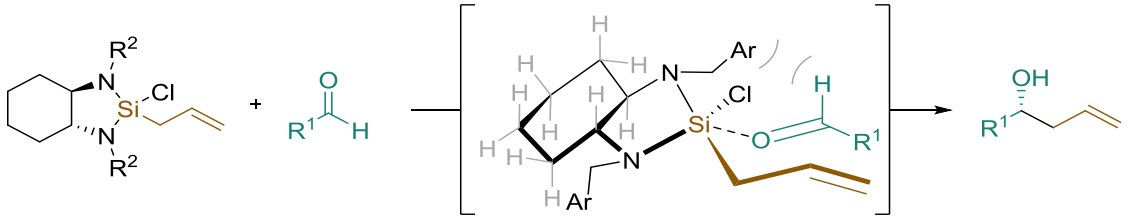


Figure 22. Asymmetric allylation

The asymmetric version of the allyl metal addition to an aldehyde has been widely studied. Indeed, chirality mostly steams from chiral ligands attached to the metal center, which is usually boron, titanium, silicon or tin. Most well-established methodologies include those developed by BROWN, ROUSH, KECK, COREY or LEIGHTON which have been used in many examples of total synthesis.[130]

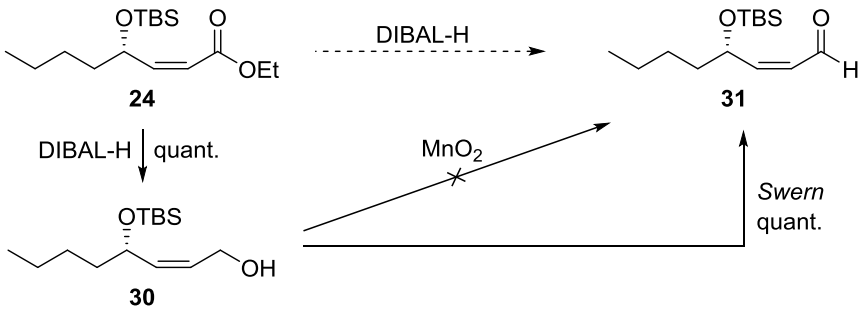
4.1 Leighton allylation

Among all the options available, the Leighton allylation was chosen due to the simplicity of the procedure that involves the simple mixture of a diazasilane and an aldehyde without the need for supplementary additives. The key to the easy procedure was to develop an allyl silane in which the silyl center is constricted in a 5-membered ring that provides silane with enough Lewis acid character to activate the aldehyde for the allyl nucleophilic addition. Therefore, the same reagent acts as both Lewis acid and allyl donor. Moreover, the chirality of the silacycle furnishes highly asymmetric allylated products[131] through a chair-like transition state (*Scheme 75*).[132]



Scheme 75. Chair-like transition state of Leighton's allylation

To perform such an allylation, ester **24** needed to be converted to the corresponding aldehyde. Partial reduction of the ester was first attempted with DIBAL-H, but a mixture of starting material, aldehyde and alcohol was obtained. Instead, full reduction of the ester was achieved quantitatively with two equivalents of DIBAL-H, and the oxidation of the resulting allylic alcohol **30** to the desired aldehyde with manganese(IV) oxide was attempted, yet no reaction occurred. Alternatively, SWERN oxidation produced aldehyde **31** in quantitative yield.



Scheme 76. Ester reduction to aldehyde

As we noticed that aldehyde **31** started to decompose after two days in the freezer, it was prepared and freshly used in the allylation step in the same day. First, commercially available Leighton silane **32** (*Figure 23*) was added to the aldehyde in DCM at 0 °C and stirred overnight as indicated in the literature.[133] ^{1}H NMR of the crude showed a mixture of starting aldehyde (*Z*), isomerized aldehyde (*E*) and just traces of allylated *Z* product (*entry 1, Table 20*). Apparently, the allylic OTBS *Z*-aldehyde **31** was a challenging substrate that needed to be activated in order to achieve a successful allylation. As described by LEIGHTON years later, scandium(III) triflate could be added in catalytic amounts to enhance the reactivity of deactivated aldehydes, thus improving the scope and providing lower reaction times for the allylation reaction.[134] Therefore, addition of the metal catalyst was tested, but similar results were obtained (*entry 2, Table 20*).

We were disappointed by such surprising and unexpected results, which arose the suspicion of the fine state of silane **32**, which maybe had partially decomposed. In fact,

this silane can be briefly handled in air, but it should be stored under nitrogen or argon to avoid its hydrolysis. ^{1}H NMR of silane **32** revealed other peaks that did not correspond to the allylating reagent and could be assigned to the hydrolyzed diamine. For instance, the benzylic system integrated much more than expected compared to the integration of the allyl moiety (*in blue and green respectively, Figure 23*). Moreover, the same silane was tested with benzaldehyde as a model substrate with very poor results according to the ^{1}H NMR of the crude, confirming the hypothesis.

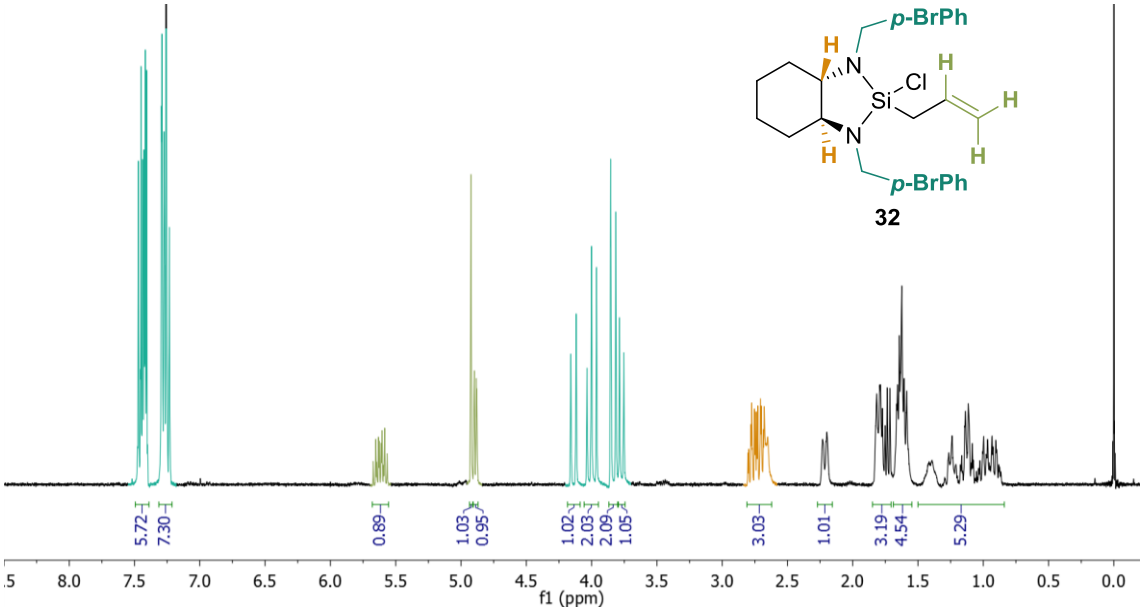
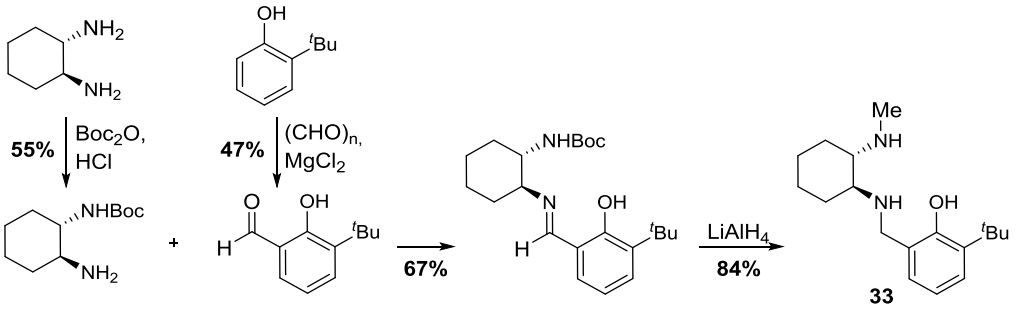


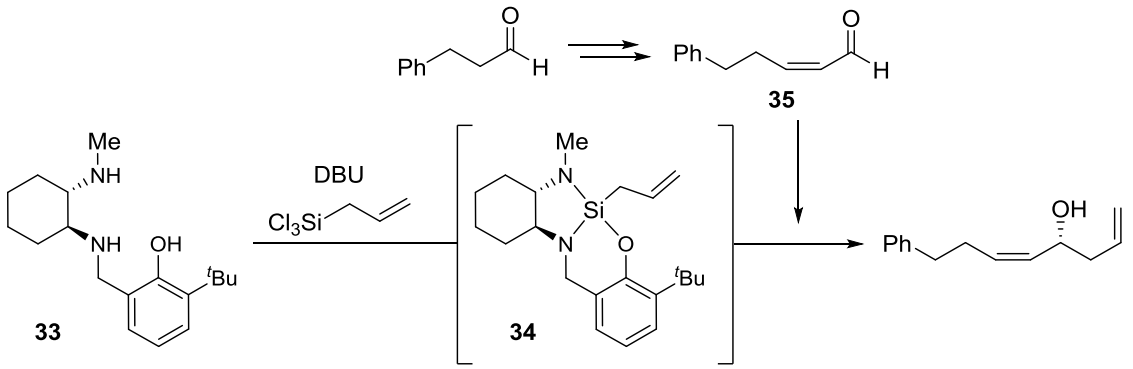
Figure 23. ^{1}H NMR of silane **32**

After these tests, silane **32** was discarded as an option to perform the allylation reaction. Luckily, LEIGHTON also described the synthesis of a crystalline diamine that can be stored without any special requirements and allows the one-pot synthesis of the allyl silane and subsequent allylation reaction.[135] Additionally, the diamine ligand can be recovered after the allylation reaction. It was speculated that a freshly prepared silane would not render isomerization problems and would give better allylation results. Therefore, diamine **33** was prepared as described in the literature. Formylation of 2-*tert*-butylphenol produced an aldehyde that was mixed with the monoprotected 1,2-diaminociclohexane to form the corresponding imine. Finally, the imine was reduced with $LiAlH_4$ to yield the desired diamine ligand **33** (*Scheme 77*).



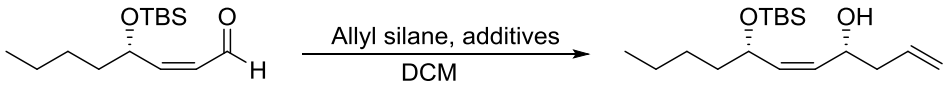
Scheme 77. Synthesis of diamine **33**

Considering that allylation of aldehyde **31** had proven to be quite challenging due to isomerization of the double bond, and that this step is found at a late stage of the synthesis, a model *Z* α,β-unsaturated aldehyde (**35**) was prepared to examine the reaction. The diamine ligand was mixed with trichlorosilane in the presence of DBU for the preformation of the diaza-silacycle, and then the model aldehyde was added (*Scheme 78*). To our pleasure, the ^{1}H NMR of the crude showed the formation of the desired product keeping the *Z* geometry of the double bond.



Scheme 78. Allylation of a model substrate with **34**

The same conditions were then applied to aldehyde **31**. Now significant amounts of allylated product were observed in the ^{1}H NMR of the crude mixture. However, these translated to just 35% of isolated alcohol **36** (*entry 3, Table 20*). In addition, *E*-aldehyde and *E*-allylated product were also isolated in minor quantities despite them not being identified in the ^{1}H NMR of the crude mixture. For the purpose of minimizing isomerization of the aldehyde the reaction was repeated at lower temperature, a change that improved the yield to 49%, although traces of *E* by-products were isolated again (*entry 4, Table 20*).



31 **36**

Entry	silane	additives	Conditions	Isolated Yield	^{1}H NMR (crude)
1	**32**	-	0 °C, 16 h	-	Aldehyde *Z* and *E*, traces of **36**
2	**32**	$Sc(OTf)_3$	rt, 16 h	-	Aldehyde *Z* and *E*, traces of **36** and others
3	**34**	-	0 °C, 2.5 h	35%	**36**
4	**34**	-	–20 °C, 16 h	49%	**36**

Table 20. Leighton allylation

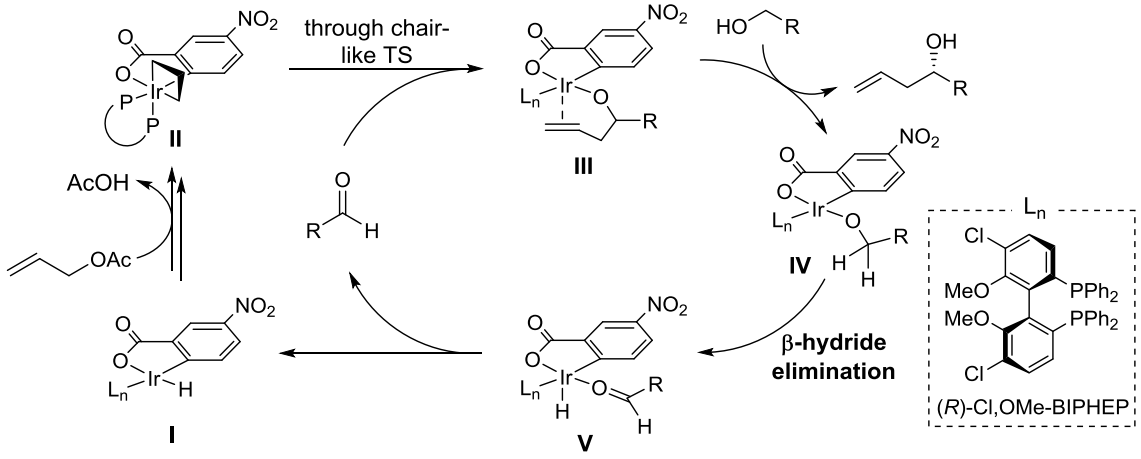
In summary, a change of the silane from **32** to **34** improved the results and allowed the isolation of **36** in moderate yields. Interestingly, just one diastereomer was observed by ^{1}H NMR, pointing to a great stereoselectivity of the allylation reaction. However, the allylation yield could not be improved satisfactorily, which opened the investigation to other allylation avenues.

4.2 Krische allylation

KRISCHE developed a catalytic allylation procedure that does not require the preformation of an organometallic reagent or the use of stoichiometric chiral modifiers.[136] Moreover, there is no need to functionalize the substrate to an aldehyde since the corresponding alcohol can be used instead, which acts as reductant species and the required aldehyde is formed during the catalytic cycle. Considering that *Z*-unsaturated aldehyde **31** decomposed relatively fast and it had led to isomerization problems before, the evasion of its formation was an interesting feature that made Krische allylation interesting for the synthesis of umuravumbolide.

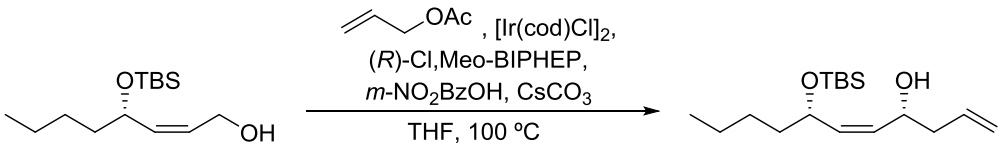
This iridium catalyzed allylation permits the coupling between allyl acetate and alcohols through a transfer hydrogenation process (*Scheme 79*).[137] One of the intermediates of the cycle is an *ortho*-cyclometalated complex between iridium and nitrobenzoic acid which also contains chiral phosphine ligands (L_n) and a hydride (**I**). After oxidative addition of allyl acetate and the loss of acetic acid, the key catalytic active species (**II**), a π-allyl iridium complex, is formed. This then catalyzes the allylation of the desired aldehyde through a closed chair-like transition state. Substitution in **III** of the alkoxide generated with the starting alcohol releases the desired product and forms a complex with a coordination site available (**IV**), which permits a β-hydride elimination

from the alcohol to form intermediate **V**. Finally intermediate **I** is regenerated by dissociation of the aldehyde, which will be allylated in a following cycle.



Scheme 79. Krische mechanism

Since the aldehyde to be allylated is generated during the catalytic cycle it exists in the reaction mixture for a short period of time. Therefore, the isomerization of such species was no longer a concern. Application of the experimental conditions described in the literature to alcohol **30** delivered a clean crude mixture in which the starting alcohol was present in significant amounts (*entry 1, Table 21*). In a second attempt, the reaction was repeated with double the amount of catalyst loading (5 mol%), which nicely improved the conversion and resulted in a 73% isolated yield of the desired allylation product **36** (*entry 2, Table 21*). Since the crude mixtures were still clean, a longer reaction was set up, but results were the same as in 20 h (*entry 3, Table 21*). Finally, scale up of the reaction raised the yield to an excellent level (*entry 4, Table 21*). It is important to notice that high stereoselectivities were achieved (95:5) in all the examples.

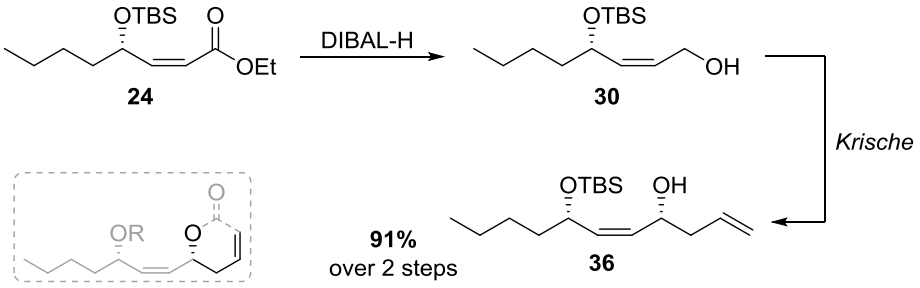


Entry	Catalyst	Time	Isolated Yield
1	2.5%	20 h	(37%)[a]
2	5%	20 h	73%
3	5%	30 h	73%
4[b]	5%	20 h	91%

[a]Conversion calculated by ^{1}H NMR of the crude; [b]2.4 mmol scale.

Table 21. Krische allylation

In summary, allylation of the *Z*-unsaturated carbonyl compound was a more challenging step than initially expected due to isomerization problems associated with the Leighton allylation. This problem was circumvented using the Krische catalytic hydrogenative allylation, which does not require preformation of the aldehyde species, and finally, excellent yields and diastereoselectivities were reached for the obtention of alcohol **36** (*Scheme 80*).



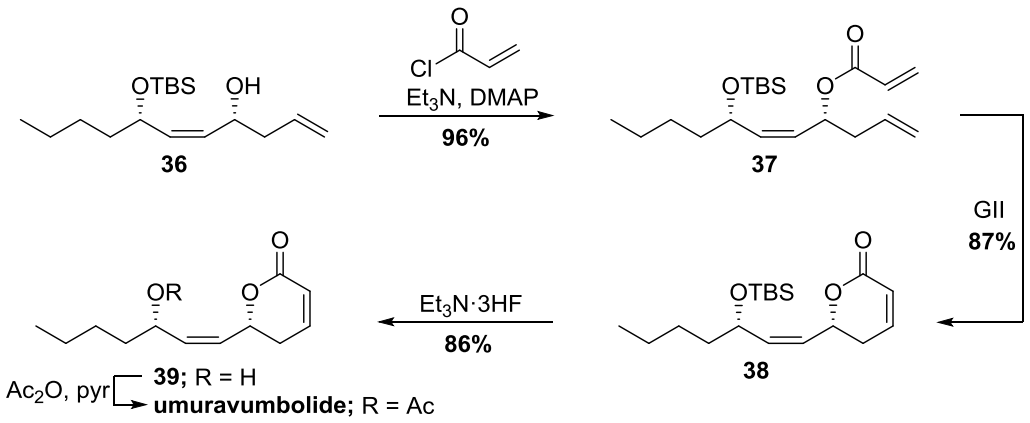
Scheme 80. Construction of the second stereocenter

5. Final steps

At this point the key steps of the synthesis of umuravumbolide were overcome, so the synthesis continued with the acylation of the free alcohol in **36** with acryloyl chloride to set up the stage for the construction of the pyrone ring. Acylation catalyzed by DMAP took place smoothly affording acrylic ester **37** in a high yield (*Scheme 81*).

Then, the pyrone cycle was formed by ring-closing metathesis (RCM). A first attempt with Hoveyda-Grubbs catalyst resulted in a complex mixture of decomposed products. Much better results were obtained using Grubbs II carbene, which allowed the obtention of the pyrone ring (**38**) in an 87% yield (*Scheme 81*).

To obtain deacetylumuravumbolide (**39**), the TBS protected alcohol was first treated with TBAF. Unfortunately, the basic character of this reagent led to a ring-opening of the pyrone. When $Et_3N{\cdot}3HF$ was used instead, as described in the literature,[113] **39** was obtained in a high yield. Finally, acylation of the free alcohol with acetic anhydride afforded umuravumbolide in quantitative yield (*Scheme 81*).

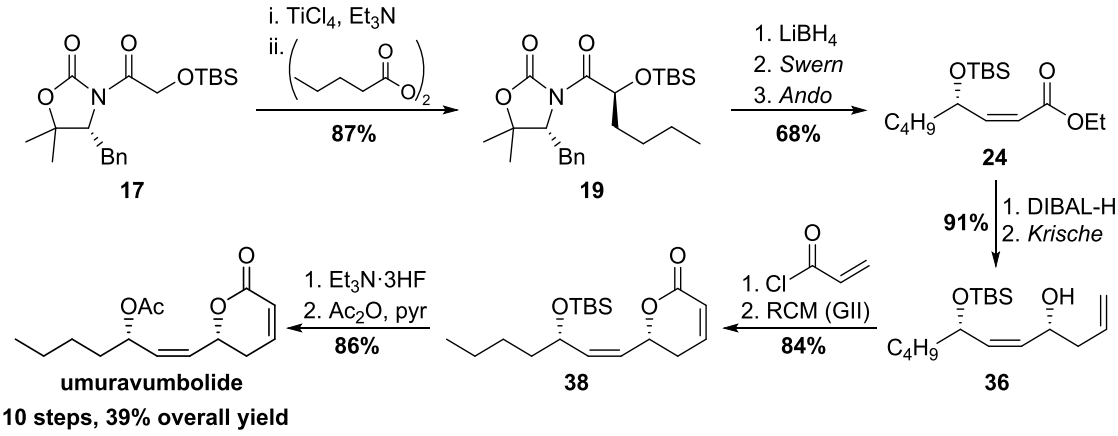


Scheme 81. Final steps of the synthesis

6. Outline

Umuravumbolide was obtained in just 10 steps and 8 flash column purifications, which makes this synthesis one of the shortest described. The great stereoselectivities obtained in three key steps of the synthesis permitted the description of a new route to umuravumbolide with a 39% overall yield, which is the highest reported to date (*Scheme 82*). These key steps are:

- the alkylation of a titanium enolate with dipentanoyl peroxide to generate the first oxygen-containing stereocenter, which is obtained as an already protected alcohol.
- an Ando modification of the HWE olefination to render the *Z*-double bond in the side chain.
- a Krische allylation to form the stereocenter found in the pyrone ring.



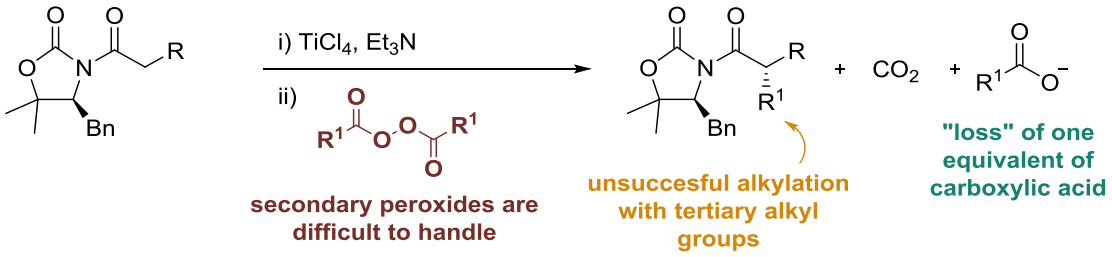
Scheme 82. Total synthesis of umuravumbolide

CHAPTER III

Alkylation of Titanium Enolates with *tert*-Butyl Peresters

1. Introduction

The reaction of a broad range of titanium enolates with alkyl diacyl peroxides proved to be a useful methodology to introduce inactivated primary and even secondary alkyl groups. Despite the success of such a transformation, the use of diacyl peroxides entails some disadvantages. Firstly, due to its symmetry, the synthesis of the peroxide requires two equivalents of the corresponding carboxylic acid, one of which is consumed as a carboxylate anion. This jeopardizes the atom economy of the overall alkylation procedure, which is a major drawback if the carboxylic acid has a high value. Furthermore, while the preparation of primary alkyl acyl peroxides was easy, secondary analogues were more difficult to obtain and handle. What is more, the preparation of the secondary peroxide and subsequent alkylation were performed the same day to minimize degradation problems. Finally, this methodology does not allow the insertion of tertiary alkyl groups because the necessary peroxides could not be obtained in any case.



Scheme 83. Disadvantages of the alkylation with peroxides

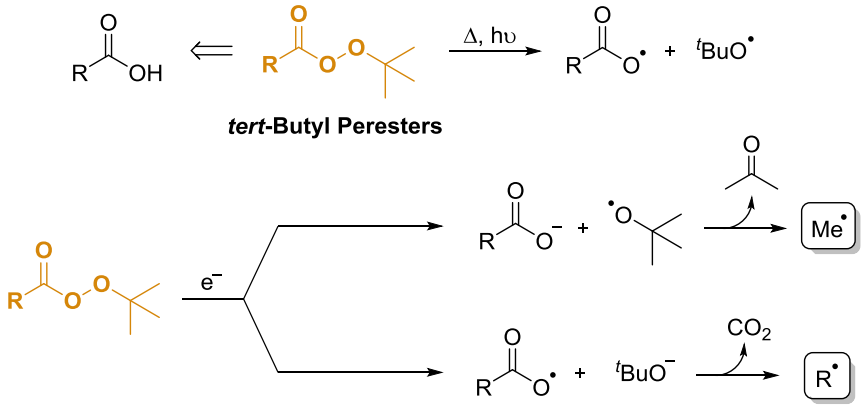
All these reasons considered; the group decided that it was necessary to find a substitute of diacyl peroxides that could (partly) solve these weak points.

1.1 *tert*-Butyl peresters

tert-Butyl peresters were selected as candidates because of their close structure to diacyl peroxides. They can be prepared through a diverse range of procedures, for example, coupling a carboxylic acid with a hydroperoxide or from acyl chlorides and hydroperoxides. *tert*-Butyl peresters, due to the tertiary alkyl group, are stable enough to even be purified by silica,* and similarly to diacyl peroxides, they are redox-active species able to render alkyl radicals upon heating, irradiation or transition-metal prompted reduction.

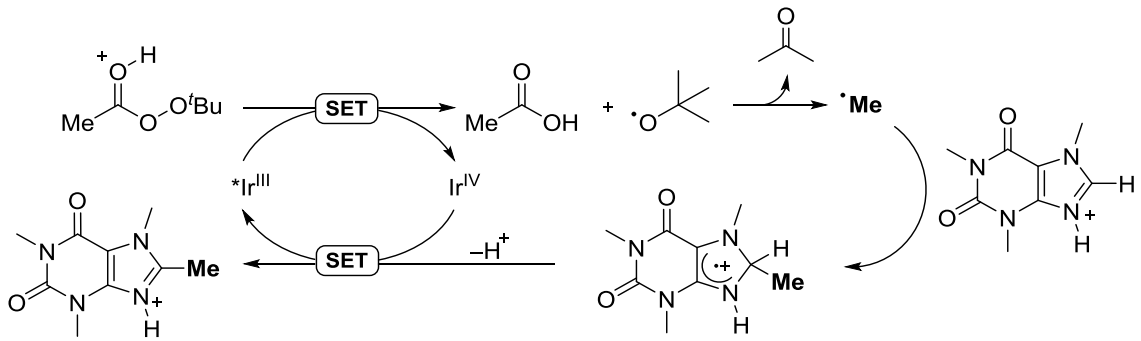
*Other peresters are thermally unstable and potentially explosive

Thermolysis and photolysis of peresters operate closely to peroxides. Homolysis of the O-O bond results in the formation of an acyloxy radical, yet this time, a *tert*-butoxy radical is also generated. Instead, single reduction of peresters leads to a dilemma; a carboxylate anion and an alkoxy radical can be formed as a result, or alternatively, the reduced compound can split into an acyloxy radical and a *tert*-butoxide anion (*Scheme 84*). None of the options are much clearly favored over the other. Anyhow, both paths can generate alkyl radicals; if an alkoxy radical is formed, β-fragmentation of a C–C bond would lead to a methyl radical and acetone. On the contrary, if an acyloxy radical is formed instead, its subsequent decarboxylation renders an alkyl radical as with diacyl peroxides. Examples of either pathways can be found in the literature; however, it is not clear which factors are responsible for the difference in scission patterns. DUSSAULT suggested that this divergence could be impacted by the metal that is being used as a reducing agent, suggesting that copper(I) favors the *tert*-butoxy radical formation while iron(II) favors the acyloxy radical generation.[138]



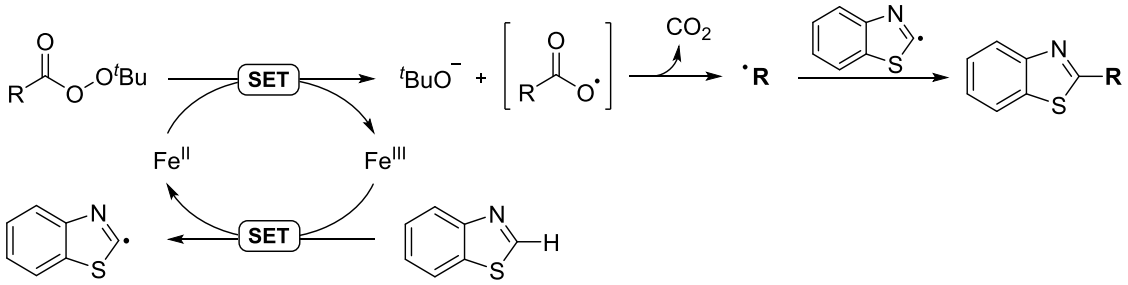
Scheme 84. *tert*-Butyl peresters decomposition

In 2014 DIROCCO reported the radical methylation of heterocycles present in biologically active molecules (*Scheme 85*). This case of late-stage functionalization was achieved on account of the mild conditions offered by the photoredox mediated scission of the perester. In this example, the homolysis of the perester renders a *tert*-butoxy radical that suffers another homolytic scission to provide the methyl radical. The alkyl radical was trapped by different heterocycles, eventually leading to methylated products.



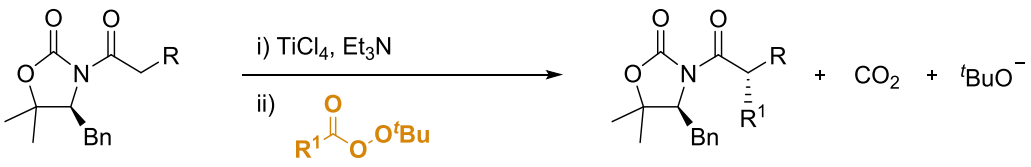
Scheme 85. DiRocco alkylation of heterocycles

Conversely, Bao described the alkylation of heterocycles using *tert*-butyl peresters as alkyl radical sources (*Scheme 86*). In her studies the perester was reduced by iron(II) leading to an acyloxy radical that, after the release of CO_2, generated the corresponding alkyl radical that would be introduced into the heterocycle. This was just an opposite scission example of the perester chemistry described by DiRocco.



Scheme 86. Bao alkylation of heterocycles

As alkyl peresters are able to react in a similar way to diacyl peroxides, the alkylation of titanium enolates with these species was the next reaction to study. It was also an especially attracting investigation line because, contrary to diacyl peroxides, the preparation of *tert*-butyl peresters from tertiary carboxylic acids had already been described. Meaning that, if the reaction worked as predicted (*Scheme 87*), the alkylation with a tertiary alkyl group could be feasible.

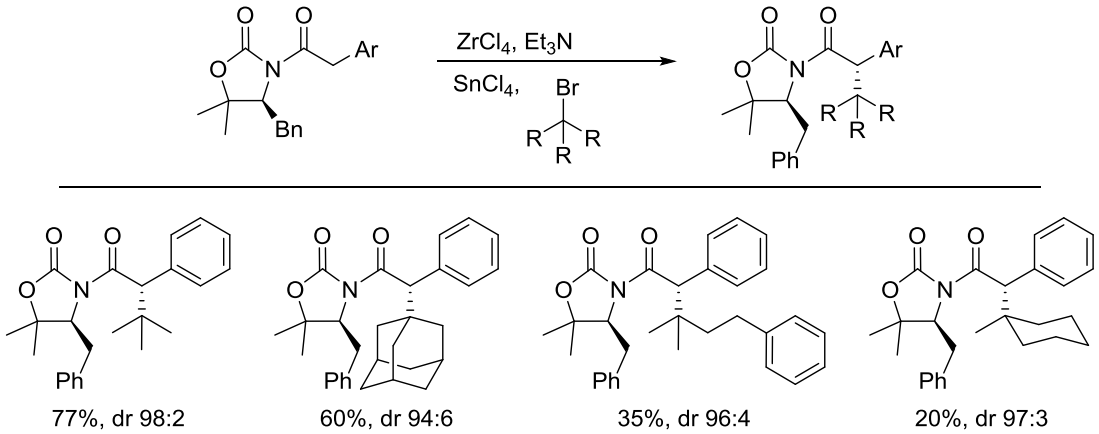


Scheme 87. Alkylation of titanium enolates with *tert*-butyl peresters

1.2 Tertiary α-alkylation of carbonyl compounds

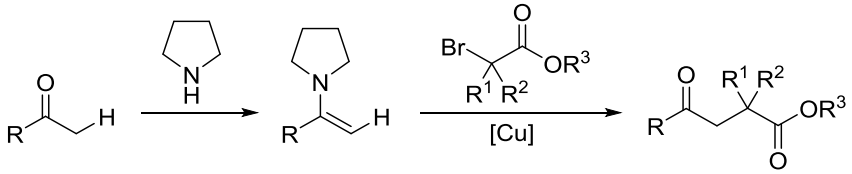
As described in the introduction, the alkylation with tertiary alkyl groups is a challenging transformation that has rarely been accomplished.

One example is the tertiary alkylation of aryl acetic derivatives described by ZAKARIAN (*Scheme 88*). In there, tin(IV) chloride is used as a Lewis acid to activate tertiary alkyl halides that react with a zirconium(IV) enolate.[52] The yields for the alkylation are strongly dependent on the alkyl halide used; good yields are obtained for *tert*-butyl and adamantyl moieties, but other tertiary groups give poor results. Nonetheless, excellent diastereoselectivities were obtained in all the examples.



Scheme 88. ZAKARIAN tertiary alkylation of zirconium enolates

Another example of a tertiary alkylation has recently been described by NISHIKATA (*Scheme 89*).[139] This combines the enamine catalysis of ketones with the copper catalyzed radical generation. In this example, the homolysis of α-disubstituted α-bromocarbonyl compounds is triggered by copper(I) to render tertiary alkyl radicals after the scission of the C–Br bond. The radicals generated recombine with the enamine species to give alkylated products, which are obtained as a racemic mixture. Moderate to excellent yields were obtained for all the examples explored, yet the alkylation scope was limited to carbonyl-containing alkyl groups.

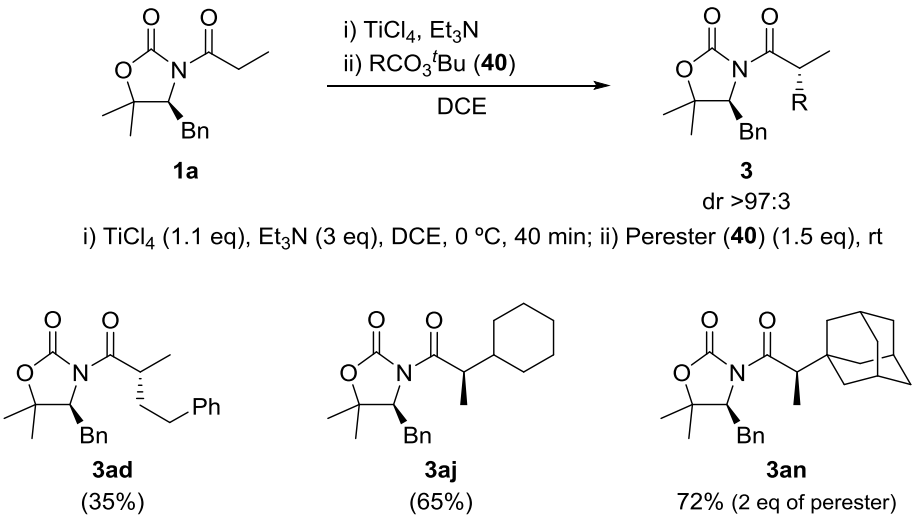


Scheme 89. NISHIKATA tertiary alkylation of enamines with α-bromocarbonyl compounds

2. Preliminary results and optimization

As the tertiary alkylation of titanium enolates seemed an appealing possibility, preliminary tests were performed to investigate the alkylation of titanium enolates with *tert*-butyl peresters containing tertiary alkyl groups. For this, *tert*-butyl peresters[†] from different carboxylic acids were added to a titanium enolate under the conditions used in the alkylation with diacyl peroxides (solvent, temperature, base...), results are summarized in *Scheme 90*.

Firstly, a primary alkylation was attempted with the perester derived from hydrocinnamic acid. Unfortunately, a low conversion of the alkylated product was observed in the ^{1}H NMR of the crude mixture. On the good side, just one diastereomer was observed. Better results were obtained when the alkylation was performed with the secondary perester containing a cyclohexyl ring, which gave around 65% conversion to alkylated product and, again, as a single diastereomer. Finally, surprisingly good results were obtained when 1-adamantane-carboxylic acid was used; the conversion was almost 90% of just one diastereomer in a clean crude mixture. Since it was the first time obtaining such product, it was isolated (72% yield) and fully characterized to confirm its structure.

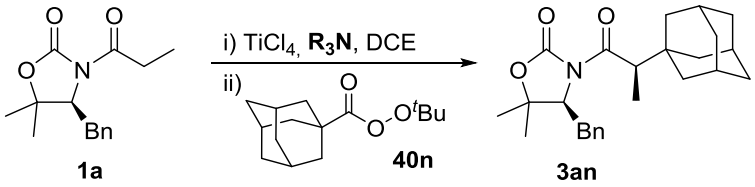


Scheme 90. Preliminary results of the alkylation with *tert*-butyl peresters

[†] The preparation of peresters will be explained in *section 3.1*

2.1 Optimization

These results, especially the *tert*-alkylation, were a clear invitation to the optimization of the reaction conditions. In this case, **1a** and perester **40n** were selected as model substrates. Gladly, the yield was not affected by a lower amount of perester used (*entries 1 and 2, Table 22*). However, slightly poorer yields were observed when the temperature was lowered, regardless the equivalents of perester used (*entries 3 and 4, Table 22*). Finally, the swapping of triethylamine for Hünig's base to form the enolate did not seem to have a huge impact on the alkylation (*entry 5, Table 22*). Unfortunately, this short optimization did not improve the preliminary results a lot.



i) $TiCl_4$ (1.1 eq), **R_3N** (3 eq), DCE, 0 °C, 40 min; ii) **40n** (**X eq**), **Temperature**

Entry	R_3N	40n	Temperature	Isolated Yield
1	Et_3N	2.0 eq	rt	72%
2	Et_3N	1.5 eq	rt	74%
3	Et_3N	2.0 eq	0 °C	60%
4	Et_3N	1.5 eq	0 °C	58%
5	*i*-Pr_2NEt	1.5 eq	rt	66%

Table 22. Optimization of the reaction conditions

2.2 Identification of by-products

Assuming that the previously established conditions in Chapter I were also the most suitable for the alkylation with peresters, another tertiary example, the *tert*-butyl group, was sought. The diastereoselectivity was excellent but just a moderate yield of the *tert*-butylated product (**3ap**) was obtained (48%). It was also noticed that the reaction was slower. In fact, TLC analysis indicated that there was still starting material in the reaction mixture after 2 h, a time at which the reaction had been assumed finished from previous knowledge with peroxides. To confirm that the reaction had certainly finished, a second batch reaction was set for 16 h, yet a similar yield was obtained (42%).

As previously observed, the ^1H NMR of the reaction crude mixture revealed the formation of different by-products (*Figure 24*). The bottom spectrum shows a signal of the starting material as a reference; a doublet of doublets from the oxazolidinone proton at ~4.5 ppm (*in orange*). The spectrum after 2 h indicated the presence of starting

material. This also shows two representative signals of the expected product **3ap** (*in blue*), the oxazolidinone proton at ~4.55 ppm and the quartet from the proton COCH. However, a quartet at ~4.65 ppm was proof of the formation of another product not seen before (*in red*). Importantly, another quartet was hidden at around 4.60 ppm. It was later understood that the two quadruplets belonged to two diastereomers of the same by-product (**41a**), which were formed at ~1:1 ratio. Finally, in the top spectrum at 16 h there was no starting material left, although the isolated yield of alkylated product was the same as in 2 h. In view of these spectra, it was concluded that no more alkylation was occurring after some point, and the enolate just reacted to form the by-product.

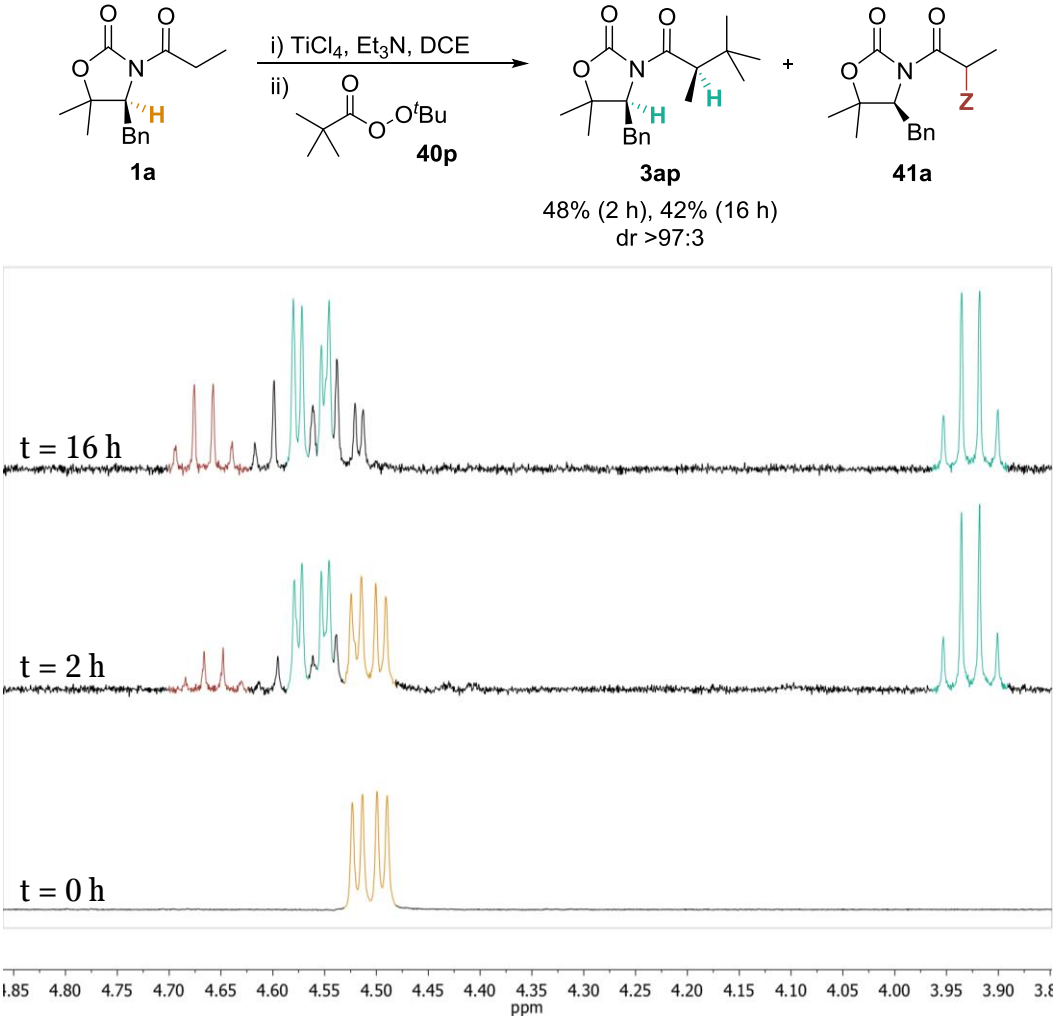
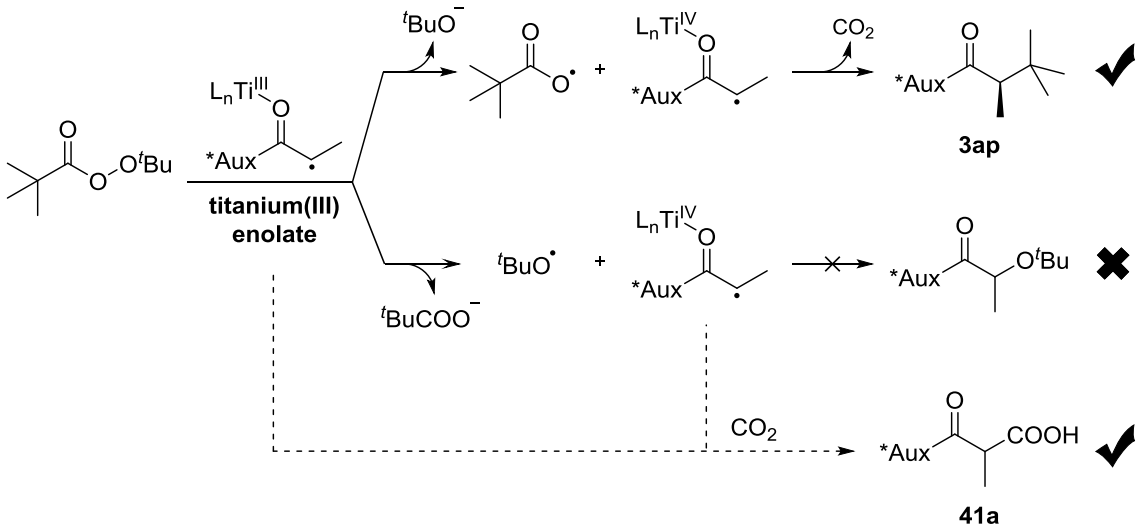


Figure 24. Diagnostic peaks observed in ^{1}H NMR of the crude mixture of the alkylation with **40p**

As discussed in the introduction of this Chapter, *tert*-butyl peresters may be reduced through two patterns of scission. One of them leads to an acyloxy radical that decarboxylates to give an alkyl radical, which would be responsible for the desired alkylated product (*first path, Scheme 91*). The other path generates a *tert*-butoxy radical

instead, so it was initially thought that the structure of the by-product corresponded to the recombination of a titanium enolate with such a *tert*-butoxy radical (*second path, Scheme 91*). The structure of this by-product would be consistent with the deshielded quartet observed in the ^{1}H NMR. Surprisingly, one of the diastereomers of the by-product was isolated and fully characterized, which indicated that the structure did not correspond to a *tert*-butylated product but to a carboxylated adduct (*third line, Scheme 91*), probably resulting from the addition of CO_2 to the titanium enolate.



Scheme 91. By-product formation hypothesis

2.3 Kinetic studies

The formation of such a by-product was surprising, especially because it had not been observed when a diacyl peroxide was used to obtain an alkyl radical (*Chapter I, Section 3*). As a matter of fact, a carboxylated by-product was neither observed when the alkylation was carried out with the *tert*-butyl perester containing an adamantyl as an alkyl group instead of a *tert*-butyl. To further comprehend the differences between those alkyl groups, a kinetic study was performed in each case. *Figure 25* shows that the reaction with adamantyl perester is clearly faster than that with *tert*-butyl counterpart. This is probably due to the adamantyl structure embedding a tricycloalkane backbone consisting of three fused cyclohexanes so that the carbon atoms are ensembled as the smallest diamond. The nature of such a structure entails the formation of a rigid pyramidalized bridgehead radical, which possesses a higher reactivity than more planar alkyl radicals such as *tert*-butyl.[140]

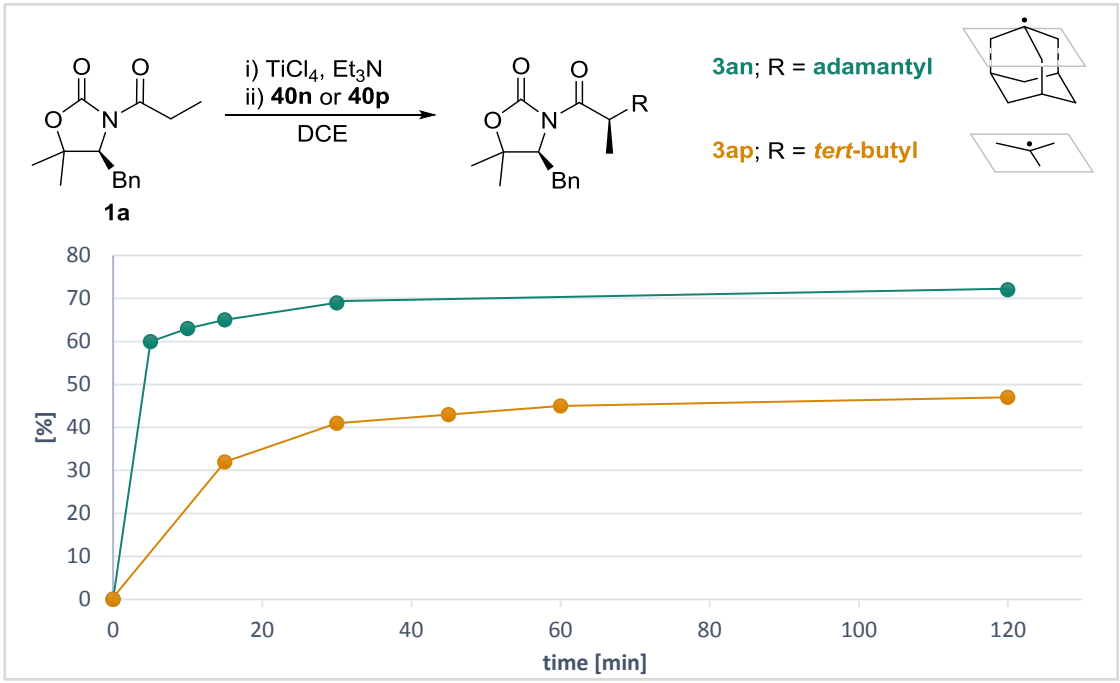


Figure 25. Alkylated product proportion in the crude mixture (by ^{1}H NMR)

In turn, the crude proportion of alkylated product (**3ap**) and carboxylated adduct (**41a**) dependence on time is represented in *Figure 26*. It can be observed that the formation of by-product does not start until past 15 min, but, while the alkylation reaches a plateau after 2 h (*in blue*), the carboxylation increases slowly (*in orange*). These results are in accordance with the alkylation results obtained after 2 and 16 h, in which the alkylated product was obtained in the same isolated yield. However, a significant amount of starting material was observed by ^{1}H NMR after 2 h, while after 16 h, only the alkylated product and both diastereomers of the carboxylated derivative were detected (*Figure 24*).

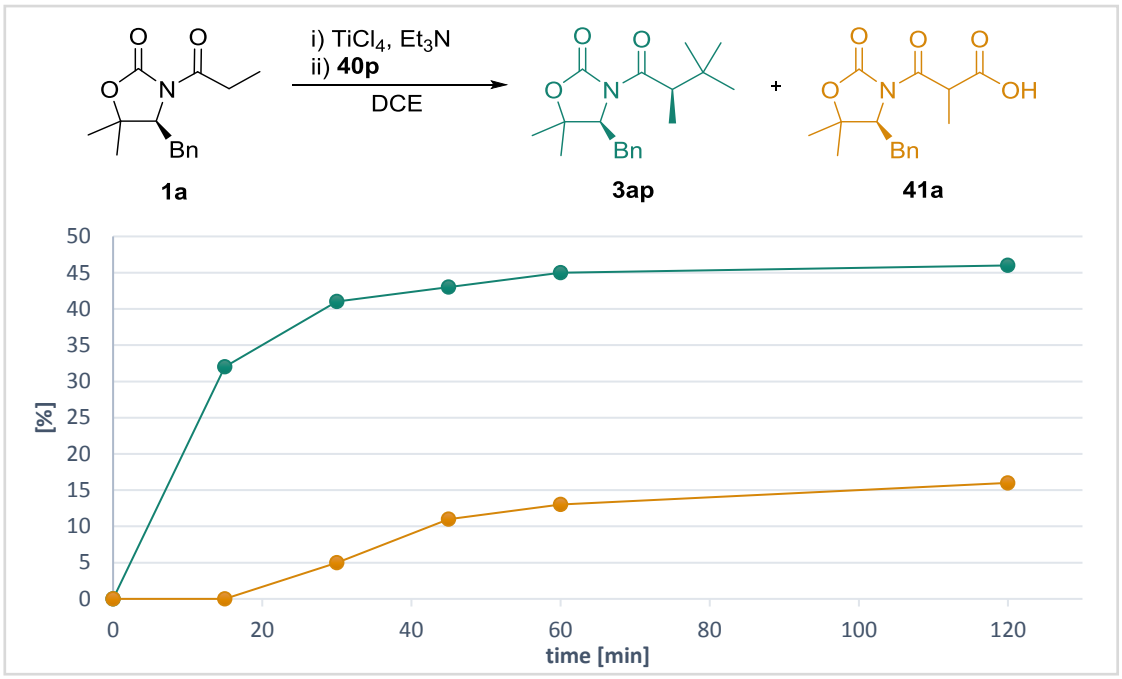
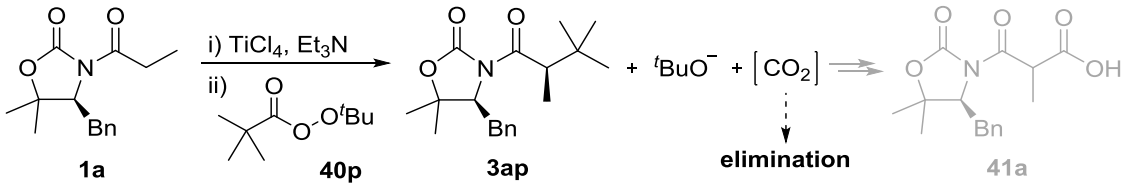


Figure 26. Alkylated and acid derivative proportion in the crude mixture (by ^{1}H NMR)

2.4 Elimination of the acid derivative

Once the structure of the acid derivative was elucidated, the suppression or at least reduction of its formation was attempted. Since it is believed that the generation of such compound comes from the CO_2 released during the decarboxylation of the perester, a comprehensive study of how to eliminate the gas from the reaction mixture was launched (*Scheme 92*).[‡]



Scheme 92. Attempts to eliminate carbon dioxide of the reaction mixture

- Amount of perester: More equivalents of the perester could make the reaction to be faster. Hence, the released CO_2 would not have time to react with the enolate so similar results to adamantyl would be obtained. Unfortunately, the amount of perester did not have any influence in the alkylation yield.
- Amount of $TiCl_4$: The CO_2 could coordinate to titanium, so it could be activated to react with the enolate species. However, tests with greater or lower equivalents of $TiCl_4$ did not alter the results.

[‡] Details can be found in the Experimental Section.

- Base: As previously experienced, changes of the trialkylamine used to form the enolate could impact the result of the reaction. In this case, neither DIPEA nor trimethylamine improved the results.
- Temperature: Given that CO_2 solubility should be lowered at higher temperatures, the reaction was performed at 35, 40 and 45 °C. Once again, no improvement was observed.
- Bubbling N_2: The displacement of CO_2 was attempted by bubbling nitrogen through the reaction mixture. However, just the partial evaporation of the solvent was achieved, getting even poorer results.
- Chemical trap: as described in the literature,[141] carbodiimides, under the right conditions could trap CO_2 to form organic carbonates in the presence of alcohols. In this case, *tert*-butoxide together with a carbodiimide could react with the released CO_2 and hopefully suppress by-product formation. Therefore, DCC and DIC were added in two different reactions mixtures, but formation of the by-product was still observed.

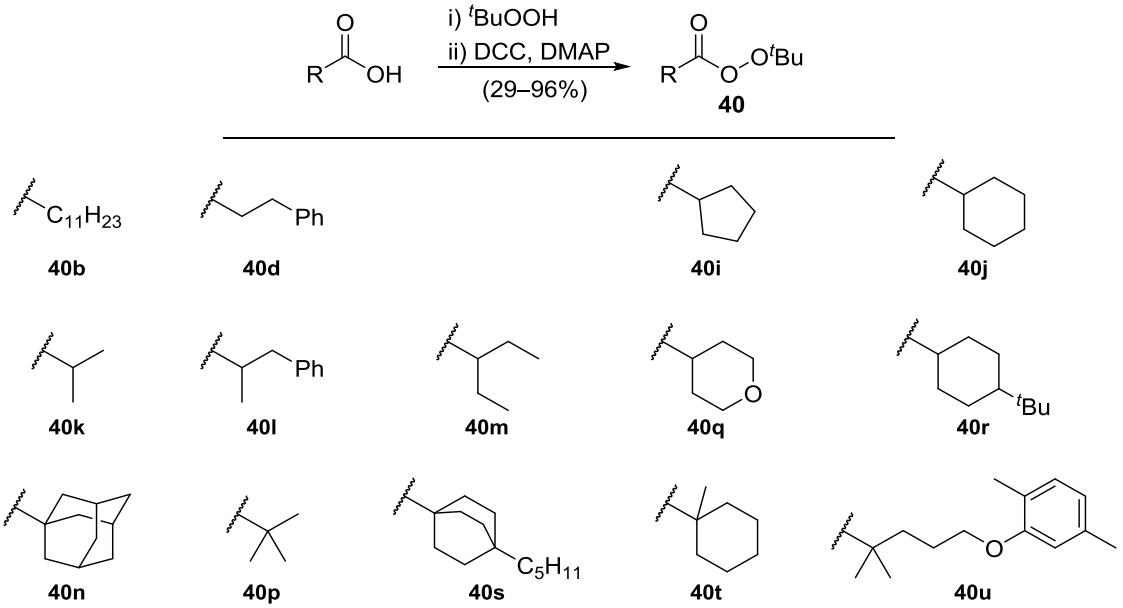
Unluckily, all the attempts to minimize the formation of the carboxylated adduct were unsuccessful. Nonetheless, the tertiary alkylation of enolates is, as stated, extremely challenging, so it was decided that it was worth continuing with its study.

3. Scope assessment

3.1 Peresters scope

A collection of peresters from different carboxylic acids was prepared to assess the scope of the reaction (*Scheme 93*). Such a group included primary, secondary and tertiary peresters exhibiting different steric hindrance. For their preparation, the corresponding acid was coupled with *tert*-butyl hydroperoxide using a carbodiimide and DMAP as a catalyst, obtaining moderate to excellent yields for all the examples.§

§ Details can be found in the Experimental Section

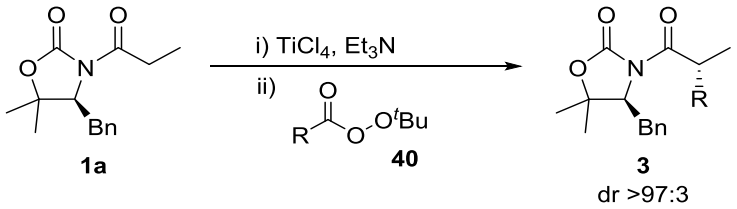


Scheme 93. Preparation of *tert*-butyl peresters

Then, each perester was added to the titanium enolate of *N*-acyl oxazolidinone **1a** according to the conditions established in the optimization section. Following the trend observed in the preliminary results, primary peresters yielded alkylated products in very low yields (*entries 1 and 2, Table 23*). On the contrary, secondary groups gave good yields overall. For cycles, cyclopentyl gave a slightly lower yield than cyclohexyl whereas an ether functional group lowered the results to a moderate yield (*entries 3-5, Table 23*). In turn, isopropyl gave a slightly higher yield than the 1-ethyl-1-propyl partner, probably due to steric reasons (*entries 6 and 7, Table 23*). Remarkably, the diastereoselectivity was excellent in all cases. For gaining further insights, two tests were also run. Firstly, the 2-methylhydrocinnamic acid was used to compare the results with those from diacyl peroxides (*entry 8, Table 23*). Similarly to the peroxides, the alkylated product was obtained in good yields but the control on the β stereocenter was poor (dr 2:1). Then, the alkylation with a 4-*tert*butylcyclohexyl group was attempted; the yield obtained was lower than the non-substituted cycle, and poor diastereoselectivity of the second stereocenter was obtained again (dr 3:1, *entry 9, Table 23*).

Then, other tertiary alkyl *tert*-butyl peresters were assessed. As the rigid adamantyl substituent had provided great alkylation results, another bridgehead radical was attempted; the bicyclo[2.2.2]octane derivative (**40s**). Surprisingly, this example gave worse results than expected, being comparable to those obtained with the *tert*-butyl example (*entries 10-12, Table 23*). Other non-rigid structures, with higher steric

hindrance than the *tert*-butyl substituent gave poor results (*entries 13 and 14, Table 23*), similar to those obtained by ZAKARIAN (*Scheme 88*).



i) $TiCl_4$ (1.1 eq), Et_3N (3 eq), DCE, 0 °C, 40 min; ii) perester (**40**) (1.5 eq), rt

Entry	Perester	R	Product	Isolated Yield
1	**40b**	$C_{11}H_{23}$	**3ab**	25%
2	**40d**	CH_2CH_2Ph	**3ad**	19%
3	**40i**	C_5H_9	**3ai**	52%
4	**40j**	C_6H_{11}	**3aj**	60%
5	**40q**	4-tetrahydropyrane	**3aq**	43%
6	**40k**	*i*-Pr	**3ak**	64%
7	**40m**	$CH(CH_2CH_3)_2$	**3am**	58%
8	**40l**	CH(Me)Bn	**3al**	77%[a]
9	**40r**	4-^{t}BuC_6H_{10}	**3ar**	46%[b]
10	**40n**	1-adamantyl	**3an**	74%
11	**40s**	4-C_5H_{11}-bicyclo[2.2.2]oct-1-yl	**3as**	39%
12	**40p**	^{t}Bu	**3ap**	48%
13[c]	**40t**	1-MeC_6H_{10}	**3at**	17%
14	**40u**	4-OR^2-1,1-dimethylbutyl	**3au**	23%

[a]dr 2:1; [b]dr 3:1; [c]5 eq of Et_3N and 2 eq of perester

Table 23. Scope of *tert*-butyl peresters

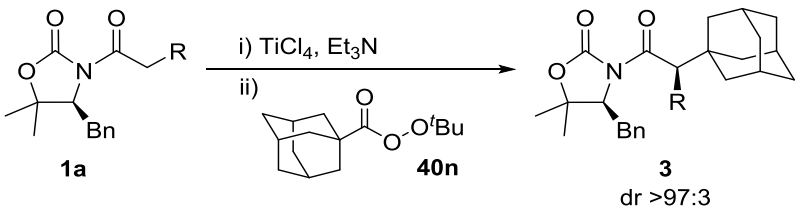
All in all, alkylation with primary alkyl groups rendered very poor yields. Instead, secondary alkylation proceeded with moderate to good yields. Finally, tertiary alkylation was possible, but it turns out to be strongly dependent on the alkyl group attached during the alkylation.

3.2 Enolates scope

Once the impact of the perester was studied, the assessment of the enolates to achieve a tertiary alkylation started. Nil Sanosa, during his master thesis, also worked on these studies.[142] For that, 1-adamantyl perester (**40n**) was used. As observed with diacyl peroxides, an increase of the steric hindrance of the enolate chain seriously impacted the reaction and produced lower alkylation yields (*entries 1 and 2, Table 24*). Then, the alkylation with unsaturated functionalities was assessed. A phenyl substituent in the enolate allowed the insertion of adamantyl with acceptable yields, similar to those obtained with a double bond (*entries 3 and 4, Table 24*). Curiously, the shortening of the

chain bearing an olefin resulted in a dramatic erosion of the yield (*entry 5, Table 24*). A triple bond also gave acceptable alkylation yields (*entry 6, Table 24*). To our pleasure, the introduction of an ester group in the enolate afforded very good results (*entry 7, Table 24*). Poorer results were obtained when an aliphatic chain containing a terminal bromine (**1y**) was employed due to the formation of other by-products (*entry 8, Table 24*) such as those arising from the cyclization of **1y** with the loss of the bromine atom.

Furthermore, an acyl substrate containing an α-phenyl substituent (**1z**) was studied to compare our methodology to that reported by ZAKARIAN (*Scheme 88*). Similar good results were obtained for the alkylation with adamantyl (*entry 9, Table 24*), but the parallel reaction with perester **40p** gave a poorer yield of the corresponding *tert*-butyl alkylated product (**3ap**) (*entry 10, Table 24*). Finally, heteroatom-containing enolates were assessed. The OTBS silyl ether gave good yields, which remained unchanged with the scale up of the reaction to 6.5 mmol (*entry 11, Table 24*). As in Chapter I, the alkylation of the α-pyrrole derivative proceeded smoothly in great yields, at scales ranging from 0.5 to 6.4 mmol (*entry 12, Table 24*). At last, the alkylation of an enolate with an α-bromine was attempted, but no alkylation product was observed, and the starting *N*-acyl oxazolidinone **1r** was decomposed instead.



i) $TiCl_4$ (1.1 eq), Et_3N (3-5 eq), DCE, 0 °C, 40 min; ii) perester **40n** (1.5 eq), rt

Entry	*N*-Acyl ox.	R	Product	Isolated Yield
1	**1a**	Me	**3an**	74%
2	**1b**	Et	**3bn**	53%
3	**1d**	Bn	**3dn**	44%
4	**1e**	$(CH_2)_2CH=CH_2$	**3en**	41%
5	**1s**	$CH_2CH=CH_2$	**3sn**	24%
6	**1f**	$(CH_2)_2C\equiv CH$	**3fn**	49%
7	**1g**	$(CH_2)_2COOMe$	**3gn**	67%
8	**1y**	$(CH_2)_3CH_2Br$	**3yn**	34%
9	**1z**	Ph	**3zn**	61%
10[a]	**1z**	Ph	**3zp**	26%
11[b]	**1h**	OTBS	**3hn**	69%
12[c]	**1v**	pyrrole	**3vn**	62%
13	**1r**	Br	**3rn**	-

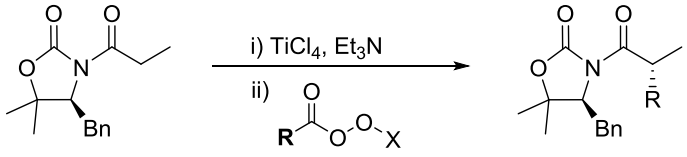
[a]Using perester **40p**; [b]6.5 mmol scale; [c] –20 °C to rt, 6.4 mmol scale

Table 24. Scope of enolates

In brief, the alkylation of *N*-acyl oxazolidinones with adamantyl *tert*-butyl perester proceeded in good yields for acyl groups containing alkyl chains and functional groups such as ester, α-phenyl and α-heteroatoms. Slightly lower yields were obtained with unsaturated side chains.

3.3 Comparison of methodologies

The alkylation with *tert*-butyl peresters compliments the alkylation with diacyl peroxides in terms of suitable alkylating agents. The procedure described in Chapter I allowed the alkylation of a wide array of titanium enolates with primary alkyl groups. On the contrary, the alkylation with primary alkyl groups is not suitable if peresters are used. A clear example is the comparison between the formation of the same product using either the diacyl peroxide or the perester (*entries 1 and 2, Table 25*). For the alkylation with secondary groups both methodologies are useful. However, it is important to say that yields from diacyl peroxides are usually slightly higher than those obtained with *tert*-butyl peresters, whereas it is more difficult to handle the former reagent (*entries 3–6, Table 25*). Nonetheless, the control of the stereochemistry in the β-stereocenter was poor in both scenarios (*entry 7, Table 25*). Finally, the addition of a tertiary alkyl group was not possible by means of diacyl peroxides, but peresters allowed the *tert*-alkylation of a broad scope of titanium enolates (*entries 8 and 9*, *Table 25*).



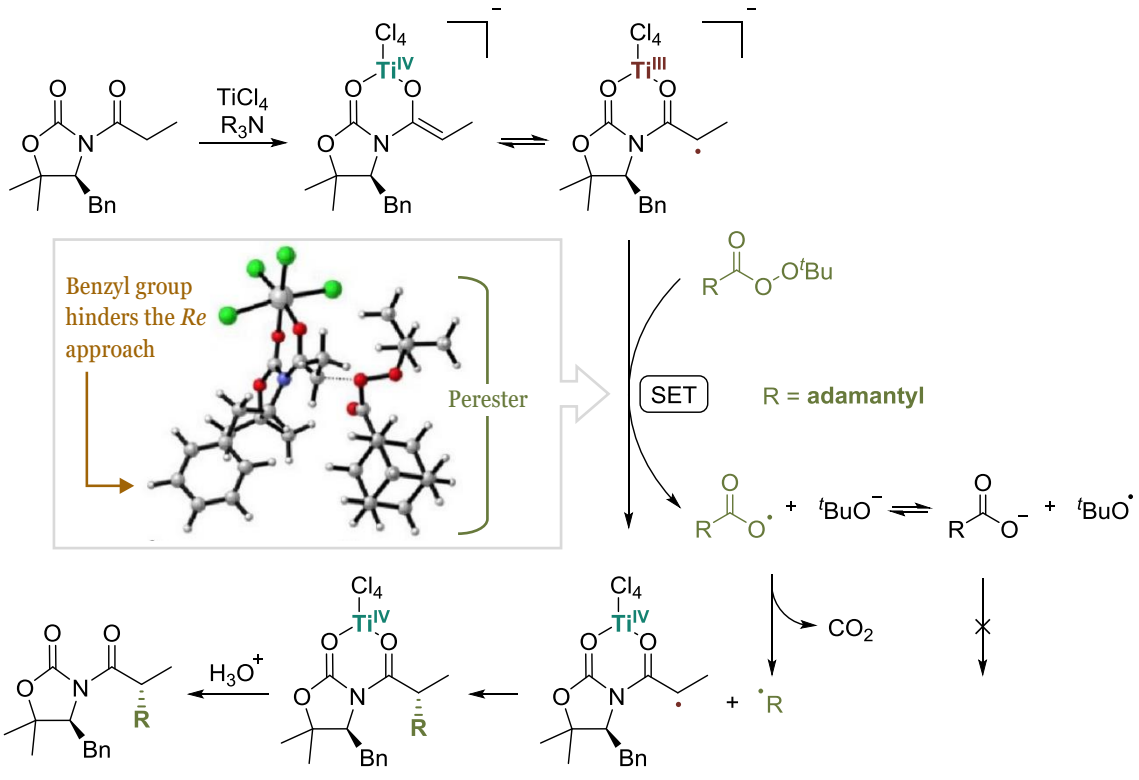
Entry	Alkyl type	R	Product	Isolated Yield (3)	
				Diacyl peroxide	*tert*-Butyl perester
1	Primary	$C_{11}H_{23}$	**3ab**	95%	19%
2		$(CH_2)_2Ph$	**3ad**	93%	25%
3	Secondary	C_5H_9	**3ai**	70%	52%
4		C_6H_{11}	**3aj**	74%	60%
5		*i*-Pr	**3ak**	77%	64%
6		$CH(CH_2CH_3)_2$	**3am**	57%	58%
7		CH(Me)Bn	**3al**	75% (dr 2:1)	77% (dr 2:1)
8	Tertiary	Adamantyl	**3an**	-	74%
9		^{t}Bu	**3ap**	-	48%

Table 25. Comparison of methodologies

4. Other studies

4.1 Mechanistic studies

It was hypothesized that the alkylation with peresters proceeded through a similar mechanism as the one proposed for the alkylation with peroxides. Even so, computational studies were carried out by GÓMEZ-BENGOA's group using **1a** and adamantyl perester (**40n**) as model reacting partners. Calculations agreed to the hypothesis that a SET from the enolate to the perester would trigger the scission of the O-O bond of the latter. However, in this case the perester could split in two different patterns: forming a carboxylate anion or an acyloxy radical. The computational analysis unveiled that both species could be in equilibrium (*Scheme 94*). Despite this equilibrium, the acyloxy radical is very unstable and it spontaneously undergoes a decarboxylation reaction ($\Delta\Delta G^{\ddagger} < 5$ kcal/mol), leading to the formation of an alkyl radical. On the other hand, decomposition of the carboxylate anion is kinetically and thermodynamically prevented. Considering the fate of the species in both ends of the equilibrium, a Curtin-Hammett model could explain the formation of the tertiary alkyl radical. Finally, recombination of the radical with the enolate species leads to the alkylated product through a carbon-carbon bond forming step.



Scheme 94. Mechanistic hypothesis

Again, the short distance between the enolate and perester that is required for a SET process to occur accounts for the high diastereoselectivity of the reaction. Due to the interaction between the benzyl group of the chiral auxiliary and the adamantyl moiety of the perester, the approach of the reagents is much favored through the *Si* π-face of the enolate. Representations of the *Si* and *Re* approaches keeping the electron transfer distance C---O at 1.8 Å is shown in *Figure 27*. In this case, the difference in energy between both approaches is 7.6 kcal/mol, which agrees with the high diastereoselectivity observed.

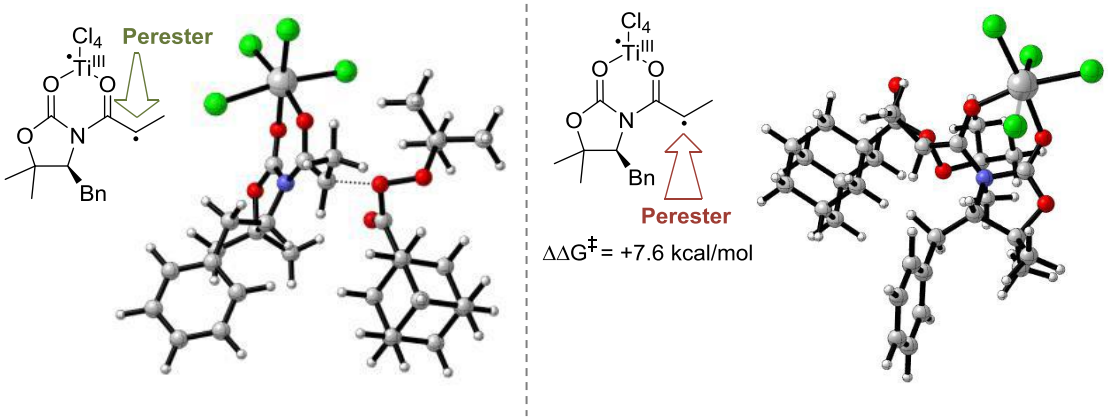


Figure 27. Approaches of the perester to both diastereotopic π-faces of the enolate

4.2 X-ray analysis

To prove the configuration of the major diastereomer, the secondary alkylated products obtained in this chapter were compared with the same alkylated products obtained in Chapter I, which confirmed that their absolute configuration was as predicted. Additionally, the X-ray diffraction analysis of a *tert*-butyl alkylated product was performed. In this case, product **3ap** was recrystallized to perform such analysis, which corroborated the *R* configuration of the new stereocenter, that is the product that results from the perester approaching the less hindered *Si* π-face of the enolate (*Figure 28*).

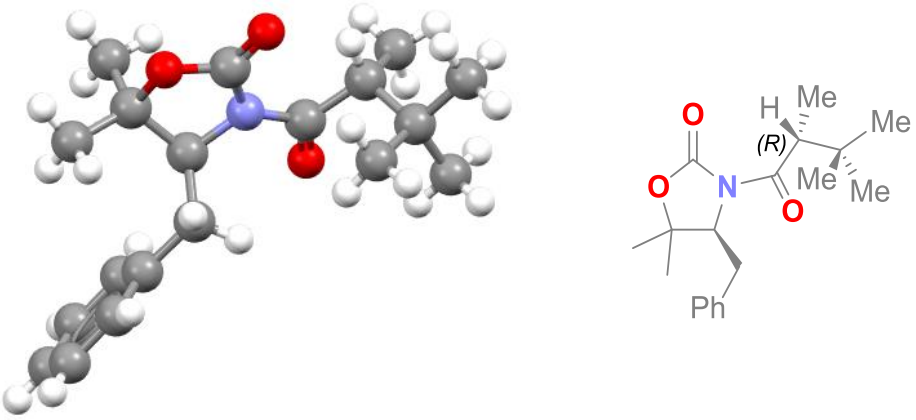


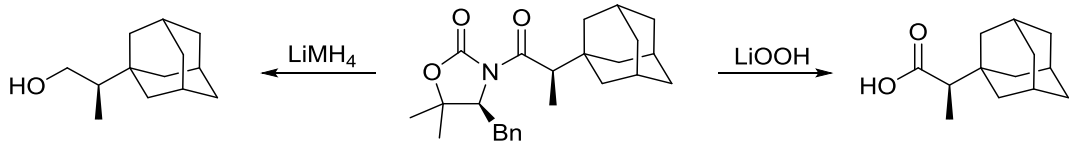
Figure 28. X-ray analysis of **3ap**

5. Cleavage of the chiral auxiliary

The particular structure of adamantyl not only confers its bridgehead radical an enhanced reactivity. The rigidity, symmetry and bulkiness of this substituent have made adamantane derivatives an attractive motif for the development of catalysts.[143] In addition, the lipophilicity and stability of this scaffold has improved the pharmacokinetics of several drugs.[144] Moreover, adamantane, being larger than benzene, occupies space in three dimensions due to its spherical shape, unlike flat benzene, which fills more or less space depending on its orientation. This makes adamantane a good scaffold to improve the selectivity of certain drugs.[144,145] Because of its outstanding properties, the functionalization of small molecules with the adamantyl moiety is of great interest. Therefore, the removal of the chiral auxiliary to render enantiopure derivatives containing adamantyl was next assessed.

Initially, the simplest alkylation product (**3an**) was chosen. Removal of the chiral auxiliary under reductive conditions ($LiBH_4$) was attempted. Unfortunately, after the addition of 6 equivalents of hydride and 7 h the reaction had not been completed (70% conversion was measured by ^1H NMR of the crude), and alcohol **42** was obtained in 64% yield (*entry 1, Table 26*). Probably the steric hindrance of adamantyl was the reason why the cleavage was slow. In another attempt, $LiAlH_4$ was used as a stronger reducing agent. As expected, the use of $LiAlH_4$ produced a full conversion of **3an** but the alkylated product was isolated again in 64% yield (*entry 2, Table 26*). Alternatively, oxidative conditions were applied to remove the auxiliary. In this case, the reaction was even slower than the formation of the alcohol; after 5 equivalents of LiOOH and two days of reaction just 16% of the corresponding carboxylic acid (**43**) was obtained, the rest being unreacted

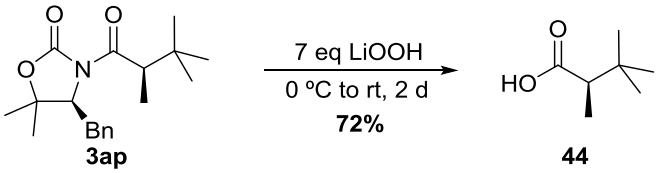
starting material (*entry 3, Table 26*). A second attempt with double the amount of peroxide was carried out, but just a slight increase to 22% yield was achieved (*entry 4, Table 26*).



Entry	Product	Cleavage reagent	Temperature	time	Isolated Yield
1	**42**	6 eq $LiBH_4$	0 °C to rt	7 h	64%
2	**42**	6 eq $LiAlH_4$	–78 °C to –20 °C	7.5 h	64%
3	**43**	5 eq LiOOH	0 °C to rt	2 d	16%
4	**43**	10 eq LiOOH	rt	3 d	22%

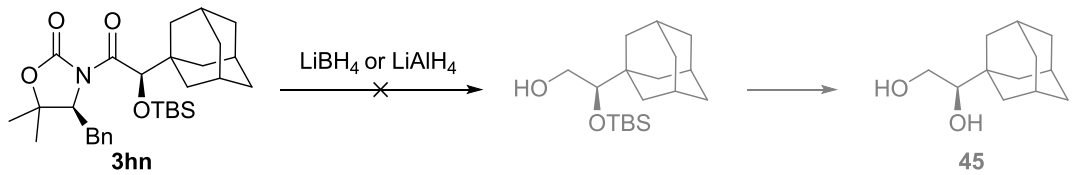
Table 26. Removal of the chiral auxiliary from **3an**

These results suggest that the hindrance of the adamantyl group and the bulkiness of the chiral auxiliary thwart the nucleophilic attack to the carbonyl. To prove that hypothesis, the removal of the chiral auxiliary from **3ap**, with a *tert*-butyl as a smaller group was attempted (*Scheme 95*). Although the reaction was not fully completed after two days, a much larger yield of carboxylic acid (**44**) was obtained this time (72%).



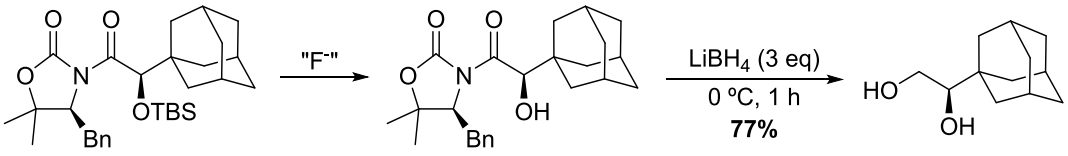
Scheme 95. Removal of the chiral auxiliary from **3ap**

After the work on the aliphatic substrate, the objective was to obtain an optically pure diol **45**. The plan was to start with the cleavage of the auxiliary from **3hn**, and then to remove the TBS protecting group (*Scheme 96*). Regrettably, no reaction was observed at all when $LiBH_4$ was employed, whereas the use of $LiAlH_4$ produced unclean crudes, probably leading to hemiaminal species as observed in Chapter II (*page 79, Scheme 68*). These results were not surprising given that the OTBS group is much larger than the methyl of the previous example, which had already showed difficulties in the removal.



Scheme 96. Initial route to **45**

At this point the strategy was changed. The deprotection of the alcohol was performed, hoping that the posterior removal of the chiral auxiliary would be easier. Unclean crudes were obtained with TBAF, while the treatment of **3hn** with 3HF·Et$_3$N complex afforded the deprotected product (**46**) in 56% yield. Unfortunately, there was still starting material in the reaction crude, so the reaction was repeated at 40 °C for 3 days, which led to the formation of an unknown by-product that could not be separated by column chromatography. To minimize the formation of such by-product, the reaction was repeated at 40 °C but just stirred for 16 h, which afforded a clearer crude and the alcohol in 62% yield. Then, reductive removal of the auxiliary from **46** was much easier; full conversion was achieved at 0 ºC within 1 h, and diol **45** was obtained in 77% yield. Moreover, the chiral auxiliary was recovered in quantitative yield.



3hn **46** **45**

Entry	F$^-$ source	T	time	Isolated Yield	Observations
1	1.5 eq TBAF	rt	3.5 h	-	unclean crude
2	8 eq Et$_3$N·3HF	rt	20 h	56%	not completed
3	8 eq Et$_3$N·3HF	40 °C	3 d	-	by-product observed
4	8 eq Et$_3$N·3HF	40 °C	16 h	62%	-

Table 27. Final route to **45**

Finally, it was thought that it would be interesting to synthesize the β-aminoethanol analogue since it may be a key building block of numerous bioactive compounds, natural products, chiral ligands and auxiliaries and even organocatalysts (*Figure 29*).[146–150]

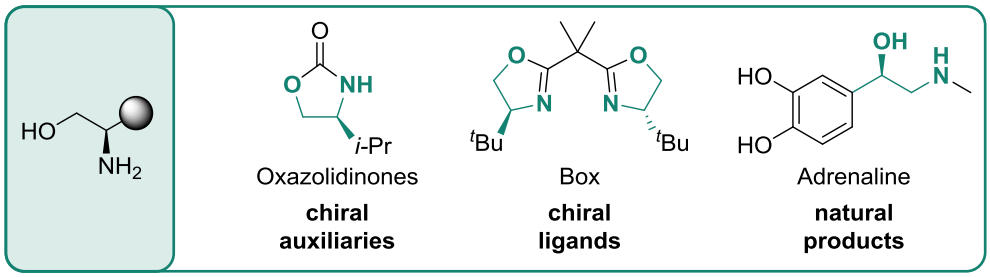
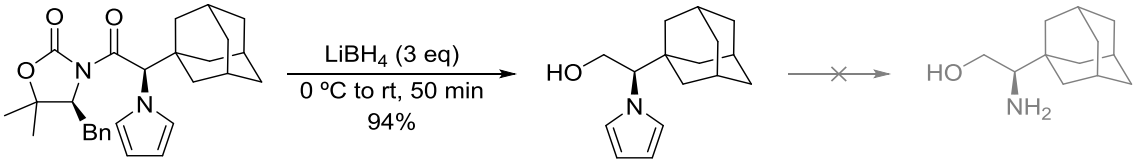


Figure 29. Presence of β-aminoalcohols

As we initially did for the diol, the first route was to remove the auxiliary and then to deprotect the nitrogen inside the pyrrole moiety. This time, the cleavage of the auxiliary from **3vn** was successful at the first attempt; indeed, alcohol **47** was obtained in excellent

yield (94%) and the auxiliary was recovered almost quantitatively in less than 1 h. On the contrary, deprotection of the nitrogen proved to be troublesome. It was described in the literature that pyrrole scission in a similar compound could be achieved using hydroxylamine and microwave heating, but these conditions did not work for this studied case.[151] Ozonolysis was also described as an alternative procedure, so it was performed on alcohol **47**. ^{1}H NMR of the crude mixture seemed to show the signals of the aminol product, which was also observed by HPLC-MS. However, there were many other products, probably derived from the thiourea that was used for the reducing quench. Purification of the product was extremely difficult due to its low solubility in organic solvents. A recrystallization was attempted, but all the products co-crystallized. Then, the direct neutralization of the crude followed by column chromatography was attempted, but purifications were difficult since the product was not observed by any TLC stain, and it usually coeluted with a major by-product. Finally, the direct protection of the resulting amine with Cbz was attempted, to obtain a product that would be easier to purify, but unfortunately, no protection reaction was observed.



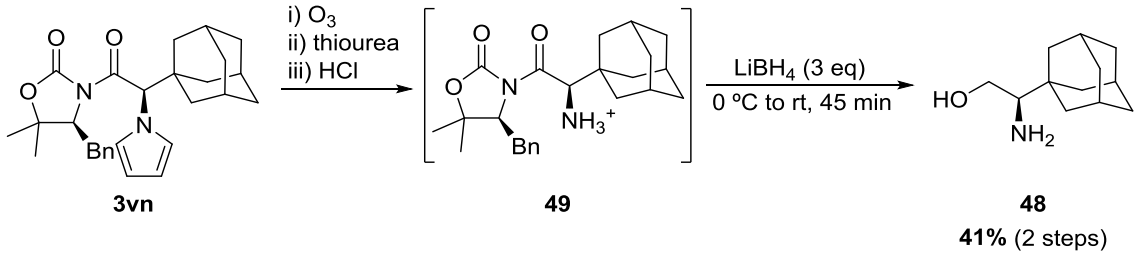
3vn **47** **48**

Entry	Deprotection	Observations
1	$NH_2OH{\cdot}HCl$, μwave, 120 °C	Starting material recovered
2	Ozonolysis	Aqueous work-up
3		Recrystallization
4		Neutralization with K_2CO_3 and column
5		Neutralization with Et_3N and column
6		Neutralization with NaOH and column
7		Direct protection with Cbz

Table 28. Initial route to **48**, deprotection of the pyrrole

After these failures, the order of the steps was changed. We speculated that it would be easier to isolate the deprotected product if the chiral auxiliary was still attached. Hence, ozonolysis was directly performed on **3vn** (*Scheme 97*) and the desired ammonium salt **49** was successfully obtained, which was used in the next step without further purification. Finally, removal of the chiral auxiliary with $LiBH_4$ afforded the desired aminoalcohol **48** in less than 1 h with a 41% overall yield. The resultant β-aminoalcohol was soluble in most organic solvents and was indeed observed after

permanganate TLC stain. Moreover, NMR spectra perfectly matched those reported in the literature.[152]

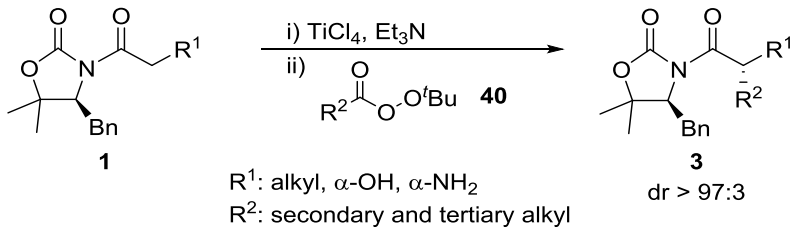


Scheme 97. Final route to **48**

To sum up, removal of the chiral auxiliary and deprotection of the hydroxy and amino groups was quite challenging due to the extremely hindered alkylated compounds obtained after the alkylation with adamantyl *tert*-butyl perester. However, appropriate sequences have been found to isolate the enantiomerically pure 1,2-diol **45** and the β-aminoalcohol **48** containing an adamantyl group.

6. Outline

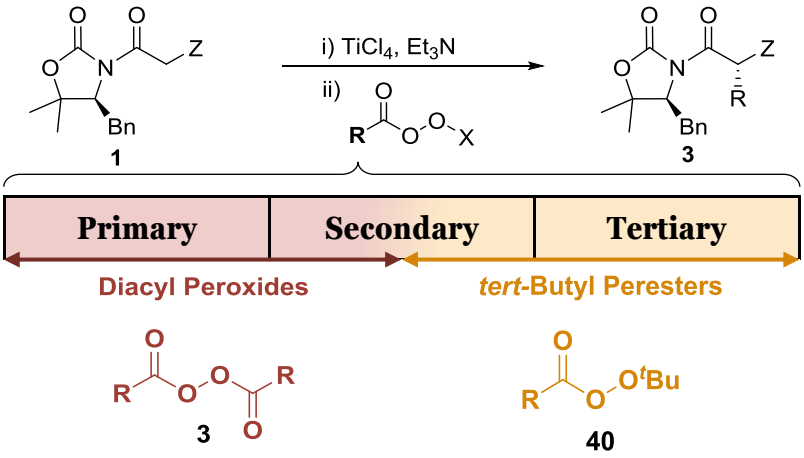
In this chapter, the radical alkylation of titanium enolates with *tert*-butyl peresters derived from carboxylic acids was fully studied (*Scheme 98*). Despite the formation of a carboxylated by-product that diminishes some alkylation yields, this alkylation allows the stereocontrolled introduction of secondary and tertiary alkyl groups for a wide range of titanium enolates. This is a challenging transformation that has been reported on few occasions. Not to mention the ease of the procedure and the mild conditions required for such alkylation, together with the reproducibility of the results after being scaled up to a 2-gram scale.



Scheme 98. Alkylation of titanium enolates with *tert*-butyl peresters

Such an alkylation procedure fulfils the gaps found in the alkylation with diacyl peroxides since it allows the introduction of tertiary groups, which was not possible in Chapter I (*Scheme 99*). However, it does not cover the alkylation with primary alkyl groups. All in all, choosing the right reagent to perform a radical alkylation of titanium

enolates will depend on the **R** group to be attached. If it is primary, diacyl peroxides should be used. For secondary alkyl groups, both, diacyl peroxides and *tert*-butyl peresters are suitable reagents, although the use of peresters would be recommended due to their easier manipulation. Finally, tertiary alkyl groups can only be incorporated using *tert*-butyl peresters.



Scheme 99. Comparison of methodologies

CHAPTER IV

Expansion of the Biradical Reactivity

The radical alkylation of titanium enolates with diacyl peroxides or *tert*-butyl peresters had proved to be highly successful, but these methodologies presented some drawbacks that could be improved. Firstly, the alkylation with secondary or tertiary groups had been achieved with poor to good yields, which were negatively impacted by the formation of a carboxylated by-product due to the release of carbon dioxide. Additionally, stoichiometric amounts of titanium tetrachloride were required to perform such transformations. Therefore, to exploit the biradical character of enolates, alternative procedures to overcome such limitations would first be required. Hence, the need for new methodologies was addressed through a two-fold approach: on one hand, the search for another redox active species to substitute diacyl peroxides or *tert*-butyl peresters, and, on the other hand, the quest for another transition metal to replace titanium, that is a metal that could also render biradical enolates but at the same time, could be used under catalytic premises.

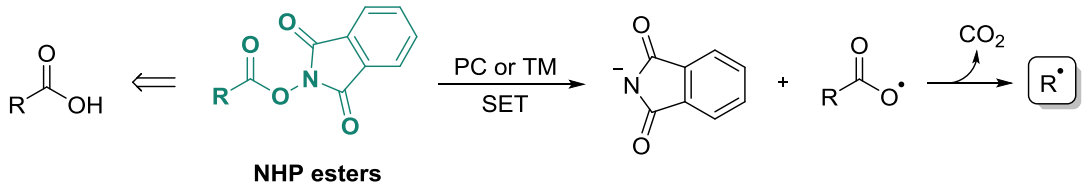
1. Looking for other redox active species

At the beginning, radical chemistry used alkyl halides as raw materials to obtain alkyl radicals. Unfortunately, organotin species were then required. Nowadays, there are many other species to generate alkyl radicals without the need for toxic reagents. An important group of these radical precursors renders alkyl radicals through a reductive treatment. Actually, diacyl peroxides or *tert*-butyl peresters are members of this group but not the most broadly used. In the first part of this chapter, the screening of other species to produce alkyl radicals upon reductive conditions is described.

1.1 Introduction

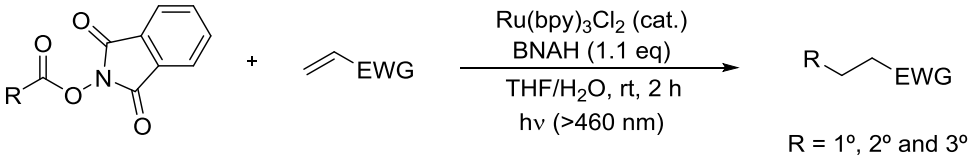
Active esters: *N*-hydroxyphthalimide (NHP) esters

Studies on the decarboxylation of NHP esters is a very active area in radical chemistry. These species are easy to handle, readily prepared from carboxylic acids, and a vast range of reducing conditions has been described to trigger the homolysis of the O–N bond and subsequently provide primary, secondary, or tertiary radical species after a decarboxylation process (*Scheme 100*). These redox active esters have thus been used in a broad range of reactions, from radical additions to alkenes or alkynes to Csp^3-Csp^3 or Csp^3-Csp^2 radical couplings, as well as carbon-heteroatom couplings.[80]



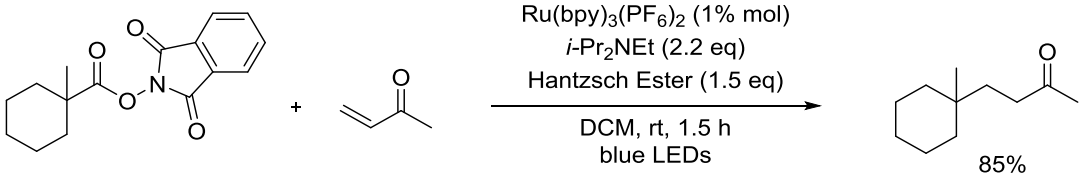
Scheme 100. NHP esters

N-Hydroxyphthalimide esters were first described by ODA and OKADA in 1988 for the UV-photochemical decarboxylation of carboxylic acids.[153] Later, they reported such a decarboxylation using visible light and a ruthenium photocatalyst, leading to primary, secondary or tertiary alkyl radical intermediates that could be trapped with electron-poor olefins.[16]



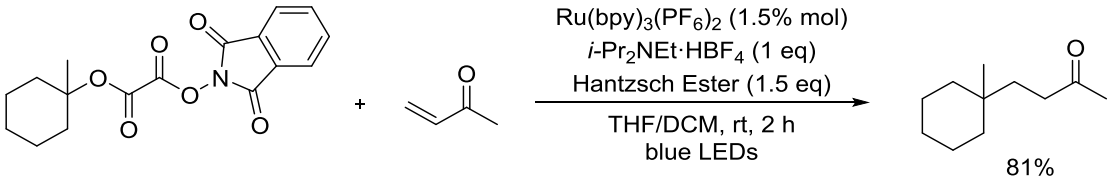
Scheme 101. Decarboxylation of NHP esters by ODA and OKADA

Although these studies reported the generation of alkyl radicals under mild conditions, poor attention was given to them until OVERMAN adapted the procedure to accomplish the synthesis of (-)-aplyviolene.[154] In there, the hydrolysis of the product due to the aqueous media reported by ODA and OKADA prompted the use of dichloromethane as the solvent and the Hantzsch ester as the reducing agent. These changes enabled the same reaction to be carried out under anhydrous conditions, thus, avoiding hydrolysis issues. After that, OVERMAN completed a comprehensive study of the radical generation through these species and the radical quench with electron-poor alkenes.[155]



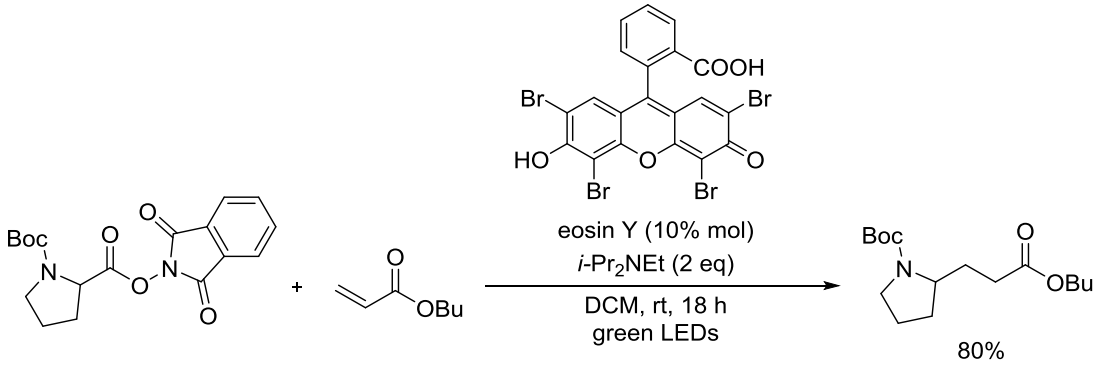
Scheme 102. Decarboxylation of NHP esters by OVERMAN

Moreover, OVERMAN described the generation of alkyl radicals from *N*-phthalimidoyl oxalates, which are analogue compounds that can be prepared from tertiary alcohols instead of carboxylic acids.[156,157] However, oxalates are less stable than NHP esters and they performed slightly worse than their analogues.



Scheme 103. Decarboxylation of N-phthalimidoyl oxalates by OVERMAN

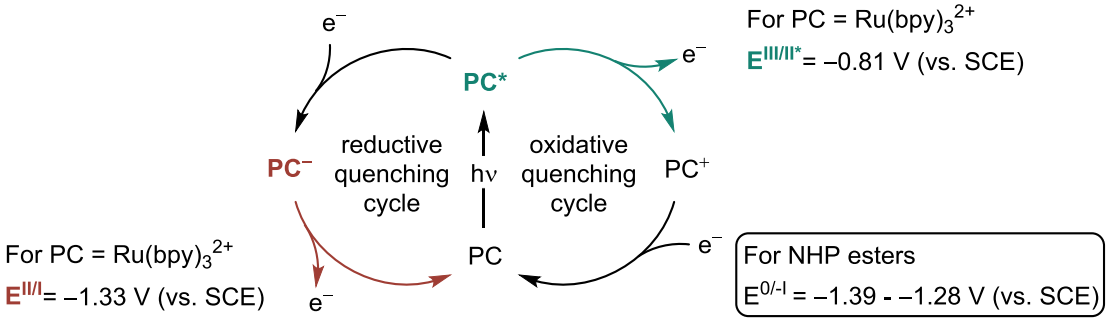
In the previous examples, NHP esters were reduced in the presence of a ruthenium photocatalyst. However, other transition metals, such as iridium, or organic photocatalysts have been recently used to reduce such redox active esters. For instance, KÖNIG used eosin-Y, an organic dye, as a photocatalyst to generate a broad variety of radicals that were trapped with electron-deficient alkenes.[158]



Scheme 104. KÖNIG metal-free decarboxylation of NHP esters

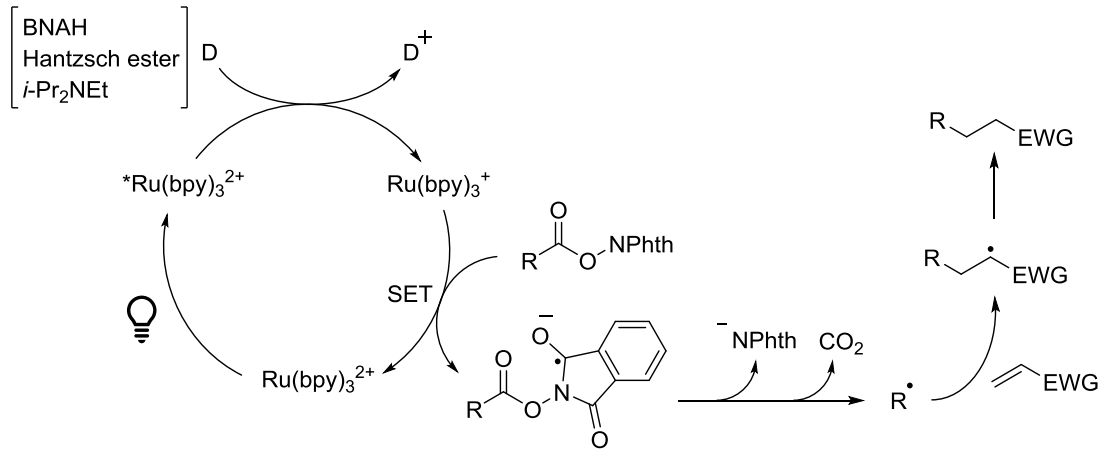
Photocatalysis, either from transition metals or organic dyes, is nowadays one of the main tools to attain the decarboxylation of NHP esters. In these cases, two different catalytic cycles can be considered, because once the photocatalyst (PC) has been excited, it can easily undergo either reduction or oxidation reactions (*Scheme 105*). A reductive quenching cycle occurs if the excited photocatalyst is reduced, and a single-electron oxidant is required to regenerate the photocatalyst to its initial oxidation state. In turn, the oxidation of the excited photocatalyst involves an oxidative quenching that requires an electron donor to close the cycle. In the case of NHP esters, a reducing complex is necessary in order to achieve the cleavage of such species. In a reductive quenching cycle, the catalyst must firstly be reduced by an additional reductant to generate PC^{-}, which can act as a reductant to achieve our purpose (*red in Scheme 105*). Instead, in an oxidative quenching cycle, the excited catalyst could directly reduce the active esters (*blue in Scheme 105*). The choice between these two options will depend on the reducing potentials of each species. The excited state of the catalyst used in the initial studies, $Ru(bpy)_3^{2+}$, is unable to reduce the NHP esters according to the potentials in the

literature (–0.81 V vs –1.3 V aprox. respectively),[13,153] whereas the reduced $Ru(bpy)_3^{+}$ has enough reducing potential to achieve the electron-transfer to the ester (–1.33 V vs –1.3 V aprox. respectively).



Scheme 105. Photocatalytic cycles

According to the mechanism described in the literature, the ruthenium photocatalyst is excited upon visible light irradiation. The resultant excited catalyst is reduced by an additional donor species (D) to form a ruthenium(I) complex that prompts the scission of the redox active ester upon a SET process. The radical anion formed is cleaved through the weak O–N bond to generate phthalimide and a radical intermediate that decarboxylates to afford the desired carbon centered radical. Addition of the radical to electron-poor alkenes affords another radical species that can be quenched by either hydrogen atom abstraction or reduced to a carbanion and eventually protonated (*Scheme 106*).

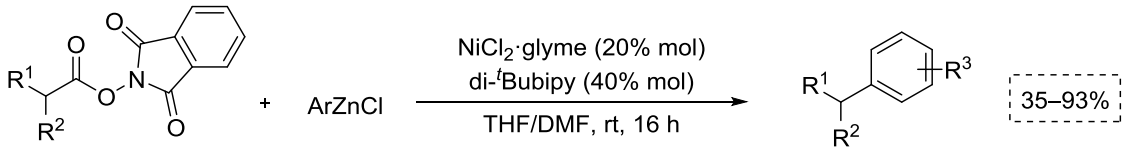


Scheme 106. Mechanism of decarboxylation of NHP esters

Initially, the donor species (D) to obtain ruthenium(I) was an organic reductant: BNAH in the procedure described by ODA and OKADA, and Hantzsch ester or DIPEA in OVERMAN's conditions. With the generalized use of NHP esters, other species have been

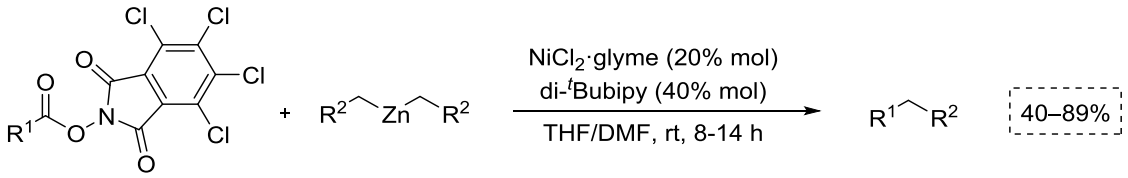
used as reductants; for instance, another transition metal in dual catalysis systems, or even a radical intermediate in the reaction pathway.

On the contrary, the reduction of NHP esters has also been described using a transition metal, without the need for light. An example is the nickel catalyzed alkyl-aryl coupling described by BARAN.[159] In this work, secondary carboxylic acids are converted into the corresponding redox active esters, these are reduced by a nickel(II) complex and the resultant radical is coupled with an aryl zinc reagent (*Scheme 107*).



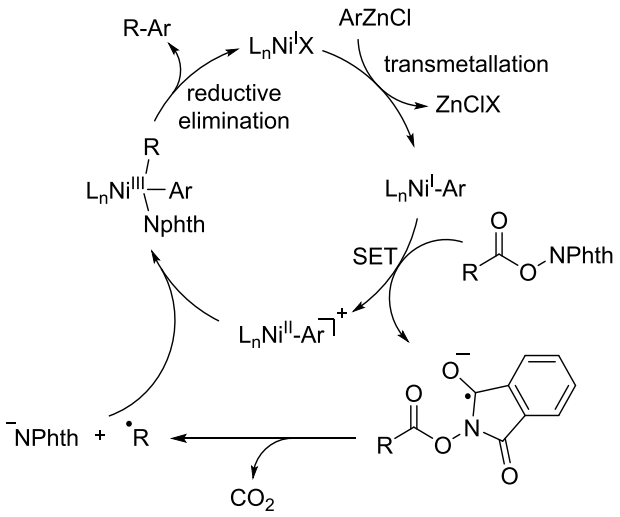
Scheme 107. Nickel catalyzed aryl-alkyl coupling from NHP esters

Parallelly, BARAN developed the nickel(II) catalyzed alkyl-alkyl coupling between redox active esters and dialkylzinc reagents. This time, the more active tetrachloro-substituted NHP ester derivative is used because it gives higher yields (*Scheme 108*).[160]



Scheme 108. Nickel catalyzed alkyl-alkyl coupling from NHP esters

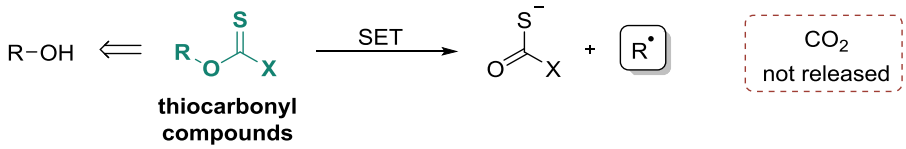
In other examples the reduction of redox active esters by transition metals has been reported with iron or copper catalysts, or with zinc as a stoichiometric reductant.[161–163] In these cases, the low valent metal is responsible for the reduction of redox active esters so that a radical is generated. In turn, an additional reductant or the radical intermediates themselves are responsible for the regeneration of the oxidation state of the catalyst. A description of a nickel catalyzed alkyl-aryl cross coupling is shown in *Scheme 109*.



Scheme 109. Mechanism of a nickel catalyzed cross coupling using NHP esters

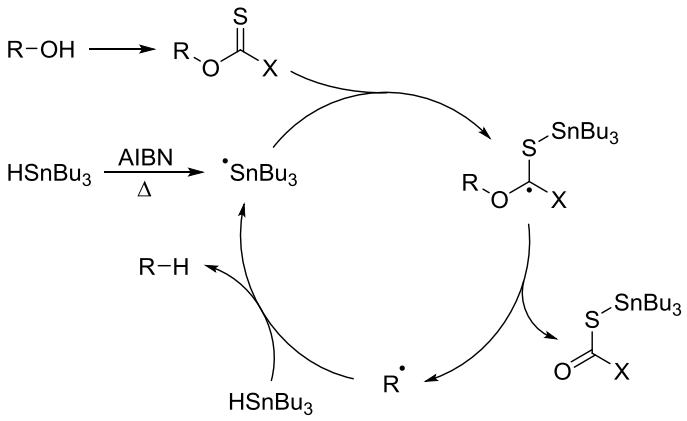
Thiocarbonyl compounds

The redox active esters previously described react like diacyl peroxides or *tert*-butyl peresters since all these species release carbon dioxide upon reductive fragmentation. Nonetheless, carbon dioxide was responsible for the formation of a carboxylated by-product during the alkylation with peresters (*see Chapter III, Section 2.2*). Therefore, other radical precursors that do not release carbon dioxide during the cleavage were considered. Within this category, we paid a special attention to thiocarbonyl compounds used in Barton-McCombie decarboxylation (*Scheme 110*).



Scheme 110. Thiocarbonyl compounds

In 1975, BARTON and MCCOMBIE reported the radical deoxygenation of secondary alcohols through a thiocarbonyl intermediate.[12] In their work, AIBN was used as a radical initiator to form alkyltin radicals, which provoked the scission of the thiocarbonyl compound upon addition to the sulfur atom (*Scheme 111*). Then, the alkyl radical formed reacted with trialkyltin hydride through hydrogen atom abstraction to render the deoxygenated alkane and generate another alkyltin radical. This reaction entailed a great advancement because it allowed the deoxygenation of complex structures containing a broad variety of functional groups, a transformation that was impossible using ionic methodologies.



Scheme 111. Barton-McCombie mechanism

Moreover, different derivatives were described by changing the X group (*Figure 30*), which provided thiocarbonyl derivatives with different properties and reactivities. Xanthate derivatives from tertiary alcohols are usually unstable due to elimination reactions. On the other hand, xanthates derived from primary alcohols are more difficult to cleave because the generation of primary alkyl radicals is more challenging. This process can be favored by higher temperatures, yet competition between the cleavage of the C-O or the C-S arises. This problem can be circumvented by changing the thiocarbonyl derivative, for instance, to an aryl thionocarbonate.

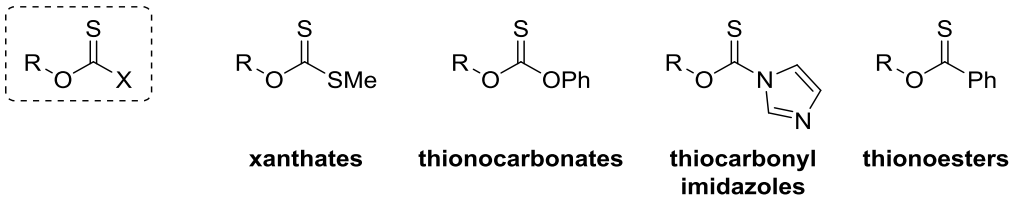
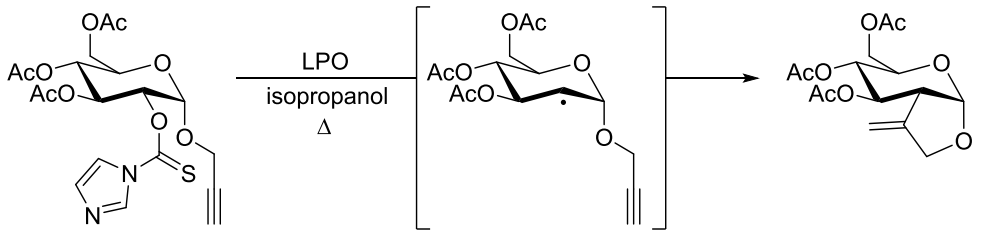


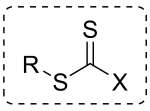
Figure 30. Thiocarbonyl compounds for Barton-McCombie decarboxylation

Despite this procedure being initially reported to deoxygenate secondary alcohols, it was later adopted as a new method to generate alkyl radicals for other transformations such as additions to π-bonds.[164] In the following tin-free example (*Scheme 112*), stoichiometric amounts of dilauroyl peroxide (instead of organotin reagents) were used to initiate the scission of the thiocarbonylimidazolate. Then, the radical formed was trapped by the triple bond through an intramolecular cyclization.[165]



Scheme 112. Intramolecular Barton-McCombie cyclization

Inspired by BARTON and MCCOMBIE, CSIRO agency invented the "reversible addition-fragmentation chain transfer" (RAFT) polymerization.[166] This process consists of a free radical polymerization controlled by a thiocarbonylthio derivative, commonly known as a RAFT reagent, which includes dithioesters, dithiocarbamates, dithiocarbonates or xanthates. Similarly to the previous examples, changes in the X group modify the reactivity of these reagents (*Figure 31*).



RAFT reagent general structure

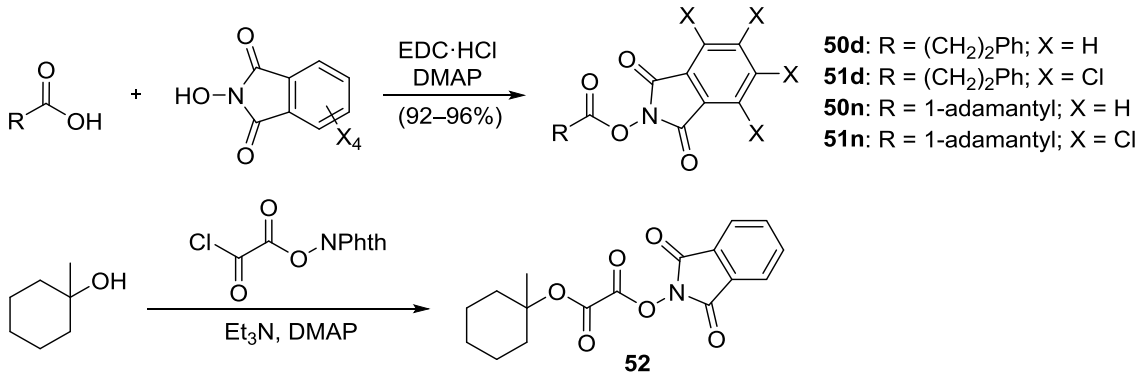
Figure 31. RAFT polymerization

1.2 Preparation of redox active species

To perform a screening of new radical precursors that could react with titanium enolates, a range of redox active species were prepared. Among those, primary and tertiary alkyl groups were included in the structures.

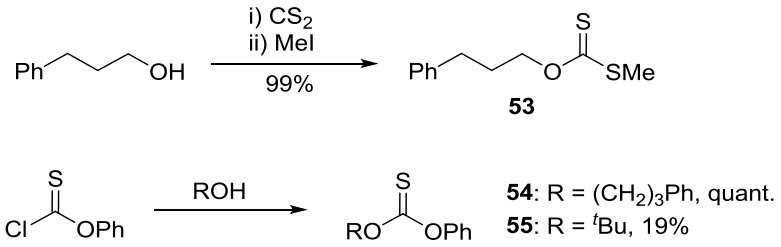
N-Hydroxyphthalimide esters (NHP esters)

N-(Acyloxy)phthalimides were prepared by EDC-mediated coupling of alkyl carboxylic acids with *N*-hydroxyphthalimide catalyzed by DMAP (*Scheme 113*). Reagents with and without chlorine substituents in the phthalimide moiety were prepared for a primary (**50d** and **52d** from hydrocinnamic acid) and a tertiary (**50n** and **51n** from 1-adamantane carboxylic acid) substrates. All the NHP esters were obtained with excellent yields. Besides, the oxalate **52** was prepared from the tertiary 1-methylciclohexanol by acylation with the oxalyl derivative.



Scheme 113. Preparation of NHP esters and oxalates

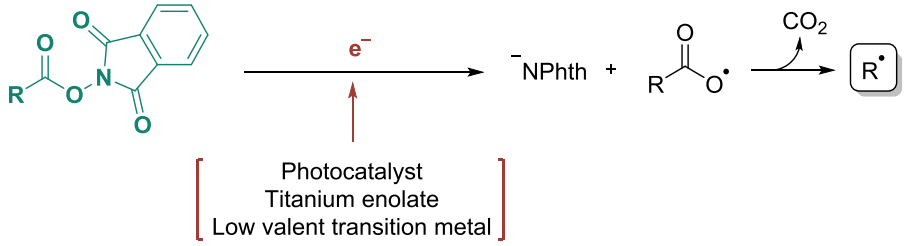
In parallel, a small group of thiocarbonyl compounds was also prepared (*Scheme 114*). Firstly, a xanthate derivative was synthesized from 3-phenylpropanol, carbon disulfide, and methyl iodide (**53**) in excellent yield. Then, phenyl thiocarbonates **54** and **55** were prepared from phenoxythiocarbonyl chloride, and 3-phenylpropanol or *tert*-butanol in quantitative and poor yields respectively.



Scheme 114. Preparation of xanthates and thiocarbonates

1.3 Test results

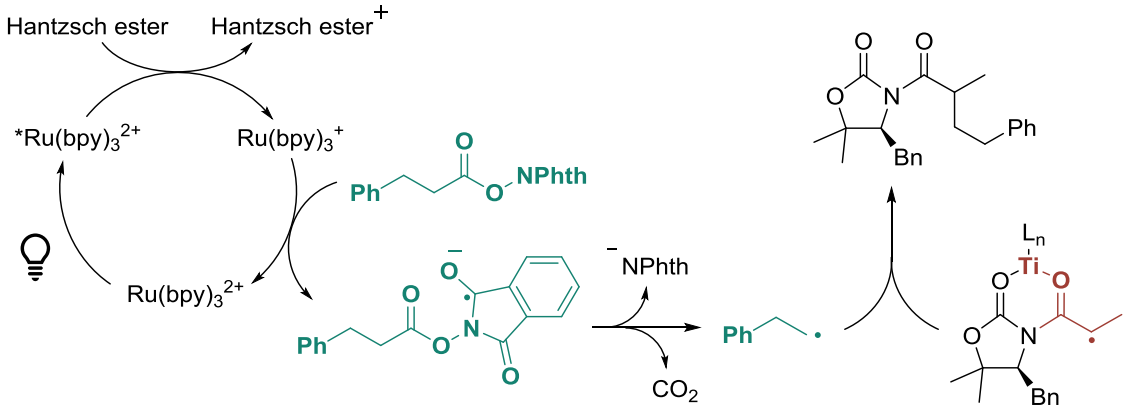
The reaction of such radical precursors with titanium enolates was then studied. As seen in the introduction, the NHP esters can render alkyl radicals upon its reductive scission. To achieve this, different reductant species have been described in the literature, from photocatalysts to transition metal catalysts. In the following tests, we considered distinct approaches to achieve the reduction of such esters in which the reductant species was different: a photocatalyst, the titanium enolate itself or a transition metal added stoichiometrically (*Scheme 115*).



Scheme 115. Approaches taken for the decarboxylation of NHP esters

Photochemical reduction of NHP esters

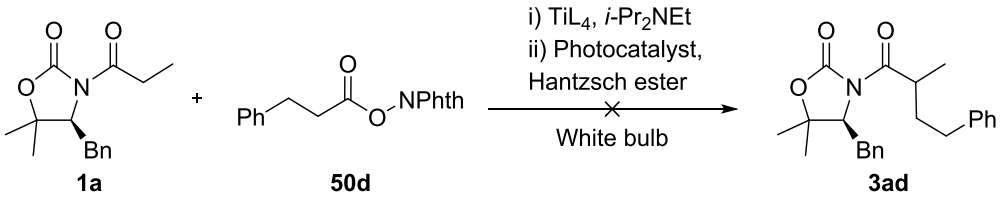
Firstly, the photochemical generation of alkyl radicals was assessed. The initial experiments were based on the conditions described by OVERMAN,[154] which seemed compatible with the conditions employed to prepare the titanium enolates since the solvent and the trialkylamine were identical. Indeed, OVERMAN used a ruthenium catalyst together with Hantzsch ester as a reducing species to form the nucleophilic radicals, which were trapped by an electron-poor olefin. It was hypothesized that alkyl radicals could be trapped by titanium enolates instead (*Scheme 116*).



Scheme 116. Attempts to combine photoredox generation of radicals with titanium enolates

Blank reactions with methyl vinyl ketone as a radical trap were performed to check that the reagents and conditions were suitable to activate **50d**. Then, the same conditions were applied to the titanium enolate of **1a**, which was added to the mixture of **50d**, the ruthenium catalyst, and Hantzsch ester. The mixture was stirred for 16 h under irradiation from a white bulb. However, no decomposition of any of the starting materials was observed (*entry 1, Table 29*). Considering that ester **50d** could interact with titanium and thus be inactivated, an excess of **50d** was used, but the same negative results were obtained (*entries 2 and 3, Table 29*). Following the same hypothesis, one of the chlorides of the titanium enolate was replaced by a bulkier isopropoxide ligand to hinder the titanium and avoid coordination with the redox active ester, yet again, starting materials

were recovered (*entry 4, Table 29*). Then, the titanium enolate was prepared with 0.5 equivalents of titanium tetrachloride so that two *N*-acyl oxazolidinone molecules (**1a**) would coordinate to titanium,[73] and consequently elude the coordination of the NHP ester. However, only starting materials were observed by ^{1}H NMR of the crude (*entry 5, Table 29*). On a different note, it was considered that the deep dark solution of the enolate could absorb the light, which would prevent the excitation of the ruthenium catalyst. To preclude that option, the reaction mixture was diluted ten-fold, but the results obtained were the same (*entry 6, Table 29*). It should be mentioned that even with the dilution, the solution did not turn more transparent to human eyes. Then, the ruthenium catalyst was replaced by an organic dye; eosin Y as KÖNIG described,[158] but no changes were observed from the previous experiments (*entry 7, Table 29*). Finally, to discard interactions between the titanium enolate and the photocatalyst, an experiment with 150 mol% of eosin Y was set up, but the starting materials were recovered, again without any decomposition (*entry 8, Table 29*).



1a **50d** **3ad**

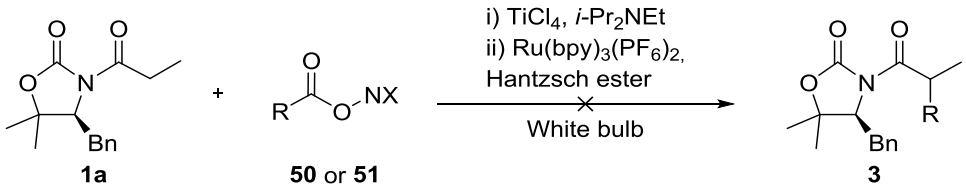
i) TiL_4 (X eq), *i*-Pr_2NEt (2.2 eq), DCM, 0 ºC, 40 min; ii) **50d** (X eq), Photocatalyst (X mol%), Hantzsch ester (1.5 eq), 16 h, rt, white bulb

Entry	TiL_4	Conc.	50d	Photocatalyst
1	$TiCl_4$ (1.1 eq)	0.2 M	0.7 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%
2	$TiCl_4$ (1.1 eq)	0.2 M	2.1 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%
3	$TiCl_4$ (1.1 eq)	0.2 M	3.1 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%
4	$TiCl_3$*i*-PrO (1.1 eq)	0.2 M	1.0 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%
5	$TiCl_4$ (0.5 eq)	0.2 M	1.5 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%
6	$TiCl_4$ (1.1 eq)	0.02 M	1.0 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%
7	$TiCl_4$ (1.1 eq)	0.2 M	1.5 eq	EOSIN Y 15 mol%
8	$TiCl_4$ (1.1 eq)	0.2 M	1.5 eq	EOSIN Y 150 mol%

Table 29. Photochemical activation of **50d**

In view of the failure of our efforts with ester **50d**, other esters were used. Firstly, the same reaction was attempted with the more active ester **51d**, containing four chlorine atoms in the phthalimide group. Once again, the ^{1}H NMR of the crude showed unmodified starting materials (*entry 1, Table 30*). Then, in order to facilitate the generation of the alkyl radical, the alkyl group of the NHP ester was changed to adamantyl, because it would render a tertiary radical that should be easier to generate.

However, neither **50n** or **51n** esters were altered during the reaction with the titanium enolate (*entries 2 and 3, Table 30*).



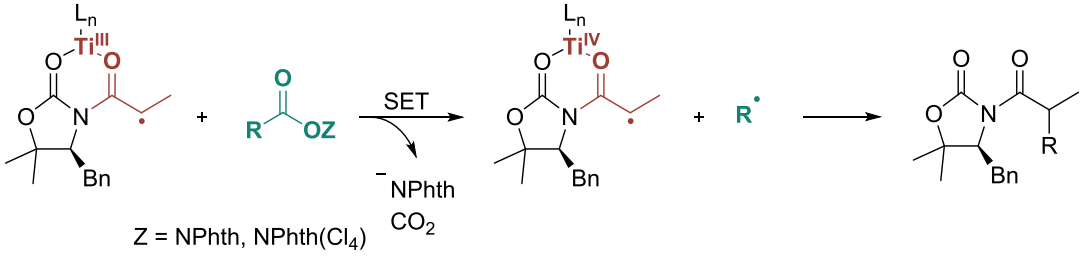
i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (2.2 eq), DCM, 0 °C, 40 min; ii) **50** or **51** (1.4 eq), $Ru(bpy)_3(PF_6)_2$ (1 mol%), Hantzsch ester (1.5 eq), 16 h, rt, white bulb

Entry	*N*-Acyloxy phthalimide	R	X
1	**51d**	2-phenylethyl	3,4,5,6-tetrachlorophthalimide
2	**50n**	1-adamantyl	phthalimide
3	**51n**	1-adamantyl	3,4,5,6-tetrachlorophthalimide

Table 30. Photochemical activation of other NHP esters

Non-photochemical reduction of NHP esters

Although the decarboxylation of redox active esters was firstly described using a photocatalyst as a reducing species, BARAN demonstrated that it could also be achieved by a transition metal catalyst without the need for light, as shown in the introduction (*Chapter IV, Section 1.1*). Thus, we hypothesized that the titanium enolate itself could act as a reducing agent to provoke the decarboxylation of NHP esters, without the need for a photocatalyst species (*Scheme 117*). In fact, we thought of a mechanism similar to that described in Chapters I and III, in which the scission of diacyl peroxides or *tert*-butyl peresters was achieved by a SET from the titanium enolate. Therefore, another set of experiments was launched using NHP esters and *N*-phthalimidoyl oxalates (*Scheme 117*).

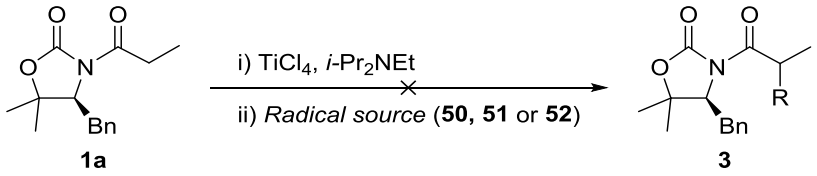


Scheme 117. Hypothetical reduction of redox active esters with titanium enolates

According to those ideas, **50d** was added to a solution of the titanium enolate of **1a** without any additive, but no reaction took place (*entry 1, Table 31*). Then, the same reaction was repeated at a higher temperature to facilitate the scission of the NHP ester,

but it did not work either (*entry 2, Table 31*). Similarly, the more active **51d** ester was then considered, but the same negative results were obtained (*entry 3, Table 31*). At this point, any direct reaction of titanium enolates with NHP esters was discarded. However, the oxalates described by OVERMAN seemed a promising alternative as a radical source.[157] Therefore, the alkylation reaction was attempted by adding oxalate **52** to the titanium enolate, but no alkylation product was observed (*entry 4, Table 31*).

After these experiments, it was assumed that titanium enolates could not reduce NHP esters on their own. Additionally, as seen in the previous section, photochemistry did not aid the decarboxylation of redox active species. In a last approach, the use of a stoichiometric metal reductant was considered. However, the addition of zinc(0) together with **50d** did not work (*entry 5, Table 31*). Neither did work the reaction of the titanium enolate with the tertiary ester **50n** and zinc(0) nor manganese(0) (*entries 6 and 7, Table 31*).



i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (2.2 eq), DCM, 0 °C, 40 min; ii) Radical source (1.5 eq), 16 h, rt

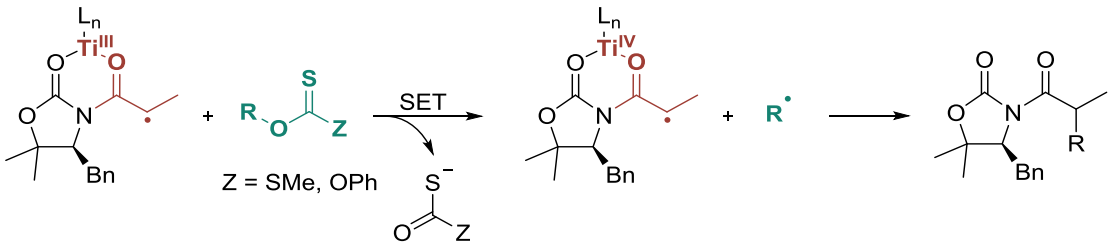
Entry	Radical source	R	Additive	Temp.
1	**50d**	2-phenylethyl	-	rt
2[a]	**50d**	2-phenylethyl	-	70 °C
3	**51d**	2-phenylethyl	-	rt
4	**52**	1-methylciclohexyl	-	rt
5	**50d**	2-phenylethyl	$Zn^{(0)}$ 1.5 eq	rt
6	**50n**	1-adamantyl	$Zn^{(0)}$ 1.5 eq	rt
7	**50n**	1-adamantyl	$Mn^{(0)}$ 2.5 eq	rt

[a]in DCE

Table 31. Addition of redox active esters and oxalates to titanium enolates

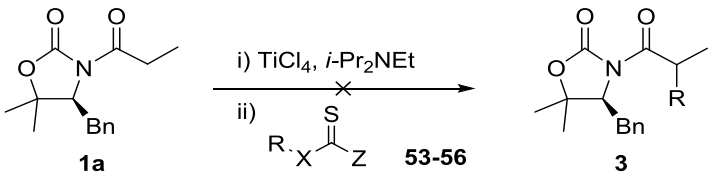
Addition of thiocarbonyl compounds to titanium enolates

After these unsuccessful experiments, NHP esters were abandoned and thiocarbonyl compounds were investigated. Diverging from diacyl peroxides, *tert*-butyl peresters or NHP esters, thiocarbonyl compounds do not release carbon dioxide after their scission (*Scheme 118*). This could entail an advantage considering that the adduct between titanium enolates and carbon dioxide had been observed in the past.



Scheme 118. Reduction of thiocarbonyl compounds with titanium enolates

However, the addition of xanthate **53** to titanium enolate did not work neither at room temperature nor at a high temperature (*entries 1 and 2, Table 32*) and the starting materials were recovered unmodified. Similar results were obtained when a primary (**54**) or a tertiary (**55**) thiocarbonate were used (*entries 3 and 4, Table 32*). Finally, the addition of the commercially available RAFT reagent **56** did not give any better results (*entry 5, Table 32*).



i) $TiCl_4$ (1.1 eq), *i*-Pr_2NEt (2.2 eq), DCM, 0 °C, 40 min; ii) **thiocarbonate** (1.5 eq), 16 h, rt

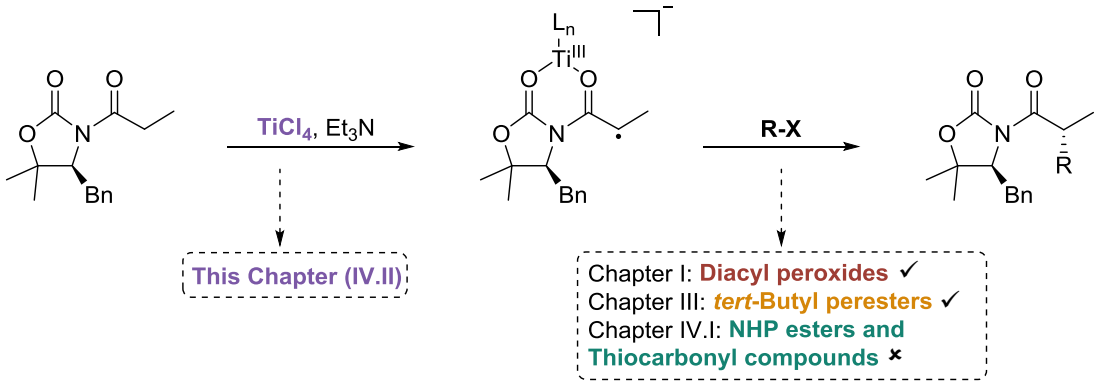
Entry	Radical source	Z	X	R	T
1	**53**	SMe	O	3-phenylpropyl	rt
2[a]	**53**	SMe	O	3-phenylpropyl	70 °C
3	**54**	OPh	O	3-phenylpropyl	rt
4	**55**	OPh	O	*tert*-butyl	rt
5	**56**	Ph	S	benzyl	rt

[a]in DCE

Table 32. Addition of thiocarbonyl compounds to titanium enolates

2. Looking for a titanium substitute

The objective of this chapter was to find a radical alkylation methodology that could overcome the constraints found in previous Chapters. To do so, the efforts were initially focused on finding a substitute for diacyl peroxides or *tert*-butyl peresters. However, none of the candidates gave the desired alkylated product. Instead, this section will focus on finding a titanium replacement so that another metal can be used to form an enolate that also exhibits biradical character (*Scheme 119*).



Scheme 119. Quest for a metal

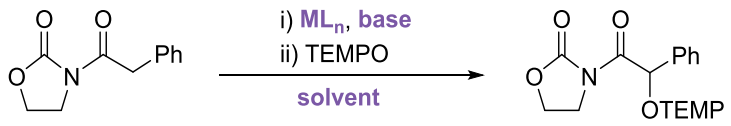
2.1 Introduction

Up to this point, the thesis has been centered on titanium enolates prepared with stoichiometric amounts of titanium tetrachloride and a trialkylamine base. The catalytic use of this metal is prevented because titanium(IV) strongly coordinates to species such as carbonyls or ethers, which makes it difficult to participate in catalytic cycles. It was thus imperative that the alkylations described, although one-pot, required two steps; first the formation of the titanium enolate, and after 40 minutes, the addition of the radical source. Consequently, the set-up of the reactions is long. And finally, titanium tetrachloride can be used with a narrow variety of solvents because it also coordinates to most of them. The substitution of titanium by another transition metal seemed a good strategy since it could be beneficial in terms of catalysis, which would allow the straightforward set-up of the reactions and this other enolate would, hopefully, be compatible with a wider range of solvents.

The objective was to find another transition metal that could form a new type of metal enolate possessing a biradical character, thus exhibiting similar reactivity upon diacyl peroxides and *tert*-butyl peresters. And maybe, this new type of enolate could react with other redox active species, or at least, it could be compatible with the photoredox

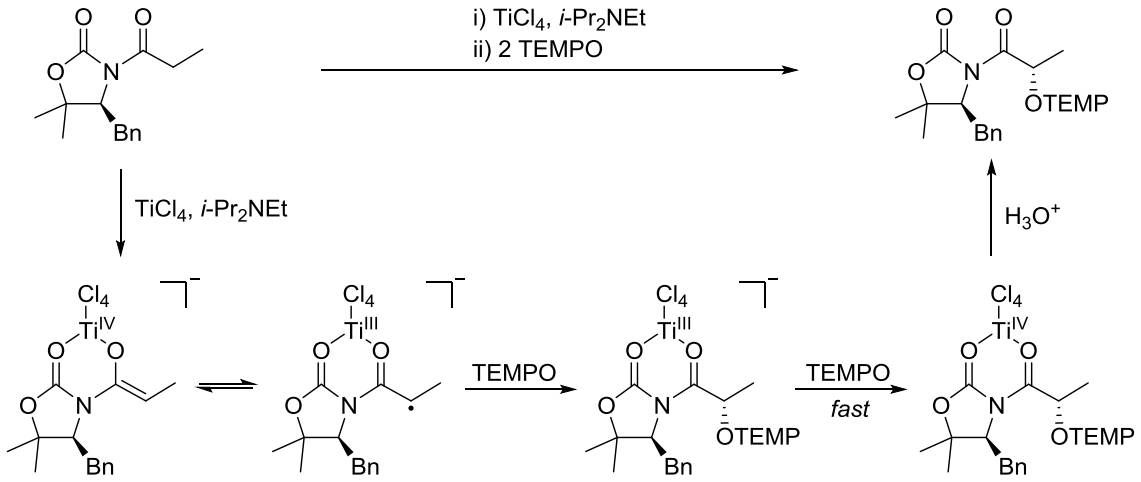
decarboxylation of NHP esters, which was unsuccessful until now. The task was daunting since a lot of variables should be considered. Firstly, many transition metals are available, and these can be found in a variety of oxidation states and forming different salts or complexes. Secondly, the capability of the complex to allow soft enolizations with the appropriate base should also be considered. Finally, the solvent was another key component that should be evaluated.

In order to facilitate the search of a new metal enolate, the chiral auxiliary was removed because stereoselectivity at these early stages was not a priority, yet the naked oxazolidinone was left to provide another coordination point to the metal (*Scheme 120*). Furthermore, an α-phenyl group was incorporated to facilitate the enolization. At the same time, the phenyl group would make the substrate visible in the UV, which would ease the monitoring of the reactions. Finally, instead of directly pursuing the alkylation of the new enolate, TEMPO was used to trap the enolate. TEMPO is a free radical that it is broadly used as a probe to determine if a reaction goes through a radical intermediate. Therefore, if the aminoxylated product was formed, it could suggest that an enolate with a biradical character had been formed (*Scheme 120*).



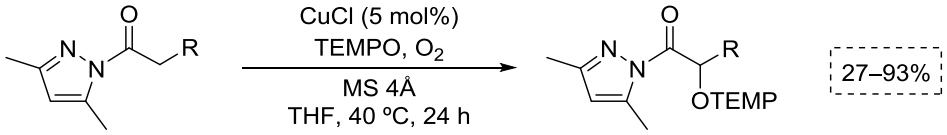
Scheme 120. Simplified research of another biradical enolate

As seen in the general introduction, the same reactivity using titanium enolates from chiral *N*-acyl oxazolidinones was described by our group and ZAKARIAN a few years ago. In these studies it was observed that a second equivalent of TEMPO was required due to the fast oxidation of titanium(III) species to titanium(IV) (*Scheme 121*). Importantly, it was also verified that conventional nucleophilic enolates such as sodium enolates do not react with TEMPO.[75]



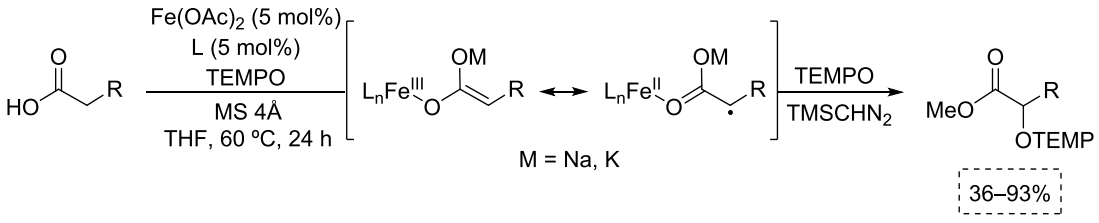
Scheme 121. Proposed mechanism for the aminoxylation of titanium enolates

Some examples in the literature describe a catalytic version of similar transformations. In 2017, YAZAKI and OHSHIMA reported the aminoxylation of acylpyrazole derivatives under catalytic conditions.[167] In their work, an aerobic atmosphere was required to generate the active copper catalyst that acted as both: Lewis acid and Brønsted base (*Scheme 122*).



Scheme 122. Catalytic aminoxylation of acylpyrazoles

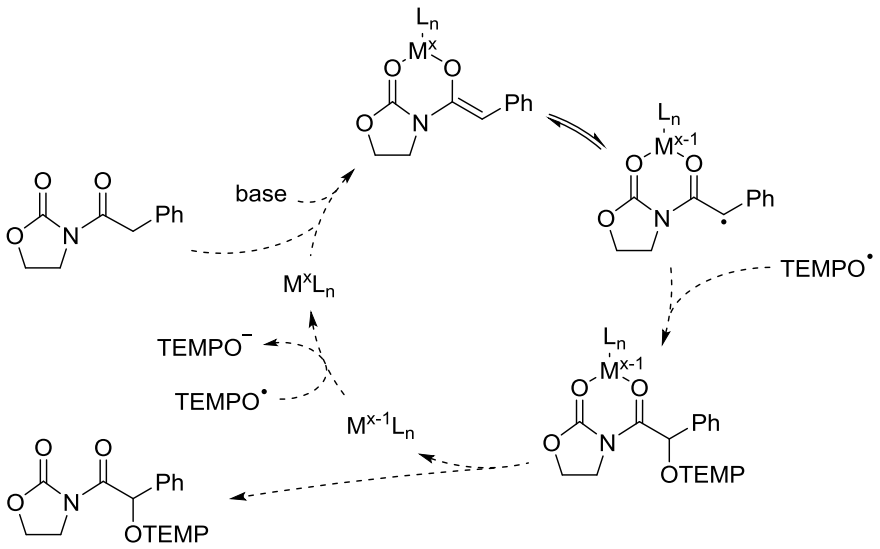
Later, in 2020, the same authors published similar work in which carboxylic acids are directly oxidized with TEMPO.[168] This time, a combination of a redox active iron catalyst and alkali carboxylates (present within the molecular sieves) generates a heterobimetallic endiolate species, which becomes a highly reactive biradical species that recombines with TEMPO to afford the aminoxylated product (*Scheme 123*).



Scheme 123. Catalytic aminoxylation of carboxylic acids

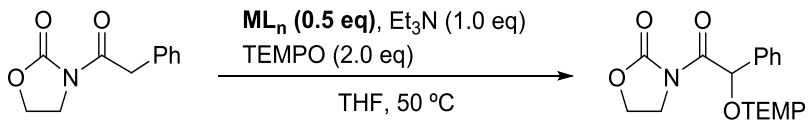
Our previous experience and the abovementioned examples were used to set the starting point of the screening of a substitute for titanium (*Scheme 124*). It was envisaged

that other transition metals (M^x) could coordinate to the *N*-acyl oxazolidinone in a similar fashion to titanium tetrachloride in order to achieve a soft enolization with a tertiary amine. Then, if a suitable substitute was found, the enolate might participate in a valence tautomerism equilibrium, similar to titanium enolates, and it would then react with the free radical TEMPO to afford the aminoxylated product. Considering this, another oxidant should be present in order to regenerate the initial oxidation state of the aforementioned metal (M^{x-1}) to close the catalytic cycle, therefore, an extra equivalent of TEMPO was added to the reaction mixture. A putative catalytic cycle of such a transformation is represented in *Scheme 124*.



Scheme 124. Initial hypothesis

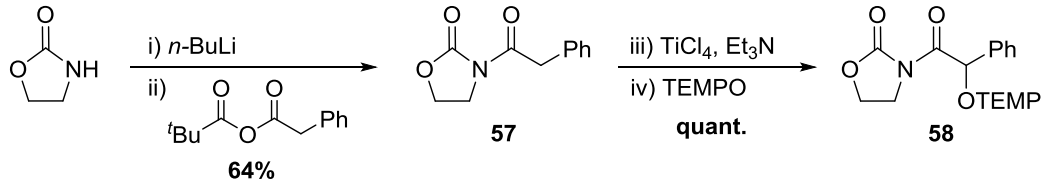
According to such a plan, the reaction conditions to perform the screening of a titanium substitute were defined (*Scheme 125*). Firstly, as for titanium enolates, triethylamine was chosen as a base to form the enolate. Secondly, two equivalents of TEMPO were required to obtain full conversion if a catalytic cycle was in action. Finally, tetrahydrofuran and moderate temperatures were initially selected following the YAZAKI and OHSHIMA examples.



Scheme 125. Experimental conditions to screen new transition metals

2.2 Preparation of starting materials

Parallel to the choice of the conditions for the screening, a method to rapidly analyze the results would be welcomed. To perform a ^{1}H NMR of each test, tedious aqueous work-ups were required so, to avoid them, the results were evaluated by direct HPLC-MS analysis of the reaction crudes instead. In order to confirm the formation of the expected product, 1,3-oxazolidinone was acylated following a standard procedure to obtain **57** in good yields, which would be used as model substrate to conduct the screening experiments. Then, *N*-phenylacetyl oxazolidinone **57** was aminoxylated with TEMPO through the formation of a titanium enolate as previously described (*Scheme 126*)[76] to quantitatively yield a racemic mixture of **58** that would be used as a standard.



i) *n*-BuLi (1.3 eq), THF, –78 °C, 15 min; ii) *t*BuCOOCOCH$_2$Ph (1.3 eq), –78 °C to rt, 2 h; iii) $TiCl_4$ (1.1 eq), Et_3N (1.1 eq), DCM, 0 °C, 40 min; ii) TEMPO (2.1 eq), rt

Scheme 126. Preparation of *N*-acyl oxazolidinone and a standard of the product

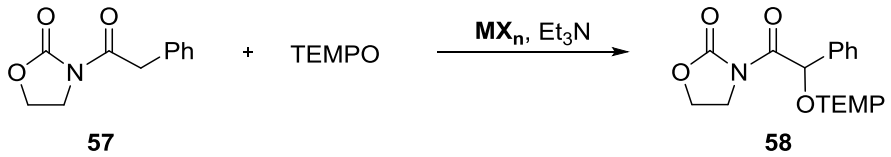
HPLC-MS chromatographic analysis of the starting material **57** and the product **58** were performed to characterize their retention time. Additionally, a calibration line was measured using **57** and **58** to calculate approximate proportions of these species in the crude mixture. For further details see the Experimental Section.

2.3 Screening results

Screening of metal compounds

A wide range of copper, cobalt, and iron salts were initially screened. We were pleased to observe that copper(II) acetate, which was soluble in the reaction conditions, readily afforded a significant amount of aminoxylated product (*entry 1, Table 33*). On the contrary, other copper(II) salts gave none or very poor results (*entries 2-4, Table 33*). Similar positive results were obtained with copper(I) acetate (*entry 5, Table 33*) since TEMPO could oxidize copper(I) to copper(II). Importantly, other copper(I) salts did not give any product (*entries 6-8, Table 33*). For instance, copper(I) triflate reacted with TEMPO to give a deep green product, even before the solvent was added to the mixture.

Other metals did not give as good results, and no product was observed from cobalt(II), iron(II) or iron(III) compounds tested (*entries 9-13, Table 33*).



57 **58**

MX_n (0.5 eq), Et_3N (1.0 eq), TEMPO (2.0 eq), THF, 50 °C, 16 h

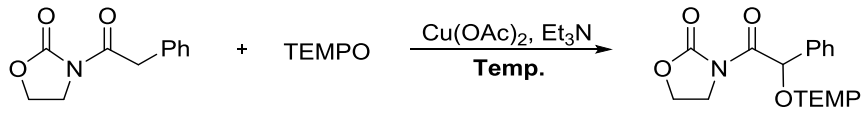
Entry	M	MX_n	Solubility	Conversion (HPLC-MS)
1	Cu^{II}	$Cu(OAc)_2$	✓	41%
2		$CuCl_2$	×	-
3		$CuBr_2$	✓	-
4		$Cu(acac)_2$	×	<10%
5	Cu^{I}	CuOAc	×	35%
6		CuCl	×	-
7		CuBr	~	-
8		CuOTf	✓	-
9	Co^{II}	$CoCl_2$	~	-
10		$Co(OAc)_2$	×	-
11	Fe^{II}	$Fe(OAc)_2$	×	-
12	Fe^{III}	$FeCl_3$	×	-
13		$Fe(acac)_3$	✓	-

Table 33. Screening of metal salts and complexes

The encouraging results obtained with copper acetates triggered a further search for better and milder conditions. For that, copper(II) acetate was selected.

Screening of the temperature

Once the salt was selected, a small screening of temperature was performed. Indeed, a rise of the temperature to 70 °C afforded a great conversion (*entry 1, Table 34*). On the contrary, temperatures below 50 °C yielded poor conversions (*entries 3 and 4, Table 34*). After this screening, 70 °C was chosen as the temperature for further experiments.



57 **58**

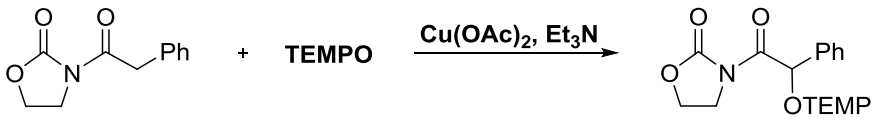
$Cu(OAc)_2$ (0.5 eq), Et_3N (1.0 eq), TEMPO (2.0 eq), THF, **temp.**, 16 h

Entry	Temperature	Conversion (HPLC-MS)
1	70 °C	>90%
2	50 °C	41%
3	rt	<10%
4	0 °C	<10%

Table 34. Temperature screening

Blanks

Before any other conditions were assessed, some blank experiments were carried out for a better understanding of the reaction and to test our hypothesis. First the catalyst was studied; a blank reaction with no copper acetate gave no product at all (*entry 1, Table 35*), which proved that the catalyst is required, and it may have an impact in the generation of the enolate. Then, a reaction with a 10 mol% of catalyst loading was set up, which, as predicted, gave lower conversion than 50 mol% (*entries 2 and 3, Table 35*). However, to appreciate better the changes in the conversion results, 10 mol% was selected for the following experiments, since a 50 mol% loading afforded almost quantitative conversions. Then, the amount of TEMPO was studied. A second equivalent of TEMPO was needed to reoxidize the catalyst to its original oxidation state. However, less equivalents or more equivalents of TEMPO did not change the conversion results (*entries 4-6, Table 35*). It was then rationalized that small conversions of around 25% would leave enough equivalents of unreacted TEMPO, which could be responsible for the oxidation of the catalyst. Hence, as an exception, the catalyst loading was increased again to 50 mol%. In this case, fewer equivalents of TEMPO gave a significantly lower conversion (*entries 7 and 8, Table 35*). That would match with the hypothesis that TEMPO not only combines with the enolate, but it also oxidizes copper(I).



57 58

$Cu(OAc)_2$ (0.5 eq), **Et_3N (1.0 eq)**, **TEMPO (2.0 eq)**, THF, 70 °C, 16 h

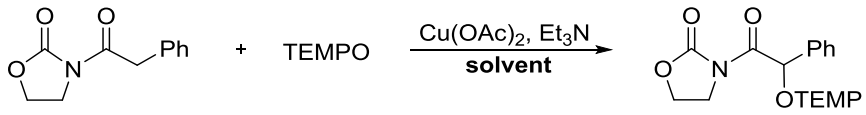
Entry	Item	$Cu(OAc)_2$	Et_3N	TEMPO	Conversion (HPLC-MS)
1		×			-
2	$Cu(OAc)_2$	10%	1.0 eq	2.0 eq	23%
3		50%			>90%
4				1.0 eq	24%
5	TEMPO	10%	1.0 eq	2.0 eq	23%
6				3.0 eq	25%
7	TEMPO	50%	1.0 eq	1.0 eq	63%
8				2.0 eq	>90%
9			-		<10%
10	Et_3N	10%	1.0 eq	2.0 eq	23%
11			2.0 eq		27%

Table 35. Blank experiments

Finally, the impact of the base was assessed; an absence of base gave really poor conversions (*entry 10, Table 35*), which matches the hypothesis because since the enolate could not be formed. Instead, a higher amount of base did not have any impact on the results (*entry 11, Table 35*).

Solvent screening

The screening of conditions was continued by assessing the solvent. In comparison to tetrahydrofuran, acetonitrile gave much better conversions (*entry 2, Table 36*). Other polar and non-protic solvents such as 1,2-dichloroethane, dimethylformamide, dimethyl sulfoxide or ethyl acetate gave a range of conversions between the first two (*entries 3-6, Table 36*). Isopropanol was also tested, it gave low conversions likely given that it is a protic solvent, thus, incompatible with the formation of an enolate (*entry 7, Table 36*). Finally, it was observed that the HPLC-MS spectrum of the reaction crude in acetonitrile did not show any TEMPO left. Therefore, the same reaction was repeated using three equivalents of the free radical instead, as a result, almost quantitative conversions were achieved (*entry 8, Table 36*). Therefore, acetonitrile and three equivalents of TEMPO were used for further experiments.



57 **58**

$Cu(OAc)_2$ (0.1 eq), Et_3N (1.0 eq), TEMPO (2.0 eq), **solvent**, 70 °C, 16 h

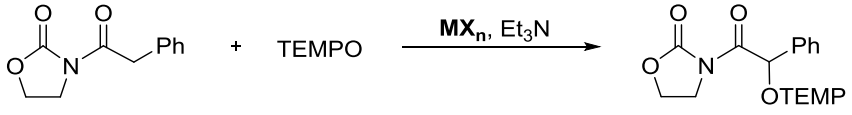
Entry	Solvent	Conversion (HPLC-MS)
1	THF	23%
2	ACN	57%
3	DCE	25%
4	DMF	35%
5	DMSO	39%
6	EtOAc	41%
7	IPA	<10%
8[a]	ACN	>90%

[a]3.0 eq of TEMPO were used.

Table 36. Solvent screening

Reassessment of other salts in acetonitrile

At these early stages of the project, we deemed it necessary to check if other salts would show reactivity when acetonitrile was used. Therefore, selected examples were repeated; this time, copper(II) chloride showed some reactivity while it had not in THF (*entry 1, Table 37*). Then copper(II) acetylacetonate showed largely better results than those obtained with THF (*entry 2, Table 37*). Finally, cobalt(II) acetate gave poor conversion by HPLC-MS (*entry 3, Table 37*). Although these results obtained with acetonitrile were better in all the cases, especially for copper acetylacetonate, the conversion obtained with copper acetate was still better (*entry 8, Table 36*). Consequently, no changes were applied after these tests.



57 **58**

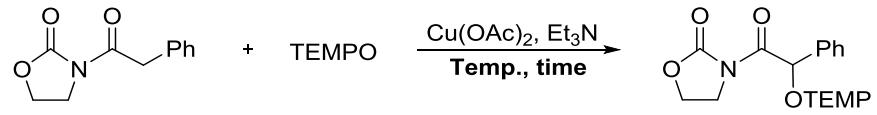
MX_n (0.5 eq), Et_3N (1.0 eq), TEMPO (2.0 eq), **ACN**, 70 °C, 16 h

Entry	M	MX_n	Soluble	Conversion (HPLC-MS)	in THF
1	Cu^{II}	$CuCl_2$	~	14%	-
2		$Cu(acac)_2$	✓	83%	<10%
3	Co^{II}	$Co(OAc)_2$	×	<10%	-

Table 37. Reassesment of other salts (MX_n) in acetonitrile

Reassessment of temperature and time

Taking in consideration a future stereoselectivity challenge, a lower temperature would be highly convenient. Since acetonitrile gave almost quantitative conversions at 70 °C, a screening of lower temperatures was performed. It was found that quantitative conversions were also achieved if the temperature was lowered to 40 ºC (*entries 1-3, Table 38*). At 30 ºC good conversions were also obtained, but at lower temperatures the results dropped significantly (*entries 4 and 5, Table 38*). Finally, the reaction at room temperature was repeated for longer reaction times, and greater conversions were measured by HPLC-MS. However, the reaction crude was messier than in previous examples since other peaks appeared in the spectrum (*entry 6, Table 38*).



57 **58**

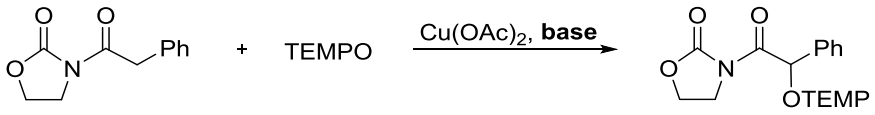
$Cu(OAc)_2$ (0.1 eq), Et_3N (1.0 eq), TEMPO (3.0 eq), ACN, **Temp.**, **time**

Entry	T	time	Conversion (HPLC-MS)
1	70 °C	16 h	>90%
2	50 °C	16 h	>90%
3	40 °C	16 h	>90%
4	30 °C	16 h	83%
5	rt	16 h	29%
6	rt	72 h	82%

Table 38. Reassessment of temperature and time

Screening of the base

Finally, other bases were examined for the formation of the enolate. These experiments were performed at 30 °C, a temperature at which the conversion was not complete, to better appreciate differences in the results. As shown in *Table 39*, neither DIPEA nor lutidine afforded competitive results compared to triethylamine.



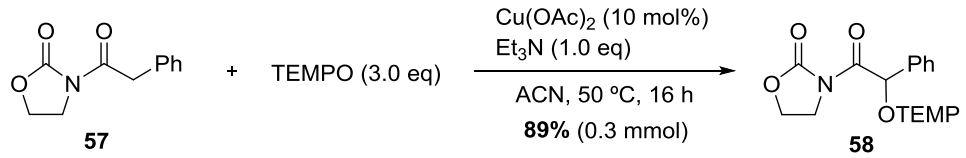
57 **58**

$Cu(OAc)_2$ (0.1 eq), **base** (1.0 eq), TEMPO (3.0 eq), ACN, 30 °C, 16 h

Entry	base	Conversion (HPLC-MS)
1	Et_3N	83%
2	*i*-Pr_2NEt	18%
3	2,6-lutidine	<10%

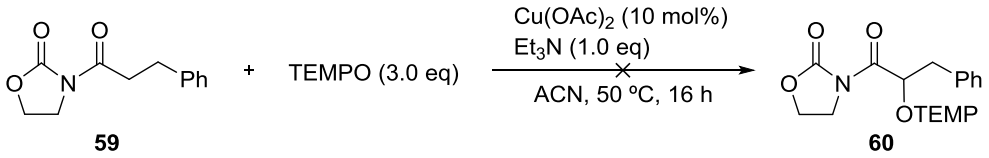
Table 39. Base screening

After the screening of different conditions, it was concluded that the best choice involved using 10 mol% of copper(II) acetate, three equivalents of TEMPO and one equivalent of triethylamine, acetonitrile as solvent and stirring the mixture at 50 °C for 16 h. These conditions were scaled up to 0.3 mmol, which allowed the purification of the product with an isolated yield of 89%, which nicely matched with the conversion established by HPLC-MS (*Scheme 127*).



Scheme 127. Aminoxylation of **57**

Finally, another *N*-acyl oxazolidinone was prepared and used under the same conditions. Noteworthy, in this case the formation of the enolate was more challenging because the phenyl group in the α-position was shifted by the addition of a methylene group. Unfortunately, no product formation was observed (*Scheme 128*). Further studies should thus be performed to enable this transformation and stronger bases or the addition of ligands to coordinate to copper should be brought into play. Nonetheless, these are out of the reach of this thesis.

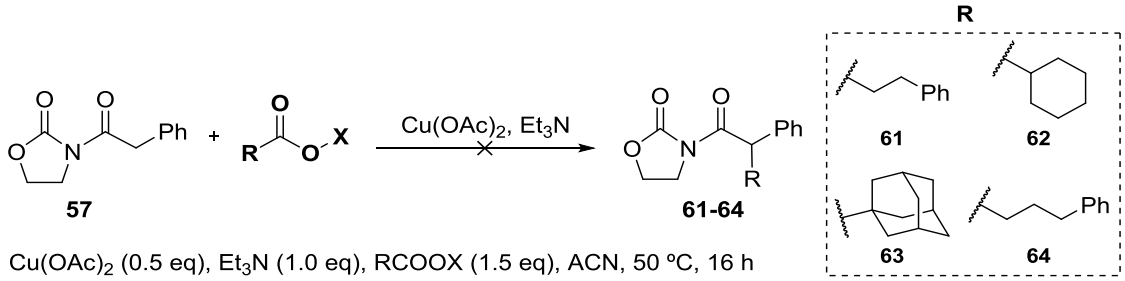


Scheme 128. Aminoxylation of **59**

2.4 Other radical sources

Finally, the good results obtained for the aminoxylation of *N*-phenylacetyl oxazolidinone **57** with copper encouraged us to find the new boundaries of this catalytic approach. Indeed, we envisaged that if copper and titanium enolates showed a similar behavior with TEMPO, copper enolates might also engage radical alkylation transformations as titanium enolates do. Therefore, the conditions found in the previous section were used to seek the copper catalytic alkylation of *N*-acyl oxazolidinones. For that, a small screening of alkyl radical sources (peroxides, peresters, NHP esters...) that had already been used throughout the course of the thesis was performed. During the screening, redox active species that rendered differently substituted alkyl radicals were used. For instance, a primary diacyl peroxide was tested, while the *tert*-butyl peresters screened would afford secondary and tertiary alkyl radicals (*entries 1-3, Table 40*). Then, a primary NHP ester was tested as well as the more active chlorinated analogue (*entries 4 and 5, Table 40*). Additionally, a tertiary chlorinated NHP ester was also examined (*entry 6, Table 40*). Finally, an example of a primary thiocarbamate was essayed (*entry 7, Table 40)*. Unfortunately, none of such substrates afforded any trace of alkylated

product. That is probably because the putative copper enolate is unable to provoke the reductive breaking of the species tested during the screening.

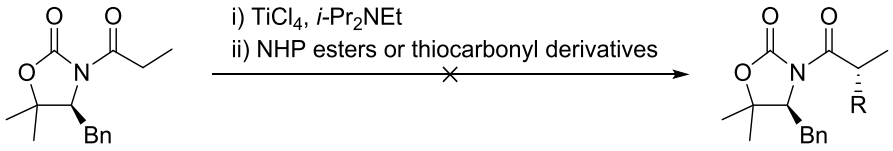


Entry	Radical source	RCOOX	R	X	Product
1	peroxide	**2d**	2-phenylethyl	OCOR	**61**
2	perester	**40j**	ciclohexyl	O^{t}Bu	**62**
3		**40n**	adamantyl		**63**
4	NHP ester	**50d**	2-phenylethyl	NPhth	**61**
5	NHP ester (Cl_4)	**51d**	2-phenylethyl	NPhth(Cl_4)	**61**
6		**51n**	adamantyl		**63**
7	thiocarbonate	**54**	3-phenylpropyl	different structure	**64**

Table 40. Screening of other radical sources

3. Outline

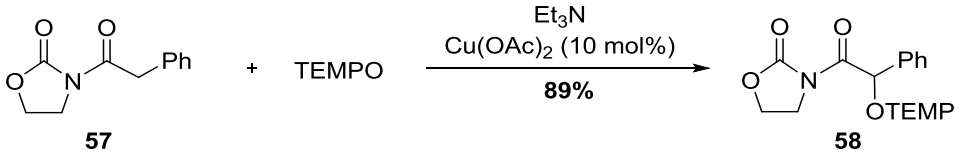
In the first part of this chapter, the search for a redox active species that could render alkyl radicals to alkylate titanium enolates was undertaken. First, the photochemical reduction of *N*-hydroxyphthalimide esters was attempted without any success. Neither the titanium enolate nor an additional low-valent metal were able to reduce an array of NHP esters. Then, the alkylation of titanium enolates was attempted with thiocarbonyl derivatives, as in BARTON-MCCOMBIE decarboxylation, but no reaction was observed either. Therefore, no other species were found that could react with titanium enolates in a similar fashion to diacyl peroxides or *tert*-butyl peresters (*Scheme 129*).



Scheme 129. Attempted alkylation of titanium enolates with other redox active species

On the other hand, the search for an enolate that reacted similarly to titanium enolates in terms of radical reactivity was attempted. For that, TEMPO was used as a probe throughout the screening of metal complexes to produce the desired enolate with

a biradical character. Finally, it was found that copper acetate afforded the corresponding aminoxylated adduct. From there, a comprehensive analysis of temperature, solvent, and base was performed. At the end, the radical aminoxylation of an *N*-acyl oxazolidinone was completed using catalytic amounts of copper acetate in excellent yields (*Scheme 130*).

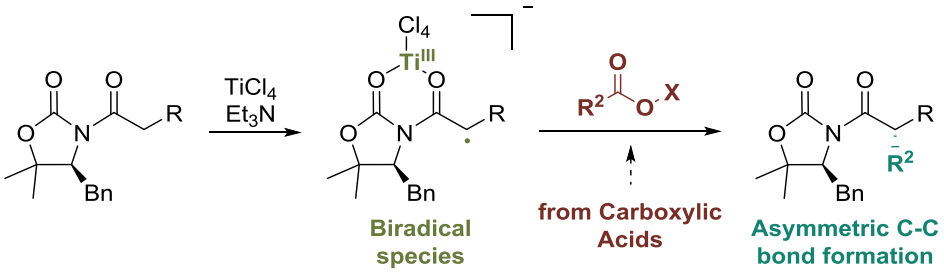


57 **58**

Scheme 130. Catalytic aminoxylation of *N*-Acyl oxazolidinone

SUMMARY AND CONCLUSIONS

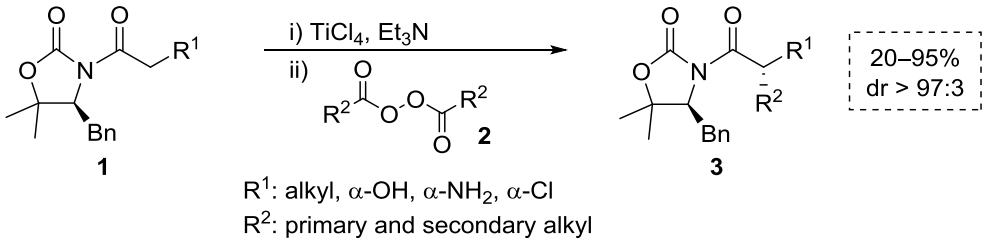
Considering that radical approaches have proven to be an appealing alternative to heterolytic methodologies, the radical-like reactivity of titanium enolates has been exploited to develop new α-alkylation methodologies that allow the introduction of a wide range of alkyl groups. Thus, a narrow scope of alkylating agents for reported methods, which are mainly restricted to privileged structures, has been fulfilled. For that, while other approaches use alkyl halides as electrophiles, in this thesis, alkyl groups have been introduced from carboxylic acids as raw materials (*Scheme 131*).



Scheme 131. Radical alkylation of titanium enolates with carboxylic acid derivatives

In **Chapter I**, the stereoselective alkylation of titanium enolates with diacyl peroxides was described. During these studies, experimental evidence led to a second optimization of the alkylation reaction. New conditions were found so that the diastereoselectivity of the reaction was maintained while the conversion was dramatically increased, which resulted in a remarkable improvement in results. The configuration of the new stereocenter formed was confirmed by X-ray analysis. Importantly, a mechanistic proposal supported by computational studies was described. Finally, the applicability of the alkylation reaction was proved by the short synthesis of arundic acid *via* two different pathways.

In summary, this Chapter describes the stereoselective radical alkylation of titanium enolates with diacyl peroxides under mild conditions. The resultant procedure enables the insertion of primary as well as secondary alkyl groups, which was not available by other reported methods (*Scheme 132*).

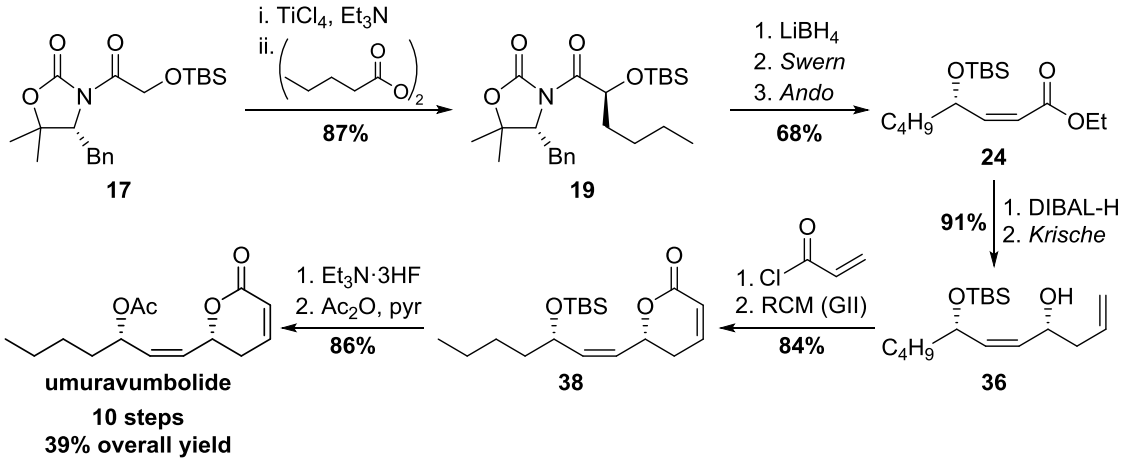


Scheme 132. Alkylation of titanium enolates with diacyl peroxides

The results in chapter I were published in:

"Stereoselective Decarboxylative Alkylation of Titanium(IV) Enolates with Diacyl Peroxides", Gómez-Palomino, A.; Pérez-Palau, M.; Romea, P.; Urpí, F.; Del Olmo, M.; Hesse, T.; Fleckenstein, S.; Gómez-Bengoa, E.; Sotorríos, L; Font-Bardia, M. *Org. Lett.* **2020**, 22, 199.

Chapter II describes the total synthesis of umuravumbolide, a substituted α-pyrone that is found in a medicinal plant in Central Africa. Key steps of the synthesis include the previously studied stereoselective alkylation of a glycolate derivative through the formation of a titanium enolate that rendered the oxygen containing stereocenter in the side chain with a great diastereoselectivity. An Ando olefination was used to selectively form the *Z*-double bond. Then, an asymmetric Krische allylation allowed the introduction of the second stereocenter in a highly stereocontrolled catalytic transformation. The rest of the pyrone was synthetized by acylation with acryloyl chloride followed by ring-closing metathesis. The total synthesis consisted of 10 steps, which included highly diastereoselective transformations that allowed the obtention of umuravumbolide with an outstanding overall yield of 39% (*Scheme 133*).



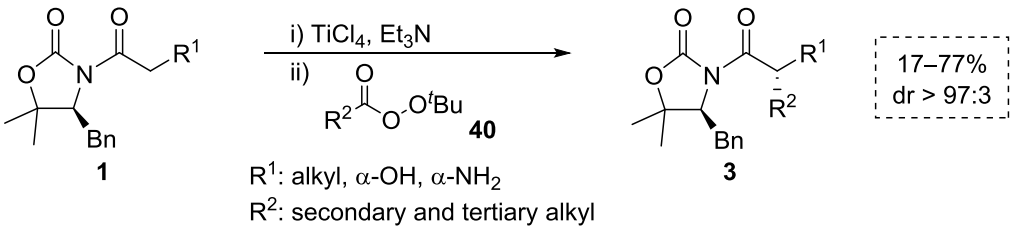
Scheme 133. Total synthesis of umuravumbolide

The results in chapter II are under revision in:

"An Optimized Asymmetric Synthesis of Umuravumbolide", Pérez-Palau, M.; Balaguer-García, E.; Romea, P.; Urpí, F. *ACS Omega*.

In **Chapter III** the alkylation of titanium enolates with *tert*-butyl peresters was investigated. Following a wide optimization of the reaction conditions, moderate to excellent results were achieved. Furthermore, the scope of the peresters for the alkylation was examined as well as the enolates suitable for such transformation. Again, the configuration of the new stereocenter formed was confirmed by X-ray analysis. The cleavage of the chiral auxiliary resulted challenging owing to the high steric hindrance of the alkylated products. Finally, a mechanism was proposed, which is similar to that of the alkylation with peroxides and it was also supported by computational studies.

This developed procedure permits the alkylation of titanium enolates with tertiary and secondary alkyl groups under mild conditions and great diastereoselectivities (*Scheme 134*). Yields for the secondary alkylation are similar to those achieved with diacyl peroxides. Moderate to good yields are achieved for the tertiary alkylation. All in all, this method compliments the alkylation described in Chapter I in terms of suitable alkylating agents.

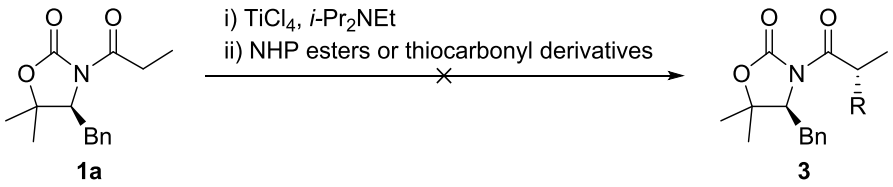


Scheme 134. Alkylation of titanium enolates with tert-butyl peresters

The results in Chapter III have been published in:

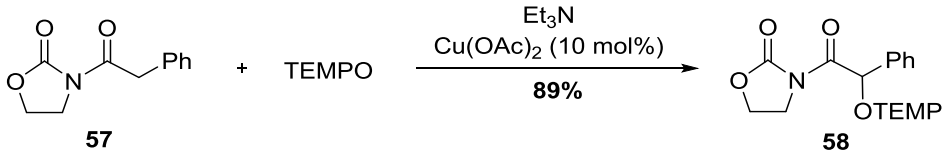
"Stereoselective Alkylation of Chiral Titanium(IV) Enolates with *tert*-Butyl Peresters", Pérez-Palau, M.; Sanosa, N.; Romea, P.; Urpí, F.; López, R.; Gómez-Bengoa, E.; Font-Bardia, M. *Org. Lett.* **2021**, 23, 8852.

In **Chapter IV** a surrogate for diacyl peroxides and *tert*-butyl peresters was investigated. Unexpectedly, neither NHP esters nor thiocarbonyl derivatives afforded alkylated products (*Scheme 135*). Further seeking for other redox active species could be continued in the future, for example with Barton esters or aryliodine (III) carboxylates. However, the final efforts were focused on the substitution of titanium aiming to find a metal whose enolates could undergo radical reactions under catalytic premises.



Scheme 135. Unsuccessful alkylation of titanium enolates with other redox active species

Indeed, the catalytic aminoxylation of the *N*-acyl oxazolidinone **57** was achieved with copper(II) acetate. Preliminary experiments suggested that such a transformation may proceed through a copper enolate, which would manifest radical character by reacting with the free radical TEMPO. The assessment of solvent, temperature and base allowed the isolation of the aminoxylated product in an excellent yield (*Scheme 136*).



Scheme 136. Catalytic aminoxylation of copper enolates

In the near future, the next step would be to attempt a stereoselective version of the aminoxylation reaction by the addition of chiral ligands, for instance the bis(oxazoline)-type ligands. Finally, the effect of ligands in copper enolates should be studied to see if the redox properties of the latter can be modulated, thus allowing copper enolates to act as reducing agents against redox active species such as peroxides or NHP esters. Then, the dream for a catalytic asymmetric alkylation of carboxylic acid derivatives might be a reality (*Scheme 137*).

Scheme 137. Future perspectives for the catalytic alkylation of carboxylic acid derivatives

EXPERIMENTAL SECTION

Table of Contents – Experimental Section

General methods

Unless otherwise noted, reactions were conducted in oven-dried glassware under inert atmosphere of N_2 with anhydrous solvents. The solvents and reagents were dried and purified when necessary according to standard procedures. Commercially available reagents were used as received.

Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates and analyzed by UV (254 nm) and stained with phosphomolybdic acid or $KMnO_4$; column chromatographies were carried under low pressure (flash) conditions and performed on SDS silica gel 60 (35–70 μm). Eluents are indicated in brackets in each case. R_f values are approximate.

Melting points (Mp) were determined with a Stuart SMP10 apparatus and are uncorrected.

Specific rotations ($[\alpha]_D^{20}$) were determined at 20 °C on a Perkin-Elmer 241 MC polarimeter equipped with a sodium lamp (λ 589 nm, D-line). Concentration (g/dL) and solvent used are indicated in brackets.

IR spectra (Attenuated Total Reflectance, ATR) were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer and only the more representative frequencies (ν) are reported in cm^{-1}.

^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded at room temperature on a Varian Mercury 400, a Bruker 400 Avance III or a Bruker 500 Avance Neo. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ 0.00 for ^1H NMR) and $CDCl_3$ (δ 77.0 for ^{13}C NMR). Data are reported as follows: chemical shift (number of protons, multiplicity, coupling constant(s)); multiplicity is reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; hept, heptuplet; oct, octet; m, multiplet; br, broad signal (and their corresponding combinations); coupling constants (*J*) are quoted in Hz. Where necessary, 2D techniques (COSY, HSQC) were also used to assist on structure elucidation.

High resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

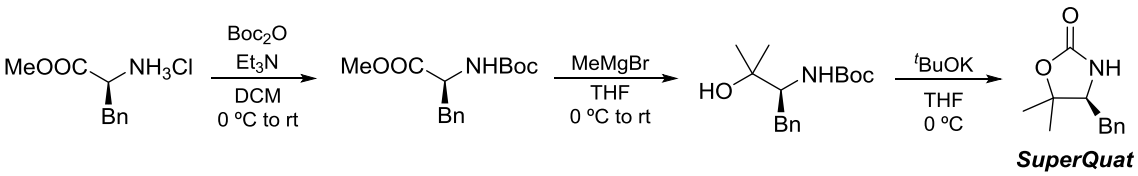
High performance liquid chromatography – mass spectra (HPLC-MS) chromatograms were obtained with a Waters Alliance HT 2795 coupled with a photodiode array Waters PDA 2996 and a Waters ZQ 2000 spectrometer.

Preparation of Starting Materials

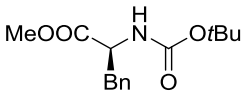
1. Preparation of Chiral Auxiliaries

(*S*)-4-Benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (*SuperQuat*)

It was prepared according to the procedure described by Davies.[169]

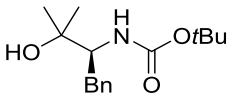


Methyl (*S*)-*N*-*tert*-butoxycarbonylphenylalaninate



Neat Et_3N (6.6 mL, 47 mmol) was added dropwise to a solution of methyl (*S*)-phenylalaninate hydrochloride (10.22 g, 47 mmol) in DCM (75 mL) at 0 °C and the resultant mixture was stirred for 10 min. A solution of Boc_2O (10.35 g, 47 mmol) in DCM (20 mL) was added via *cannula*. The reaction mixture was stirred for 10 min at 0 °C, allowed to warm to rt and stirred overnight. The reaction was quenched with 0.5 M citric acid (80 mL). The layers were separated, and the organic layer was washed with 0.5 M citric acid (2 × 80 mL), brine (80 mL), and dried with anhydrous $MgSO_4$. The solution was concentrated to afford methyl (*S*)-*N*-*tert*-butoxycarbonylphenylalaninate (12.72 g, 45 mmol, 96% yield) as a yellow oil.

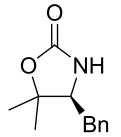
(*S*)-3-Amino-*N*-*tert*-butyloxocarbonyl-2-methyl-4-phenyl-2-butanol



A 3 M solution of MeMgBr in Et_2O (100 mL, 0.3 mol) was added dropwise to a solution of methyl (*S*)-*N*-*tert*-butoxycarbonylphenylalaninate (20.70 g, 74 mmol) in THF (100 mL) at 0 °C and the resulting mixture was stirred at rt for 2.5 days. The reaction mixture was quenched at 0 °C with 40 mL of MeOH (**CAUTION**: slow addition, release of gas) and a few minutes later water (15 mL) was added. The mixture was filtered through Celite® and eluted with EtOAc (50 mL). The solvent of the filtrate was evaporated under reduced pressure and the residue was dissolved in Et_2O (100 mL). The solution was dried with anhydrous $MgSO_4$ and filtered through Celite®. The solvent of the filtrate was evaporated and the residue was dissolved in DCM, dried again with

anhydrous $MgSO_4$ and concentrated to give (*S*)-3-amino-*N*-*tert*-butyloxocarbonyl-2-methyl-4-phenyl-2-butanol (15.98 g, 57 mmol, 77%) as a white solid.

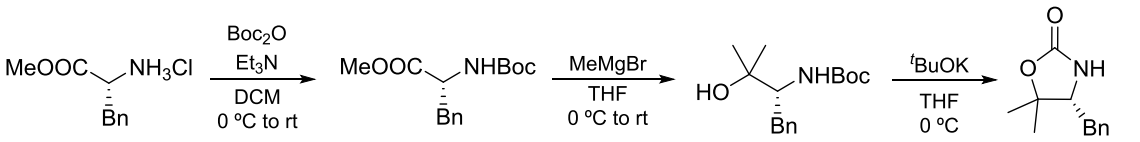
(*S*)-4-Benzyl-5,5-dimethyl-1,3-oxazolidin-2-one



SuperQuat

Solid ^{t}BuOK (4.46 g, 40 mmol) was added in one portion to a solution of (*S*)-3-amino-*N*-*tert*-butyloxocarbonyl-2-methyl-4-phenyl-2-butanol (9.25 g, 33 mmol) in THF (110 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and quenched with 20 mL of sat NH_4Cl (slow addition). The mixture was concentrated under reduced pressure and the residue was partitioned between water and EtOAc (50 mL each). The aqueous layer was extracted with further EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (40 mL) and dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by flash column chromatography (50:50 hexanes/EtOAc) to the title compound (***SuperQuat***) (6.37 g, 31 mmol, 94% yield, 69% overall yield) as a white solid. **Mp** 60–62 °C; $\mathbf{R_f}$ (98:2 hexanes/EtOAc) 0.4; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –98.9 (*c* 1.0, $CHCl_3$), [lit.[1] $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –103.5 (*c* 1.0, $CHCl_3$)]; **IR** (ATR) ν br 3500–3100, 2981, 1740, 1389, 1373, 1282, 1190 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36–7.17 (5H, m, Ar<u>H</u>), 5.18 (1H, br s, N<u>H</u>), 3.70 (1H, dd, *J* = 10.5, 4.1 Hz, C<u>H</u>N), 2.83 (1H, dd, *J* = 13.4, 4.1 Hz, C<u>H</u>$_x$H$_y$Ph), 2.69 (1H, dd, *J* = 13.4, 10.5 Hz, CH$_x$<u>H</u>$_y$Ph), 1.46 (3H, s, C<u>H</u>$_3$), 1.45 (3H, s, C<u>H</u>$_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 157.9 (C), 136.8 (C), 129.0 (CH), 128.8 (CH), 127.1 (CH), 83.1 (C), 63.0 (CH), 37.0 (CH_2), 27.5 (CH_3), 21.9 (CH_3).

(*R*)-4-Benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (*entSuperQuat*)

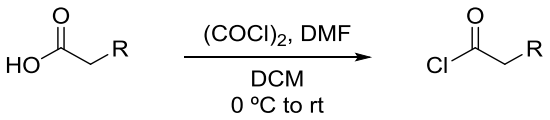


entSuperQuat

It was prepared following the same procedure as for ***SuperQuat*** from methyl (*R*)-phenylalaninate hydrochloride with a 53% overall yield. $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ +98.2 (*c* 1.0, $CHCl_3$).

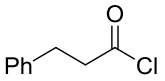
2. Preparation of Acyl Chlorides

General Procedure 1



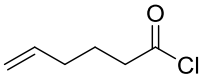
Two drops of DMF and $(COCl)_2$ (0.61 mL, 7.2 mmol) were added dropwise to a solution of the corresponding carboxylic acid (6.0 mmol) in DCM (20 mL) at 0 °C. The reaction mixture was stirred overnight at rt. The volatiles were removed in *vacuo* obtaining the acyl chloride, which was used in the next step without further purification.

3-Phenylpropanoyl chloride



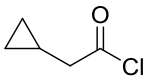
It was prepared following General Procedure 1 from 3-phenylpropanoic acid (901 mg, 6.0 mmol). 3-Phenylpropanoyl chloride was obtained quantitatively and used in the next step without further purification. Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.19 (5H, m, Ar$\underline{H}$), 3.21 (2H, t, J = 7.5 Hz, COC$\underline{H}_2$), 3.02 (2H, t, J = 7.5 Hz, PhC$\underline{H}_2$).

5-Hexenoyl chloride



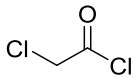
It was prepared following General Procedure 1 from 5-hexenoic acid (0.46 mL, 3.9 mmol) and $(COCl)_2$ (0.40 mL, 4.7 mmol). 5-Hexenoyl chloride was obtained quantitatively and used in the next step without further purification. Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.75 (1H, ddt, J = 17.0, 10.2, 6.7 Hz, C$\underline{H}$=CH_2), 5.09–5.01 (2H, m, CH=C$\underline{H}_2$), 2.90 (2H, t, J = 7.3 Hz, COC$\underline{H}_2$), 2.16–2.11 (2H, m, C$\underline{H}_2$CH=CH_2), 1.86–1.79 (2H, m, $COCH_2C\underline{H}_2$).

Cylcopropylacetyl chloride



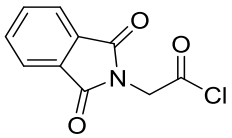
It was prepared following General Procedure 1 from cyclopropylacetic acid (0.38 mL, 3.9 mmol) and $(COCl)_2$ (0.40 mL, 4.7 mmol). Cyclopropylacetyl chloride was obtained almost quantitatively and used in the next step without further purification. Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.78 (2H, d, J = 7.0 Hz, COC$\underline{H}_2$), 1.19–1.06 (1H, m, $CH_2C\underline{H}$), 0.69–0.61 (2H, m, $CH(C\underline{H}_xH_y)_2$), 0.33–0.17 (2H, m, $CH(CH_x\underline{H}_y)_2$).

2-Chloroacetyl chloride



It was prepared following General Procedure 1 from chloroacetic acid (580 mg, 6.1 mmol) and $(COCl)_2$ (0.62 mL, 7.3 mmol). 2-Chloroacetyl chloride was obtained quantitatively and used in the next step without further purification. Colorless oil.

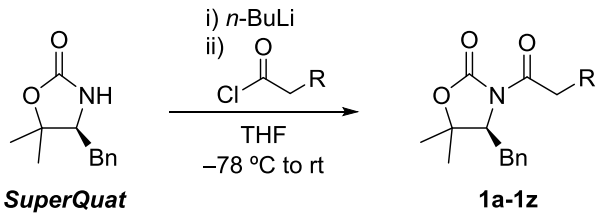
2-Phthalimidoacetyl chloride



It was prepared following General Procedure 1 from phthalimidoacetic acid (821 mg, 4 mmol) and $(COCl)_2$ (406 µL, 4.8 mmol). 2-Phthalimidoacetyl chloride was obtained quantitatively and used in the next step without further purification. Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95–7.90 (2H, m, ArH), 7.82–7.77 (2H, m, ArH), 4.83 (2H, s, CH_2).

3. Preparation of *N*-Acyl Oxazolidinones (1)

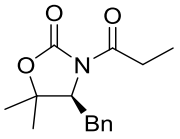
General Procedure 2



SuperQuat **1a-1z**

A 2.5 M solution of *n*-BuLi in hexanes (2.2 mL, 5.5 mmol) was added dropwise to a solution of oxazolidinone ***SuperQuat*** (1.03 g, 5.0 mmol) in THF (25 mL) at −78 °C under nitrogen. The solution was stirred for 15 min and the corresponding acyl chloride (6.5 mmol) was added dropwise. The final mixture was stirred at −78 °C for 20 min, allowed to warm to rt and stirred for 2 h. The reaction mixture was quenched with sat NH_4Cl (10 mL) and concentrated. The residue was partitioned between water and EtOAc (20 mL each). The aqueous layer was extracted with further EtOAc (2 × 20 mL). The combined organic extracts were washed with sat $NaHCO_3$ (50 mL), brine (50 mL), and dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by flash column chromatography to afford the acylated oxazolidinones (**1a-1z**).

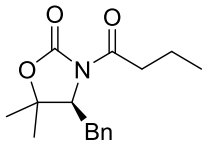
(*S*)-4-Benzyl-5,5-dimethyl-*N*-propanoyl-1,3-oxazolidin-2-one (1a)



1a

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (2.12 g, 10.3 mmol), *n*-BuLi (2.5 M in hexanes, 4.5 mL, 11.3 mmol) and propionyl chloride (1.2 mL, 13.4 mmol). Purification of the crude product by flash column chromatography (90:10 hexanes/EtOAc) afforded **1a** (2.59 g, 9.9 mmol, 96% yield) as a white solid. **Mp** 62–63 °C, [lit.[170] **Mp** 61-62 °C]; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.2; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –40.0 (*c* 1.1, $CHCl_3$), [lit.[170] $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –39.8 (*c* 1.0, $CHCl_3$)]. **IR** (KBr) ν 2977, 2941, 1766, 1702, 1356, 1276, 1231, 1210, 1160, 1112, 1073 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.20 (5H, m, ArH), 4.51 (1H, dd, *J* = 9.5, 4.0 Hz, CHN), 3.15 (1H, dd, *J* = 14.2, 4.0 Hz, CH_xH_yPh), 2.93 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 2.88 (1H, dd, *J* = 14.2, 9.5 Hz, CH_xH_yPh), 1.37 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 1.14 (3H, t, *J* = 7.3 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ174.2 (C), 152.6 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 82.1 (C), 63.4 (CH), 35.3 (CH_2), 29.3 (CH_2), 28.5 (CH_3), 22.2 (CH_3), 8.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438, found: 262.1436.

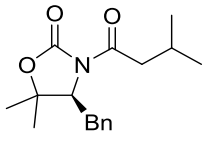
(*S*)-4-Benzyl-*N*-butanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (1b)



1b

It was prepared following General Procedure 2 from butyryl chloride (0.67 mL, 6.5 mmol). Purification of the crude product by flash column chromatography (90:10 hexanes/EtOAc) afforded **1b** (1.24 g, 4.5 mmol, 90% yield) as a white solid. **Mp** 69–71 ºC; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.35; $[\alpha]_D^{22}$ –41.2(*c* 1.0, $CHCl_3$), [lit.[171] $[\alpha]_D^{22}$ –44.6 (*c* 1.0, $CHCl_3$)]; **IR** (ATR) ν 2959, 2928, 1766, 1690 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.21 (5H, m, ArH), 4.51 (1H, dd, *J* = 9.5, 4.0 Hz, CHN), 3.14 (1H, dd, *J* = 14.3, 4.0 Hz, CH_xH_yPh), 2.92–2.84 (3H, m, $COCH_2$, CH_xH_yPh), 1.73–1.61 (2H, m, $COCH_2CH_2$), 1.37 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 0.97 (3H, t, *J* = 7.4 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.4 (C), 152.6 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 82.0 (C), 63.4 (CH), 37.4 (CH_2), 35.3 (CH_2), 28.5 (CH_3), 22.2 (CH_3), 17.7 (CH_2), 13.6 (CH_3); **HRMS** (+ESI): *m/z* calc. for $C_{16}H_{21}NNaO_3$ $[M+Na]^+$: 298.1414, found: 298.1419.

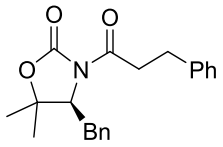
(*S*)-4-Benzyl-5,5-dimethyl-*N*-(3-methylbutanoyl)-1,3-oxazolidin-2-one (1c)



1c

It was prepared following General Procedure 2 from isovaleryl chloride (0.79 mL, 6.5 mmol). Purification of the crude product by flash column chromatography (90:10 hexanes/EtOAc) afforded **1c** (1.39 g, 4.8 mmol, 96% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ –33.9 (*c* 1.1, $CHCl_3$), [lit.[172] $[\alpha]_D^{25}$ –38.0 (*c* 0.5, $CHCl_3$)]; **IR** (NaCl) ν 2959, 2871, 1778, 1699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.18 (5H, m, ArH), 4.52 (1H, dd, *J* = 9.5, 3.9 Hz, CHN), 3.14 (1H, dd, *J* = 14.4, 3.9 Hz, CH_xH_yPh), 2.88 (1H, dd, *J* = 14.4, 9.5 Hz, CH_xH_yPh), 2.83 (1H, dd, *J* = 15.9, 7.0 Hz, $COCH_xH_y$), 2.79 (1H, dd, *J* = 15.9, 6.9, $COCH_xH_y$), 2.22–2.09 (1H, m, $CH(CH_3)_2$), 1.37 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 0.97 (3H, d, *J* = 6.7 Hz, $CHCH_3$), 0.96 (3H, d, *J* = 6.7 Hz, $CHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.9 (C), 152.6 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 82.0 (C), 63.4 (CH), 44.0 (CH_2), 35.4 (CH_2), 28.5 (CH_3), 25.1 (CH), 22.5 (CH_3), 22.4 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{17}H_{24}NO_3$ $[M+H]^+$: 290.1751, found: 290.1751.

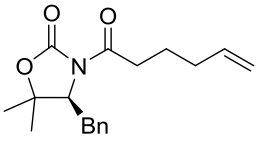
(S)-4-Benzyl-5,5-dimethyl-N-(3-phenylpropanoyl)-1,3-oxazolidin-2-one (1d)



1d

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (616 mg, 3.0 mmol), *n*-BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol) and 3-phenylpropanoyl chloride (1.01 g, 6 mmol). Purification of the crude product by flash column chromatography (90:10 hexanes/EtOAc) afforded **1d** (1.01 g, 2.99 mmol, 99% yield) as a colorless oil. $\mathbf{R_f}$ (85:15 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −27.1 (*c* 1.05, $CHCl_3$), [lit.[171] $[\alpha]_D^{22}$ −27.8 (*c* 1.0, $CHCl_3$)]; **IR** (NaCl) ν 3029, 2982, 2933, 1776, 1699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.14 (10H, m, ArH), 4.49 (1H, dd, *J* = 9.6, 4.0 Hz, CHN), 3.32–3.17 (2H, m, $COCH_2$), 3.12 (1H, dd, *J* = 14.4, 4.0 Hz, $CHCH_xH_yPh$), 3.02–2.88 (2H, m, CH_2CH_2Ph), 2.85 (1H, dd, *J* = 14.4, 9.6 Hz, $CHCH_xH_yPh$), 1.36 (3H, s, CCH_3), 1.31 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.6 (C), 152.5 (C), 140.4 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 126.8 (CH), 126.2 (CH), 82.2 (C), 63.4 (CH), 37.1 (CH_2), 35.2 (CH_2), 30.4 (CH_2), 28.4 (CH_3), 22.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found: 338.1753.

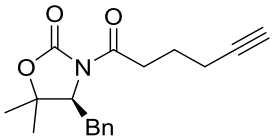
(*S*)-4-Benzyl-*N*-(5-hexenoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1e)



1e

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (616 mg, 3.0 mmol), *n*-BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol) and 5-hexenoyl chloride (517 mg, 3.9 mmol). Purification of the crude product by flash column chromatography (90:10 hexanes/EtOAc) afforded **1e** (858 mg, 2.85 mmol, 95% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −30.9 (*c* 1.7, $CHCl_3$); **IR** (NaCl) ν 3065, 2978, 2936, 1778, 1698 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH), 5.80 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, $CH=CH_2$), 5.06–4.96 (2H, m, $CH=CH_2$), 4.51 (1H, dd, *J* = 9.5, 4.0 Hz, CHN), 3.13 (1H, dd, *J* = 14.3, 4.0 Hz, CH_xH_yPh), 2.94–2.90 (2H, m, $COCH_2$), 2.88 (1H, dd, *J* = 14.3, 9.5 Hz, CH_xH_yPh), 2.14–2.07 (2H, m, $CH_2CH=CH_2$), 1.78–1.69 (2H, m, $COCH_2CH_2$), 1.37 (3H, s, CCH_3), 1.35 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.3 (C), 152.6 (C), 137.8 (CH), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 115.2 (CH_2), 82.1 (C), 63.4 (CH), 35.3 (CH_2), 34.9 (CH_2), 33.0 (CH_2), 28.5 (CH_3), 23.4 (CH_2), 22.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found: 302.1753.

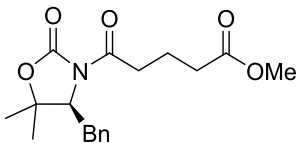
(*S*)-4-Benzyl-3-(5-hexynoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1f)



1f

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (410 mg, 2.0 mmol), *n*-BuLi (2.5 M in hexanes, 1.4 mL, 2.2 mmol) and 5-hexynyl chloride (391 mg, 3.0 mmol). Purification of the crude product by flash column chromatography (90:10 hexanes/EtOAc) afforded **1f** (557 mg, 1.86 mmol, 93% yield) as a white solid. **Mp** 61–62 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ –40.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3289, 2967, 2923, 1761, 1701 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.21 (5H, m, ArH), 4.51 (1H, dd, *J* = 9.2, 4.3 Hz, NCH), 3.12 (1H, dd, *J* = 14.3, 4.3 Hz, CH_xH_yPh), 3.04 (2H, t, *J* = 7.4 Hz, COCH), 2.89 (1H, dd, *J* = 14.3, 9.2 Hz, CH_xH_yPh), 2.28-2.23 (2H, m, $CH_2C{\equiv}CH$), 1.98 (1H, t, *J* = 2.7 Hz, C≡CH), 1.91–1.80 (2H, m, $COCHCH_2$), 1.38 (3H, s, CCH_3), 1.37 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.6 (C), 152.6 (C), 136.8 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 83.4 (C), 82.2 (C), 69.1 (CH), 63.3 (CH), 35.4 (CH_2), 34.3 (CH_2), 28.4 (CH_3), 22.9 (CH_2), 22.2 (CH_3), 17.7 (CH_2); **HRMS** (+ESI): *m/z* calcd. for $C_{18}H_{21}NNaO_3$ $[M+Na]^+$: 322.1414, found: 322.1426.

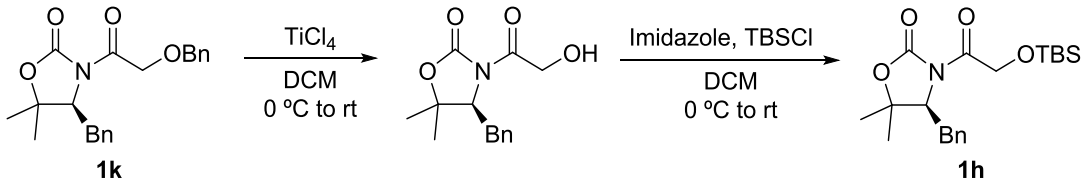
(*S*)-4-Benzyl-*N*-(5-methoxy-5-oxopentanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1g)



1g

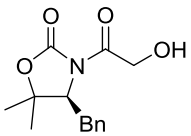
It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (616 mg, 3.0 mmol), *n*-BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol) and methyl glutaryl chloride (0.54 mL, 3.9 mmol). Purification of the crude product by flash column chromatography (85:15 hexanes/EtOAc) afforded **1g** (936 mg, 2.81 mmol, 94% yield) as a white solid. **Mp** 54–56 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ –31.6 (*c* 2.0, $CHCl_3$); **IR** (KBr) ν 2945, 1772, 1724, 1704 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH), 4.51 (1H, dd, *J* = 9.3, 4.2 Hz, CHN), 3.67 (3H, s, OCH_3), 3.13 (1H, dd, *J* = 14.3, 4.2 Hz, CH_xH_yPh), 2.99–2.93 (2H, m, $COCH_2$), 2.88 (1H, dd, *J* = 14.3, 9.3 Hz, CH_xH_yPh), 2.40–2.34 (2H, m, CH_2COOCH_3), 2.00–1.91 (2H, m, $COCH_2CH_2$), 1.38 (3H, s, CCH_3), 1.36 (3H, s, CCH_3).; **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.4 (C), 172.6 (C), 152.6 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 82.3 (C), 63.4 (CH), 51.5 (CH_3), 35.4 (CH_2), 34.8 (CH_2), 33.0 (CH_2), 28.5 (CH_3), 22.2 (CH_3), 19.4 (CH_2); **HRMS** (+ESI): *m/z* calcd. for $C_{18}H_{24}NO_5$ $[M+H]^+$: 334.1649, found: 334.1657.

(*S*)-4-Benzyl-*N*-(*tert*-butyldimethylsilyloxy)acetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1h)



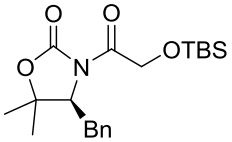
1k **1h**

(*S*)-4-Benzyl-*N*-hydroxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one



Neat $TiCl_4$ (1.3 mL, 11.4 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone **1k**[**] (2.02 g, 5.7 mmol) in DCM (45 mL) at 0 °C. The reaction mixture was stirred at rt for 30 min and quenched with sat NH_4Cl (20 mL) at 0 °C. The mixture was extracted with DCM (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (from 100:0 to 60:40 hexanes/EtOAc) and (*S*)-4-benzyl-*N*-hydroxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (1.43 g, 5.4 mmol, 95% yield) was obtained as a colorless oil. $\mathbf{R_f}$ (70:30 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −41.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3482, 2981, 2931, 1778, 1699, 1603, 1497 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.22 (5H, m, Ar<u>H</u>), 4.72 (1H, d, *J* = 18.6 Hz, COC<u>H</u>$_x$H$_y$), 4.64 (1H, d, *J* = 18.6 Hz, COCH$_x$<u>H</u>$_y$), 4.52 (1H, dd, *J* = 9.4, 4.3 Hz, NC<u>H</u>), 3.20 (1H, dd, *J* = 14.4, 4.2 Hz, C<u>H</u>$_x$H$_y$Ph), 2.92 (1H, dd, *J* = 14.4, 9.4 Hz, CH$_x$<u>H</u>$_y$Ph), 1.41 (3H, s, CC<u>H</u>$_3$), 1.39 (3H, s, CC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.5 (C), 152.1 (C), 136.3 (C), 128.9 (CH), 128.7 (CH), 127.0 (CH), 83.9 (C), 63.4 (CH), 63.2 (CH_2), 35.1 (CH_2), 28.6 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{14}H_{18}NO_4$ $[M+H]^+$: 264.1230, found: 264.1222.

(*S*)-4-Benzyl-*N*-*tert*-butyldimethylsilyloxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (**1h**)



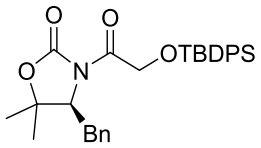
1h

Imidazole (327 mg, 4.8 mmol) and TBSCl (332 mg, 2.2 mmol) were added to a solution of (*S*)-4-benzyl-*N*-hydroxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (524 mg, 2.0 mmol) in DCM (10 mL) at 0 °C. The mixture was stirred for 72 h at rt and diluted with Et_2O (15 mL). The organic layer was washed with water (15 mL), 10% citric acid aqueous solution (15 mL), brine (15 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure.

[**] For preparation of **1k** see page 173

Purification of the crude product by flash column chromatography (from 95:5 to 90:10 hexanes/EtOAc) afforded **1h** (696 mg, 1.8 mmol, 92% yield) as a white solid. **Mp** 78–79 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ –26.6 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2949, 2925, 2852, 1759, 1726, 1351, 1297, 1166, 1159 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH), 4.89 (1H, d, *J* = 18.3 Hz, $COCH_xH_y$), 4.75 (1H, d, *J* = 18.3 Hz, $COCH_xH_y$), 4.51 (1H, dd, *J* = 10.0, 3.4 Hz, NCH), 3.24 (1H, dd, *J* = 14.4, 3.4 Hz, $NCHCH_xH_yPh$), 2.88 (1H, dd, *J* = 14.4, 10.0 Hz, $NCHCH_xH_yPh$), 1.36 (3H, s,CCH_3), 1.35 (3H, s, CCH_3), 0.94 (9H, s, $SiC(CH_3)_3$), 0.12 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.9 (C), 152.6 (C), 136.7 (C), 129.0 (CH), 128.7 (CH), 126.8 (CH), 83.5 (C), 64.4 (CH_2), 63.4 (CH), 35.0 (CH_2), 28.6 (CH_3), 25.8 (CH_3), 22.4 (CH_3), 18.4 (C), –5.4 (CH_3), –5.5 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{20}H_{32}NO_4Si$ $[M+H]^+$: 378.2095, found: 378.2098.

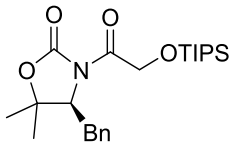
(*S*)-4-Benzyl-*N*-(*tert*-butyldiphenylsilyloxy)acetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1i)



1i

Imidazole (266 mg, 3.9 mmol) and TBDPSCl (940 µL, 3.6 mmol) were added to a solution of (*S*)-4-benzyl-*N*-hydroxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (790 mg, 3.0 mmol) in DCM (6 mL) at 0 °C. The mixture was stirred for 5 h at rt and quenched with sat $NaHCO_3$ (10 mL). The mixture was extracted with DCM (3 × 10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Purification of the crude product by flash column chromatography (from 60:40 to 50:50 hexanes/DCM) afforded **1i** (1.35 g, 2.7 mmol, 90% yield) as a colorless oil. $\mathbf{R_f}$ (80:20 toluene/DCM) 0.4; $[\alpha]_D^{20}$ –12.9(*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2930, 2856, 1772, 1717, 1427 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71–7.69 (4H, m, ArH), 7.45–7.34 (6H, m, ArH), 7.31–7.20 (5H, m, ArH), 4.93 (1H, d, *J* = 18.2 Hz, $COCH_xH_y$), 4.78 (1H, d, *J* = 18.2 Hz, $COCH_xH_y$), 4.43 (1H, dd, *J* = 10.2, 3.0 Hz, NCH), 3.10 (1H, dd, *J* = 14.5, 3.0 Hz, $CHCH_xH_y$), 2.76 (1H, dd, *J* = 14.5, 10.2 Hz, $CHCH_xH_y$), 1.29 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.12 (9H, br s, $C(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.2 (C), 152.3 (C), 136.7 (C), 135.6 (CH), 135.6 (CH), 132.9 (C), 132.9 (C), 129.8 (CH), 129.0 (CH), 128.6 (CH), 127.7 (CH), 126.8 (CH), 83.4 (C), 64.6 (CH_2), 63.2 (CH), 34.8 (CH_2), 28.6 (CH_3), 26.8 (CH_3), 22.3 (CH_3), 19.3 (C); **HRMS** (+ESI): *m/z* calcd. for $C_{30}H_{39}N_2O_4Si$ $[M+NH_4]^+$: 519.2674, found: 519.2673.

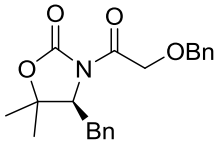
(*S*)-4-Benzyl-*N*-(triisopropylsilyloxy)acetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1j)



1j

2,6-Lutidine (360 µL, 3.1 mmol) and TIPSOTf (840 µL, 3.1 mmol) were added to a solution of (*S*)-4-benzyl-*N*-hydroxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (632 mg, 2.4 mmol) in DCM (10 mL) at 0 °C. The mixture was stirred for 72 h at rt and diluted with MeOH (3 mL) and Et_2O (15 mL). The organic layer was washed with sat $NaHCO_3$ (20 mL), 1M HCl solution (20 mL), brine (20 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Purification of the crude product by flash column chromatography (90:10 hexanes/EtOAc) afforded **1j** (903 mg, 2.2 mmol, 90% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −18.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2941, 2891, 2864, 1774, 1720, 1463 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43–7.14 (5H, m, Ar<u>H</u>), 4.96 (1H, d, *J* = 18.2 Hz, COC<u>H</u>$_x$H$_y$), 4.83 (1H, d, *J* = 18.2 Hz, COCH$_x$<u>H</u>$_y$), 4.52 (1H, dd, *J* = 10.1, 3.3 Hz, NC<u>H</u>), 3.26 (1H, dd, *J* = 14.5, 3.3 Hz, NCHC<u>H</u>$_x$H$_y$), 2.87 (1H, dd, *J* = 14.5, 10.1 Hz, NCHCH$_x$<u>H</u>$_y$), 1.36 (3H, s, C<u>H</u>$_3$), 1.35 (3H, s, C<u>H</u>$_3$), 1.22–1.13 (3H, m, 3 × C<u>H</u>(CH$_3$)$_2$), 1.10–1.05 (18H, m, 3 × CH(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.7 (C), 152.6 (C), 136.8 (C), 129.0 (CH), 128.7 (CH), 126.8 (CH), 83.5 (C), 64.4 (CH_2), 63.4 (CH), 35.0 (CH_2), 28.7 (CH_3), 22.4 (CH_3), 17.9 (CH_3), 12.0 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{23}H_{38}NO_4Si$ $[M+H]^+$: 420.2565, found: 420.2567.

(*S*)-4-Benzyl-*N*-(2-(benzyloxy)acetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1k)

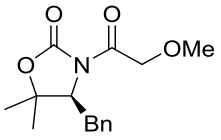


1k

It was prepared following <u>General Procedure 2</u> from oxazolidinone ***SuperQuat*** (1.23 g, 6.0 mmol), *n*-BuLi (2.5 M in hexanes, 2.7 mL, 6.6 mmol) and 2-benzyloxyacetyl chloride (1.25 mL, 7.8 mmol). Purification of the crude product by flash column chromatography (85:15 hexanes/EtOAc) afforded **1k** (1.98 g, 5.6 mmol, 93% yield) as a thick oil. $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −31.8 (*c* 1.0, $CHCl_3$), [lit.[173] $[\alpha]_D^{22}$ −33.9 (*c* 1.0, $CHCl_3$)]; **IR** (NaCl) ν 3029, 2980, 1769, 1711, 1354, 1259, 1126, 1099 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.18 (10H, m, Ar<u>H</u>), 4.73 (1H, d, *J* = 17.8 Hz, COC<u>H</u>$_x$H$_y$), 4.63 (1H, d, *J* = 17.8 Hz, COCH$_x$<u>H</u>$_y$), 4.62 (2H, s, OC<u>H</u>$_2$Ph), 4.52 (1H, dd, *J* = 9.5, 3.9 Hz, NC<u>H</u>), 3.20 (1H, dd, *J* = 14.4, 3.9 Hz, NCHC<u>H</u>$_x$H$_y$Ph), 2.89 (1H, dd, *J* = 14.4, 9.5 Hz, NCHCH$_x$<u>H</u>$_y$Ph), 1.38 (3H, s, CC<u>H</u>$_3$), 1.36 (3H, s, CC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.3 (C), 152.5 (C), 137.2 (C), 136.6 (C), 129.0

(CH), 128.7 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 126.9 (CH), 83.6 (C), 73.3 (CH_2), 69.7 (CH_2), 63.3 (CH), 35.1 (CH_2), 28.6 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{21}H_{24}NO_4$ $[M+H]^+$: 354.1700, found: 354.1693.

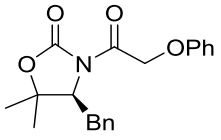
(*S*)-4-Benzyl-*N*-2-methoxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (1l)



1l

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (411 mg, 2.0 mmol), *n*-BuLi (2.5 M in hexanes, 880 µL, 2.2 mmol) and 2-methoxyacetyl chloride (245 µL, 2.6 mmol). Purification of the crude product by flash column chromatography (80:20 hexanes/EtOAc) afforded **1l** (524 mg, 1.9 mmol, 94% yield) as a colorless oil. $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ −36.1(*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2982, 2930, 1767, 1712 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.18 (5H, m, ArH), 4.65 (1H, d, *J* = 17.8 Hz, $COCH_xH_y$), 4.54 (1H, d, *J* = 17.8 Hz, $COCH_xH_y$), 4.52 (1H, dd, *J* = 9.5, 3.9 Hz, NCH), 3.45 (3H, s, OCH_3), 3.21 (1H, dd, *J* = 14.4, 3.9 Hz, CH_xH_yPh), 2.90 (1H, dd, *J* = 14.4, 9.5 Hz, CH_xH_yPh), 1.40 (3H, s, CCH_3), 1.38 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.2 (C), 152.5 (C), 136.6 (C), 129.0 (CH), 128.7 (CH), 126.9 (CH), 83.6 (C), 72.2 (CH_2), 63.2 (CH), 59.4 (CH_3), 35.1 (CH_2), 28.6 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{15}H_{20}NO_4$ $[M+H]^+$: 278.1387, found: 278.1391.

(*S*)-4-Benzyl-*N*-2-methoxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (1m)

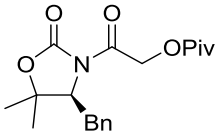


1m

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (411 mg, 2.0 mmol), *n*-BuLi (2.5 M in hexanes, 880 µL, 2.2 mmol) and 2-phenoxyacetyl chloride (366 µL, 2.6 mmol). Purification of the crude product by flash column chromatography (80:20 hexanes/EtOAc) afforded **1m** (638 mg, 1.9 mmol, 94% yield) as a white solid. **Mp** 71–73 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −37.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2977, 1766, 1725, 1494, 1354, 1296, 1254, 1226, 1166 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33–7.21 (7H, m, ArH), 7.03–6.95 (1H, m, ArH), 6.95–6.90 (2H, m, ArH), 5.27 (1H, d, *J* = 17.6 Hz, $COCH_xH_y$), 5.16 (1H, d, *J* = 17.6 Hz, $COCH_xH_y$), 4.54 (1H, dd, *J* = 9.8, 3.7 Hz, NCH), 3.26 (1H, dd, *J* = 14.4, 3.7 Hz, $NCHCH_xH_y$), 2.92 (1H, dd, *J* = 14.4, 9.8 Hz, $NCHCH_xH_y$), 1.42 (3H, s, CH_3), 1.39 (3H, s, CH_3); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 168.7 (C), 157.8 (C), 152.6 (C), 136.5 (C), 129.5 (CH), 129.0 (CH), 128.7 (CH), 126.9 (CH), 121.7 (CH), 114.8 (CH), 84.0 (C), 67.6 (CH_2), 63.5

(CH), 35.0 (CH_2), 28.7 (CH_3), 22.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{20}H_{25}N_2O_4$ $[M+NH_4]^+$: 357.1809, found: 357.1813.

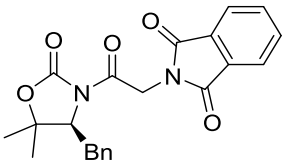
(*S*)-4-Benzyl-5,5-dimethyl-*N*-(2-pivaloyloxyacetyl)-1,3-oxazolidin-2-one (1n)



1n

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (411 mg, 2.0 mmol), *n*-BuLi (2.5 M in hexanes, 880 µL, 2.2 mmol) and 2-pivaloylacetyl chloride (464 mg, 2.6 mmol). Purification of the crude product by flash column chromatography (90:10 hexanes/EtOAc) afforded **1n** (680 mg, 2.0 mmol, 98% yield) as a white solid. **Mp** 125–128 °C; **R_f** (80:20 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −6.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2974, 1773, 1739, 1714, 1392, 1357, 1264, 1141, 1104 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, Ar$\underline{H}$), 5.24 (1H, d, *J* = 17.0 Hz, COC$\underline{H}_xH_y$), 5.11 (1H, d, *J* = 17.0 Hz, COCH$_x\underline{H}_y$), 4.50 (1H, dd, *J* = 10.2, 3.2 Hz, C$\underline{H}$N), 3.26 (1H, dd, *J* = 14.6, 3.2 Hz, C$\underline{H}_xH_y$Ph), 2.88 (1H, dd, *J* = 14.6, 10.2 Hz, C$\underline{H}_xH_y$Ph), 1.38 (3H, s, CC$\underline{H}_3$), 1.36 (3H, s, CC$\underline{H}_3$), 1.28 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.9 (C), 167.5 (C), 152.5 (C), 136.6 (C), 128.9 (CH), 128.7 (CH), 126.8 (CH), 83.9 (C), 63.3 (CH), 63.2 (CH_2), 38.7 (C), 34.8 (CH_2), 28.7 (CH_3), 27.1 (CH_3), 22.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{19}H_{25}NNaO_5$ $[M+Na]^+$: 370.1625, found: 370.1631.

(*S*)-4-Benzyl-*N*-phthalimidoacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (1o)

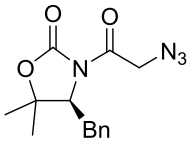


1o

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (616 mg, 3.0 mmol), *n*-BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol) and phthalimidoacetyl chloride (894 mg, 3.9 mmol). Purification of the crude product by flash column chromatography (80:20 hexanes/EtOAc) afforded **1o** (771 mg, 2.0 mmol, 65% yield) as a white solid. **Mp** 69–72 °C; **R_f** (70:30 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ +1.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2980, 1774, 1716, 1405, 1268, 1102 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91–7.87 (2H, m), 7.77–7.72 (2H, m, Phth), 7.77–7.72 (2H, m, Phth), 7.32–7.14 (5H, m, Ar$\underline{H}$), 5.08 (1H, d, *J* = 18.2 Hz, COC$\underline{H}_xH_y$), 5.03 (1H, d, *J* = 18.2 Hz, COCH$_x\underline{H}_y$), 4.48 (1H, dd, *J* = 10.0, 3.2 Hz, NC$\underline{H}$), 3.24 (1H, dd, *J* = 14.5, 3.2 Hz, C$\underline{H}_xH_y$Ph), 2.91 (1H, dd, *J* = 14.5, 10.0 Hz, CH$_x\underline{H}_y$Ph), 1.41 (6H, s, 2 × C$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 167.6 (C), 166.8 (C), 152.6 (C), 136.5 (C), 134.1 (CH), 132.1 (C), 128.9 (CH), 128.7 (CH), 126.8 (CH), 123.6 (CH), 83.7 (C), 63.9 (CH), 41.7 (CH_2), 34.8 (CH_2), 28.8

(CH_3), 22.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{22}H_{20}N_2NaO_5$ $[M+Na]^+$: 415.1271, found: 415.1264.

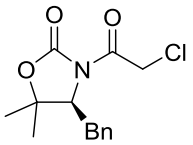
(*S*)-*N*-Azidoacetyl-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (1p)



1p

A solution of NaN_3 (569 mg, 8.8 mmol) in DMSO (10 mL) was added to a solution of **1q** (620 mg, 2.2 mmol) and **1r** (424 mg, 1.3 mmol) in THF (10 mL) at rt. The mixture was stirred at rt for 72 h and concentrated under reduced pressure. The residue was partitioned between water and EtOAc (15 mL each), the organic phase was washed with water (10 mL), brine (10 mL) and dried with anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure. Purification of the crude product through a short pad of silica (80:20 hexanes/EtOAc) afforded **1p** (884 mg, 3.1 mmol, 88% yield) as a white solid. **Mp** 61–62 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.4; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –27.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3060, 3029, 2957, 2118, 1776, 1711, 1391, 1357, 1259, 1236, 1188, 1105, 1028 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, Ar$\underline{H}$), 4.53 (1H, dd, *J* = 9.5, 4.2 Hz, NC$\underline{H}$), 4.51 (1H, d, *J* = 18.4 Hz, COC$\underline{H}_x$H$_y$), 4.43 (1H, d, *J* = 18.4 Hz, COCH$_x\underline{H}_y$), 3.21 (1H, dd, *J* = 14.4, 4.2 Hz, C$\underline{H}_x$H$_y$Ph), 2.91 (1H, dd, *J* = 14.4, 9.5 Hz, CH$_x\underline{H}_y$Ph), 1.41 (3H, s, C$\underline{H}_3$), 1.39 (3H, s, C$\underline{H}_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 168.0 (C), 152.3 (C), 136.3 (C), 129.0 (CH), 128.8 (CH), 127.0 (CH), 83.7 (C), 63.5 (CH), 52.8 (CH_2), 35.1 (CH_2), 28.5 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{14}H_{16}N_4NaO_3$ $[M+Na]^+$: 311.1115, found: 311.1116.

(*S*)-4-Benzyl-*N*-chloroacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (1q)

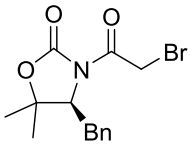


1q

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (960 mg, 4.7 mmol), *n*-BuLi (2.5 M in hexanes, 2.0 mL, 5.2 mmol) and chloroacetyl chloride (689 mg, 6.1 mmol). Purification of the crude product by flash column chromatography (80:20 hexanes/EtOAc) afforded **1q** (632 mg, 2.2 mmol, 48% yield) as a white solid. **Mp** 89–91 °C; $\mathbf{R_f}$ (70:30 hexanes/EtOAc) 0.6; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –35.3 (*c* 1.0, $CHCl_3$), [lit.[172] (enant.) $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +32.0 (*c* 0.5, $CHCl_3$)]; **IR** (ATR) ν 2973, 1786, 1710, 1358, 1239, 1105 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.20 (5H, m, Ar$\underline{H}$), 4.78 (1H, d, *J* = 15.9 Hz, COC$\underline{H}_x$H$_y$), 4.66 (1H, d, *J* = 15.9 Hz, COCH$_x\underline{H}_y$), 4.52 (1H, dd, *J* = 9.7, 3.7 Hz, NC$\underline{H}$), 3.22 (1H, dd, *J* = 14.4, 3.7 Hz, C$\underline{H}_x$H$_y$Ph), 2.90 (1H, dd, *J* = 14.4, 9.7 Hz, CH$_x\underline{H}_y$Ph), 1.41 (3H, s, CC$\underline{H}_3$), 1.38 (3H, s, CC$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 166.3 (C), 152.3 (C), 136.4 (C), 129.0 (CH), 128.8 (CH), 127.0 (CH), 83.6 (C),

64.0 (CH), 43.8 (CH_2), 35.0 (CH_2), 28.6 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{14}H_{17}ClNO_3$ $[M+H]^+$: 282.0891, found: 282.0898.

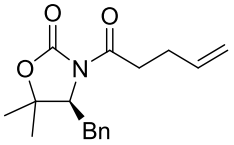
(*S*)-4-Benzyl-*N*-bromoacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (1r)



1r

LiBr (3.00 g, 35 mmol) was added to a solution of **1q** (374 mg, 1.35 mmol) in THF (7 mL) and the mixture was stirred at rt for 72 h. The reaction mixture was quenched with H_2O (15 ml) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (40 mL) and dried over anhydrous $MgSO_4$. **1r** (632 mg, 2.2 mmol, 48% yield) was obtained without further purification as a white solid. **Mp** 52–54 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ –25.8 (*c* 1.0, $CHCl_3$), [lit.[173] $[\alpha]_D^{25}$ –26.7 (*c* 1.0, $CHCl_3$)]; **IR** (ATR) ν 2968, 1779, 1697, 1354, 1327, 1272, 1208, 1178, 1157, 1100 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.22 (5H, m, Ar$\underline{H}$), 4.58 (1H, d, *J* = 12.4 Hz, COC$\underline{H}_xH_y$), 4.51 (1H, dd, *J* = 9.7, 3.8 Hz, NC$\underline{H}$), 4.44 (1H, d, *J* = 12.4 Hz, COC$\underline{H}_xH_y$), 3.19 (1H, dd, *J* = 14.4, 3.8 Hz, NCHC$\underline{H}_xH_y$), 2.91 (1H, dd, *J* = 14.4, 9.7 Hz, NCHC$\underline{H}_xH_y$), 1.40 (3H, s, C$\underline{H}_3$), 1.39 (3H, s, C$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 166.1 (C), 152.0 (C), 136.4 (C), 128.9 (CH), 128.6 (CH), 126.8 (CH), 83.2 (C), 63.9 (CH), 34.8 (CH_2), 28.5 (CH_3), 28.3 (CH_2), 22.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{14}H_{17}BrNNaO_3$ $[M+Na]^+$: 348.0206, found: 348.0202.

(*S*)-4-Benzyl-*N*-(5-pentenoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1s)

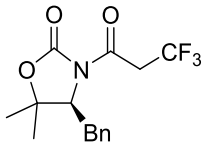


1s

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (616 mg, 3.0 mmol), *n*-BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol) and 5-pentenoyl chloride (391 mg, 3.3 mmol). Purification of the crude product by flash column chromatography (90:10 hexanes/EtOAc) afforded **1s** (294 mg, 1.02 mmol, 34% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ –34.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2980, 1774, 1698, 1376, 1355, 1276, 1233, 1209, 1182, 1160, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.33–7.20 (5H, m, Ar$\underline{H}$), 5.84 (1H, ddt, *J* = 16.8, 10.2, 6.5 Hz, C$\underline{H}$=CH_2), 5.10–5.05 (1H, m, CH=C$\underline{H}_xH_y$), 5.03–4.99 (1H, m, CH=C$H_x\underline{H}_y$), 4.51 (1H, dd, *J* = 9.6, 3.9 Hz, C$\underline{H}$N), 3.14 (1H, dd, *J* = 14.4, 3.9 Hz, C$\underline{H}_xH_y$Ph), 3.03 (2H, t, *J* = 7.4 Hz, COC$\underline{H}_2$), 2.87 (1H, dd, *J* = 14.4, 9.6 Hz, C$H_x\underline{H}_y$Ph), 2.43–2.37 (2H, m, C$\underline{H}_2$CH=CH_2), 1.37 (3H, s, CC$\underline{H}_3$), 1.36 (3H, s, CC$\underline{H}_3$); **^{13}C NMR** (100.6

MHz, $CDCl_3$) δ 172.8 (C), 152.6 (C), 136.9 (C), 136.7 (CH), 129.0 (CH), 128.6 (CH), 126.8 (CH), 115.6 (CH_2), 82.2 (C), 63.5 (CH), 35.4 (CH_2), 34.9 (CH_2), 28.5 (CH_3), 28.3 (CH_2), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{17}H_{21}NNaO_3$ $[M+Na]^+$: 310.1414, found: 310.1416.

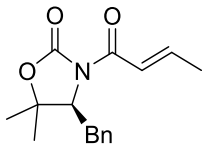
(*S*)-4-Benzyl-*N*-2,2,2-trifluoropropanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (1t)



1t

Et_3N (730 µL, 5.2 mmol) and PivCl (640 µL, 5.2 mmol) were added to a solution of 2,2,2-trifluoropropanoic acid (460 µL, 5.2 mmol) in THF (25 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 90 min and afterwards it was cooled to −78 °C. Meanwhile, a 2.5 M solution of *n*-BuLi in hexanes (1.8 mL, 4.4 mmol) was added dropwise to a solution of oxazolidinone ***SuperQuat*** (821 mg, 4.0 mmol) in THF (10 mL) at −78 °C and stirred for 15 min. The resulting solution was added to the first mixture via *cannula*. The reaction mixture was stirred at −78 °C for 20 min and it was allowed to warm to rt and stirred for 2 h. The mixture was quenched with sat NH_4Cl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with sat $NaHCO_3$ (40 mL), brine (40 mL) and dried with anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure. Purification of the crude by flash column chromatography (90:10 hexanes/EtOAc) afforded **1t** (448 mg, 1.4 mmol, 35% yield) as a white solid. **Mp** 65−66 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −22.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2982, 2925, 1773, 1709, 1405, 1356, 1274, 1239, 1210, 1160, 1082 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35−7.20 (5H, m, ArH), 4.54 (1H, dd, *J* = 9.5, 4.0 Hz, NCH), 3.94 (1H, dq, *J* = 17.0, 9.8 Hz, $COCH_xH_y$), 3.81 (1H, dq, *J* = 17.0, 9.8 Hz, $COCH_xH_y$), 3.18 (1H, dd, *J* = 14.4, 4.0 Hz, $NCHCH_xH_y$), 2.91 (1H, dd, *J* = 14.4, 9.5 Hz, $NCHCH_xH_y$), 1.41 (3H, s, CH_3), 1.38 (3H, s, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 163.4 (q, J_{CF} = 3.7 Hz, C), 152.3 (C), 136.3 (C), 129.0 (CH), 128.8 (CH), 127.0 (CH), 123.5 (q, J_{CF} = 276.7 Hz, CF_3), 83.1 (C), 63.6 (CH), 39.8 (q, J_{CF} = 29.9 Hz, CH_2), 35.1 (CH_2), 28.5 (CH_3), 22.2 (CH_3); **^{19}F NMR** (376 MHz, $CDCl_3$) δ −62.8 (t, J_{FH} = 9.8 Hz); **HRMS** (+ESI): *m/z* calcd. for $C_{15}H_{20}F_3N_2O_3$ $[M+NH_4]^+$: 333.1421, found: 333.1419.

(*S*)-4-Benzyl-*N*-(2-butenoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (1u)

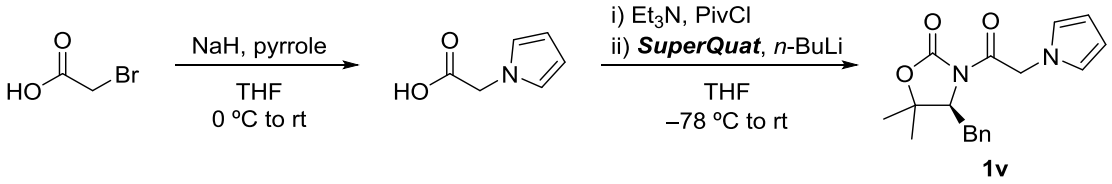


1u

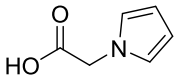
It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (1.03 g, 5.0 mmol), *n*-BuLi (2.5 M in hexanes, 2.6 mL, 6.5 mmol) and 2-butenoyl chloride (620 µL, 6.5

mmol). Purification of the crude product by flash column chromatography (80:20 hexanes/EtOAc) afforded **1u** (1.10 g, 4.0 mmol, 80% yield) as a white solid. **Mp** 91–95 °C; **R_f** (80:20 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ –41.0 (*c* 1.0, $CHCl_3$), [lit.[174] $[\alpha]_D^{25}$ –40.3 (*c* 0.8, $CHCl_3$)]; **IR** (ATR) ν 3029, 2975, 1764, 1682, 1634, 1353, 1336, 1290, 1235, 1184, 1090 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33–7.20 (6H, m, ArH, COCH=CH), 7.14 (1H, dq, *J* = 15.2, 6.8 Hz, COCH=CH), 4.55 (1H, dd, *J* = 9.8, 3.5 Hz, NCH), 3.22 (1H, dd, *J* = 14.4, 3.5 Hz, CH_xH_yPh), 2.88 (1H, dd, *J* = 14.4, 9.8 Hz, CH_xH_yPh), 1.96 (3H, dd, *J* = 6.8, 1.6 Hz, CH=CHCH_3), 1.37 (3H, s, CH_3), 1.35 (3H, s, CH_3); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 165.2 (C), 152.6 (C), 146.5 (CH), 137.1 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 122.2 (CH), 82.1 (C), 63.7 (CH), 35.2 (CH_2), 28.5 (CH_3), 22.3 (CH_3), 18.5 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{16}H_{19}NNaO_3$ $[M+Na]^+$: 296.1257, found: 296.1263.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-(2-(1*H*-*N*-pyrrolyl)acetyl)-1,3-oxazolidin-2-one (1v)

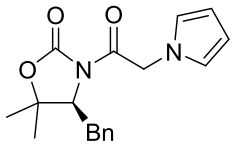


2-(1*H*-*N*-Pyrrolyl)acetic acid



Pyrrole (800 µL, 11.5 mmol) was added to a mixture of NaH 60% dispersion in mineral oil (500 mg, 12.5 mmol) in THF (10 mL) at 0 °C. A solution of bromoacetic acid (695 mg, 5.0 mmol) in THF (2 mL) was added to the reaction mixture via cannula (**CAUTION**: release of gas). The reaction mixture was allowed to warm to rt, stirred for 16 h and finally quenched by slow addition of water (5 mL). The mixture was concentrated under reduced pressure and the residue was partitioned between water and EtOAc (10 mL each). The aqueous phase was acidified with 2 M HCl to pH = 1. The acidified aqueous phase was extracted with EtOAc (2 × 20 mL), the combined organic phases were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to obtain 2-(1*H*-*N*-pyrrolyl)acetic acid (593 mg, 4.7 mmol, 95% yield) as a brown solid. The product was used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.84 (1H, br s, COOH), 6.66–6.65 (2H, m, 2 × NCH=CH), 6.23–6.22 (2H, m, 2 × NCH=CH), 4.69 (1H, m, $COCH_2$).

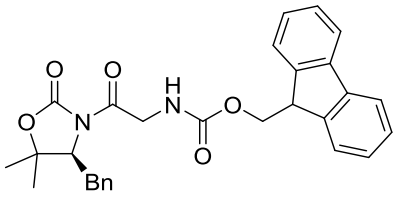
(*S*)-4-Benzyl-5,5-dimethyl-*N*-(2-(1*H*-*N*-pyrrolyl)acetyl)-1,3-oxazolidin-2-one (**1v**)



1v

Et_3N (660 µL, 4.7 mmol) and PivCl (580 µL, 4.7 mmol) were added to a solution of 2-(1*H*-*N*-pyrrolyl)acetic acid (588 mg, 4.7 mmol) in THF (25 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 90 min and afterwards it was cooled to −78 °C. Meanwhile, a 1.4 M solution of *n*-BuLi in hexanes (2.8 mL, 4.0 mmol) was added dropwise to a solution of oxazolidinone ***SuperQuat*** (739 mg, 3.6 mmol) in THF (13 mL) at −78 °C and stirred for 15 min. The resulting solution was added to the first mixture via cannula. The reaction mixture was stirred at −78 °C for 20 min and it was allowed to warm to rt and stirred for 2 h. The mixture was quenched with sat NH_4Cl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with sat $NaHCO_3$ (50 mL), brine (50 mL) and dried with anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure. Purification of the crude by flash column chromatography (from 85:15 to 70:30 hexanes/EtOAc) afforded **1v** (890 mg, 2.9 mmol, 79% yield) as a brown solid. **Mp** 161–164 °C; $\mathbf{R_f}$ (70:30 hexanes/EtOAc) 0.6; $[\alpha]_D^{20}$ −30.4 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2935, 1767, 1724, 1500, 1353, 1255, 1667 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.14 (5H, m, ArH), 6.62 (2H, t, *J* = 2.1 Hz, 2 × NCH=CH), 6.22 (2H, t, *J* = 2.1 Hz, 2 × NCH=CH), 5.28 (1H, d, *J* = 18.3 Hz, $COCH_xH_y$), 5.18 (1H, d, *J* = 18.3 Hz, $COCH_xH_y$), 4.49 (1H, dd, *J* = 9.6, 3.9 Hz, NCH), 3.20 (1H, dd, *J* = 14.3, 3.9 Hz, $NCHCH_xH_y$), 2.89 (1H, dd, *J* = 14.3, 9.6 Hz, $NCHCH_xH_y$), 1.42 (3H, s, CCH_3), 1.38 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.8 (C), 152.7 (C), 136.4 (C), 129.1 (CH), 128.7 (CH), 126.9 (CH), 122.0 (CH), 109.0 (CH), 83.6 (C), 63.8 (CH), 52.7 (CH_2), 35.0 (CH_2), 28.6 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{18}H_{21}N_2O_3$ $[M+H]^+$: 313.1547, found: 313.1548.

(*S*)-4-Benzyl-*N*-[2-((9-fluorenylmethyl)oxycarbonylamino)acetyl]-5,5-dimethyl-1,3-oxazolidin-2-one (1w)

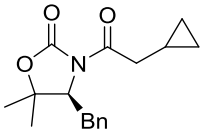


1w

Et_3N (710 µL, 5.1 mmol) and PivCl (630 µL, 5.1 mmol) were added to a solution of Fmoc glycine (1.52 g, 5.1 mmol) in THF (25 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 90 min and afterwards it was cooled to −78 °C. Meanwhile, a 2.5 M solution of *n*-BuLi in hexanes (1.7

mL, 4.3 mmol) was added dropwise to a solution of oxazolidinone ***SuperQuat*** (800 mg, 3.9 mmol) in THF (10 mL) at −78 °C and stirred for 15 min. The resulting solution was added to the first mixture via *cannula*. The reaction mixture was stirred at −78 °C for 20 min and it was allowed to warm to rt and stirred for 2 h. The mixture was quenched with sat NH_4Cl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with sat $NaHCO_3$ (40 mL), brine (40 mL) and dried with anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure. Purification of the crude by flash column chromatography (from 90:10 to 60:40 hexanes/EtOAc) afforded **1v** (990 mg, 2.0 mmol, 52% yield) as a white solid. **Mp** 115–117 °C; $\mathbf{R_f}$ (70:30 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −15.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3374, 2982, 1765, 1737, 1715, 1531, 1377, 1354, 1267, 1226, 1160, 1105, 1044 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 7.5 Hz, ArH), 7.61 (2H, d, *J* = 7.5 Hz, ArH), 7.40 (2H, t, *J* = 7.4 Hz, ArH), 7.33–7.29 (4H, m, ArH), 7.27–7.21 (3H, m, ArH), 5.42–5.35 (1H, br m, NH), 4.64 (1H, dd, *J* = 19.2, 6.0 Hz, OCH_xH_y), 4.53–4.47 (2H, m, OCH_xH_y, NCH), 4.41 (2H, d, *J* = 7.3 Hz, $COCH_2$), 4.27–4.22 (1H, m, OCH_2CH), 3.20 (1H, dd, *J* = 14.3, 3.4 Hz, CH_xH_yPh), 2.89 (1H, dd, *J* = 14.4, 9.6 Hz, CH_xH_yPh), 1.39 (3H, s, CH_3), 1.38 (3H, s, CH_3); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 169.7 (C), 156.3 (C), 152.3 (C), 143.8 (C), 141.3 (C), 136.6 (C), 129.0 (CH), 128.7 (CH), 127.7 (CH), 127.0 (CH), 126.9 (CH), 125.1 (CH), 119.9 (CH), 83.5 (C), 67.2 (CH_2), 63.6 (CH), 47.1 (CH), 45.5 (CH_2), 35.1 (CH_2), 28.6 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{29}H_{28}N_2NaO_5$ $[M+Na]^+$: 507.1890, found: 507.1893.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-(cyclopropylacetyl)-1,3-oxazolidin-2-one (1x)



1x

It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (616 mg, 3.0 mmol), *n*-BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol) and cyclopropylacetyl chloride (367 mg, 3.9 mmol). Purification of the crude product by flash column chromatography (80:20 hexanes/EtOAc) afforded **1x** (337 mg, 1.17 mmol, 39% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ −29.4 (*c* 1.1, $CHCl_3$); **IR** (NaCl) ν 3025, 2996, 2973, 1768, 1696, 1353, 1089 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH), 4.53 (1H, dd, *J* = 9.5, 3.8 Hz, NCH), 3.17 (1H, dd, *J* = 14.4, 3.8 Hz, $NCHCH_xH_yPh$), 2.89 (1H, dd, *J* = 14.4, 9.5 Hz, $NCHCH_xH_yPh$), 2.86–2.88 (2H, m, $COCH_2$), 1.38 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 1.15–1.03 (1H, m, $COCH_2CH$), 0.59–0.52 (2H, m, $CH(CH_xH_y)_2$), 0.21–0.16 (2H, m, $CH(CH_xH_y)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.1 (C), 152.6 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 82.2 (C), 63.5 (CH), 40.7 (CH_2), 35.3 (CH_2), 28.5 (CH_3), 22.3 (CH_3), 6.3 (CH), 4.2 (CH_2), 4.2 (CH_2); **HRMS** (+ESI): *m/z* calcd. for $C_{17}H_{21}NNaO_3$ $[M+Na]^+$: 310.1414, found: 310.1412.

Chapter I

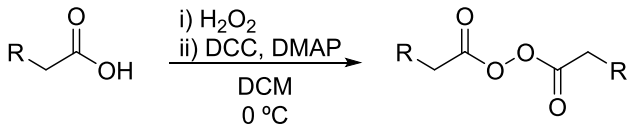
Alkylation of Titanium Enolates with Diacyl Peroxides

1. Preparation of diacyl peroxides

Caution: Diacyl peroxides have potential to explode and should be handled with care!

General Procedure 3 - Primary Peroxides

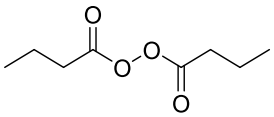
Primary diacyl peroxides were synthesized according to the literature.[87]



2a-2h

A 30% solution of H_2O_2 (100 µL, 1.0 mmol) was added to a solution of the corresponding carboxylic acid (3.4 mmol) in DCM (10 mL) at 0 °C. The resultant solution was vigorously stirred for 10 min at 0 °C. Then, DMAP (41 mg, 0.34 mmol) and DCC (763 mg, 3.7 mmol) were added in one portion and the reaction was vigorously stirred at 0 °C for 2 h. After the addition of hexanes (50 mL), the mixture was filtered, dried with anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography to afford the diacyl peroxide.

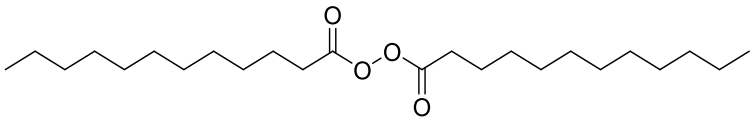
Dibutanoyl peroxide (2a)



2a

It was prepared following General Procedure 3 from butanoic acid (311 µL, 3.4 mmol). The residue was purified by flash column chromatography (70:30 hexanes/DCM) to afford **2a** (179 mg, 1.0 mmol, 59% yield) as a colorless oil. **IR** (ATR) ν 2969, 2939, 2879, 1777, 1121, 1041 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (4H, t, *J* = 7.3 Hz, 2 × COC$\underline{H}_2$), 1.79–1.68 (4H, m, 2 × $COCH_2C\underline{H}_2$), 1.02 (6H, t, *J* = 7.4 Hz, 2 × $C\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.0 (C), 31.8 (CH_2), 18.4 (CH_2), 13.4 (CH_3). ***Note**: peroxide **2a** cannot be monitored by TLC.*

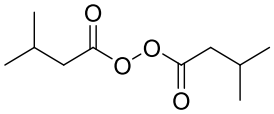
Dilauroyl peroxide (LPO, 2b)



2b

It was prepared following General Procedure 3 from lauric acid (6.61 g, 33 mmol), 30% H_2O_2 (970 µL, 9.7 mmol), DMAP (403 mg, 3.3 mmol) and DCC (7.49 g, 36 mmol). The residue was purified by column chromatography (80:20 hexanes/DCM) to afford **2b** (3.71 g, 9.3 mmol, 93% yield) as a white solid. $\mathbf{R_f}$ (80:20 hexanes/DCM) 0.5; **IR** (ATR) ν 2963, 2914, 2848, 1772, 1130, 1099, 1070, 1060 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (4H, t, J = 7.5 Hz, 2 × $COCH_2$), 1.77–1.65 (4H, m, 2 × $COCH_2CH_2$), 1.42–1.18 (32H, m, 2 × $(CH_2)_8CH_3$), 0.93–0.82 (6H, m, 2 × CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.2 (C), 31.9 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 24.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

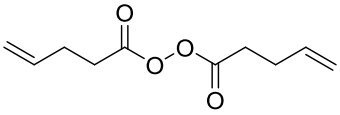
Di(3-methylbutanoyl) peroxide (2c)



2c

It was prepared following General Procedure 3 from isovaleric acid (1.1 mL, 10 mmol), 30% H_2O_2 (300 µL, 3.0 mmol), DMAP (122 mg, 1.0 mmol) and DCC (2.27 g, 11.0 mmol). The residue was purified by flash column chromatography (70:30 hexanes/DCM) to afford **2c** (960 mg, 4.7 mmol, 95% yield) as a colorless oil. **IR** (ATR) ν 2962, 2875, 1777, 1138, 1050 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.31 (4H, d, J = 7.1 Hz, 2 × $COCH_2$), 2.24–2.11 (2H, m, 2 × CH_2CH), 1.03 (12H, d, J = 6.6 Hz, 4 × CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.3 (C), 38.8 (CH_2), 25.9 (CH), 22.1 (CH_3). ***Note**: peroxide **2c** cannot be monitored by TLC.*

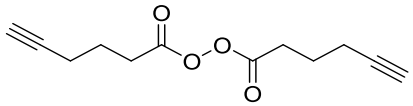
Di(4-pentenoyl) peroxide (2e)



2e

It was prepared following General Procedure 3 from 4-pentenoic acid (347 µL, 3.4 mmol). The residue was purified by flash column chromatography (70:30 hexanes/DCM) to afford **2e** (247 mg, 1.2 mmol, 73% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/DCM) 0.5; **IR** (ATR) ν 3082, 2982, 2927, 1778, 1642, 1060 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 (2H, ddt, J = 16.8, 10.2, 6.3 Hz, 2 × $CH=CH_2$), 5.14–5.05 (4H, m, 2 × $CH=CH_2$), 2.56–2.52 (4H, m, 2 × $COCH_2$), 2.49–2.44 (4H, m, 2 × $CH_2CH=CH_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.5 (C), 135.4 (CH), 116.5 (CH_2), 29.3 (CH_2), 28.5 (CH_2).

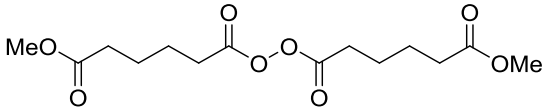
Di(5-hexynoyl) peroxide (2f)



2f

It was prepared following General Procedure 3 from 5-hexynoic acid (375 µL, 3.4 mmol). The residue was purified by flash column chromatography (60:40 hexanes/DCM) to afford **2f** (266 mg, 1.2 mmol, 71% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/DCM) 0.3; **IR** (ATR) ν 3290, 2944, 1775, 1082 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.60 (4H, t, *J* = 7.3 Hz, 2 × $COCH_2$), 2.33 (4H, td, *J* = 7.3, 2.6 Hz, 2 × $CH_2C{\equiv}CH$), 2.01 (2H, t, *J* = 2.6 Hz, 2 × $C{\equiv}CH$), 1.94 (4H, quint, *J* = 7.3 Hz, 2 × $COCH_2CH_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.6 (C), 82.4 (C), 69.7 (CH), 28.6 (CH_2), 23.5 (CH_2), 17.6 (CH_2).

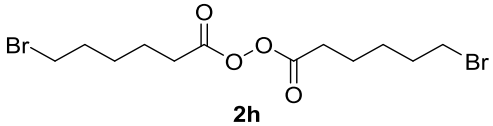
Di(6-methoxy-6-oxohexanoyl) peroxide (2g)



2g

It was prepared following General Procedure 3 from *O*-methyladipic acid (741 µL, 5.0 mmol), 30% H_2O_2 (150 µL, 1.5 mmol), DMAP (61 mg, 0.5 mmol) and DCC (1.13 g, 5.5 mmol). The residue was purified by flash column chromatography (70:30 hexanes/EtOAc) to afford **2g** (639 mg, 2.0 mmol, 81% yield) as a white solid. $\mathbf{R_f}$ (70:30 hexanes/EtOAc) 0.3; **IR** (ATR) ν 2952, 1809, 1705, 1436, 1169 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.68 (6H, s, 2 × CH_3), 2.48–2.44 (8H, m, 4 × $COCH_2$), 2.37–2.34 (8H, m, 4 × $COCH_2CH_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.5 (C), 168.8 (C), 51.6 (CH_3), 33.4 (CH_2), 29.6 (CH_2), 24.2 (CH_2), 24.1 (CH_2).

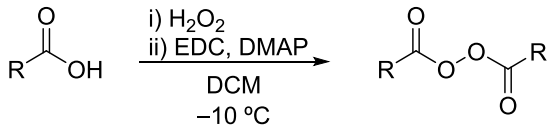
Di(6-bromohexanoyl) peroxide (2h)



2h

It was prepared following General Procedure 3 from 6-bromohexanoic acid (975 mg, 5.0 mmol), 30% H_2O_2 (150 µL, 1.5 mmol), DMAP (61 mg, 0.5 mmol) and DCC (1.13 g, 5.5 mmol). The residue was purified by flash column chromatography (50:50 hexanes/DCM) to afford **2h** (767 mg, 2.0 mmol, 80% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/DCM) 0.3; **IR** (ATR) ν 2932, 2860, 2116, 1776, 1049 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.41 (4H, t, *J* = 6.7 Hz, 2 × CH_2Br), 2.46 (4H, *J* = 7.4 Hz, 2 × $COCH_2$), 1.93–1.86 (4H, m, 2 × CH_2CH_2Br), 1.79–1.72 (4H, m, 2 × $COCH_2CH_2$), 1.59–1.51 (4H, m, $COCH_2CH_2CH_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.9 (C), 33.1 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 27.4 (CH_2), 23.9 (CH_2).

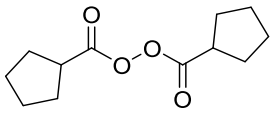
General Procedure 4 – Secondary Peroxides



2i-2o

A 30% solution of H_2O_2 (500 μL, 5.0 mmol) was added to a solution of the corresponding carboxylic acid (10.0 mmol) in DCM (15 mL) at –10 °C. The resultant solution was stirred for 10 min at –10 °C. Then, DMAP (122 mg, 1.0 mmol) and EDC·HCl (2.11 g, 11.0 mmol) were added in one portion with DCM (15 mL) and the reaction was stirred at –10 °C for 2 h. Then, the mixture was extracted with 10% citric acid (30 mL), dried with anhydrous $MgSO_4$ and concentrated. The residue was purified by filtration through a short pad of alumina (hexanes/DCM) to afford the diacyl peroxide. *Secondary diacyl peroxides decompose rapidly, they should be prepared and used as soon as possible (2 days maximum).*

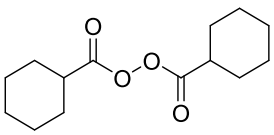
Di(cyclopentanecarboxyl) peroxide (2i)



2i

It was prepared following General Procedure 4 from cyclopentanecarboxylic acid (1.1 mL, 10.0 mmol). The residue was purified by filtration through a short pad of alumina (80:20 hexanes/DCM) to afford **2i** (543 mg, 2.4 mmol, 48% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.91–2.83 (2H, m, 2 × COC<u>H</u>), 2.01–1.58 (16H, m, CH(C<u>H</u>$_2$)$_4$).

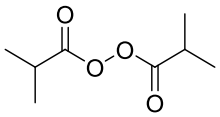
Di(cyclohexanecarboxyl) peroxide (2j)



2j

It was prepared following General Procedure 4 from cyclohexanecarboxylic acid (1.28 g, 10.0 mmol). The residue was purified by filtration through a short pad of alumina (80:20 hexanes/DCM) to afford **2j** (374 mg, 1.5 mmol, 30% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.49–2.41 (2H, m, 2 × COC<u>H</u>), 1.98–1.27 (20H, m, 2 × CH(C<u>H</u>$_2$)$_5$).

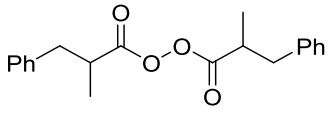
Di(2-methylpropanoyl) peroxide (2k)



2k

It was prepared following General Procedure 4 from isobutyric acid (930 μL, 10.0 mmol). The residue was purified by filtration through a short pad of alumina (80:20 hexanes/DCM) to afford **2k** (279 mg, 1.6 mmol, 32% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.74 (2H, sext, *J* = 7.0 Hz, 2 × COC**H**), 1.29 (12H, d, *J* = 7.0 Hz, 4 × CHC**H**$_3$).

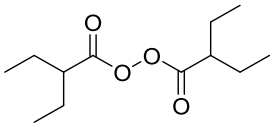
Di(2-methyl-3-phenylpropanoyl) peroxide (2l)



2l

It was prepared following General Procedure 4 from 2-methyl-3-phenylpropanoic acid (1.64 g, 10.0 mmol). The residue was purified by filtration through a short pad of alumina (80:20 hexanes/DCM) to afford **2l** (556 mg, 1.7 mmol, 34% yield, dr 1:1) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.11 (10H, m, Ar**H**), 3.16–3.09 (2H, m, 4 × C**H**$_x$H$_y$Ph) 2.91–2.86 (2H, m, 4 × CH$_x$**H**$_y$Ph), 2.76–2.71 (2H, m, 4 × COC**H**), 1.27 (6H, d, *J* = 5.6 Hz, 2 × C**H**$_3$ diast 1), 1.25 (6H, d, *J* = 5.6 Hz, 2 × C**H**$_3$ diast 2).

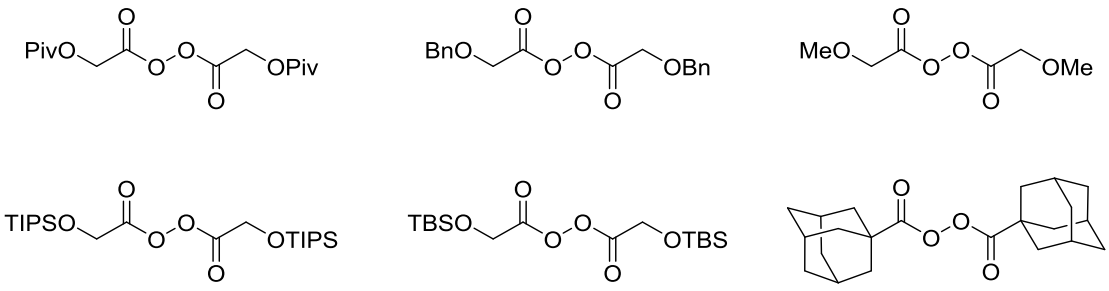
Di(2-ethylbutanoyl) peroxide (2m)



2m

It was prepared following General Procedure 4 from 2-ethylbutanoic acid (1.3 mL, 10.0 mmol). The residue was purified by filtration through a short pad of alumina (80:20 hexanes/DCM) to afford **2m** (511 mg, 2.2 mmol, 44% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.37 (2H, tt, *J* = 8.8, 5.4 Hz, 2 × COC**H**), 1.81–1.55 (8H, m, 4 × $CHCH_2$), 1.03–0.96 (12H, m, 4 × CH_2C**H**$_3$).

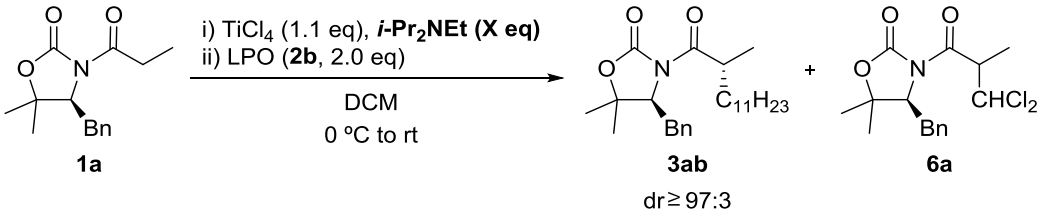
Unsuccessful preparation of diacyl peroxides



2. Second optimization

2.1. Screening of equivalents of base

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-propanoyl oxazolidinone **1a** (131 mg, 0.50 mmol) in DCM (2 mL) at 0 °C. After 5 min, *i*-Pr_2NEt (**X mmol**) was added dropwise and the solution was stirred for 40 min at 0 °C. Then, dilauroyl peroxide (**2b**) (399 mg, 1 mmol) was added and the resultant mixture was stirred at rt for 2 h. The reaction was quenched with sat NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The resulting crude mixtures were analyzed by ^1H NMR and purified by flash column chromatography (90:10 hexanes/EtOAc) to afford **3ab**. Results are summarized in *Table 41*.

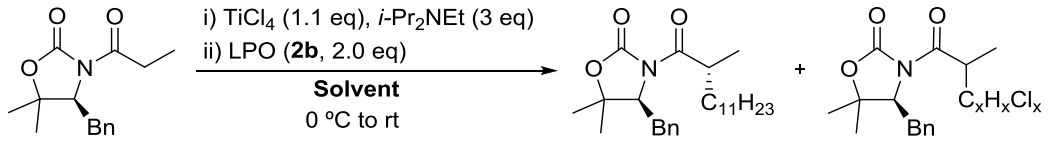


Entry	*i*-Pr_2NEt	^1H NMR crude			Yield (3ab)
		1a	3ab	6a	
1	1 eq	18	67	15	66%
2	2 eq	16	67	17	66%
3	3 eq	11	67	22	67%

Table 41. Screening of equivalents of base

2.2. Screening of solvents

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-propanoyl oxazolidinone **1a** (131 mg, 0.50 mmol) in **Solvent** (2 mL) at 0 °C. After 5 min, *i*-Pr_2NEt (260 µL, 1.5 mmol) was added dropwise and the solution was stirred for 40 min at 0 °C. Then, dilauroyl peroxide (**2b**) (399 mg, 1 mmol) was added and the resultant mixture was stirred at rt for 2 h. The reaction was quenched with sat NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The resulting crude mixtures were analyzed by ^1H NMR and purified by flash column chromatography (90:10 hexanes/EtOAc) to afford **3ab** and by-products **6a**, **7a**, **8a**. Results are summarized in *Table 42*.



1a **3ab** **6a, 7a, 8a**

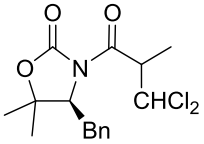
dr ≥97:3

Entry	solvent	byprod.	$C_xH_yCl_z$	^{1}H NMR crude			Yield
				1a	3ab	byprod.	
1	DCE	-	-	-	100	-	76%
2	DCM	**6a**	$CHCl_2$	18	67	15	66%
3	TCE	**7a**	CCl_2CHCl_2	60	20	20	-
4	$CHCl_3$	**8a**	CCl_3	22	19	59	-
5[a]	CCl_4	**8a**	CCl_3	54	-	27	-

[a]The rest of material was found as dimer of the starting material.

Table 42. Screening of Solvents

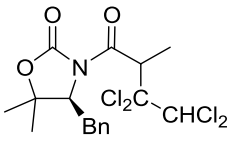
(4*S*)-4-Benzyl-*N*-(3,3-dichloro-2-methylpropanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (6a)



6a

R_f (90:10 hexanes/EtOAc) 0.4; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.20 (5H, m, ArH), 6.06 (1H, d, *J* = 7.5 Hz, CHCl$_2$), 4.58-4.50 (2H, m, CHN, COCH), 3.23 (1H, dd, *J* = 14.6, 3.0 Hz, CH$_x$H$_y$Ph), 2.85 (1H, dd, *J* = 14.6, 10.3 Hz, CH$_x$H$_y$Ph), 1.44 (3H, d, *J* = 6.8 Hz, CHCH$_3$), 1.38 (3H, s, CCH$_3$), 1.34 (3H, s, CCH$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.0 (C), 152.1 (C), 136.6 (C), 128.9 (CH), 128.8 (CH), 126.9 (CH), 82.7 (C), 73.6 (CH), 63.9 (CH), 49.4 (CH), 34.8 (CH_2), 28.7 (CH_3), 22.4 (CH_3), 14.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{16}H_{20}Cl_2NO_3$ $[M+H]^+$: 344.0815, found: 344.0821.

(4*S*)-4-Benzyl-5,5-dimethyl-*N*-(3,3,4,4-tetrachloro-2-methylbutanoyl)-1,3-oxazolidin-2-one (7a)

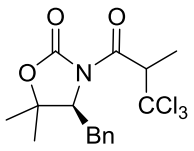


7a

R_f (90:10 hexanes/EtOAc) 0.3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.15 (5H, m, ArH), 6.23 (1H, s, CHCl$_2$), 5.00 (1H, q, *J* = 6.9 Hz, COCH), 4.49 (1H, dd, *J* = 9.5, 3.9 Hz, CHN), 3.16 (1H, dd, *J* = 14.5, 3.9 Hz, CH$_x$H$_y$Ph), 2.92 (1H, dd, *J* = 14.5, 9.5 Hz, CH$_x$H$_y$Ph), 1.65 (3H, d, *J* = 6.9 Hz, CHCH$_3$), 1.38 (3H, s, CCH$_3$), 1.37 (3H, s, CCH$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.2 (C), 151.7 (C), 136.5 (C), 129.0 (CH), 128.8 (CH), 127.0 (CH), 94.8 (C), 82.7 (C), 76.9 (CH),

64.1 (CH), 49.2 (CH), 35.1 (CH_2), 28.5 (CH_3), 22.1 (CH_3), 15.6 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{17}H_{20}Cl_4NO_3$ $[M+H]^+$: 426.0192, found: 426.0203.

(4*S*)-4-Benzyl-5,5-dimethyl-*N*-(3,3,3-trichloro-2-methylpropanoyl)-1,3-oxazolidin-2-one (8a)

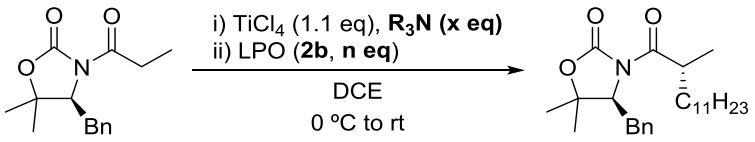


8a

R_f (90:10 hexanes/EtOAc) 0.4; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.18 (5H, m, Ar<u>H</u>), 5,31 (1H, q, *J* = 6.7 Hz, COC<u>H</u>), 4.56 (1H, dd, *J* = 10.5, 2.9 Hz, C<u>H</u>N), 3.31 (1H, dd, *J* = 14.5, 2.9 Hz, C<u>H</u>$_x$H$_y$Ph), 2.85 (1H, dd, *J* = 14.5, 10.5 Hz, CH$_x$<u>H</u>$_y$Ph), 1.64 (3H, d, *J* = 6.7 Hz, CHC<u>H</u>$_3$), 1.38 (3H, s, CC<u>H</u>$_3$), 1.34 (3H, s, CC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.9 (C), 152.1 (C), 136.6 (C), 128.9 (CH), 128.7 (CH), 126.9 (CH), 99.2 (C), 82.4 (C), 64.1 (CH), 55.6 (CH), 34.6 (CH_2), 28.7 (CH_3), 22.4 (CH_3), 15.6 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{16}H_{19}Cl_3NO_3$ $[M+H]^+$: 378.0425, found: 378.0429.

2.3. Survey of the alkylation in DCE

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-propanoyl oxazolidinone **1a** (131 mg, 0.50 mmol) in DCE (2 mL) at 0 °C. After 5 min, **R_3N** (1.5 mmol) was added dropwise and the solution was stirred for 40 min at 0 °C. Then, dilauroyl peroxide (**2b**) (**n eq**) was added and the resultant mixture was stirred at rt for 2 h. The reaction was quenched with sat NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The resulting crude mixtures were analyzed by ^{1}H NMR and purified by flash column chromatography (90:10 hexanes/EtOAc) to afford **3ab**. Results are summarized in *Table 43*.



1a **3ab**

dr ≥ 97:3

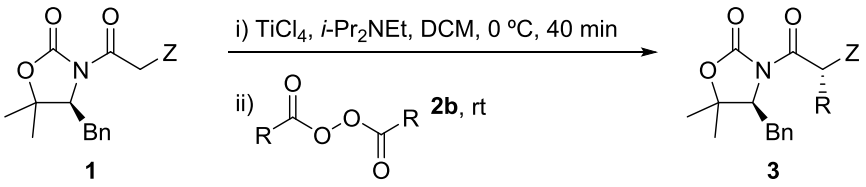
Entry	base	$TiCl_4$	LPO (2b)	^{1}H NMR crude conversion	Yield
1	*i*-Pr_2NEt	1.1 eq	2 eq	quantitative	76%
2	Et_3N	1.1 eq	2 eq	quantitative	90%
3	Et_3N	0.5 eq	2 eq	50%	-
4	Et_3N	1.1 eq	1.5 eq	quantitative	87%
5[a]	Et_3N	1.1 eq	1.5 eq	quantitative	93%
6[a]	Et_3N (2 eq)	1.1 eq	1.5 eq	quantitative	84%

[a]reaction time: 15 min

Table 43. Survey of the Alkylation in DCE

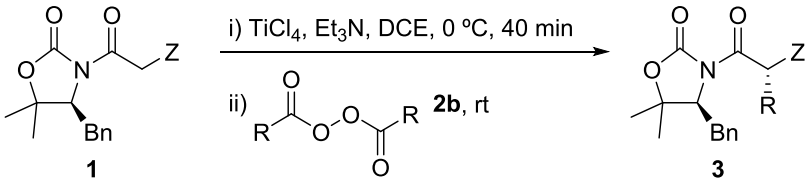
3. Scope of the alkylation

General Procedure 5 – 1st Methodology (before second optimization)



Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone (0.50 mmol) in DCM (2 mL) at 0 °C. After 5 min, *i*-Pr_2NEt (95 µL, 0.55 mmol) was added dropwise and the resultant deep purple mixture was stirred at 0 °C for 40 min. A solution of the peroxide (1.5 mmol) in DCM (1 mL) was added via *cannula*. The reaction was allowed to warm to rt and stirred for 2 to 16 h. Then, it was quenched with sat NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The residue was purified by flash column chromatography to afford the corresponding alkylated products as a single diastereomer.

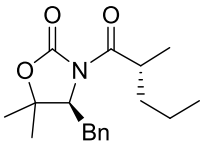
General Procedure 6 – 2nd Methodology



Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone (0.50 mmol) in DCE (2 mL) at 0 °C. After 5 min, Et_3N (210 µL, 1.5 mmol) was added dropwise and the resultant deep purple mixture was stirred at 0 °C for 40 min. A solution of the peroxide (0.75 to 1.0 mmol) in DCE (1 mL) was added via *cannula*. The reaction was allowed to warm to rt and stirred for 15 to 60 min. Then, it was quenched with sat NH_4Cl (3 mL). The layers were separated and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The residue was purified by flash column chromatography to afford the corresponding alkylated products as a single diastereomer.

3.1. Scope of diacyl peroxides

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methylpentanoyl]-1,3-oxazolidin-2-one (3aa)



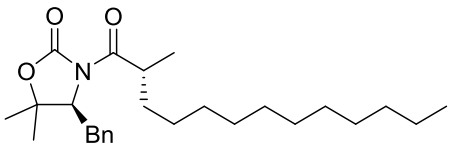
3aa

1st Methodology (Alejandro Gómez-Palomino)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (261 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and peroxide **2a** (261 mg, 1.5 mmol) for 15 min. Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded **3aa** (264 mg, 0.87 mmol, 87% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −41.7 (*c* 1.5, $CHCl_3$); **IR** (ATR) ν 3027, 2958, 2926, 2872, 1774, 1691 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32−7.20 (5H, m, ArH), 4.53 (1H, dd, *J* = 9.7, 3.7 Hz, CHN), 3.77 (1H, sext, *J* = 6.8 Hz, COCH), 3.12 (1H, dd, *J* = 14.4, 3.7 Hz, CH_xH_yPh), 2.87 (1H, dd, *J* = 14.4, 9.7 Hz, CH_xH_yPh), 1.74−1.66 (1H, m, $COCHCH_xH_y$), 1.38−1.27 (3H, m, $COCHCH_xH_y$, CH_2CH_3), 1.36 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.15 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 0.90 (3H, t, *J* = 7.1 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.7 (C), 152.3 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.8 (C), 63.6 (CH), 37.4 (CH), 36.0 (CH_2), 35.4 (CH_2), 28.6 (CH_3), 22.3 (CH_2), 20.2 (CH_2), 16.8 (CH_3), 14.1 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{26}NO_3$ $[M+H]^+$: 304.1907, found: 304.1914.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methyltridecanoyl]-1,3-oxazolidin-2-one (3ab)



3ab

1st Methodology

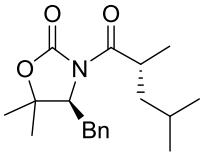
It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol) and peroxide **2b** (618 mg, 1.55 mmol) for 2.0 h. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3ab** (158 mg, 0.38 mmol, 76% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol) and peroxide **2b** (299 mg, 0.75 mmol) for 15 min. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3ab** (194 mg, 0.47 mmol, 93% yield)

as a colorless oil. **R_f** (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −46.4 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2922, 2852, 1774, 1697, 1351, 1096 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, ArH), 4.52 (1H, dd, *J* = 9.7, 3.6 Hz, CHN), 3.74 (1H, sext, *J* = 6.8 Hz, COCH), 3.12 (1H, dd, *J* = 14.3, 3.6 Hz, CH_xH_yPh), 2.87 (1H, dd, *J* = 14.3, 9.7 Hz, CH_xH_yPh), 1.74–1.66 (1H, m, $COCHCH_xH_y$), 1.36 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.25 (19H, br s, $COCHCH_xH_y(CH_2)_9$), 1.15 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 0.87 (3H, t, *J* = 6.8 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.7 (C), 152.3 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.8 (C), 63.6 (CH), 37.6 (CH), 35.4 (CH_2), 33.8 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2) 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.5 (CH_3), 27.0 (CH_2), 22.6 (CH_2), 22.3 (CH_3), 16.8 (CH_3), 14.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{26}H_{42}NO_3$ $[M+H]^+$: 416.3159, found: 416.3165.

(*S*)-4-Benzyl-*N*-[(*R*)-2,4-dimethylpentanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3ac)



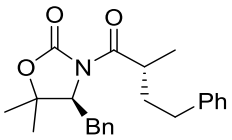
3ac

1st Methodology (Alejandro Gómez-Palomino)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (261 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and peroxide **2c** (303 mg, 1.5 mmol) for 15 min. Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded **3ac** (266 mg, 0.84 mmol, 84% yield) as a colorless oil. **R_f** (90:10 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ −43.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3059, 3027, 2955, 2926, 2872, 1770, 1691 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, ArH), 4.53 (1H, dd, *J* = 9.7, 3.8 Hz, CHN), 3.88 (1H, sext, *J* = 6.9 Hz, COCH), 3.12 (1H, dd, *J* = 14.4, 3.8 Hz, CH_xH_yPh), 2.88 (1H, dd, *J* = 14.4, 9.7 Hz, CH_xH_yPh), 1.64 (1H, dt, *J* = 12.9, 6.9 Hz , $COCHCH_xH_y$), 1.59–1.49 (1H, m, $CH(CH_3)_2$), 1.37 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.23–1.13 (1H, m, $COCHCH_xH_y$), 1.14 (3H, d, *J* = 6.9 Hz, $COCHCH_3$), 0.91 (3H, d, *J* = 6.5 Hz, $CH(CH_3)_2$), 0.89 (3H, d, *J* = 6.5 Hz, $CH(CH_3)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 178.0 (C), 152.3 (C), 137.0 (C), 129.1 (CH), 128.6 (CH), 126.7 (CH), 81.8 (C), 63.6 (CH), 42.7 (CH_2), 35.6 (CH), 35.4 (CH_2), 28.6 (CH_3), 25.7 (CH), 22.9 (CH_3), 22.3 (CH_3), 22.2 (CH_3), 17.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2064, found: 318.2067.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methyl-4-phenylbutanoyl]-1,3-oxazolidin-2-one (3ad)



3ad

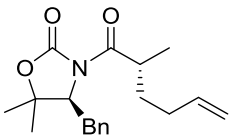
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1a** (79 mg, 0.30 mmol), $TiCl_4$ (37 µL, 0.33 mmol), *i*-Pr_2NEt (58 µL, 0.33 mmol) and peroxide **2d** (277 mg, 0.93 mmol) for 30 min. Purification of the residue by flash column chromatography (40:60 hexanes/DCM) afforded **3ad** (95 mg, 0.26 mmol, 87% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol) and peroxide **2d** (224 mg, 0.75 mmol) for 15 min. Purification of the residue by flash column chromatography (40:60 hexanes/DCM) afforded **3ad** (174 mg, 0.48 mmol, 95% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −53.2 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2924, 2854, 1777, 1696, 1603, 1496, 1455 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.15 (10H, m, ArH), 4.53 (1H, dd, *J* = 9.6, 3.8 Hz, NCH), 3.82 (1H, h, *J* = 6.8 Hz, COCH), 3.09 (1H, dd, *J* = 14.4, 3.8 Hz, $NCHCH_xH_yPh$), 2.86 (1H, dd, *J* = 14.4, 9.6 Hz, $NCHCH_xH_yPh$), 2.67–2.52 (2H, m, CH_2CH_2Ph), 2.10–2.01 (1H, m, $CH_xH_yCH_2Ph$), 1.70–2.61 (1H, m, $CH_xH_yCH_2Ph$), 1.36 (3H, s,CCH_3), 1.35 (3H, s, CCH_3), 1.21 (3H, d, *J* = 6.8 Hz, $CHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.1 (C), 152.3 (C), 141.8 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 126.8 (CH), 125.9 (CH), 81.9 (C), 63.6 (CH), 37.7 (CH), 35.7 (CH_2), 35.4 (CH_2), 33.6 (CH_2), 28.6 (CH_3), 22.3 (CH_3), 16.9 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{23}H_{28}NO_3$ $[M+H]^+$: 366.2064, found: 366.2056.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methyl-5-hexenoyl]-1,3-oxazolidin-2-one (3ae)



3ae

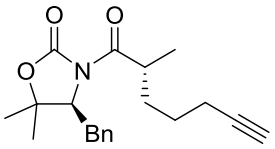
1st Methodology (Alejandro Gómez-Palomino)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (261 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and peroxide **2e** (298 mg, 1.5 mmol) for 15 min. Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc)

afforded **3ae** (293 mg, 0.89 mmol, 93% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −53.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3060, 2024, 2971, 2932, 1767, 1692, 1350, 1277, 1239, 1093 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, ArH), 5.80 (1H, ddt, *J* = 16.8, 10.0, 6.7 Hz, CH=CH_2), 5.07–4.98 (1H, m, CH=CH_xH_y), 4.97–4.93 (1H, m, CH=CH_xH_y), 4.53 (1H, dd, *J* = 9.7, 3.8 Hz, CHN), 3.77 (1H, sext, *J* = 6.8 Hz, COCH), 3.13 (1H, dd, *J* = 14.4, 3.8 Hz, CH_xH_yPh), 2.87 (1H, dd, *J* = 14.4, 9.7 Hz, CH_xH_yPh), 2.11–2.01 (2H, m, CH_2CH=CH_2), 1.85 (1H, ddt, *J* = 13.6, 8.7, 6.8 Hz, COCHCH_xH_y), 1.50–1.41 (1H, m, COCHCH_xH_y), 1.37 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.17 (3H, d, *J* = 6.8 Hz, COCHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.3 (C), 152.3 (C), 138.0 (CH), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 114.9 (CH_2), 81.9 (C), 63.7 (CH), 37.2 (CH), 35.4 (CH_2), 32.8 (CH_2), 31.3 (CH_2), 28.5 (CH_3), 22.3 (CH_3), 16.9 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1907, found: 316.1914.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methyl-6-heptynoyl]-1,3-oxazolidin-2-one (3af)



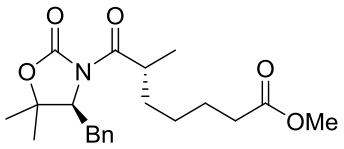
3af

1st Methodology (Alejandro Gómez-Palomino)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (261 mg, 1.0 mmol), $TiCl_4$ (122 μL, 1.1 mmol), Et_3N (420 μL, 3.0 mmol) and peroxide **2f** (363 mg, 1.5 mmol) for 15 min. Purification of the residue by flash column chromatography (from 95:5 to 90:10 hexanes/EtOAc) afforded **3af** (296 mg, 0.91 mmol, 91% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ −49.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3284, 3069, 3027, 2974, 2929, 2863, 1767, 1694, 1274, 1236, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH), 4.53 (1H, dd, *J* = 9.5, 4.0 Hz, CHN), 3.79–3.73 (1H, m, COCH), 3.11 (1H, dd, *J* = 14.3, 4.0 Hz, CH_xH_yPh), 2.89 (1H, dd, *J* = 14.3, 9.5 Hz, CH_xH_yPh), 2.21–2.16 (2H, m, CH_2C≡CH), 1.95 (1H, t, *J* = 2.7 Hz, C≡CH), 1.82–1.75 (1H, m, COCHCH_xH_y), 1.55–1.47 (3H, m, COCHC$H_xH_yCH_2$), 1.38 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 1.17 (3H, d, *J* = 6.8 Hz, COCHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.1 (C), 152.3 (C), 136.8 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 84.1 (C), 81.9 (C), 68.5 (CH), 63.6 (CH), 37.3 (CH), 35.5 (CH_2), 32.8 (CH_2), 28.5 (CH_3), 25.9 (CH_2), 22.2 (CH_3), 18.5 (CH_2), 16.9 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1907, found: 328.1911.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-(2-methyl-7-methoxy-7-oxoheptanoyl)]-1,3-oxazolidin-2-one (3ag)



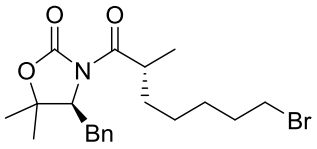
3ag

1st Methodology (Alejandro Gómez-Palomino)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (231 mg, 0.90 mmol), $TiCl_4$ (110 µL, 0.99 mmol), Et_3N (380 µL, 2.7 mmol) and peroxide **2g** (566 mg, 1.8 mmol) for 15 min. Purification of the residue by flash column chromatography (85:15 hexanes/EtOAc) afforded **3ag** (257 mg, 0.69 mmol, 77% yield) as a colorless oil. $\mathbf{R_f}$ (85:15 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −43.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2974, 2936, 2856, 1770, 1733, 1695, 1233, 1154, 1084 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, ArH), 4.52 (1H, dd, *J* = 9.6, 3.9 Hz, CHN), 3.74 (1H, sext, *J* = 6.8 Hz, COCH), 3.65 (3H, s, OCH_3), 3.11 (1H, dd, *J* = 14.3, 3.9 Hz, CH_xH_yPh), 2.88 (1H, dd, *J* = 14.3, 9.6 Hz, CH_xH_yPh), 2.30 (2H, t, *J* = 7.5 Hz, CH_2CO_2Me), 1.76–1.68 (1H, m, $COCHCH_xH_y$), 1.62 (2H, quint, *J* = 7.5 Hz, $CH_2CH_2CO_2Me$), 1.42–1.28 (3H, m, $COCHCH_xH_yCH_2$), 1.37 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.15 (3H, d, *J* = 6.8 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.3 (C), 174.0 (C), 152.3 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 81.9 (C), 63.6 (CH), 51.4 (CH_3), 37.5 (CH), 35.4 (CH_2), 33.8 (CH_2), 33.3 (CH_2), 28.5 (CH_3), 26.5 (CH_2), 24.8 (CH_2), 22.3 (CH_3), 16.8 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{30}NO_5$ $[M+H]^+$: 376.2118, found: 376.2123.

(*S*)-4-Benzyl-*N*-[(*R*)-(7-bromo-2-methyl-heptanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3ah)



3ah

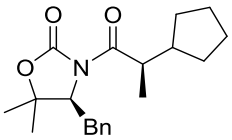
1st Methodology (Alejandro Gómez-Palomino)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (261 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and peroxide **2h** (582 mg, 1.5 mmol) for 15 min. Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded **3ah** (373 mg, 0.91 mmol, 91% yield) as a colorless oil. $\mathbf{R_f}$ (40:60 hexanes/DCM) 0.3;

$[\alpha]_D^{20}$ −54.9 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3059, 3027, 2970, 2929, 2850, 1770, 1688, 1347, 1233, 1154, 1093 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32−7.20 (5H, m, ArH), 4.53 (1H, dd, *J* = 9.6, 3.9 Hz, CHN), 3.74 (1H, sext, *J* = 6.7 Hz, COCH), 3.39 (2H, t, *J* = 6.8 Hz, CH_2Br), 3.11 (1H, dd, *J* = 14.4, 3.9 Hz, CH_xH_yPh), 2.89 (1H, dd, *J* = 14.4, 9.6 Hz, CH_xH_yPh), 1.89−1.81 (2H, m, CH_2CH_2Br), 1.76−1.68 (1H, m, $COCHCH_xH_y$), 1.47−1.40 (2H, m, $CH_2CH_2CH_2Br$), 1.37 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 1.35−1.13 (3H, m, $COCHCH_xH_yCH_2$), 1.15 (3H, d, *J* = 6.8 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.4 (C), 152.3 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 81.9 (C), 63.6 (CH), 37.5 (CH), 35.4 (CH_2), 33.8 (CH_2), 33.5 (CH_2), 32.5 (CH_2), 28.5 (CH_3), 28.1 (CH_2), 26.1 (CH_2), 22.3 (CH_3), 16.8 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{29}BrNO_3$ $[M+H]^+$: 410.1325, found: 410.1332.

(*S*)-4-Benzyl-*N*-[(*R*)-2-cyclopentylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3ai)



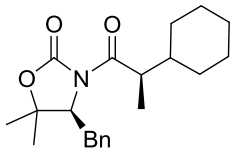
3ai

1st Methodology (Alejandro Gómez-Palomino)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol) and peroxide **2i** (226 mg, 1.0 mmol) for 60 min. Purification of the residue by flash column chromatography (93:7 hexanes/EtOAc) afforded **3ai** (116 mg, 0.35 mmol, 70% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ −55.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2945, 2857, 1770, 1688, 1270, 1169, 1093 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33−7.20 (5H, m, ArH), 4.54 (1H, dd, *J* = 10.1, 3.3 Hz, CHN), 3.72 (1H, dq, *J* = 9.1, 6.8 Hz, COCH), 3.18 (1H, dd, *J* = 14.4, 3.3 Hz, CH_xH_yPh), 2.85 (1H, dd, *J* = 14.4, 10.1 Hz, CH_xH_yPh), 2.17−2.06 (1H, m, $CH(CH_2)_4$), 1.81−1.46 (6H, m, $CH(CH_2)_4$), 1.35 (3H, s, CCH_3), 1.33 (3H, s, CCH_3), 1.26−1.14 (2H, m, $CH(CH_2)_4$), 1.18 (3H, d, *J* = 6.8 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.9 (C), 152.4 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.7 (C), 63.8 (CH), 43.4 (CH), 42.4 (CH), 35.2 (CH_2), 30.8 (CH_2), 29.8 (CH_2), 28.6 (CH_3), 25.2 (CH_2), 25.0 (CH_2), 22.4 (CH_3), 16.2 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{28}NO_3$ $[M+H]^+$: 330.2064, found: 330.2072.

(*S*)-4-Benzyl-*N*-[(*R*)-2-cyclohexylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3aj)



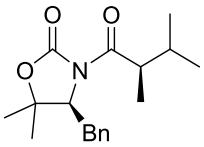
3aj

1st Methodology (Alejandro Gómez-Palomino)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol) and peroxide **2j** (254 mg, 1.0 mmol) for 60 min. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3aj** (127 mg, 0.37 mmol, 74% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −71.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2923, 2851, 1768, 1689, 1451, 1375, 1347, 1274, 1236, 1201, 1093 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH), 4.56 (1H, dd, *J* = 9.9, 3.6 Hz, CHN), 3.68 (1H, quint, *J* = 6.9 Hz, COCH), 3.15 (1H, dd, *J* = 14.3, 3.6 Hz, CH_xH_yPh), 2.87 (1H, dd, *J* = 14.3, 9.9 Hz, CH_xH_yPh), 1.75–1.59 (6H, m, $CH(CH_2)_5$, $CH(CH_2)_5$), 1.36 (3H, s, CCH_3), 1.33 (3H, s, CCH_3), 1.29–1.13 (3H, m, $CH(CH_2)_5$), 1.12–1.05 (1H, m, $CH(CH_2)_5$), 1.11 (3H, d, *J* = 6.9 Hz, $COCHCH_3$), 1.03–0.93 (1H, m, $CH(CH_2)_5$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.5 (C), 152.4 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.7 (C), 63.7 (CH), 42.6 (CH), 40.8 (CH), 35.4 (CH_2), 31.3 (CH_2), 28.7 (CH_2), 28.6 (CH_3), 26.4 (CH_2), 26.3 (CH_2), 26.3 (CH_2), 22.4 (CH_3), 13.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{30}NO_3$ $[M+H]^+$: 344.2220, found: 344.2222.

(*S*)-4-Benzyl-*N*-[(*R*)-2,3-dimethylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3ak)



3ak

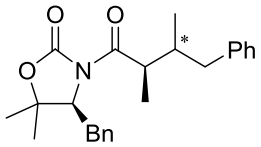
1st Methodology (Alejandro Gómez-Palomino)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol), and peroxide **2k** (174 mg, 1.0 mmol) for 60 min. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3ak** (118 mg, 0.39 mmol, 77% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −53.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3024, 2964, 2926, 2869, 1767, 1688 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH),

4.56 (1H, dd, *J* = 10.0, 3.5 Hz, C<u>H</u>N), 3.65 (1H, quint, *J* = 6.8 Hz, COC<u>H</u>), 3.16 (1H, dd, *J* = 14.4, 3.5 Hz, C<u>H</u>$_x$H$_y$Ph), 2.85 (1H, dd, *J* = 14.4, 10.0 Hz, CH$_x$<u>H</u>$_y$Ph), 2.03 (1H, oct, *J* = 6.8 Hz, COCHC<u>H</u>), 1.35 (3H, s, CC<u>H</u>$_3$), 1.33 (3H, s, CC<u>H</u>$_3$), 1.11 (3H, d, *J* = 6.8 Hz, COCHC<u>H</u>$_3$), 0.96 (3H, d, *J* = 6.8 Hz, CH(C<u>H</u>$_3$)$_2$), 0.87 (3H, d, *J* = 6.8 Hz, CH(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.4 (C), 152.4 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.7 (C), 63.7 (CH), 43.3 (CH), 35.3 (CH_2), 30.8 (CH), 28.6 (CH_3), 22.4 (CH_3), 21.0 (CH_3), 18.2 (CH_3), 12.9 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{26}NO_3$ $[M+H]^+$: 304.1907, found: 304.1914.

(4*S*)-4-Benzyl-*N*-[(2*R*)-2,3-dimethyl-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3al)



3al

<u>1st Methodology</u> (Alejandro Gómez-Palomino)

<u>2nd Methodology</u>

It was prepared following <u>General Procedure 6</u> from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol) and peroxide **2l** (326 mg, 1.0 mmol) for 60 min. Purification of the residue by flash column chromatography (from 60:40 to 35:65 hexanes/DCM) afforded **3al** as a mixture of diastereomers (142 mg, 0.37 mmol, 75% yield, dr 2:1) as a colorless oil. The diastereomers were separated by a second flash column chromatography (from 60:40 to 35:65 hexanes/DCM) and characterized individually.

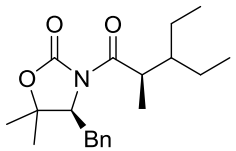
Major diastereomer

R$_f$ (70:30 hexanes/DCM) 0.2; $[\alpha]_D^{20}$ −58.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2968, 2926, 1771, 1685, 1495, 1454, 1359, 1232, 1101 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.11 (10H, m, Ar<u>H</u>), 4.57 (1H, dd, *J* = 9.9, 3.6 Hz, NC<u>H</u>), 3.80 (1H, qd, *J* = 6.9, 5.6 Hz, COC<u>H</u>), 3.11 (1H, dd, *J* = 14.4, 3.6 Hz, NCHC<u>H</u>$_x$H$_y$), 2.84 (1H, dd, *J* = 14.4, 9.9 Hz, NCHCH$_x$<u>H</u>$_y$), 2.77 (1H, dd, *J* = 12.9, 3.9 Hz, CH$_3$CHC<u>H</u>$_x$H$_y$Ph), 2.35 (1H, dd, *J* = 12.9, 10.3 Hz, CH$_3$CHCH$_x$<u>H</u>$_y$Ph), 2.26–2.16 (1H, m, COCHC<u>H</u>), 1.35 (3H, s, CC<u>H</u>$_3$), 1.34 (3H, s, CC<u>H</u>$_3$), 1.15 (3H, d, *J* = 6.9 Hz, COCHC<u>H</u>$_3$), 0.74 (3H, d, *J* = 6.8 Hz, COCHCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.0 (C), 152.3 (C), 140.8 (C), 136.9 (C), 129.3 (CH), 129.0 (CH), 128.7 (CH), 128.1 (CH), 126.8 (CH), 125.9 (CH), 81.8 (C), 63.6 (CH), 42.7 (CH), 41.9 (CH_2), 37.5 (CH), 35.4 (CH_2), 28.7 (CH_3), 22.4 (CH_3), 14.2 (CH_3), 12.2 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{24}H_{30}NO_3$ $[M+H]^+$: 380.2220, found: 380.2224.

Minor diastereomer

R_f (70:30 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ −55.4 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2970, 2933, 1770, 1692, 1496, 1454, 1350, 1234, 1089 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.09 (10H, m, ArH), 4.57 (1H, dd, *J* = 10.1, 3.3 Hz, NCH), 3.84 (1H, qd, *J* = 6.8, 5.2 Hz, COCH), 3.18 (1H, dd, *J* = 14.3, 3.3 Hz, $NCHCH_xH_y$), 2.91–2.80 (2H, m, $NCHCH_xH_y$, $CH_3CHCH_xH_yPh$), 2.26–2.11 (2H, m, $COCHCH$, $CH_3CHCH_xH_yPh$), 1.36 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.25 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 0.85 (3H, d, *J* = 6.3 Hz, $COCHCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.1 (C), 152.4 (C), 140.7 (C), 137.0 (C), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.2 (CH), 126.8 (CH), 125.8 (CH), 81.8 (C), 63.8 (CH), 42.7 (CH), 38.7 (CH_2), 37.9 (CH), 35.3 (CH_2), 28.7 (CH_3), 22.4 (CH_3), 17.2 (CH_3), 13.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{24}H_{30}NO_3$ $[M+H]^+$: 380.2220, found: 380.2221.

(*S*)-4-Benzyl-*N*-[(*R*)-3-ethyl-2-methylpentanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3am)



3am

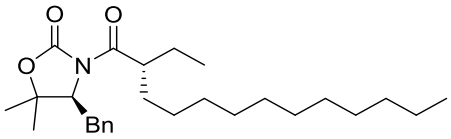
1st Methodology (not performed)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol) and peroxide **2m** (230 mg, 1.0 mmol) for 60 min. Purification of the residue by flash column chromatography (from 99.5:0.5 to 95:5 hexanes/EtOAc) afforded **3am** (94 mg, 0.28 mmol, 57% yield) as a colorless oil. **R_f** (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −44.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2963, 2933, 1770, 1694, 1351, 1275, 1231, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.29 (4H, m, ArH), 7.26–7.20 (1H, m, ArH), 4.56 (1H, dd, *J* = 10.1, 3.4 Hz, NCH), 3.88 (1H, quint, *J* = 6.8 Hz, COCH), 3.16 (1H, dd, *J* = 14.3, 3.4 Hz, $NCHCH_xH_y$), 2.83 (1H, dd, *J* = 14.3, 10.1 Hz, $NCHCH_xH_y$), 1.74–1.62 (1H, m, $CH(CH_2CH_3)_2$), 1.52–1.36 (2H, m, $2\times CH_xH_yCH_3$), 1.35 (3H, s, CCH_3), 1.31 (3H, s, CCH_3), 1.29–1.17 (2H, m, $2 \times CH_xH_yCH_3$), 1.08 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 0.92 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 0.85 (3H, t, *J* = 7.5 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 178.0 (C), 152.3 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.6 (C), 63.7 (CH), 42.8 (CH), 39.7 (CH), 35.2 (CH_2), 28.7 (CH_3), 23.6 (CH_2), 22.5 (CH_3), 21.3 (CH_2), 12.6 (CH_3), 11.2 (CH_3), 11.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{20}H_{29}NNaO_3$ $[M+Na]^+$: 354.2040, found: 354.2047.

3.1. Scope of *N*-acyl oxazolidinones

(*S*)-4-Benzyl-*N*-[(*R*)-2-ethyltridecanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3bb)



3bb

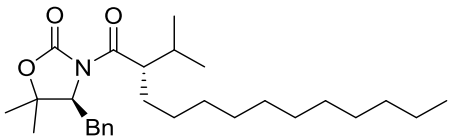
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1b** (275 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), *i*-Pr_2NEt (190 µL, 1.1 mmol) and peroxide **2b** (1.236 g, 3.1 mmol) for 4.5 h. Purification of the residue by flash column chromatography (70:30 hexanes/DCM) afforded **3bb** (272 mg, 0.63 mmol, 63% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1b** (275 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and peroxide **2b** (598 mg, 1.5 mmol) for 30 min. Purification of the residue by flash column chromatography (97:3 hexanes/EtOAc) afforded **3bb** (377 mg, 0.88 mmol, 88% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −35.1 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2925, 2854, 1779, 1696, 1392, 1352, 1234, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.20 (5H, m, ArH), 4.55 (1H, dd, *J* = 9.8, 3.5 Hz, CHN), 3.76 (1H, tt, *J* = 8.0, 5.5 Hz, COCH), 3.12 (1H, dd, *J* = 14.4, 3.5 Hz, CH_xH_yPh), 2.89 (1H, dd, *J* = 14.4, 9.8 Hz, CH_xH_yPh), 1.73–1.62 (2H, m, $COCHCH_xH_yCH_2$, $COCHCH_xH_yCH_3$), 1.58–1.49 (1H, m, $COCHCH_xH_yCH_2$), 1.48–1.41 (1H, m, $COCHCH_xH_yCH_3$), 1.36 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.24 (18H, br s, $COCHCH_2(CH_2)_9$, 0.90 (3H, t, *J* = 7.4 Hz, $CHCH_2CH_3$), 0.87 (3H, t, *J* = 6.8 Hz, $CH_2CH_2CH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.2 (C), 152.4 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.7 (C), 63.7 (CH), 44.2 (CH), 35.5 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.5 (CH_3), 27.1 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 22.2 (CH_3), 14.1 (CH_3), 11.7 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{27}H_{44}NO_3$ $[M+H]^+$: 430.3316, found: 430.3321.

(*S*)-4-Benzyl-*N*-[(*S*)-2-isopropyltridecanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3cb)



3cb

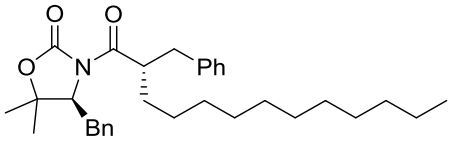
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1c** (289 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), *i*-Pr_2NEt (190 µL, 1.1 mmol) and peroxide **2b** (1.236 g, 3.1 mmol) for 20 h. Purification of the residue by flash column chromatography (70:30 hexanes/DCM) afforded **3cb** (166 mg, 0.37 mmol, 37% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1c** (289 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and peroxide **2b** (598 mg, 1.5 mmol) for 90 min. Purification of the residue by flash column chromatography (97:3 hexanes/EtOAc) afforded **3cb** (288 mg, 0.65 mmol, 65% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −29.1 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2925, 2854, 1779, 1693, 1497, 1469, 1096 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH), 4.56 (1H, dd, *J* = 10.0, 3.3 Hz, CHN), 3.75 (1H, ddd, *J* = 10.4, 7.4, 3.7 Hz, COCH), 3.14 (1H, dd, *J* = 14.4, 3.3 Hz, CH_xH_yPh), 2.89 (1H, dd, *J* = 14.4, 10.0 Hz, CH_xH_yPh), 1.98–1.86 (1H, m, $CH(CH_3)_2$), 1.72–1.64 (1H, m, $COCHCH_xH_y$), 1.57–1.50 (1H, m, $COCHCH_xH_y$), 1.34 (6H, s, $C(CH_3)_2$), 1.24 (18H, br s, $COCHCH_2(CH_2)_9$), 0.96 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 0.94 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 0.86 (3H, t, *J* = 6.9 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.0 (C), 152.5 (C), 137.2 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.5 (C), 63.9 (CH), 48.7 (CH), 35.5 (CH_2), 31.9 (CH_2), 30.9 (CH), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.5 (CH_3), 27.3 (CH_2), 22.7 (CH_2), 22.2 (CH_3), 20.9 (CH_3), 19.5 (CH_3), 14.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{28}H_{46}NO_3$ $[M+H]^+$: 444.3472, found: 444.3475.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*S*)-2-undecyl-3-phenylpropanoyl]-1,3-oxazolidin-2-one (3db)



3db

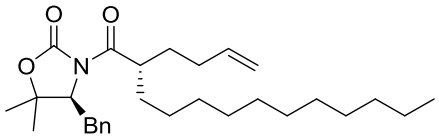
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1d** (337 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), *i*-Pr_2NEt (190 µL, 1.1 mmol) and peroxide **2b** (1.236 g, 3.1 mmol) for 20 h. Purification of the residue by flash column chromatography (70:30 hexanes/DCM) afforded **3db** (216 mg, 0.44 mmol, 44% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1d** (337 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and peroxide **2b** (598 mg, 2.0 mmol) for 60 min. Purification of the residue by flash column chromatography (97:3 hexanes/EtOAc) afforded **3db** (329 mg, 0.67 mmol, 67% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/DCM) 0.4; $[\alpha]_D^{20}$ +27.5 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2925, 1778, 1696, 1604, 1496, 1455 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.03 (10H, m, ArH), 4.31 (1H, dd, *J* = 9.5, 3.7 Hz, CHN), 4.35–4.28 (1H, m, COCH), 3.05 (1H, dd, *J* = 14.4, 3.7 Hz, NCHCH_xH_yPh), 2.94–2.73 (3H, m, NCHCH_xH_yPh, COCHCH_2Ph), 1.78–1.69 (1H, m, COCHC$H_xH_y$$CH_2$), 1.57–1.49 (1H, m, COCHC$H_xH_y$$CH_2$), 1.24 (21H, br s, C$CH_3$, COCHC$H_2$($CH_2$)$_9$), 0.87 (3H, t, *J* = 6.9 Hz, CH_2CH_3), 0.84 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.4 (C), 152.3 (C), 139.3 (C), 137.0 (C), 129.1 (CH), 128.6 (CH), 128.3 (CH), 126.7 (CH), 126.2 (CH), 81.7 (C), 63.5 (CH), 44.3 (CH), 39.0 (CH_2), 35.5 (CH_2), 33.0 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.6 (CH_3), 27.1 (CH_2), 22.7 (CH_2), 22.1 (CH_3), 14.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{32}H_{45}NO_3$ $[M+H]^+$: 492.3472, found: 492.3478.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*S*)-2-undecyl-5-hexenoyl]-1,3-oxazolidin-2-one (3eb)



3eb

1st Methodology

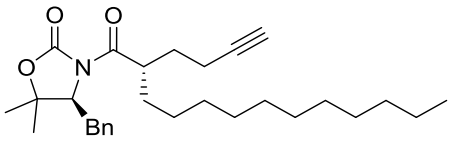
It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1e** (211 mg, 0.70 mmol), $TiCl_4$ (85 µL, 0.77 mmol), *i*-Pr_2NEt (134 µL, 0.77 mmol) and peroxide **2b** (865 mg, 2.17 mmol) for 2.0 h. Purification of the residue by flash column chromatography (50:50 hexanes/DCM) afforded **3eb** (170 mg, 0.37 mmol, 53% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1e** (301 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and peroxide **2b** (598 mg, 1.5 mmol) for 30 min. Purification of the residue by flash column chromatography (97:3 hexanes/EtOAc) afforded **3eb** (273 mg, 0.60 mmol, 60% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ −22.0 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2925, 2854, 1779, 1696, 1352, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, ArH), 5.78 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, CH=CH_2), 5.00 (1H, dq, *J* = 17.0, 1.5 Hz, CH=CH_xH_y), 4.96–4.93 (1H, m, CH=CH_xH_y), 4.54 (1H, dd, *J* = 9.8, 3.6 Hz, CHN), 3.83 (1H, dtd, *J* = 8.6, 7.5, 5.7 Hz, COCH), 3.12 (1H, dd, *J* = 14.4, 3.6 Hz, CH_xH_yPh), 2.88 (1H, dd, *J* = 14.4, 9.8 Hz, CH_xH_yPh), 2.08–2.03 (2H, m, CH_2CH=CH_2),

1.86–1.77 (1H, m, C$\underline{H}_x$H$_y$CH$_2$CH=CH$_2$), 1.70–1.61 (1H, m, COCHC$\underline{H}_x$H$_y$CH$_2$CH$_2$), 1.60–1.51 (1H, m, CH$_x\underline{H}_y$CH$_2$CH=CH$_2$), 1.50–1.41 (1H, m, COCHCH$_x\underline{H}_y$CH$_2$CH$_2$), 1.36 (3H, s, CCH$_3$), 1.34 (3H, s, CCH$_3$), 1.25 (18H, br s, COCHCH$_2$(C$\underline{H}_2$)$_9$), 0.87 (3H, t, *J* = 7.0 Hz, CH$_2$C$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, CDCl$_3$) δ 176.9 (C), 152.3 (C), 138.1 (CH), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 114.9 (CH$_2$), 81.7 (C), 63.7 (CH), 42.3 (CH), 35.4 (CH$_2$), 32.7 (CH$_2$), 31.9 (CH$_2$), 31.7 (CH$_2$), 31.1 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 28.5 (CH$_3$), 26.9 (CH$_2$), 22.7 (CH$_2$), 22.3 (CH$_3$), 14.1 (CH$_3$); **HRMS** (+ESI): *m/z* calcd. for C$_{29}$H$_{46}$NO$_3$ [M+H]$^+$: 456.3472, found: 456.3462.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*S*)-2-undecyl-5-hexynoyl]-1,3-oxazolidin-2-one (3fb)



3fb

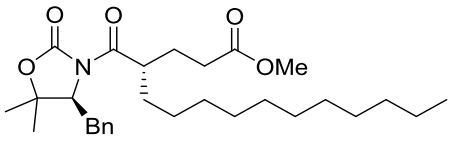
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1f** (152 mg, 0.50 mmol) and peroxide **2b** (618 mg, 1.55 mmol) for 4.0 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3fb** (109 mg, 0.24 mmol, 48% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1f** (234 mg, 0.78 mmol), TiCl$_4$ (95 µL, 0.86 mmol), Et$_3$N (320 µL, 2.3 mmol) and peroxide **2b** (478 mg, 1.2 mmol) for 90 min. Purification of the residue by flash column chromatography (97:3 hexanes/EtOAc) afforded **3fb** (286 mg, 0.63 mmol, 81% yield) as a colorless oil. **R$_f$** (90:10 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ −14.1 (*c* 1.0, CHCl$_3$); **IR** (NaCl) ν 3310, 2925, 2854, 1779, 1693, 1456, 1353, 1100 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.33–7.20 (5H, m, Ar$\underline{H}$), 4.54 (1H, dd, *J* = 9.6, 3.8 Hz, NC$\underline{H}$), 3.94 (1H, dtd, *J* = 9.2, 6.6, 5.0 Hz, COC$\underline{H}$), 3.11 (1H, dd, *J* = 14.4, 3.8 Hz, C$\underline{H}_x$H$_y$Ph), 2.89 (1H, dd, *J* = 14.4, 9.6 Hz, CH$_x\underline{H}_y$Ph), 2.28–2.13 (2H, m, C$\underline{H}_2$C≡CH), 1.95 (1H, t, *J* = 2.7 Hz, C≡C$\underline{H}$), 1.98–1.89 (1H, m, C$\underline{H}_x$H$_y$CH$_2$C≡CH), 1.76–1.60 (2H, m, CH$_x\underline{H}_y$CH$_2$C≡CH, COCHC$\underline{H}_x$H$_y$(CH$_2$)$_9$), 1.52–1.41 (m, 1H, COCHCH$_x\underline{H}_y$(CH$_2$)$_9$), 1.36 (3H, s, CC$\underline{H}_3$), 1.36 (3H, s, CC$\underline{H}_3$), 1.25 (br s, 18H, COCHCH$_2$(C$\underline{H}_2$)$_9$), 0.89–0.85 (3H, t, *J* = 6.9 Hz, CH$_2$C$\underline{H}_3$).; **^{13}C NMR** (100.6 MHz, CDCl$_3$) δ 176.3 (C), 152.2 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 83.4 (C), 81.9 (C), 69.1 (CH), 63.7 (CH), 41.8 (CH), 35.4 (CH$_2$), 32.7 (CH$_2$), 31.9 (CH$_2$), 30.0 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 28.5 (CH$_3$), 26.7 (CH$_2$), 22.7 (CH$_2$), 22.3 (CH$_3$), 16.4 (CH$_2$), 14.1 (CH$_3$); **HRMS** (+ESI): *m/z* calcd. for C$_{29}$H$_{44}$NO$_3$ [M+H]$^+$: 454.3316, found: 454.3314.

(*S*)-4-Benzyl-*N*-[(*S*)-5-methoxy-5-oxo-2-undecylpentanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3gb)



3gb

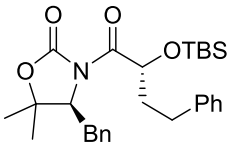
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1g** (167 mg, 0.50 mmol) and peroxide **2b** (618 mg, 1.55 mmol) for 2.0 h. Purification of the residue by flash column chromatography (89.5:10:0.5 hexanes/EtOAc/NEt_3) afforded **1gb** (125 mg, 0.26 mmol, 51% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1g** (375 mg, 1.13 mmol), $TiCl_4$ (125 µL, 1.24 mmol), Et_3N (470 µL, 3.39 mmol) and peroxide **2b** (678 mg, 1.70 mmol) for 90 min. Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded **1gb** (455 mg, 0.93 mmol, 83% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ −15.6 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2925, 2854, 1778, 1738, 1693, 1453, 1393, 1353, 1159, 1100 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, ArH), 4.55 (1H, dd, *J* = 9.7, 3.7 Hz, NCH), 3.85–3.78 (1H, m, COCH), 3.65 (3H, s, OCH_3), 3.11 (1H, dd, *J* = 14.4, 3.7 Hz, CH_xH_yPh), 2.88 (1H, dd, *J* = 14.4, 9.7 Hz, CH_xH_yPh), 2.39–2.24 (2H, m, CH_2CO), 2.05–1.94 (1H, m, $CH_xH_yCH_2CO$), 1.91–1.81 (1H, m, $CH_xH_yCH_2CO$), 1.71–1.61 (1H, m, $COCHCH_xH_y(CH_2)_9$), 1.48–1.40 (1H, m, $COCHCH_xH_y(CH_2)_9$), 1.38 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 1.24 (18H, br s, $COCHCH_2(CH_2)_9$), 0.87 (3H, t, *J* = 6.9 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.3 (C), 173.4 (C), 152.3 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 81.9 (C), 63.7 (CH), 51.6 (CH_3), 41.9 (CH), 35.4 (CH_2), 32.7 (CH_2), 31.9 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.4 (CH_3), 26.8 (CH_2), 26.8 (CH_2), 22.6 (CH_2), 22.3 (CH_3), 14.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{29}H_{46}NO_5$ $[M+H]^+$: 488.3371, found: 488.3367.

(*S*)-4-Benzyl-*N*-[(*R*)-2-*tert*-butyldimethylsilyloxy-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3hd)



3hd

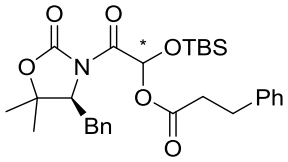
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1h** (189 mg, 0.50 mmol) and peroxide **2d** (463 mg, 1.55 mmol) for 7 h at −20 °C. Purification of the residue by flash column chromatography (from 99:01 to 90:10 hexanes/EtOAc) afforded **3hd** (150 mg, 0.31 mmol, 62% yield). **4hd** was also isolated (38 mg, 0,07 mmol, 14%) as a white solid (characterisation in the following paragraphs).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1h** (189 mg, 0.50 mmol) and peroxide **2d** (298 mg, 1.0 mmol) for 30 min at −10 °C. Purification of the residue by flash column chromatography (97:2.25:0.75 hexanes/EtOAc/EtOH) afforded **3hd** (206 mg, 0.43 mmol, 85% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −16.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2952, 2928, 2856, 1771, 1711, 1471, 1101 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.14 (10H, m, ArH), 5.42 (1H, dd, *J* = 8.4, 3.2 Hz, COCH), 4.58 (1H, dd, *J* = 9.8, 3.8 Hz, NCH), 3.06 (1H, dd, *J* = 14.4, 3.8 Hz, $NCHCH_xH_y$), 2.89–2.76 (1H, m, $CH_2CH_xH_yPh$), 2.82 (1H, dd, *J* = 14.4, 9.8 Hz, $NCHCH_xH_y$), 2.76–2.66 (1H, m, $CH_2CH_xH_yPh$), 2.08–1.98 (1H, m, $COCHCH_xH_y$), 1.90–1.79 (1H, m, $COCHCH_xH_y$), 1.37 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 0.95 (9H, s, $C(CH_3)_3$), 0.12 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.3 (C), 152.2 (C), 141.7 (C), 136.4 (C), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 126.9 (CH), 125.9 (CH), 82.9 (C), 71.4 (CH), 63.3 (CH), 37.2 (CH_2), 35.2 (CH_2), 32.1 (CH_2), 28.6 (CH_3), 25.8 (CH_3), 22.4 (CH_3), 18.4 (C), −4.8 (CH_3), −5.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{28}H_{40}NO_4Si$ $[M+H]^+$: 482.2721, found: 482.2716.

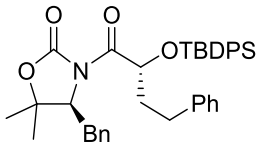
(4*S*)-Benzyl-*N*-[2-*tert*-butyldimethylsilyloxy-2-(3-phenylpropanoyloxy)-acetyl]-5,5-dimethyl-1,3-oxazolidin-2-one (4hd)



White solid; **Mp** 67–70 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ −42.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2928, 2856, 1772, 1732, 1712, 1393, 1352, 1252, 1168, 1147, 1128 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.16 (10H, m, ArH), 6.97 (1H, s, COCH), 4.47 (1H, dd, *J* = 10.0, 3.1 Hz, NCH), 3.21 (1H, dd, *J* = 14.7, 3.1 Hz, $NCHCH_xH_yPh$), 2.98 (2H, t, *J* = 7.9 Hz, CH_2CH_2Ph), 2.90 (1H, dd, *J* = 14.7, 10.0 Hz, $NCHCH_xH_yPh$), 2.79-2.63 (2H, m, CH_2CH_2Ph), 1.36 (6H, s, 2×CCH_3), 0.90 (9H, s, $C(CH_3)_3$), 0.17 (3H, s, $SiCH_3$), 0.15 (3H, s, $SiCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.6 (C), 167.2 (C), 151.5 (C), 140.2 (C), 136.7 (C), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 126.8 (CH), 126.3 (CH), 88.2 (CH), 83.3 (C), 63.9 (CH), 35.6 (CH_2),

34.7 (CH_2), 30.5 (CH_2), 28.5 (CH_3), 25.5 (CH_3), 22.3 (CH_3), 18.0 (C), -4.8 (CH_3), -5.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{29}H_{43}N_2O_6Si$ $[M+NH_4]^+$: 543.2885, found: 543.2880.

(*S*)-4-Benzyl-*N*-[(*R*)-2-*tert*-butyldiphenylsilyloxy-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3id)



3id

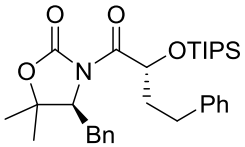
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1i** (251 mg, 0.50 mmol) and peroxide **2d** (463 mg, 1.55 mmol) for 3 h at 0 °C. Purification of the residue by flash column chromatography (95:05 hexanes/EtOAc) afforded **3id** (113 mg, 0.19 mmol, 37% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1i** (251 mg, 0.50 mmol) and peroxide **2d** (298 mg, 1.0 mmol) for 30 min at −20 °C. Purification of the residue by flash column chromatography (97:2.25:0.75 hexanes/EtOAc/EtOH) afforded **3id** (255 mg, 0.42 mmol, 84% yield) as a colorless oil. $\mathbf{R_f}$ (90:7.5:2.5 hexanes/EtOAc/EtOH) 0.3; $[\alpha]_D^{20}$ −1.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2930, 2857, 1771, 1710, 1427, 1392, 1353, 1255, 1103 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78–7.64 (4H, m, ArH), 7.44–7.32 (6H, m, ArH), 7.29–7.13 (10H, m, ArH), 5.59–5.54 (1H, m, COCH), 4.25 (1H, dd, *J* = 10.1, 3.4 Hz, NCH), 2.97 (1H, dd, *J* = 14.4, 3.4 Hz, $NCHCH_xH_y$), 2.80–2.65 (3H, m, $NCHCH_xH_y$, CH_2CH_2Ph), 2.12–1.89 (2H, m, CH_2CH_2Ph), 1.22 (3H, s, CH_3), 1.15 (9H, s, $(CH_3)_3$), 1.01 (3H, s, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.2 (C), 151.8 (C), 141.8 (C), 136.5 (C), 136.1 (CH), 135.9 (CH), 133.4 (C), 133.4 (C), 129.8 (CH), 129.7 (CH), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 126.7 (CH), 125.8 (CH), 82.5 (C), 71.5 (CH), 62.8 (CH), 37.0 (CH_2), 35.1 (CH_2), 31.3 (CH_2), 28.4 (CH_3), 27.0 (CH_3), 22.4 (CH_3), 19.6 (C); **HRMS** (+ESI): *m/z* calcd. for $C_{38}H_{43}NNaO_4Si$ $[M+Na]^+$: 628.2854, found: 628.2847.

(*S*)-4-Benzyl-*N*-[(*R*)-2-triisopropylsilyloxy-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3jd)



3jd

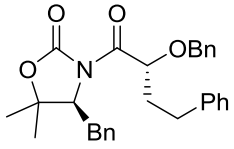
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1j** (171 mg, 0.40 mmol), $TiCl_4$ (49 µL, 0.44 mmol), *i*-Pr_2NEt (77 µL, 0.44 mmol) and peroxide **2d** (370 mg, 1.24 mmol) for 3 h at 0 °C. Purification of the residue by flash column chromatography (95:05 hexanes/EtOAc) afforded **3jd** (48 mg, 0.09 mmol, 23% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1j** (210 mg, 0.50 mmol) and peroxide **2d** (298 mg, 1.0 mmol) for 30 min at −20 °C. Purification of the residue by flash column chromatography (from 70:30 to 60:40 hexanes/DCM) afforded **3jd** (205 mg, 0.39 mmol, 78% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/DCM) 0.4; $[\alpha]_D^{20}$ −15.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2942, 2865, 1771, 1712, 1455, 1352, 1234, 1177, 1128, 1101 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.14 (10H, m, ArH), 5.66 (1H, dd, *J* = 6.1, 4.3 Hz, COCH), 4.59 (1H, dd, *J* = 10.1, 3.5 Hz, NCH), 3.07 (1H, dd, *J* = 14.4, 3.5 Hz, $NCHCH_xH_yPh$), 2.88-2.77 (2H, m, $NCHCH_xH_yPh$, $CH_2CH_xH_yPh$), 2.77-2.67 (1H, m, $CH_2CH_xH_yPh$), 2.14-2.03 (1H, m, $CH_xH_yCH_2Ph$), 2.03-1.91 (1H, m, $CH_xH_yCH_2Ph$), 1.35 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.21-1.05 (21H, m, $Si(CH(CH_3)_2)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ174.0 (C), 152.2 (C), 141.8 (C), 136.5 (C), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 126.8 (CH), 125.8 (CH), 82.8 (C), 70.9 (CH), 63.2 (CH), 37.5 (CH_2), 35.2 (CH_2), 31.0 (CH_2), 28.6 (CH_3), 22.4 (CH_3), 18.0 (CH), 12.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{31}H_{46}NO_4Si$ $[M+H]^+$: 524.3191, found: 524.3188.

(*S*)-4-Benzyl-*N*-[(*R*)-2-benzyloxy-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3kd)



3kd

1st Methodology

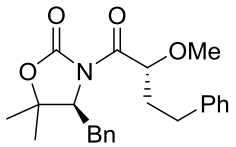
It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1k** (177 mg, 0.50 mmol) and peroxide **2d** (463 mg, 1.55 mmol) for 30 min. Purification of the residue by flash column chromatography (from 50:50 to 30:70 hexanes/DCM) afforded **3kd** (133 mg, 0.29 mmol, 58% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1k** (177 mg, 0.50 mmol) and peroxide **2d** (298 mg, 1.0 mmol) for 30 min at 0 °C. Purification of the residue by flash column chromatography (from 95:5 to 90:10 hexanes/EtOAc) afforded **3kd** (190 mg, 0.41

mmol, 82% yield) as a colorless oil. $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ +6.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2928, 1770, 1703, 1351, 1100 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.15 (15H, m, ArH), 5.08 (1H, dd, *J* = 8.8, 3.2 Hz, COCH), 4.64 (1H, d, *J* = 11.3 Hz, OCH_xH_y), 4.55 (1H, dd, *J* = 9.5, 4.1 Hz, NCH), 4.43 (1H, d, *J* = 11.3 Hz, OCH_xH_y), 3.07 (1H, dd, *J* = 14.4, 4.1 Hz, $NCHCH_xH_y$), 2.93–2.72 (2H, m, CH_2CH_2Ph), 2.83 (1H, dd, *J* = 14.4, 9.5 Hz, $NCHCH_xH_y$), 2.11–2.02 (1H, m, $COCHCH_xH_y$), 1.95–1.86 (1H, m, $COCHCH_xH_y$), 1.37 (3H, s, CCH_3), 1.32 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.1 (C), 152.1 (C), 141.4 (C), 137.5 (C), 136.4 (C), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 126.9 (CH), 125.9 (CH), 82.9 (C), 77.5 (CH), 72.5 (CH_2), 63.3 (CH), 35.2 (CH_2), 35.0 (CH_2), 32.0 (CH_2), 28.5 (CH_3), 22.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{29}H_{35}N_2O_4$ $[M+NH_4]^+$: 475.2591, found: 475.2586.

(*S*)-4-Benzyl-*N*-[(*R*)-2-methoxy-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3ld)



3ld

1st Methodology

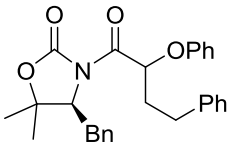
It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1l** (145 mg, 0.50 mmol) and peroxide **2d** (463 mg, 1.55 mmol) for 15 min at 0 °C. Purification of the residue by flash column chromatography (from 90:10 to 80:20 hexanes/EtOAc) afforded **3ld** (116 mg, 0.30 mmol, 61% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1l** (122 mg, 0.44 mmol), $TiCl_4$ (53 μL, 0.48 mmol), Et_3N (135 μL, 1.32 mmol) and peroxide **2d** (263 mg, 0.88 mmol) for 30 min at 0 °C. Purification of the residue by flash column chromatography (from 95:5 to 80:20 hexanes/EtOAc) afforded **3ld** (120 mg, 0.26 mmol, 60% yield) as a white solid. **Mp** 71–76 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ –14.03 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2926, 1773, 1763, 1708, 1376, 1349, 1275, 1235, 1161, 1099 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.14 (10H, m, ArH), 4.85 (1H, dd, *J* = 8.6, 3.2 Hz, COCH), 4.59 (1H, dd, *J* = 9.4, 4.3 Hz, NCH), 3.39 (3H, s, OCH_3), 3.06 (1H, dd, *J* = 14.3, 4.3 Hz, $NCHCH_xH_yPh$), 2.86–2.72 (2H, m, $COCHCH_2$), 2.85 (1H, dd, *J* = 14.3, 9.4 Hz, $NCHCH_xH_yPh$), 2.11–1.99 (1H, m, $CH_2CH_xH_yPh$), 1.90–1.76 (1H, m, $CH_2CH_xH_yPh$) 1.39 (3H, s,CCH_3), 1.37 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.0 (C), 152.2 (C), 141.4 (C), 136.4 (C), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 126.9 (CH), 125.9 (CH), 83.0 (C), 79.6 (CH), 63.3 (CH), 58.0 (CH_3), 35.3 (CH_2),

34.8 (CH_2), 31.8 (CH_2), 28.6 (CH_3), 22.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{23}H_{28}NO_4$ $[M+H]^+$: 382.2013, found: 382.2012.

(4*S*)-4-Benzyl-5,5-dimethyl-*N*-(2-phenoxy-4-phenylbutanoyl)-1,3-oxazolidin-2-one (3md)



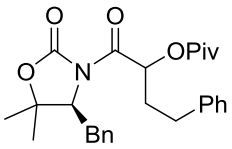
3md

1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1m** (175 mg, 0.5 mmol) and peroxide **2d** (462 mg, 1.55 mmol) for 80 min at 0 °C. Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded **3md** as a mixture of diastereomers (112 mg, 0.25 mmol, 50% yield, dr 77:23). The product was not characterized.

2nd Methodology (not performed)

(4*S*)-4-Benzyl-5,5-dimethyl-*N*-(2-pivaloyloxy-4-phenylbutanoyl)-1,3-oxazolidin-2-one (3nd)



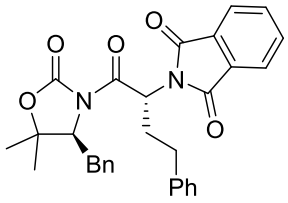
3nd

1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1n** (347 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), *i*-Pr_2NEt (192 µL, 1.1 mmol) and peroxide **2d** (925 mg, 3.1 mmol) for 6 h at 0 °C. Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded **3nd** as a mixture of diastereomers (223 mg, 0.49 mmol, 49% yield, dr 77:23). The product was not characterized.

2nd Methodology (not performed)

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-4-phenyl-2-(*N*-phthalimidyl)butanoyl]-1,3-oxazolidin-2-one (3od)



3od

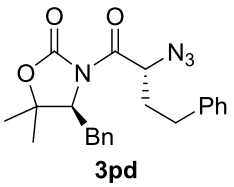
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1o** (196 mg, 0.5 mmol) and peroxide **2d** (487 mg, 1.55 mmol) for 6 h at rt. No product was observed by ^{1}H NMR of the crude mixture, just unreacted starting material.

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1o** (196 mg, 0.5 mmol) and peroxide **2d** (298 mg, 1.0 mmol) for 30 min. Purification of the residue by flash column chromatography (85:15 hexanes/EtOAc) afforded **3od** (75 mg, 0.15 mmol, 30% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ –45.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2928, 1775, 1718, 1384, 1102 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84–7.82 (2H, m, Phth), 7.73–7.71 (2H, m, Phth), 7.31–7.06 (10H, m, ArH), 5.85–5.78 (1H, m, COCH), 4.51 (1H, dd, *J* = 9.8, 3.9 Hz, NCH), 3.22 (1H, dd, *J* = 14.4, 3.9 Hz, NCHCH_xH_yPh), 2.91–2.66 (4H, m, NCHCH_xH_yPh, CH_2CH_2Ph, COCHCH_xH_y), 2.46–2.35 (1H, m, COCHCH_xH_y), 1.37 (3H, s, CH_3), 1.31 (3H, s, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.5 (C), 168.0 (C), 151.9 (C), 140.6 (C), 136.4 (C), 134.1 (CH), 131.7 (C), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 126.9 (CH), 126.0 (CH), 123.4 (2 × CH), 83.1 (C), 63.8 (CH), 54.7 (CH), 35.0 (CH_2), 33.2 (CH_2), 30.3 (CH_2), 28.4 (CH_3), 22.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{30}H_{32}N_3O_5$ $[M+NH_4]^+$: 514.2336, found: 514.2333.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-azido-4-phenylbutanoyl]-1,3-oxazolidin-2-one (3pd)



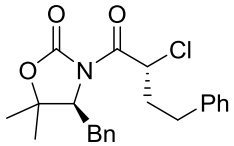
3pd

1st Methodology

Enolization following General Procedure 5 from *N*-acyl oxazolidinone **1p** (86 mg, 0.3 mmol), $TiCl_4$ (36 μL, 0.33 mmol) and *i*-Pr_2NEt (57 μL, 0.33 mmol) decomposed the starting material either at 0 °C or –78 °C.

2nd Methodology (not performed)

(*S*)-4-Benzyl-*N*-[(*R*)-2-chloro-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3qd)



3qd

1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1q** (141 mg, 0.50 mmol) and peroxide **2d** (463 mg, 1.55 mmol) for 7 h. Purification of the residue by flash column chromatography (from 60:40 to 40:60 hexanes/DCM) afforded **3qd** as a mixture of diastereomers (86 mg, 0.22 mmol, 45% yield, dr 85:15).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1q** (141 mg, 0.5 mmol) and peroxide **2d** (298 mg, 1.0 mmol) for 30 min. Purification of the residue by flash column chromatography (from 99:1 to 90:10 hexanes/EtOAc) afforded **3qd** as a mixture of diastereomers (180 mg, 0.47 mmol, 93% yield, dr 85:15) as a colorless oil. After a second flash column chromatography a small pure sample of the major diastereomer could be isolated and allowed its characterization.

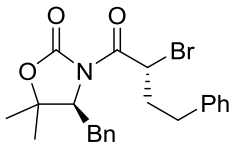
Major Diastereomer:

R_f (90:10, hexanes/EtOAc) 0.3; **IR** (ATR) ν 3020, 2995, 1759, 1710, 1370, 1167, 1098 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.17 (10H, m, ArH), 5.58 (1H, dd, *J* = 8.3, 5.4 Hz, COCH), 4.51 (1H, dd, *J* = 9.2, 4.5 Hz, NCH), 3.05 (1H, dd, *J* = 14.4, 4.5 Hz, $NCHCH_xH_y$), 2.90 (1H, dd, *J* = 14.4, 9.2 Hz, $NCHCH_xH_y$), 2.81 (1H, ddd, J = 13.7, 10.0, 5.3 Hz, $CH_2CH_xH_yPh$), 2.68 (1H, ddd, J = 13.7, 10.1, 6.3 Hz, $CH_2CH_xH_yPh$), 2.29 (1H, dddd, J = 14.0, 10.0, 6.3, 5.4 Hz, $COCHCH_xH_y$), 2.15 (1H, dddd, J = 14.0, 10.1, 8.3, 5.3 Hz, $COCHCH_xH_y$) 1.41 (3H, s, CH_3), 1.40 (3H, s, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.9 (C), 151.9 (C), 140.3 (C), 136.4 (C), 129.1 (CH), 128.7 (CH), 128.5 (CH), 128.5 (CH), 127.0 (CH), 126.3 (CH), 83.2 (C), 64.0 (CH), 55.1 (CH), 35.8 (CH_2), 35.4 (CH_2), 32.3 (CH_2), 28.5 (CH_3), 22.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{22}H_{25}ClNO_3$ $[M+H]^+$: 386.1517, found: 386.1519.

Minor Diastereomer: relevant peaks

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (1H, dd, *J* = 8.0, 5.7 Hz, COCH), 4.50 (1H, dd, *J* = 9.9, 3.5 Hz, NCH), 3.20 (1H, dd, *J* = 14.4, 3.5 Hz, $NCHCH_xH_y$), 2.89 (1H, dd, *J* = 14.4, 9.9 Hz, $NCHCH_xH_y$), 1.39 (3H, s, CH_3), 1.33 (3H, s, CH_3).

(*S*)-4-Benzyl-*N*-[(*R*)-2-bromo-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3rd)



3rd

1st Methodology

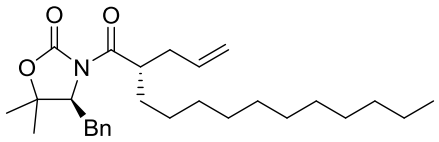
It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1r** (163 mg, 0.50 mmol) and peroxide **2d** (463 mg, 1.55 mmol) for 5 h. Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded an impure fraction of **3rd** as a mixture of diastereomers (<20% yield, dr 85:15). Product was not completely characterized.

Major Diastereomer:

R_f (90:10 hexanes/EtOAc) 0.3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.02 (10H, m, ArH), 5.62 (1H, dd, *J* = 7.7, 6.7 Hz, COCH), 4.50 (1H, dd, *J* = 9.0, 4.7 Hz, NCH), 3.05 (1H, dd, *J* = 14.3, 4.7 Hz, NCHCH_xH_y), 2.91 (1H, dd, *J* = 14.3, 9.0 Hz, NCHCH_xH_y), 2.76 (1H, ddd, *J* = 13.7, 9.4, 5.6 Hz, $CH_2CH_xH_yPh$), 2.61 (1H, ddd, *J* = 13.7, 9.7, 6.3 Hz, $CH_2CH_xH_yPh$), 2.42-2.22 (2H, m, COCHCH_2), 1.43 (3H, s, CH_3), 1.39 (3H, s, CH_3).

2nd Methodology (not performed)

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*S*)-2-undecyl-4-pentenoyl]-1,3-oxazolidin-2-one (3sb)



3sb

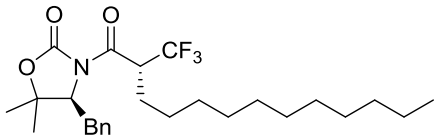
1st Methodology (not performed)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1s** (287 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and peroxide **2b** (598 mg, 1.5 mmol) for 30 min. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3sb** (244 mg, 0.55 mmol, 55% yield) as a colorless oil. **R_f** (90:10 hexanes/EtOAc) 0.3; **$[\alpha]_D^{20}$** –27.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2922, 2852, 1774, 1694, 1455, 1392, 1351, 1275, 1234, 1207, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.14 (5H, m, ArH), 5.79 (1H, ddd, *J* = 16.7, 10.1, 7.7, 6.4 Hz, CH=CH_2), 5.08–5.02 (1H, m, CH=CH_xH_y), 5.01–4.98 (1H, m, CH=CH_xH_y), 4.52 (1H, dd, *J* = 9.8, 3.7 Hz, CHN), 3.97 (1H, tt, *J* = 8.4, 5.5 Hz, COCH), 3.11

(1H, dd, *J* = 14.4, 3.7 Hz, C<u>H</u>$_x$H$_y$Ph), 2.88 (1H, dd, *J* = 14.4, 9.8 Hz, CH$_x$<u>H</u>$_y$Ph), 2.42–2.34 (1H, m, C<u>H</u>$_x$H$_y$CH=CH$_2$), 2.30–2.22 (1H, m, CH$_x$<u>H</u>$_y$CH=CH$_2$), 1.73–1.64 (1H, m, COCHC<u>H</u>$_x$H$_y$CH$_2$), 1.51–1.42 (1H, m, COCHCH$_x$<u>H</u>$_y$CH$_2$), 1.35 (3H, s, CC<u>H</u>$_3$), 1.33 (3H, s, CCH$_3$), 1.24 (18H, br s, COCHCH$_2$(C<u>H</u>$_2$)$_9$), 0.95–0.78 (3H, m, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.4 (C), 152.4 (C), 137.0 (C), 135.7 (CH), 129.1 (CH), 128.6 (CH), 126.7 (CH), 116.8 (CH_2), 81.8 (C), 63.7 (CH), 42.5 (CH), 36.7 (CH_2), 35.5 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (2 × CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.4 (CH_2), 27.0 (CH_2), 22.7 (CH_2), 22.3 (CH_3), 14.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{28}H_{44}NO_3$ $[M+H]^+$: 442.3316, found: 442.3323.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-(trifluoromethyl)tridecanoyl]-1,3-oxazolidin-2-one (3tb)



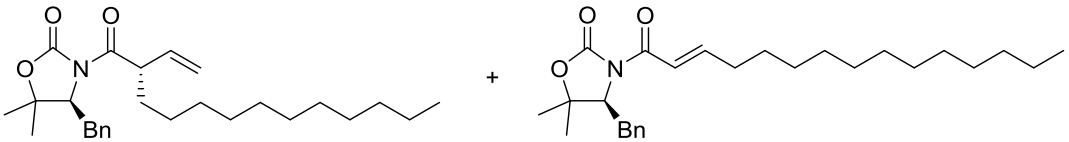
3tb

<u>1st Methodology</u> (not performed)

<u>2nd Methodology</u>

It was prepared following <u>General Procedure 6</u> from *N*-acyl oxazolidinone **1t** (158 mg, 0.5 mmol) and peroxide **2b** (299 mg, 0.75 mmol) for 30 min at –20 °C to rt. No product was observed by ^{1}H NMR of the crude mixture, just unreacted starting material.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*S*)-2-undecyl-3-butenoyl]-1,3-oxazolidin-2-one (3ub) *or* (*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*E*)-2-pentadecenoyl]-1,3-oxazolidin-2-one (9ub)



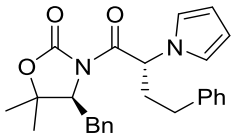
3ub **9ub**

<u>1st Methodology</u> (not performed)

<u>2nd Methodology</u>

It was prepared following <u>General Procedure 6</u> from *N*-acyl oxazolidinone **1u** (137 mg, 0.5 mmol) and peroxide **2b** (299 mg, 0.75 mmol) for 15 min. An unclean crude mixture was obtained.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-4-phenyl-2-(1H-*N*-pyrrolyl)butanoyl]-1,3-oxazolidin-2-one (3vd)



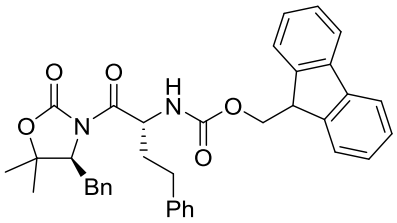
3vd

1st Methodology (not performed)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1v** (156 mg, 0.5 mmol) and peroxide **2d** (298 mg, 1.0 mmol) for 30 min at −20 °C. Purification of the residue by flash column chromatography (from 50:50 to 35:65 hexanes/DCM) afforded **3vd** (136 mg, 0.33 mmol, 66% yield) as a brown oil. $\mathbf{R_f}$ (40:60 hexanes/DCM) 0.2; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ −36.0 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2931, 1770, 1701, 1354, 1101 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31−7.17 (8H, m, ArH), 7.15−7.12 (2H, m, ArH), 6.80 (2H, m, 2 × NCH=CH), 6.19 (2H, t, *J* = 2.2 Hz, 2 × NCH=CH), 5.95 (1H, dd, *J* = 9.7, 5.1 Hz, COCH), 4.42 (1H, dd, *J* = 9.3, 4.3 Hz, NCH), 3.10 (1H, dd, *J* = 14.3, 4.3 Hz, NCHCH$_x$H$_y$Ph), 2.89 (1H, dd, *J* = 14.3, 9.3 Hz, NCHCH$_x$H$_y$Ph), 2.60−2.44 (2H, m, CH_2CH_2Ph), 1.37−1.28 (1H, m, COCHCH$_x$H$_y$), 1.26−2.16 (1H, m, COCHCH$_x$H$_y$), 1.36 (3H, s, CH_3), 1.20 (3H, s, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.7 (C), 152.3 (C), 140.5 (C), 136.4 (C), 129.1 (2 × CH), 128.7 (2 × CH), 128.4 (2 × CH), 128.4 (2 × CH), 126.9 (CH), 126.2 (CH), 120.4 (2 × CH), 108.6 (2 × CH), 83.0 (C), 63.8 (CH), 59.1 (CH), 35.3 (CH_2), 34.5 (CH_2), 32.0 (CH_2), 28.1 (CH_3), 22.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{26}H_{29}N_2O_3$ $[M+H]^+$: 417.2173, found: 417.2174.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*S*)-2-((9-fluorenylmethyl)oxycarbonylamino)-4-phenylbutanoyl]-1,3-oxazolidin-2-one (3wd)



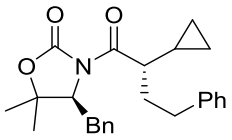
3wd

1st Methodology (not performed)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1w** (242 mg, 0.5 mmol) and peroxide **2d** (298 mg, 1.0 mmol) for 30 min at 0 °C. No product was observed by ^{1}H NMR of the crude mixture.

(*S*)-4-Benzyl-*N*-[(*S*)-2-cyclopropyl-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3xd)



3xd

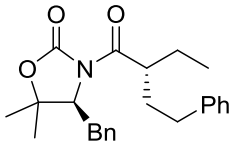
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1x** (144 mg, 0.50 mmol) and peroxide **2d** (462 mg, 1.55 mmol) for 2.0 h. Purification of the residue by flash column chromatography (from 99.5:0.5 to 94:6 hexanes/EtOAc) afforded **3xd** (109 mg, 0.28 mmol, 56% yield) as a white solid. **Mp** 68–74 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ –23.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3025, 2982, 1771, 1694, 1496, 1454, 1354, 1276, 1223, 1223, 1159, 1095 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.13 (10H, m, ArH), 4.56 (1H, dd, *J* = 9.7, 3.8 Hz, NCH), 3.28 (1H, ddd, *J* = 9.7, 8.0, 5.9 Hz, COCH), 3.07 (1H, dd, *J* = 14.4, 3.8 Hz, $NCHCH_xH_yPh$), 2.86 (1H, dd, *J* = 14.4, 9.7 Hz, $NCHCH_xH_yPh$), 2.71 (1H, ddd, *J* = 13.6, 11.2, 5.3 Hz, $CH_2CH_xH_yPh$), 2.57 (1H, ddd, *J* = 13.6, 11.5, 5.5 Hz, $CH_2CH_xH_yPh$), 2.19-2.10 (1H, m, $COCHCH_xH_y$), 1.96-1.87 (1H, m, $COCHCH_xH_y$), 1.38 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 1.10-0.99 (1H, m, COCHCH), 0.64-0.57 (1H, m, $CHCH_xH_yCH_aH_b$), 0.50-0.41 (1H m, $CHCH_xH_yCH_aH_b$), 0.32-0.22 (2H, m, $CHCH_xH_yCH_aH_b$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.5 (C), 152.6 (C), 141.9 (C), 137.0 (C), 129.1 (CH), 128.6 (CH), 128.3 (CH), 128.3 (CH), 126.8 (CH), 125.8 (CH), 82.0 (C), 63.9 (CH), 47.1 (CH), 35.4 (CH_2), 34.8 (CH_2), 33.7 (CH_2), 28.4 (CH_3), 22.2 (CH_3), 14.1 (CH), 4.6 (CH_2), 2.8 (CH_2); **HRMS** (+ESI): *m/z* calcd. for $C_{25}H_{29}NNaO_3$ $[M+Na]^+$: 414.2040, found: 414.2039.

2nd Methodology (not performed)

3.2. Scope of crossed examples

(*S*)-4-Benzyl-*N*-[(*R*)-2-ethyl-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3bd)



3bd

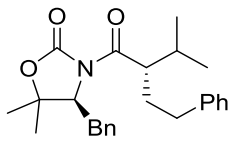
1st Methodology

It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1b** (138 mg, 0.50 mmol) and peroxide **2d** (462 mg, 1.55 mmol) for 1.2 h. Purification of the residue by flash column chromatography (50:50 hexanes/DCM) afforded **3bd** (133 mg, 0.35 mmol, 70% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1b** (138 mg, 0.5 mmol) and peroxide **2d** (224 mg, 0.75 mmol) for 15 min. Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded **3bd** (139 mg, 0.37 mmol, 73% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −35.6 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2970, 2931, 1783, 1686, 1604, 1497 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30–7.15 (10H, m, ArH), 4.55 (1H, dd, *J* = 9.7, 3.8 Hz, NCH), 3.85 (1H, tt, *J* = 8.0, 5.5 Hz, COCH), 3.08 (1H, dd, *J* = 14.4, 3.8 Hz, NCHCH$_x$H$_y$Ph), 2.87 (1H, dd, *J* = 14.4, 9.7 Hz, NCHCH$_x$H$_y$Ph), 2.65–2.50 (2H, m, CH_2CH_2Ph), 2.07–1.97 (1H, m, CH$_x$H$_y$CH$_2$Ph), 1.81–1.68 (2H, m, CH$_x$H$_y$CH$_2$Ph, CH$_x$H$_y$CH$_3$), 1.65–1.53 (1H, m, CH$_x$H$_y$CH$_3$), 1.36 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 0.93 (3H, t, *J* = 7.4 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.6 (C), 152.4 (C), 141.9 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 128.3 (CH), 128.3 (CH), 126.8 (CH), 125.8 (CH), 81.8 (C), 63.7 (CH), 44.2 (CH), 35.5 (CH_2), 33.9 (CH_2), 33.6 (CH_2), 28.5 (CH_3), 25.4 (CH_2), 22.2 (CH_3), 11.6 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{24}H_{30}NO_3$ $[M+H]^+$: 380.2220 found: 380.2214.

(*S*)-4-Benzyl-*N*-[(*S*)-2-isopropyl-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3cd)



3cd

1st Methodology

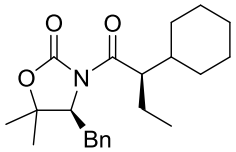
It was prepared following General Procedure 5 from *N*-acyl oxazolidinone **1c** (145 mg, 0.50 mmol) and peroxide **2d** (462 mg, 1.55 mmol) for 4.5 h. Purification of the residue by flash column

chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3cd** (78 mg, 0.20 mmol, 39% yield).

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1c** (116 mg, 0.4 mmol), $TiCl_4$ (49 µL, 0.44 mmol), Et_3N (170 µL, 1.2 mmol) and peroxide **2d** (179 mg, 0.6 mmol) for 30 min. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3cd** (105 mg, 0.27 mmol, 67% yield) as a white solid. **Mp** 82–85 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ –30.4 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 2965, 1759, 1699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.14 (10H, m, ArH), 4.57 (1H, dd, *J* = 9.8, 3.5 Hz, NCH), 3.85 (1H, ddd, *J* = 10.4, 7.0, 3.5 Hz, COCH), 3.10 (1H, dd, *J* = 14.4, 3.5 Hz, NCHCH$_x$H$_y$Ph), 2.88 (1H, dd, *J* = 14.4, 9.8 Hz, NCHCH$_x$H$_y$Ph), 2.58–2.44 (2H, m, CH_2CH_2Ph), 2.09–1.92 (2H, m, COCHCH$_x$H$_y$, CH$(CH_3)_2$), 1.82–1.78 (1H, m, COCHCH$_x$H$_y$), 1.36 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 0.98 (3H, d, *J* = 6.7 Hz, $CHCH_3$), 0.95 (3H, d, *J* = 6.8 Hz, $CHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.4 (C), 152.5 (C), 142.0 (C), 137.1 (C), 129.0 (CH), 128.7 (CH), 128.3 (CH), 128.3 (CH), 126.7 (CH), 125.8 (CH), 81.7 (C), 63.9 (CH), 48.7 (CH), 35.5 (CH_2), 33.8 (CH_2), 31.2 (CH_2), 31.0 (CH), 28.5 (CH_3), 22.2 (CH_3), 20.8 (CH_3), 19.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{25}H_{32}NO_3$ $[M+H]^+$: 394.2377, found: 394.237.

(*S*)-4-Benzyl-*N*-[(*R*)-2-cyclohexylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3bj)



3bj

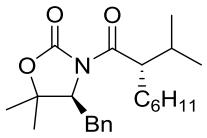
1st Methodology (not performed)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1b** (113 mg, 0.3 mmol), $TiCl_4$ (37 µL, 0.33 mmol), Et_3N (125 µL, 0.9 mmol) and peroxide **2j** (153 mg, 0.6 mmol) for 60 min. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3bj** (55 mg, 0.15 mmol, 51% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ –44.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2924, 2851, 1771, 1688, 1349, 1232, 1096 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.18 (5H, m, ArH), 4.59 (1H, dd, *J* = 9.9, 3.5 Hz, NCH), 3.69 (1H, ddd, *J* = 10.0, 7.1, 4.2 Hz, COCH), 3.14 (1H, dd, *J* = 14.4, 3.5 Hz, CH$_x$H$_y$Ph), 2.89 (1H, dd, *J* = 14.4, 9.9 Hz, CH$_x$H$_y$Ph), 1.76–1.51 (8H, m, COCHCH$_2$, Cy), 1.35 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.27–1.07 (3H, m, Cy), 1.01–0.91 (1H, m, Cy), 0.86 (3H, t, *J* = 7.4 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.9 (C), 152.5 (C), 137.1 (C), 129.0 (CH), 128.6 (CH), 126.7

(CH), 81.5 (C), 63.8 (CH), 49.5 (CH), 40.6 (CH), 35.6 (CH_2), 31.1 (CH_2), 29.5 (CH_2), 28.4 (CH_3), 26.4 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 22.2 (CH_3), 22.0 (CH_2), 11.9 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{22}H_{32}NO_3$ $[M+H]^+$: 358.2377, found: 358.2379

(*S*)-4-Benzyl-*N*-[(*R*)-2-cyclohexyl-3-methylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3cj)



3cj

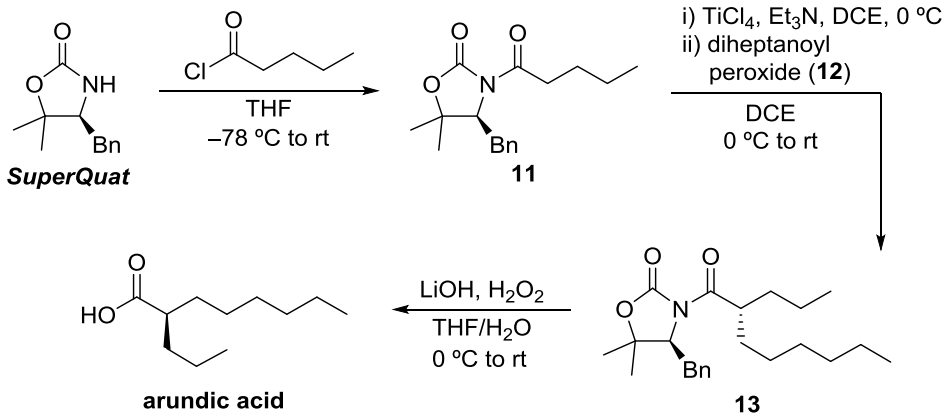
1st Methodology (not performed)

2nd Methodology

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **1c** (113 mg, 0.39 mmol), $TiCl_4$ (47 µL, 0.43 mmol), Et_3N (165 µL, 1.17 mmol) and peroxide **2j** (198 mg, 0.78 mmol) for 60 min. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3cj** (29 mg, 0.078 mmol, 20% yield) as a white solid. **Mp** 91–95 °C; **R_f** (95:5 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −29.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2920, 2851, 1765, 1682, 1448, 1235, 1208, 1174, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.20 (5H, m, ArH), 4.60 (1H, dd, *J* = 10.4, 2.9 Hz, NCH), 3.90–3.83 (1H, m, COCH), 3.19 (1H, dd, *J* = 14.5, 2.9 Hz, CH_xH_yPh), 2.88 (1H, dd, *J* = 14.5, 10.4 Hz, CH_xH_yPh), 2.19–2.05 (1H, m, $CH(CH_3)_2$) 1.90–1.56 (6H, m, Cy), 1.34 (3H, s, CCH_3), 1.31 (3H, s, CCH_3), 1.27–1.08 (4H, m, Cy), 0.98–0.88 (7H, m, $CH(CH_3)_2$), $CH(CH_3)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.1 (C), 152.7 (C), 137.35 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.2 (C), 64.0 (CH), 52.3 (CH), 38.6 (CH), 35.5 (CH_2), 30.7 (CH_2), 29.6 (CH_2), 28.5 (CH_3), 27.6 (CH), 26.5 (CH_2), 26.4 (CH_2), 26.4 (CH_2), 22.3 (CH_3), 20.5 (CH_3), 19.0 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{23}H_{34}NO_3$ $[M+H]^+$: 372.2533, found: 372.2535.

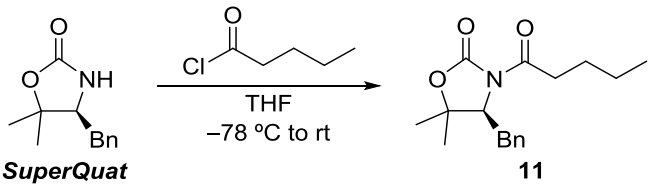
4. Synthesis of arundic acid

4.1. Route A



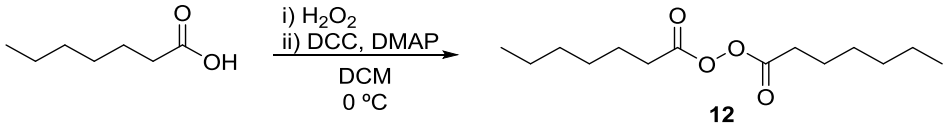
Scheme 138. Route A to arundic acid

(*S*)-4-Benzyl-5,5-dimethyl-*N*-pentanoyl-1,3-oxazolidin-2-one (11)



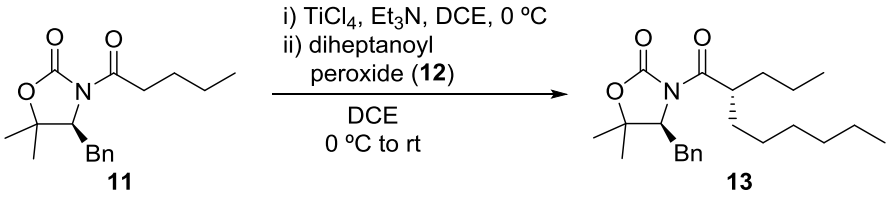
It was prepared following General Procedure 2 from oxazolidinone ***SuperQuat*** (3.70 g, 18.0 mmol), *n*-BuLi 2.5 M in hexanes (8.0 mL, 19.8 mmol) and pentanoyl chloride (2.8 mL, 23.4 mmol). Purification of the crude product by flash column chromatography (from 95:5 to 90:10 hexanes/EtOAc) afforded **11** (4.52 g, 15.6 mmol, 87% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –37.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2957, 2932, 2872, 1771, 1696, 1353, 1274, 1088 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.19 (5H, m, ArH), 4.51 (1H, dd, *J* = 9.5, 3.9 Hz, CHN), 3.14 (1H, dd, *J* = 14.3, 3.9 Hz, CH_xH_yPh), 2.94–2.86 (3H, m, CH_xH_yPh, $COCH_2$), 1.66–1.57 (2H, m, $COCH_2CH_2$), 1.42–1.32 (2H, m, $CO(CH_2)_2CH_2$), 1.37 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 0.93 (3H, t, *J* = 7.3 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.5 (C), 152.6 (C), 136.9 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 82.0 (C), 63.4 (CH), 35.3 (CH_2), 35.4 (CH_2), 28.5 (CH_3), 26.4 (CH_2), 22.2 (CH_3), 22.2 (CH_2), 13.8 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{17}H_{23}NNaO_3$ $[M+Na]^+$: 312.1570, found: 312.1572.

Diheptanoyl peroxide (12)



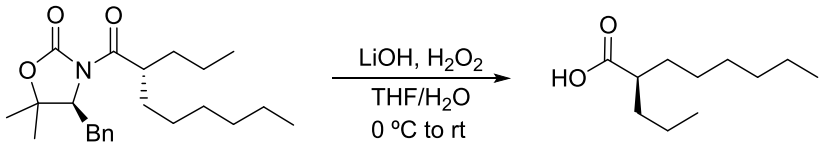
It was prepared following General Procedure 3 from heptanoic acid (7.2 mL, 50 mmol), 30% H_2O_2 (1.5 mL, 15 mmol), DMAP (611 mg, 5 mmol) and DCC (11.35 g, 55 mmol). The residue was purified by flash column chromatography (80:20 hexanes/DCM) to afford **12** (3.8 g, 14.7 mmol, 98% yield) as a colorless oil. $\mathbf{R_f}$ (hexanes/DCM 80:20) 0.3; **IR** (ATR) ν 2956, 2929, 2859, 1810, 1780, 1458, 1126, 1059 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (4H, t, J = 7.4 Hz, 2 × $COCH_2$), 1.71 (4H, quint, J = 7.4 Hz, 2 × $COCH_2CH_2$), 1.42–1.34 (4H, m, 2 × $CO(CH_2)_2CH_2$), 1.33–1.25 (8H, m, 2 × $(CH_2)_2CH_3$) 0.96–0.83 (6H, m, 2 × CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.2 (C), 31.2 (CH_2), 30.0 (CH_2), 28.6 (CH_2), 24.8 (CH_2), 22.4 (CH_2), 13.9 (CH_3).

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-propyloctanoyl]-1,3-oxazolidin-2-one (13)



It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **11** (2.60 g, 9 mmol), $TiCl_4$ (1.1 mL, 9.9 mmol), Et_3N (3.8 mL, 27 mmol) and peroxide **12** (3.50 g, 13.5 mmol) for 45 min. Purification of the residue by flash column chromatography (from 97:3 to 95:5 hexanes/EtOAc) afforded **13** (2.92 g, 7.8 mmol, 87% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ –31.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2956, 2927, 2856, 1773, 1693, 1391, 1350, 1095 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, ArH), 4.54 (1H, dd, J = 9.8, 3.5 Hz, CHN), 3.84 (1H, tt, J = 8.2, 5.5 Hz, COCH), 3.12 (1H, dd, J = 14.3, 3.5 Hz, CH_xH_yPh), 2.88 (1H, dd, J = 14.3, 9.8 Hz, CH_xH_yPh), 1.72–1.59 (2H, m, $COCHCH_xH_yCH_2CH_3$, $COCHCH_xH_y(CH_2)_4$), 1.50–1.40 (2H, m, $COCHCH_xH_yCH_2CH_3$, $COCHCH_xH_y(CH_2)_4$), 1.35 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.32–1.22 (10H, m, $COCHCH_2CH_2CH_3$, $COCHCH_2(CH_2)_4$), 0.92–0.85 (6H, m, 2 × $(CH_2)CH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.3 (C), 152.4 (C), 137.1 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.7 (C), 63.8 (CH), 42.6 (CH), 35.4 (CH_2), 34.5 (CH_2), 32.7 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 28.5 (CH_3), 27.0 (CH_2), 22.6 (CH_2), 22.2 (CH_3), 20.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{23}H_{35}NNaO_3$ $[M+Na]^+$: 396.2509, found: 396.2511.

Arundic acid



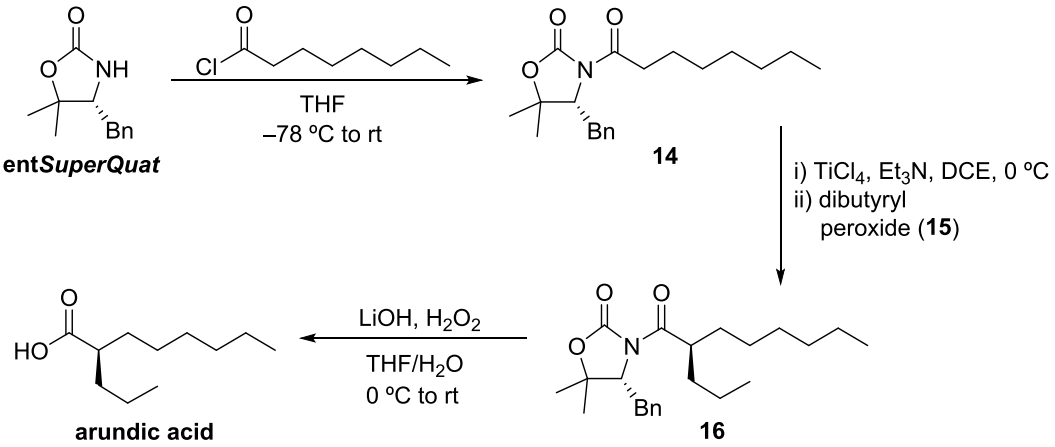
13

A 30% solution of H_2O_2 (2.4 mL, 24 mmol) and LiOH (115 mg, 4.8 mmol) were added to a solution of adduct **13** (896 mg, 2.4 mmol) in THF/H_2O 4:1 (12 mL) at 0 °C. The mixture was stirred at rt for 4.5 h and quenched by dropwise addition of 1.5 M Na_2SO_3 (12 mL) and 1 M HCl (12 mL). The mixture was extracted with Et_2O (4 × 15 mL) and the combined organic extracts were extracted with 1 M NaOH (3 × 30 mL). The combined aqueous extracts were washed with Et_2O (30 mL) and the organic extract was combined with the previous one and set apart. The aqueous phase was then acidified with 2 M HCl (pH ~2) and extracted with Et_2O (4 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford arundic acid (425 mg, 2.3 mmol, 95% yield) as a colorless oil. $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ –6.2 (*c* 1.0, CH_3OH), [lit.[106] $[\alpha]_D^{20}$ –6.5 (*c* 1.0, CH_3OH)], $[\alpha]_D^{20}$ –3.4 (*c* 1.0, $CHCl_3$), [lit.[94] $[\alpha]_D^{20}$ –5.1 (*c* 1.0, $CHCl_3$)]; **IR** (ATR) ν 2926, 2857, 1702, 1465, 1214 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.78 (1H, br s, COOH), 3.39–3.32 (1H, m, COCH), 1.67–1.57 (2H, m, $COCHCH_xH_y(CH_2)_4$, $COCHCH_xH_yCH_2CH_3$), 1.49–1.41 (2H, m, $COCHCH_xH_y(CH_2)_4$, $COCHCH_xH_yCH_2CH_3$), 1.40–1.26 (10H, m, $(CH_2)_4CH_3$, CH_2CH_3), 0.91 (3H, t, *J* = 7.3 Hz, CH_3), 0.88 (3H, t, *J* = 7.2 Hz, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 183.1 (C), 45.4 (CH), 34.3 (CH_2), 32.2 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 27.3 (CH_2), 22.6 (CH_2), 20.6 (CH_2), 14.1 (CH_3), 14.0 (CH_3); **HRMS** (-ESI): *m/z* calcd. for $C_{11}H_{21}O_2$ $[M-H]^-$: 185.1547, found: 185.1548.

Recovery of the chiral auxiliary

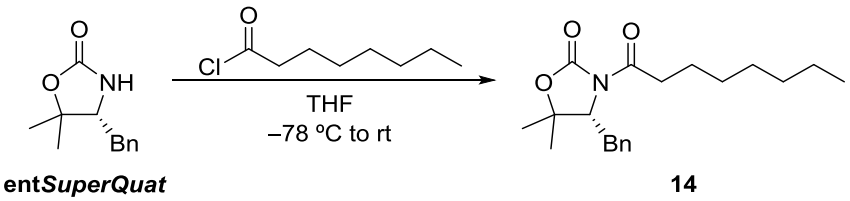
The organic extracts set apart were treated with 1 M HCl (50 mL) and water (50 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford oxazolidinone ***SuperQuat*** (482 mg, 2.35 mmol, 98% yield).

4.2. Route B



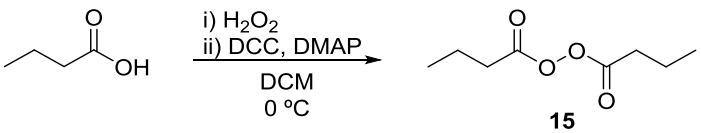
Scheme 139. Route B to arundic acid

(*R*)-4-Benzyl-5,5-dimethyl-*N*-octanoyl-1,3-oxazolidin-2-one (14)



It was prepared following General Procedure 2 from oxazolidinone **ent*SuperQuat*** (1.44 g, 7.0 mmol), *n*-BuLi 2.5 M in hexanes (3.1 mL, 7.7 mmol) and octanoyl chloride (1.55 mL, 9.1 mmol). Purification of the crude product by flash column chromatography (95:5 hexanes/EtOAc) afforded **14** (2.10 g, 6.3 mmol, 90% yield) as a colorless oil. $\mathbf{R_f}$ (95:5 hexanes/EtOAc) 0.2; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ +30.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2926, 2855, 1772, 1696, 1353, 1093 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.19 (5H, m, ArH), 4.51 (1H, dd, *J* = 9.5, 3.9 Hz, CHN), 3.14 (1H, dd, *J* = 14.3, 3.9 Hz, CH_xH_yPh), 2.93–2.83 (3H, m, CH_xH_yPh, $COCH_2$), 1.68–1.57 (2H, m, $COCH_2CH_2$), 1.37 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 1.34–1.22 (8H, m, $(CH_2)_4CH_3$), 0.91–0.85 (3H, m, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.6 (C), 152.6 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 82.0 (C), 63.4 (CH), 35.6 (CH_2), 35.4 (CH_2), 31.6 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 28.5 (CH_3), 24.4 (CH_2), 22.6 (CH_2), 22.3 (CH_3), 14.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{20}H_{30}NO_3$ $[M+H]^+$: 354.2040, found: 354.2040.

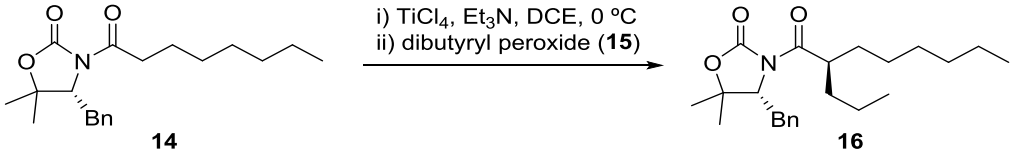
Dibutanoyl peroxide (15)



It was prepared following General Procedure 3 from butanoic acid (2.1 mL, 23.3 mmol), 30% H_2O_2 (700 µL, 7.0 mmol), DMAP (285 mg, 2.3 mmol) and DCC (5.29 g, 25.6 mmol). The residue

was purified by flash column chromatography (70:30 hexanes/DCM) to afford **15** (1.07 g, 6.1 mmol, 87% yield) as a colorless oil. **IR** (ATR) ν 2969, 2938, 2879, 1809, 1777, 1121, 1041 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (t, *J* = 7.4 Hz, 4H, 2 × $COC\underline{H}_2$), 1.76 (h, *J* = 7.4 Hz, 4H, 2 × $COCH_2C\underline{H}_2$), 1.02 (t, *J* = 7.4 Hz, 6H, 2 × $CH_2C\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.0 (C), 31.8 (CH_2), 18.4 (CH_2), 13.4 (CH_3). ***Note**: peroxide **15** cannot be monitored by TLC.*

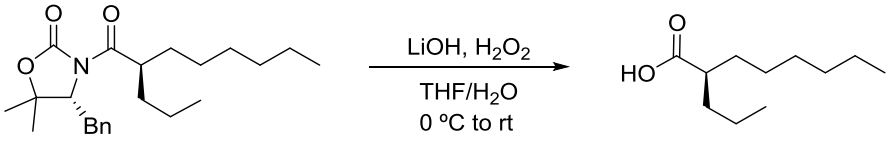
(*R*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-propyloctanoyl]-1,3-oxazolidin-2-one (16)



14 **16**

It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **14** (331 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 2.0 mmol) and peroxide **15** (348 mg, 2.0 mmol) for 30 min. Purification of the residue by flash column chromatography (from 99.5:0.5 to 95:5 hexanes/EtOAc) afforded **16** (302 mg, 0.8 mmol, 81% yield) as a colorless oil. **R_f** (90:10 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ +15.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2927, 2856, 1773, 1693, 1350, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.19 (5H, m, Ar$\underline{H}$), 4.55 (1H, dd, *J* = 9.8, 3.6 Hz, C$\underline{H}$N), 3.84 (1H, tt, *J* = 8.3, 5.5 Hz, COC$\underline{H}$), 3.12 (1H, dd, *J* = 14.4, 3.6 Hz, $C\underline{H}_xH_yPh$), 2.89 (1H, dd, *J* = 14.4, 9.8 Hz, $CH_x\underline{H}_yPh$), 1.72–1.59 (2H, m, $COCHC\underline{H}_xH_y(CH_2)_4$, $COCHC\underline{H}_xH_yCH_2CH_3$), 1.53–1.38 (2H, m, $COCHCH_x\underline{H}_y(CH_2)_4$, $COCHCH_x\underline{H}_yCH_2CH_3$), 1.35 (3H, s, $CC\underline{H}_3$), 1.34 (3H, s, $CC\underline{H}_3$), 1.33–1.20 (10H, m, $COCHCH_2(C\underline{H}_2)_4$, $COCHCH_2C\underline{H}_2CH_3$), 0.91–0.85 (6H, m, 2 × $(CH_2)C\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.3 (C), 152.4 (C), 137.0 (C), 129.1 (CH), 128.6 (CH), 126.7 (CH), 81.7 (C), 63.8 (CH), 42.5 (CH), 35.5 (CH_2), 34.9 (CH_2), 32.4 (CH_2), 31.7 (CH_2), 29.4 (CH_2), 28.4 (CH_3), 27.4 (CH_2), 22.6 (CH_2), 22.2 (CH_3), 20.3 (CH_2), 14.2 (CH_3), 14.0 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{23}H_{35}NNaO_3$ $[M+Na]^+$: 396.2509, found: 396.2507.

Arundic acid



16 **arundic acid**

A 30% solution of H_2O_2 (770 µL, 7.7 mmol) and LiOH (37 mg, 15.4 mmol) were added to a solution of adduct **16** (289 mg, 0.77 mmol) in THF/H_2O 4:1 (4 mL) at 0 °C. The mixture was stirred at rt for 4.5 h and quenched by dropwise addition of 1.5 M Na_2SO_3 (4 mL) and 1 M HCl (4 mL). The mixture was extracted with Et_2O (4 × 5 mL) and the combined organic extracts were extracted with 1 M NaOH (3 × 10 mL). The combined aqueous extracts were washed with Et_2O (10 mL) and the organic extract was combined with the previous one and set apart. The aqueous

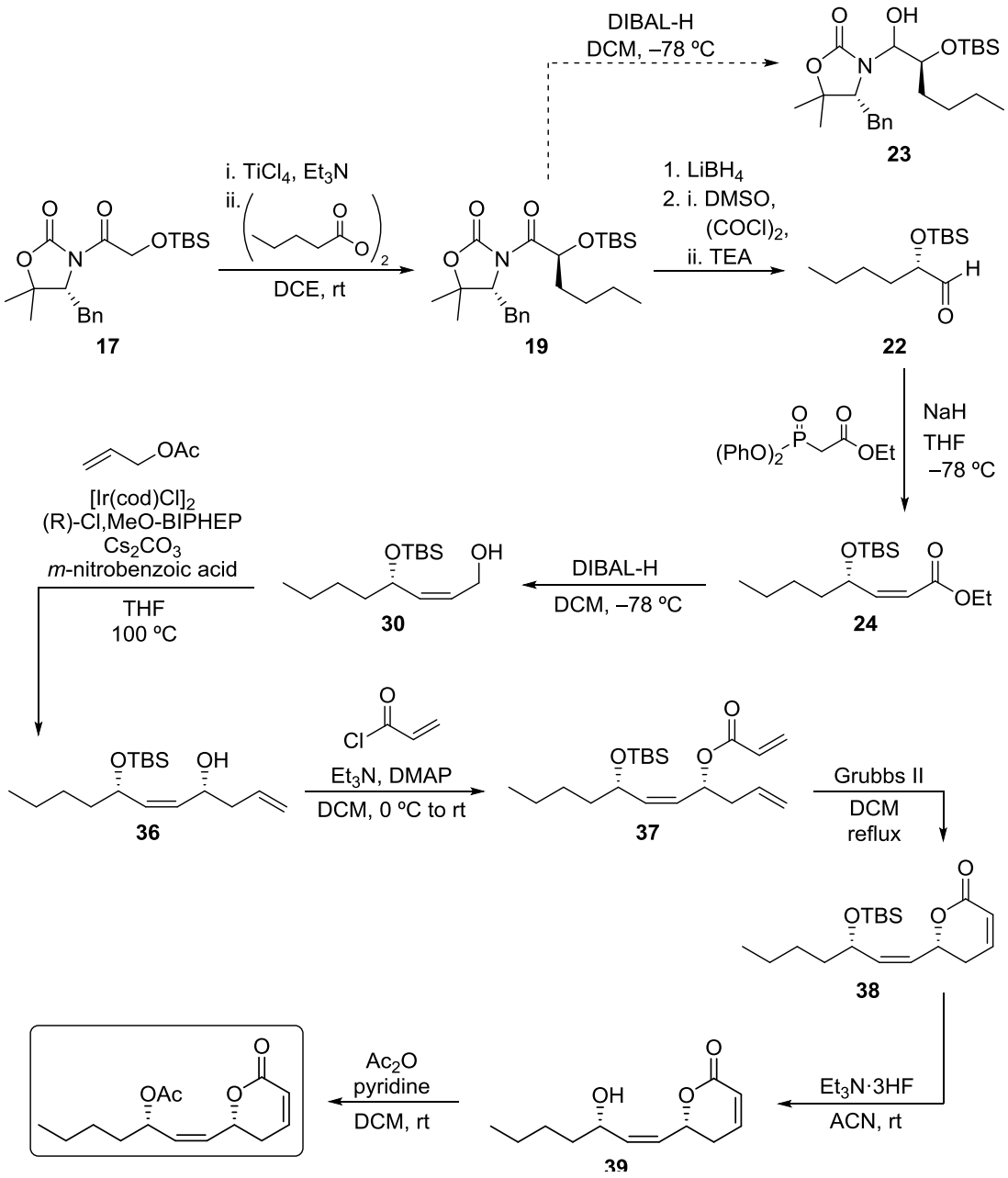
phase was then acidified with 2 M HCl (pH ~2) and extracted with Et_2O (4 × 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford arundic acid (126 mg, 0.68 mmol, 88% yield) as a colorless oil. Characterization matches with arundic acid synthesized in route A (*see page 223*).

Recovery of the chiral auxiliary

The organic extracts set apart were treated with 1 M HCl (20 mL) and water (20 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford oxazolidinone **ent*SuperQuat*** (144 mg, 0.70 mmol, 91% yield).

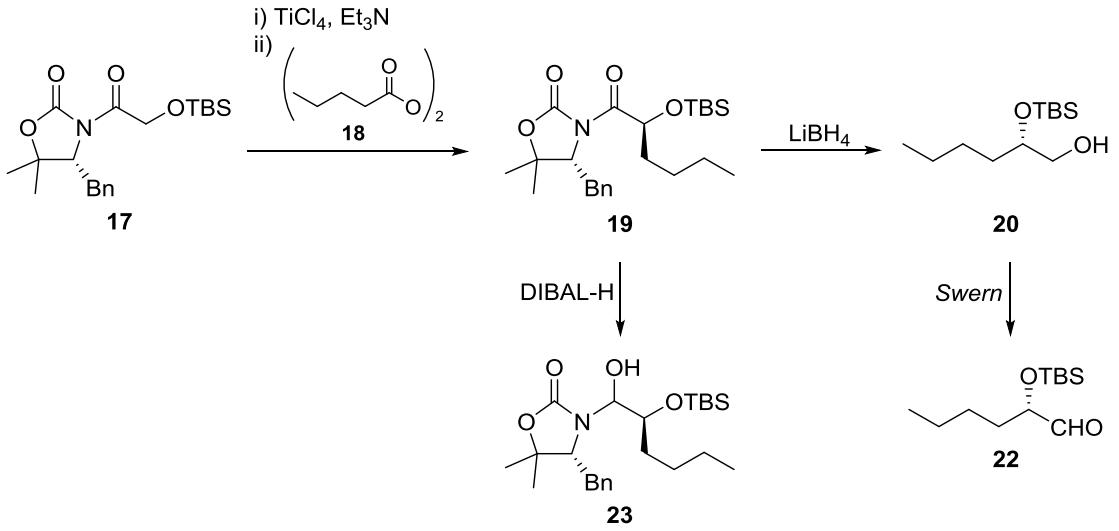
Chapter II

Total Synthesis of Umuravumbolide



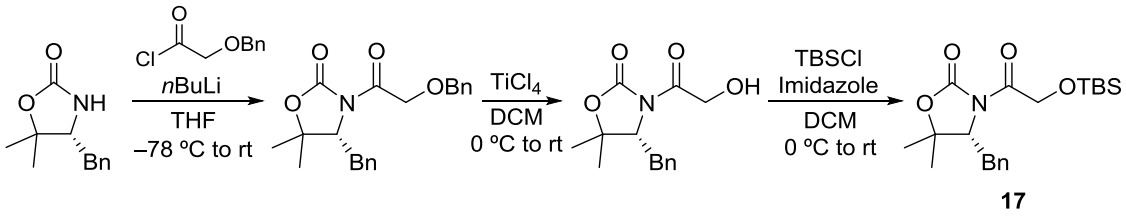
Scheme 140. Route to umuravumbolide

1. Side chain chiral center

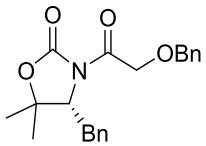


Scheme 141. Preparation of the side chain chiral center of umuravumbolide

(*R*)-4-Benzyl-*N*-(*tert*-butyldimethylsilyloxy)acetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (17)



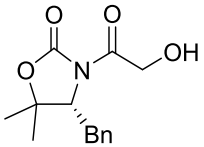
(*R*)-4-Benzyl-*N*-(2-benzyloxyacetyl)-5,5-dimethyl-1,3-oxazolidin-2-one



A 2.5 M solution of *n*-BuLi in hexanes (5.4 mL, 13.5 mmol) was added dropwise to a solution of (*R*)-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (2.52 g, 12.3 mmol) in THF (60 mL) at −78 °C. The solution was stirred for 15 min and 2-(benzyloxy)acetyl chloride (2.5 mL, 16.0 mmol) was added dropwise. The mixture was then stirred at −78 °C for 20 min, allowed to warm to rt and stirred for 2 h. The reaction mixture was quenched with sat NH_4Cl (30 mL) and concentrated. The residue was partitioned between water and EtOAc (30 mL each). The aqueous layer was extracted with further EtOAc (2 × 30 mL). The combined organic extracts were washed with sat $NaHCO_3$ (60 mL), brine (60 mL), and dried with anhydrous $MgSO_4$. The solvent was evaporated, and the residue was purified by flash column chromatography (80:20 Hexanes/EtOAc) to afford the title compound (4.01 g, 11.3 mmol, 92% yield) as a yellow oil. $\mathbf{R_f}$ (80:20 hexanes/EtOAc)

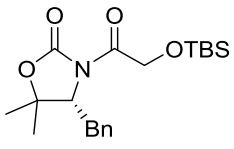
0.4; **IR** (NaCl) ν 3029, 2980, 1769, 1711, 1354, 1259, 1126, 1099 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.18 (10H, m), 4.73 (1H, d, *J* = 17.8 Hz), 4.63 (1H, d, *J* = 17.8 Hz), 4.62 (2H, s), 4.52 (1H, dd, *J* = 9.5, 3.9 Hz), 3.20 (1H, dd, *J* = 14.4, 3.9 Hz), 2.89 (1H, dd, *J* = 14.4, 9.5 Hz), 1.38 (3H, s), 1.36 (3H, s); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.3 (C), 152.5 (C), 137.2 (C), 136.6 (C), 129.0 (CH), 128.7 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 126.9 (CH), 83.6 (C), 73.3 (CH_2), 69.7 (CH_2), 63.3 (CH), 35.1 (CH_2), 28.6 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{21}H_{24}NO_4$ $[M+H]^+$: 354.1700, found: 354.1693.

(*R*)-4-Benzyl-*N*-hydroxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one



Neat $TiCl_4$ (2.5 mL, 22.7 mmol) was added dropwise to a solution of (*R*)-4-benzyl-*N*-(2-benzyloxyacetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (4.01 g, 11.4 mmol) in DCM (95 mL) at 0 °C. The reaction mixture was stirred at rt for 30 min and quenched with sat NH_4Cl (40 mL) at 0 °C. The mixture was extracted with DCM (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (from 100:0 to 60:40 hexanes/EtOAc) to afford the title compound (2.64 g, 10.0 mmol, 88% yield) as a colourless oil. **R_f** (70:30 hexanes/EtOAc) 0.3; **IR** (ATR) ν 3482, 2981, 2931, 1778, 1699, 1603, 1497 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.22 (5H, m), 4.72 (1H, d, *J* = 18.6 Hz), 4.64 (1H, d, *J* = 18.6 Hz), 4.52 (1H, dd, *J* = 9.4, 4.3 Hz), 3.20 (1H, dd, *J* = 14.4, 4.2 Hz), 2.92 (1H, dd, *J* = 14.4, 9.4 Hz), 1.41 (3H, s), 1.39 (3H, s); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.5 (C), 152.1 (C), 136.3 (C), 128.9 (CH), 128.7 (CH), 127.0 (CH), 83.9 (C), 63.4 (CH), 63.2 (CH_2), 35.1 (CH_2), 28.6 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{14}H_{18}NO_4$ $[M+H]^+$: 264.1230, found: 264.1222.

(*R*)-4-Benzyl-*N*-*tert*-butyldimethylsilyloxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (**17**)

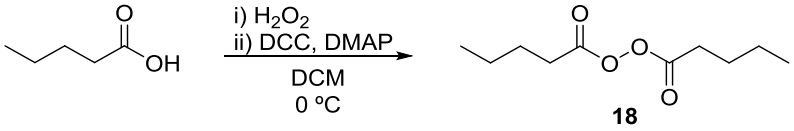


17

Imidazole (1.83 g, 27 mmol) and TBSCl (1.86 g, 12.3 mmol) were added to a solution of (*R*)-4-benzyl-*N*-hydroxyacetyl-5,5-dimethyl-1,3-oxazolidin-2-one (2.64 g, 10.0 mmol) in DCM (55 mL) at 0 °C. The mixture was stirred for 72 h at rt and diluted with Et_2O (50 mL). The organic layer was washed with water (50 mL), 10% citric acid aqueous solution (50 mL), brine (50 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Purification of the crude product by flash column chromatography (from 95:5 to 90:10

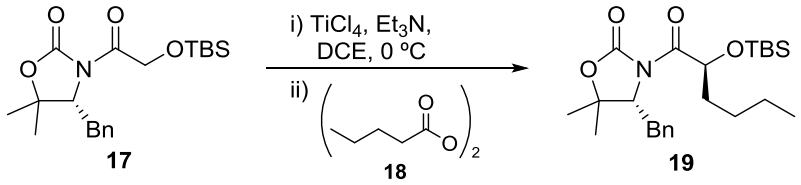
hexanes/EtOAc) afforded **17** (3.78 g, 10.0 mmol, quantitative yield) as a white solid. **Mp** 75–78 °C; **R$_f$** (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ +27.4 (*c* 1.0, $CHCl_3$); **IR** (NaCl) ν 2949, 2925, 2852, 1759, 1726, 1351, 1297, 1166, 1159 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m), 4.89 (1H, d, *J* = 18.3 Hz), 4.75 (1H, d, *J* = 18.3 Hz), 4.51 (1H, dd, *J* = 10.0, 3.4 Hz), 3.24 (1H, dd, *J* = 14.4, 3.4 Hz), 2.88 (1H, dd, *J* = 14.4, 10.0 Hz), 1.36 (3H, s), 1.35 (3H, s), 0.94 (9H, s), 0.12 (3H, s), 0.11 (3H, s); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.9 (C), 152.6 (C), 136.7 (C), 129.0 (CH), 128.7 (CH), 126.8 (CH), 83.5 (C), 64.4 (CH_2), 63.4 (CH), 35.0 (CH_2), 28.6 (CH_3), 25.8 (CH_3), 22.4 (CH_3), 18.4 (C), −5.4 (CH_3), −5.5 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{20}H_{32}NO_4Si$ $[M+H]^+$: 378.2095, found: 378.2098.

Dipentanoyl peroxide (18)



It was prepared following General Procedure 3 from pentanoic acid (3.5 mL, 32 mmol), 30% H_2O_2 (1.7 mL, 16 mmol), DMAP (391 mg, 3.2 mmol) and DCC (7.22 g, 35 mmol). The residue was purified by flash column chromatography (60:40 hexanes/DCM) to afford **18** (2.87 g, 14 mmol, 88% yield) as a colorless oil. **R$_f$** (50:50 hexanes/DCM) 0.4; **IR** (ATR) ν 2960, 2935, 2875, 1809, 1779, 1123, 1048 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.43 (4H, t, *J* = 7.4 Hz, 2 × COC<u>H</u>$_2$), 1.76–1.65 (4H, m, 2 × $COCH_2C$<u>H</u>$_2$), 1.48–1.35 (4H, m, 2 × C<u>H</u>$_2CH_3$), 0.94 (6H, t, *J* = 7.4 Hz, 2 × CH_2C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.2 (C), 29.7 (CH_2), 26.8 (CH_2), 22.1 (CH_2), 13.5 (CH_3).

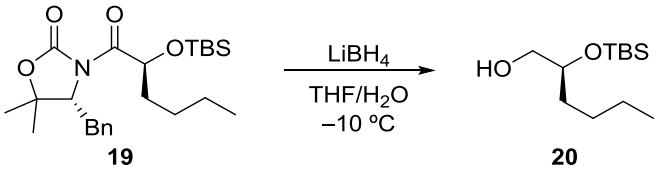
(*R*)-4-Benzyl-*N*-[(*S*)-2-*tert*-butyldimethylsilyloxyhexanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (19)



It was prepared following General Procedure 6 from *N*-acyl oxazolidinone **17** (2.27 g, 6.0 mmol), $TiCl_4$ (720 mL, 6.6 mmol), Et_3N (2.5 mL, 18 mmol) and peroxide **18** (1.82 g, 9.0 mmol) for 50 min at rt. Purification of the residue by flash column chromatography (from 99.5:0.5 to 95:5 hexanes/EtOAc) afforded **19** (2.26 g, 5.2 mmol, 87% yield) as a white solid. **Mp** 66–68 °C; **R$_f$** (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −4.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2953, 2928, 2856, 1770, 1715, 1353, 1248, 1146, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.17 (5H, m, Ar<u>H</u>), 5.34 (1H, dd, *J* = 8.2, 3.3 Hz, COC<u>H</u>), 4.58 (1H, dd, *J* = 9.7, 3.9 Hz, NC<u>H</u>), 3.09 (1H, dd, *J* = 14.4, 3.9 Hz, C<u>H</u>$_x$H$_y$Ph), 2.87 (1H, dd, *J* = 14.4, 9.7 Hz, CH$_x$<u>H</u>$_y$Ph), 1.73–1.65 (1H, m,

COCHC$\underline{H}_x$H$_y$), 1.59–1.48 (1H, m, COCHCH$_x\underline{H}_y$), 1.47–1.23 (4H, m, C$\underline{H}_2$C$\underline{H}_2$CH$_3$), 1.38 (3H, s, CC$\underline{H}_3$), 1.34 (3H, s, CC$\underline{H}_3$), 0.92–0.88 (12H, m, CH$_2$C$\underline{H}_3$, C(C$\underline{H}_3$)$_3$), 0.08 (3H, s, SiC$\underline{H}_3$), 0.06 (3H, s, SiC$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.7 (C), 152.2 (C), 136.5 (C), 129.1 (CH), 128.6 (CH), 126.8 (CH), 82.7 (C), 71.2 (CH), 63.2 (CH), 35.3 (CH_2), 35.0 (CH_2), 28.5 (CH_3), 27.5 (CH_2), 25.8 (CH_3), 22.4 (CH_2), 22.4 (CH_3), 18.4 (C), 13.9 (CH_3), −4.8 (CH_3), −5.3 (CH_3); HRMS (+ESI): *m/z* calcd. for $C_{24}H_{40}NO_4Si$ $[M+H]^+$: 434.2721, found: 434.2719.

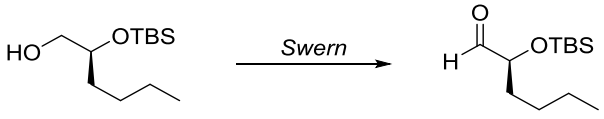
(*S*)-2-*tert*-Butyldimethylsilyloxyhexanol (20)



19 **20**

A 2.0 M solution of $LiBH_4$ in THF (14 mL, 28 mmol) was added dropwise to a solution of **19** (2.00 g, 4.6 mmol) in THF (35 mL) and H_2O (12 mL) at –10 °C. The mixture was stirred for 80 min at –10 °C and quenched with MeOH (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 × 40 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (from 95:5 to 50:50 Hexanes/EtOAc) to give recovered chiral auxiliary (869 mg, 4.2 mmol, 92% yield) as a white solid and **20** (844 mg, 3.6 mmol, 79% yield) as a colorless oil. **R_f** (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ +10.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν br 3386, 2954, 2928, 2857, 1463, 1253, 1097, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.73 (1H, tdd, *J* = 6.4, 5.4, 3.6 Hz, TBSOC$\underline{H}$), 3.56 (1H, dd, *J* = 11.0, 3.6 Hz, C$\underline{H}_x$H$_y$OH), 3.44 (1H, dd, *J* = 11.0, 5.4 Hz, CH$_x\underline{H}_y$OH), 1.94 (1H, br s, O$\underline{H}$), 1.52–1.45 (2H, m, C$\underline{H}_2$(CH$_2$)$_2$CH$_3$), 1.36–1.21 (4H, m, (C$\underline{H}_2$)$_2$CH$_3$), 0.92–0.88 (12H, m, CH$_2$C$\underline{H}_3$, C(C$\underline{H}_3$)$_3$), 0.09 (6H, s, Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 72.9 (CH), 66.3 (CH_2), 33.7 (CH_2), 27.5 (CH_2), 25.8 (CH_3), 22.8 (CH_2), 18.1 (C), 14.0 (CH_3), −4.5 (CH_3), −4.6 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{12}H_{29}O_2Si$ $[M+H]^+$: 233.1931, found: 233.1930.

(*S*)-2-*tert*-Butyldimethylsilyloxyhexanal (22)

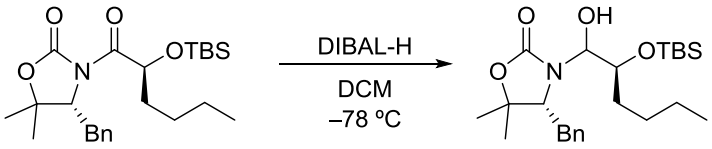


20 **22**

DMSO (656 µL, 9.2 mmol) was added dropwise to a solution of $(COCl)_2$ (423 µL, 4.9 mmol) in DCM (60 mL) at –78 °C. The resultant mixture was stirred for 10 min at –78 °C and a solution of alcohol **20** (716 mg, 3.1 mmol) in DCM (3 mL) was added via *cannula* and stirred for 10 min at –60 °C. Et_3N (2.6 mL, 18.5 mmol) was added to the reaction mixture at –78 °C and the mixture was allowed to warm to rt. The mixture was stirred for 2.3 h and then it was quenched with H_2O

(30 mL). The layers were separated, and the aqueous layer was extracted with hexanes (2 × 40 mL). The combined organic extracts were washed with H_2O (50 mL), 10% acetic acid aqueous solution (50 mL), and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure (H_2O_2 trap!) to afford quantitatively the crude reaction product **22** (729 mg) as a yellowish oil, which was used in the next step without further purification. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.7; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.59 (1H, d, J = 1.7 Hz, C<u>H</u>O), 3.96 (1H, ddd, J = 7.1, 5.7, 1.8 Hz, COC<u>H</u>), 1.65–1.59 (2H, m, CHC<u>H</u>$_2$), 1.41–1.18 (4H, m, (C<u>H</u>$_2$)$_2$CH$_3$), 0.93-0.88 (12H, m, SiC(C<u>H</u>$_3$)$_3$, CH$_2$C<u>H</u>$_3$), 0.08 (3H, s, SiC<u>H</u>$_3$), 0.08 (3H, s, SiC<u>H</u>$_3$).

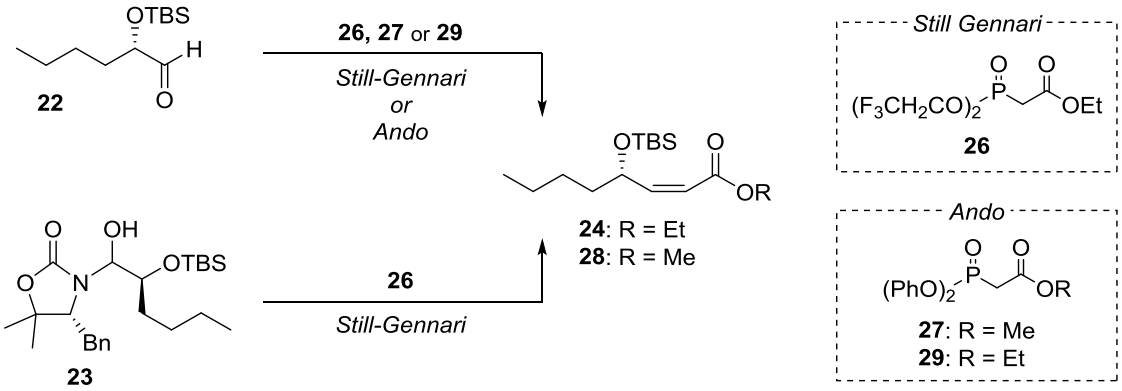
(*R*)-4-Benzyl-*N*-[(2*S*)-2-*tert*-butyldimethylsilyloxy-1-hydroxyhexyl]-5,5-dimethyl-1,3-oxazolidin-2-one (23)



19 **23**

A 1.0 M solution of DIBAL-H in toluene (800 µL, 0.80 mmol) was added to a solution of **19** (170 mg, 0.39 mmol) in DCM (2.5 mL) at –78 °C, the mixture was stirred for 30 min and quenched with MeOH (100 µL) at –78 °C. The mixture was allowed to warm to rt, rochelle's salt (3 mL) was added and the mixture was stirred at rt for 30 min. The mixture was extracted with DCM (2 × 5 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography (80:20 Hexanes/EtOAc) afforded **23** (100 mg, 0.23 mmol, 59%) as a white solid. **Mp** 90–95 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ +21.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3406 (br), 2953, 2928, 2856, 1725, 1405, 1307, 1254, 1100, 1068 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.19 (5H, m, Ar<u>H</u>), 4.57 (1H, dd, *J* = 11.1, 7.4 Hz, C<u>H</u>OH), 4.25 (1H, ddd, *J* = 7.4, 5.3, 3.6 Hz, C<u>H</u>OTBS), 4.11 (1H, dd, *J* = 8.5, 5.9 Hz, NC<u>H</u>), 3.88 (1H, d, *J* = 11.1 Hz, O<u>H</u>), 3.27 (1H, dd, *J* = 14.6, 5.9 Hz, C<u>H</u>$_x$H$_y$Ph), 2.81 (1H, dd, *J* = 14.6, 8.5 Hz, CH$_x$<u>H</u>$_y$Ph), 1.68–1.58 (1H, m, OTBSCHC<u>H</u>$_x$H$_y$), 1.57–1.43 (1H, m, OTBSCHCH$_x$<u>H</u>$_y$), 1.34 (3H, s, CC<u>H</u>$_3$), 1.29–1.20 (6H, m, CC<u>H</u>$_3$, CH$_x$<u>H</u>$_y$C<u>H</u>$_2$CH$_3$), 1.12–1.03 (1H, m,C<u>H</u>$_x$H$_y$CH$_2$CH$_3$), 0.90 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.87 (3H, t, *J* = 7.2 Hz, CH$_2$C<u>H</u>$_3$), 0.10 (3H, s, SiC<u>H</u>$_3$), 0.08 (3H, s, SiC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 157.3 (C), 136.9 (C), 128.7 (CH), 128.7 (CH), 126.8 (CH), 82.4 (C), 80.1 (CH), 72.7 (CH), 65.5 (CH), 35.1 (CH_2), 33.4 (CH_2), 27.4 (CH_3), 26.0 (CH_3), 24.8 (CH_2), 23.0 (CH_2), 22.3 (CH_3), 18.0 (C), 14.0 (CH_3), –4.2 (CH_3), –4.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{24}H_{42}NO_4Si$ $[M+H]^+$: 436.2878, found: 436.2879.

2. Side chain olefin

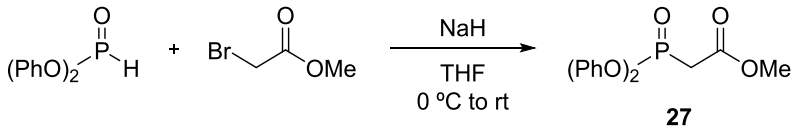


Scheme 142. Synthesis of the side chain olefin of umurvaumbolide

2.1. Preparation of phosphonates

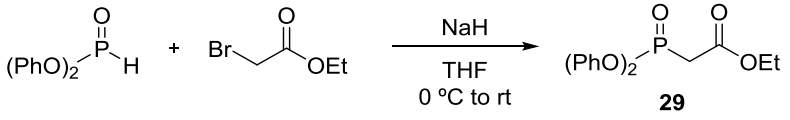
The following phosphonates were synthesized according to the literature.[127]

Methyl diphenoxyphosphorylacetate (27)



Diphenylphosphite (1.4 mL, 5.5 mmol) was added dropwise to the well-stirred suspension of NaH 60% dispersion in mineral oil (308 mg, 7.7 mmol) in THF (11 mL) at 0 °C (**CAUTION**: slow addition, release of gas). Then, a solution of methyl bromoacetate (520 µL, 5.5 mmol) in THF (14 mL) was added at 0 °C over 1 h. The resultant solution was allowed to warm to rt, stirred for 1.75 h and quenched with sat NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash column chromatography (70:30 Hexanes/EtOAc) afforded **27** (1.27 g, 4.1 mmol, 75% yield) as a colorless oil. $\mathbf{R_f}$ (80:20 Hexanes/EtOAc) 0.1; **IR** (ATR) ν 2953, 2920, 1739, 1589, 1487, 1277, 1183, 1160, 1115 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.16 (10H, m, Ar<u>H</u>), 3.76 (3H, s, C<u>H</u>$_3$), 3.28 (2H, d, J = 21.7 Hz, PC<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 165.2 (C, d, J = 6.3 Hz), 149.9 (C, d, J = 8.5 Hz), 129.8 (CH), 125.5 (CH), 120.6 (CH, d, J = 4.4 Hz), 52.8 (CH_3), 33.8 (CH_2, d, J = 137.6 Hz).

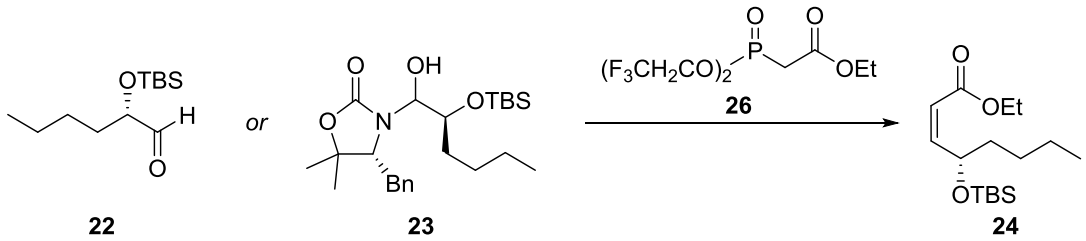
Ethyl diphenoxyphosphorylacetate (29)



Diphenylphosphite (1.4 mL, 5.5 mmol) was added dropwise to the well-stirred suspension of NaH 60% dispersion in mineral oil (308 mg, 7.7 mmol) in THF (11 mL) at 0 °C (**CAUTION**: slow addition, release of gas). Then, a solution of ethyl bromoacetate (610 µL, 5.5 mmol) in THF (14 mL) was added at 0 °C over 1 h. The resultant solution was allowed to warm to rt, stirred for 1.75 h and quenched with sat NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash column chromatography (70:30 Hexanes/EtOAc) afforded **29** (1.59 g, 4.9 mmol, 90% yield) as a colorless oil. $\mathbf{R_f}$ (80:20 Hexanes/EtOAc) 0.1; **IR** (ATR) ν 2981, 2935, 1735, 1589, 1488, 1278, 1183, 1159, 1112 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.16 (10H, m, ArH), 4.23 (2H, q, *J* = 7.2 Hz, OCH_2), 3.26 (2H, d, *J* = 21.6 Hz, PCH_2), 1.28 (3H, t, *J* = 7.1 Hz, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 164.8 (C, d, *J* = 6.4 Hz), 150.0 (C, d, *J* = 8.5 Hz), 129.8 (CH), 125.5 (CH), 120.6 (CH, d, *J* = 4.5 Hz), 62.0 (CH_2), 34.1 (CH_2, d, *J* = 137.2 Hz), 14.0 (CH_3).

2.2. Olefination reactions

Still Gennari olefination



22 **23** **24**

From aldehyde **22** with phosphonate **26** and KHDMS

Phosphonate **26** (22 µL, 0.10 mmol) was added to a solution of 18-crown-6 (58 mg, 0.22 mmol) in THF (0.5 mL) at –78 °C. Then, KHDMS (95 µL, 0.10 mmol) was added dropwise and the mixture was stirred for 10 min at –78 °C. Then a solution of aldehyde **22** (20 mg, 0.10 mmol) in THF (0.5 mL) was added via *cannula*. The mixture was stirred at –78 °C for 2 h and quenched with sat NH_4Cl (1.0 mL), allowed to warm to rt and extracted with EtOAc (2 × 3 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. ^{1}H NMR of the crude showed complete conversion to a mixture of *Z* : *E* olefinated product (dr 80:20).

From aldehyde **22** with phosphonate **26** and K_2CO_3

A solution of 18-crown-6 (58 mg, 0.22 mmol) and K_2CO_3 (41 mg, 0.30 mmol) in THF (1.0 mL) was stirred for 30 min at rt. Then, phosphonate **26** (47 µL, 0.020 mmol) was added and the mixture was cooled to –10 °C. A solution of aldehyde **22** (23 mg, 0.10 mmol) in THF (1.0 mL) was added via *cannula*. The mixture was stirred at 0 °C for 16 h and quenched with sat NH_4Cl (2

mL) and extracted with DCM (3 × 3 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. ^1H NMR of the crude showed complete conversion to a mixture of *Z* : *E* olefinated product (dr 70:30). Purification of the residue by flash column chromatography (from 90:10 to 70:30 Hexanes/DCM) afforded **24** (18 mg, 0.06 mmol, 60% yield) as a colorless oil and **25** (7 mg, 0.02 mmol, 23% yield) as a colourless oil, see characterization in page 236.

The same experiment was repeated at a lower temperature; the mixture was stirred at –20 °C for 16 h. ^1H NMR of the crude showed complete conversion to a mixture of *Z* : *E* olefinated product (dr 75:35).

From aldehyde **22** with phosphonate **26** and NaH

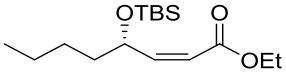
Phosphonate **26** (360 µL, 1.58 mmol) was added to a solution of NaH 60% dispersion in mineral oil (144 mg, 3.6 mmol) in THF (12 mL) at –60 °C. Then a solution of aldehyde **22** (331 mg, 1.44 mmol) in THF (2 mL) was added via *cannula*. The mixture was stirred from –60 °C to –35 °C for 1 h and quenched with sat NH_4Cl (1.0 mL), allowed to warm to rt and extracted with DCM (3 × 20 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. ^1H NMR of the crude showed complete conversion to a mixture of *Z* : *E* olefinated product (dr 89:11). Purification of the residue by flash column chromatography (from 90:10 to 70:30 Hexanes/DCM) afforded **24** (334 mg, 1.11 mmol, 77% yield) as a colourless oil and **25** (16 mg, 0.05 mmol, 4% yield) as a colourless oil, see characterization in page 236.

The same experiment was repeated at a lower temperature; the mixture was stirred at –78 °C for 1 h. ^1H NMR of the crude showed incomplete conversion (62%) to a mixture of *Z* : *E* olefinated product (dr 96:4).

From carbinol **23** with phosphonate **26** and NaH

Phosphonate **26** (126 µL, 0.55 mmol) was added to a solution of NaH 60% dispersion in mineral oil (50 mg, 1.25 mmol) in THF (3 mL) at –60 °C. Then a solution of carbinol **23** (218 mg, 0.50 mmol) in THF (2 mL) was added via *cannula*. The mixture was stirred from –60 °C to –40 °C for 2 h and quenched with sat NH_4Cl (3 mL), allowed to warm to rt and extracted with DCM (3 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. ^1H NMR of the crude showed no starting material but aldehyde **22** (40%) and mixture of *Z* : *E* olefinated product (dr 91:9). Purification of the residue by flash column chromatography (from 90:10 to 70:30 Hexanes/DCM) afforded **24** (81 mg, 0.27 mmol, 54% yield) as a colourless oil and **25** (11 mg, 0.04 mmol, 7% yield) as a colourless oil, see characterization in page 236.

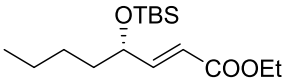
Ethyl (*S*,*Z*)-4-(*tert*-butyldimethylsilyloxy)-2-octenoate (24)



24

R$_f$ (70:30 hexanes/DCM) 0.5; $[\alpha]_D^{20}$ +7.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2956, 2929, 2857, 1720, 1252, 1183, 1116, 1080, 1049, 1031 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.14 (1H, dd, *J* = 11.7, 8.2 Hz, COCH=C<u>H</u>), 5.68 (1H, dd, *J* = 11.7, 1.3 Hz, COC<u>H</u>=CH), 5.33–5.25 (1H, m, C<u>H</u>OTBS), 4.17 (2H, q, *J* = 7.1 Hz, OC<u>H$_2$</u>), 1.62–1.25 (6H, m, CH(C<u>H$_2$</u>)$_3$), 1.29 (3H, t, *J* = 7.1 Hz, OCH$_2$C<u>H$_3$</u>), 0.88 (12H, m, C(C<u>H$_3$</u>)$_3$, (CH$_2$)$_3$C<u>H$_3$</u>), 0.05 (3H, s, SiC<u>H$_3$</u>), 0.01 (3H, s, SiC<u>H$_3$</u>); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 165.9 (C), 153.8 (CH), 117.5 (CH), 68.8 (CH), 60.1 (CH_2), 37.0 (CH_2), 27.3 (CH_2), 25.8 (CH_3), 22.6 (CH_2), 18.1 (C), 14.2 (CH_3), 14.0 (CH_3), −4.6 (CH_3), −4.9 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{16}H_{33}O_3Si$ $[M+H]^+$: 301.2193, found: 301.2191.

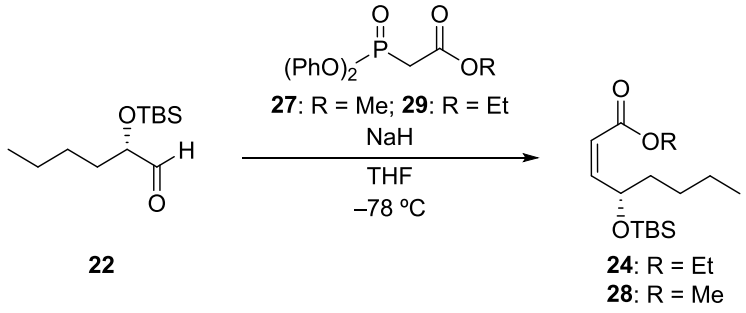
Ethyl (*S*,*E*)-4-(*tert*-butyldimethylsilyloxy)oct-2-enoate (25)



25

R$_f$ (90:10 hexanes/DCM) 0.4; **IR** (ATR) ν 2957, 2931, 2858, 1722, 1302, 1258, 1175, 1093, 1036 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.92 (1H, dd, *J* = 15.5, 4.7 Hz, C<u>H</u>=CHCOO), 5.96 (1H, dd, *J* = 15.5, 1.7 Hz, C<u>H</u>COO), 4.29 (1H, tdd, *J* = 6.1, 4.7, 1.7 Hz, C<u>H</u>OTBS), 4.24-4.16 (2H, m, COOC<u>H$_2$</u>), 1.56–1.49 (2H, m, C<u>H$_2$</u>CHO), 1.35–1.24 (7H, m, C<u>H$_2$</u>C<u>H$_2$</u>CH$_3$, CH$_2$C<u>H$_3$</u>), 0.93–0.85 (12H, m, CH$_2$CH$_2$C<u>H$_3$</u>, C(C<u>H$_3$</u>)$_3$), 0.06 (3H, s, SiC<u>H$_3$</u>), 0.03 (3H, s, SiC<u>H$_3$</u>); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 166.8 (C), 151.1 (CH), 119.7 (CH), 71.6 (CH), 60.3 (CH_2), 37.1 (CH_2), 26.9 (CH_2), 25.8 (CH_3), 22.7 (CH_2), 18.2 (C), 14.3 (CH_3), 14.0 (CH_3), −4.6 (CH_3), −4.9 (CH_3).

Ando olefination



22

24: R = Et
28: R = Me

<u>With phosphonate **27**</u>

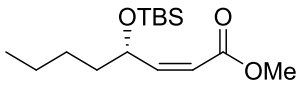
NaH 60% dispersion in mineral oil (21 mg, 0.52 mmol) was added (**CAUTION**: slow addition, release of gas) was added to a solution of phosphonate **27** (159 mg, 0.52 mmol) in THF (3 mL) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and cooled to –78 °C. Then, a solution of crude aldehyde **22** (92 mg, 0.4 mmol) in THF (6 mL) was added dropwise via *cannula* and

stirred for 2 h at –78 °C. The reaction was quenched with sat NH_4Cl (6 mL) and extracted with Et_2O (2 × 15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. ^1H NMR of the crude showed complete conversion to a mixture of *Z* : *E* olefinated product (dr 96:4). Purification of the residue by flash column chromatography (80:20 Hexanes/DCM) afforded **28** (83 mg, 0.29 mmol, 72% yield from **20**) as a colorless oil.

With phosphonate **27** and NaI

NaI (70 mg, 0.46 mmol) was added to a solution of phosphonate **27** (185 mg, 0.6 mmol) in THF (4 mL) at 0 °C. After 5 min, NaH 60% dispersion in mineral oil (25 mg, 0.6 mmol) was added (**CAUTION**: slow addition, release of gas) and the resulting mixture was stirred for 15 min and cooled to –78 °C. Then, a solution of crude aldehyde **22** (102 mg, ≈ 0.46 mmol) in THF (2 mL) was added dropwise via *cannula* and stirred for 2 h at –78 °C. The reaction was quenched with sat NH_4Cl (6 mL) and extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, concentrated under reduced pressure. ^1H NMR of the crude showed complete conversion to a mixture of ***Z*** : ***E*** olefinated product (dr 96:4). Purification of the residue by flash column chromatography (80:20 Hexanes/DCM) afforded **28** (93 mg, 0.32 mmol, 73% yield from **20**) as a colorless oil.

Methyl (*S*,*Z*)-4-(*tert*-butyldimethylsilyloxy)-2-octenoate (28)



28

R_f (70:30 Hexanes/DCM) 0.5; $[\alpha]_D^{20}$ +10.5 (*c* 1.0, $CHCl_3$), **IR** (ATR) ν 2954, 2929, 2857, 1724, 1252, 1193, 1178, 1080, 1050 cm^{-1}; **^1H NMR** (400 MHz, $CDCl_3$) δ 6.17 (1H, dd, *J* = 11.7, 8.2 Hz, COCH=C<u>H</u>), 5.69 (1H, dd, *J* = 11.7, 1.3 Hz, COC<u>H</u>=CH), 5.29 (1H, tdd, *J* = 8.2, 4.6, 1.3 Hz, C<u>H</u>OTBS), 3.71 (3H, s, OC<u>H</u>$_3$), 1.57–1.24 (6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 0.94–0.84 (12H, m, (CH$_2$)$_3$C<u>H</u>$_3$, C(C<u>H</u>$_3$)$_3$), 0.05 (3H, s, SiC<u>H</u>$_3$), 0.01 (3H, s, SiC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 166.3 (C), 154.3 (CH), 116.9 (CH), 68.7 (CH), 51.2 (CH_3), 37.0 (CH_2), 27.3 (CH_2), 25.8 (CH_3), 22.6 (CH_2), 18.1 (C), 14.0 (CH_3), –4.6 (CH_3), –4.9 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{15}H_{30}NaO_3Si$ $[M+Na]^+$: 309.1856, found: 309.1857.

With phosphonate **29**

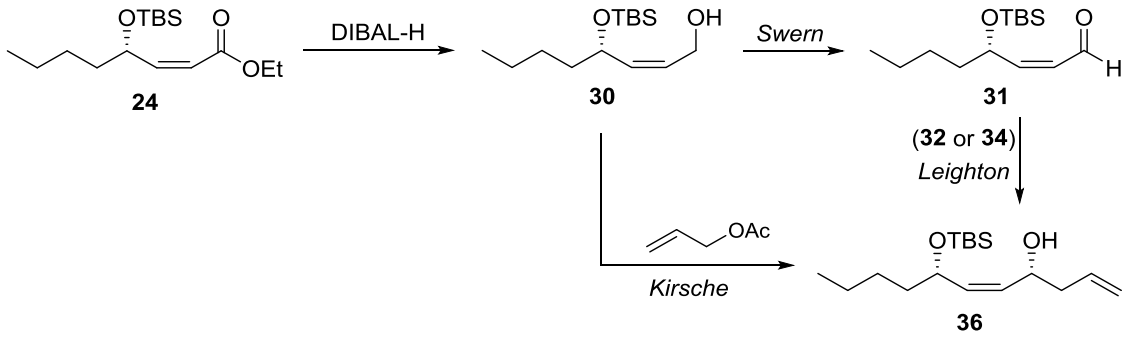
NaH 60% dispersion in mineral oil (23 mg, 0.58 mmol) was added (**CAUTION**: slow addition, release of gas) was added to a solution of phosphonate **29** (186 mg, 0.58 mmol) in THF (3 mL) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and cooled to –78 °C. Then, a solution of crude aldehyde **22** (102 mg, 0.44 mmol) in THF (3 mL) was added dropwise via *cannula* and stirred for 2 h at –78 °C. The reaction was quenched with sat NH_4Cl (6 mL) and extracted with

Et_2O (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. ^1H NMR of the crude showed complete conversion to a mixture of ***Z*** : ***E*** olefinated product (dr 96:4). Purification of the residue by flash column chromatography (80:20 Hexanes/DCM) afforded **24** (108 mg, 0.36 mmol, 82% yield from **20**) as a colorless oil, see characterization in page 236.

With phosphonate **29** and NaI

NaI (465 mg, 3.1 mmol) was added to a solution of phosphonate **29** (1.28 g, 4.0 mmol) in THF (30 mL) at 0 °C. After 5 min, NaH 60% dispersion in mineral oil (160 mg, 4.0 mmol) was added (**CAUTION**: slow addition, release of gas) and the resulting mixture was stirred for 15 min and cooled to −78 °C. Then, a solution of crude aldehyde **22** (729 mg, 3.1 mmol) in THF (8 mL) was added dropwise via *cannula* and stirred for 2 h at −78 °C. The reaction was quenched with sat NH_4Cl (20 mL) and extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. ^1H NMR of the crude showed complete conversion to a mixture of ***Z*** : ***E*** olefinated product (dr 96:4). Purification of the residue by flash column chromatography (80:20 Hexanes/DCM) afforded **24** (797 mg, 2.65 mmol, 86% yield from **20**) as a colorless oil, see characterization in page 236.

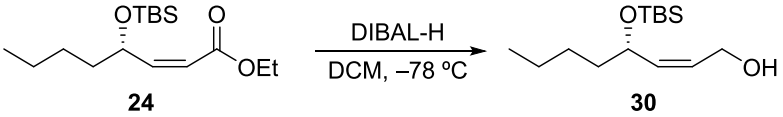
3. The pyrone stereocenter



Scheme 143. Synthesis of the pyrone stereocenter of umuravumbolide

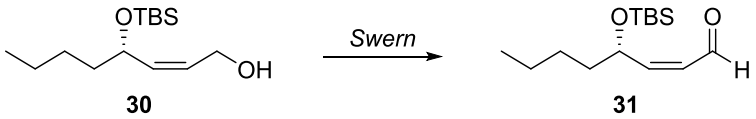
3.1. Reduction and oxidation steps

(*S*,*Z*)-4-(*tert*-Butyldimethylsilyloxy)-2-octenol (30)



A 1.0 M solution of DIBAL-H in toluene (7.5 mL, 7.5 mmol) was added dropwise to a solution of ester **24** (864 mg, 3.0 mmol) in DCM (30 mL) at –78 °C. The resultant mixture was stirred for 1 h at –78 °C and quenched with sat aqueous solution of Rochelle's salt (20 mL). The mixture was stirred for 1 h at rt. The layers were separated, and the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford quantitatively alcohol **30** (776 mg) as a colorless oil, which was used in the next step without further purification. $\mathbf{R_f}$ (90:10 hexanes/DCM) 0.2; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ +6.1 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν br 3309, 2955, 2928, 2857, 1463, 1252, 1073, 1048, 1018 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.63–5.43 (2H, m, C<u>H</u>=C<u>H</u>), 4.37 (1H, q, *J* = 7.0 Hz, C<u>H</u>OTBS), 4.27 (1H, dt, *J* = 13.4, 5.2 Hz, C<u>H</u>$_x$H$_y$OH), 4.17–4.09 (1H, m, CH$_x$<u>H</u>$_y$OH), 1.66 (1H, br t, *J* = 5.7 Hz, O<u>H</u>), 1.61–1.50 (1H, m, C<u>H</u>$_x$H$_y$(CH$_2$)$_2$), 1.45–1.35 (1H, m, CH$_x$<u>H</u>$_y$(CH$_2$)$_2$), 1.34–1.20 (4H, m, (C<u>H</u>$_2$)$_2$CH$_3$), 0.89 (12H, m, CH$_2$C<u>H</u>$_3$, C(C<u>H</u>$_3$)$_3$), 0.06 (3H, s, SiC<u>H</u>$_3$), 0.04 (3H, s, SiC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 136.0 (CH), 127.6 (CH), 69.1 (CH), 59.1 (CH_2), 38.2 (CH_2), 27.5 (CH_2), 25.8 (CH_3), 22.6 (CH_2), 18.2 (C), 14.1 (CH_3), –4.4 (CH_3), –4.8 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{14}H_{30}NaO_2Si$ $[M+Na]^+$: 281.1907, found: 281.1904.

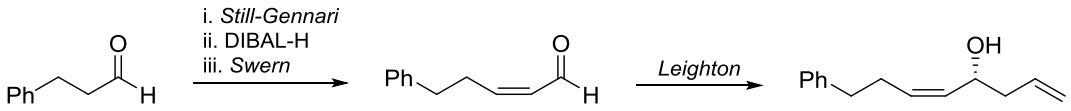
(*S*,*Z*)-4-(*tert*-Butyldimethylsilyloxy)oct-2-enal (31)



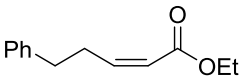
30 **31**

DMSO (43 µL, 0.60 mmol) was added dropwise to a solution of $(COCl)_2$ (27 µL, 0.32 mmol) in DCM (3.5 mL) at –78 °C. The resultant mixture was stirred for 10 min at –78 °C and a solution of alcohol **30** (52 mg, 0.20 mmol) in DCM (1 mL) was added via *cannula* and stirred for 10 min at –60 °C. Et_3N (170 µL, 1.2 mmol) was added to the reaction mixture at –78 °C and the mixture was allowed to warm to rt. The mixture was stirred for 2 h and then it was quenched with H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with hexanes (2 × 5 mL). The combined organic extracts were washed with H_2O (5 mL), 10% acetic acid aqueous solution (5 mL), and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure (H_2O_2 trap!) to afford quantitatively the crude reaction product **31** (50 mg) as a yellowish oil, which was used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.11 (1H, d, *J* = 7.7 Hz, C<u>H</u>O), 6.50 (1H, dd, *J* = 11.5, 8.3 Hz, C<u>H</u>=CHCHO), 5.91 (1H, ddd, *J* = 11.5, 7.7, 1.1 Hz, CH=C<u>H</u>CHO), 5.00–4.93 (1H, m, TBSOC<u>H</u>), 1.69–1.59 (1H, m, CHC<u>H$_x$H$_y$</u>), 1.58–1.47 (1H, m, CHCH$_x$<u>H$_y$</u>), 1.41–1.25 (4H, m, (C<u>H$_2$</u>)$_2$CH$_3$), 0.92–0.88 (12H, m, CH$_2$C<u>H$_3$</u>, C(C<u>H$_3$</u>)$_3$), 0.07 (3H, s, SiC<u>H$_3$</u>), 0.03 (3H, s, SiC<u>H$_3$</u>).

3.2. <u>Model substrate for Leighton's allylation</u>



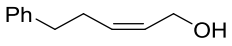
Ethyl (*Z*)-5-phenyl-2-pentenoate



Phosphonate **26** (250 µL, 1.10 mmol) was added to a solution of NaH 60% dispersion in mineral oil (100 mg, 2.5 mmol) in THF (10 mL) at –60 °C. Then a solution of hydrocinammaldehyde (130 µL, 1.00 mmol) in THF (2 mL) was added via *cannula*. The mixture was stirred from –60 °C to –35 °C for 1 h and quenched with sat NH_4Cl (1.0 mL), allowed to warm to rt and extracted with DCM (3 × 15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. ^{1}H NMR of the crude showed complete conversion to a mixture of *Z* : *E* olefinated product (dr 87:13). Purification of the residue by flash column chromatography (from 99:1 to 95:5 Hexanes/EtOAc) afforded the title compound (143 mg, 0.70 mmol, 70% yield) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.16 (5H, m, Ar<u>H</u>), 6.23 (1H, dt, *J* = 11.5, 7.5 Hz, COCH=C<u>H</u>), 5.78 (1H, dt, *J* = 11.5, 1.6 Hz, COC<u>H</u>), 4.16 (2H, q, *J* =

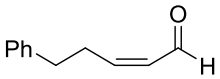
7.1 Hz, OC<u>H</u>$_2$), 3.05–2.93 (2H, m, CH=CHC<u>H</u>$_2$), 2.77 (2H, t, *J* = 7.7 Hz, C<u>H</u>$_2$Ph), 1.28 (3H, t, *J* = 7.1 Hz, C<u>H</u>$_3$).

(*Z*)-5-Phenyl-2-pentenol



A 1.0 M solution of DIBAL-H in toluene (1.7 mL, 2.5 mmol) was added dropwise to a solution of ester ethyl (*Z*)-5-phenyl-2-pentenoate (139 mg, 0.68 mmol) in DCM (7 mL) at –78 °C. The resultant mixture was stirred for 1 h at –78 °C and quenched with sat aqueous solution of Rochelle's salt (10 mL). The mixture was stirred for 1 h at rt. The layers were separated, and the aqueous layer was extracted with DCM (3 × 15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford quantitatively the title compound (≈112 mg) as a colorless oil, which was used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.15 (5H, m, Ar<u>H</u>), 5.65–5.53 (2H, m, C<u>H</u>=C<u>H</u>), 4.01 (2H, t, *J* = 5.8 Hz, C<u>H</u>$_2$OH), 2.69 (2H, t, *J* = 7.4 Hz, C<u>H</u>$_2$Ph), 2.44–2.37 (2H, m, C<u>H</u>$_2$CH$_2$Ph), 0.77 (1H, t, *J* = 5.8 Hz, O<u>H</u>).

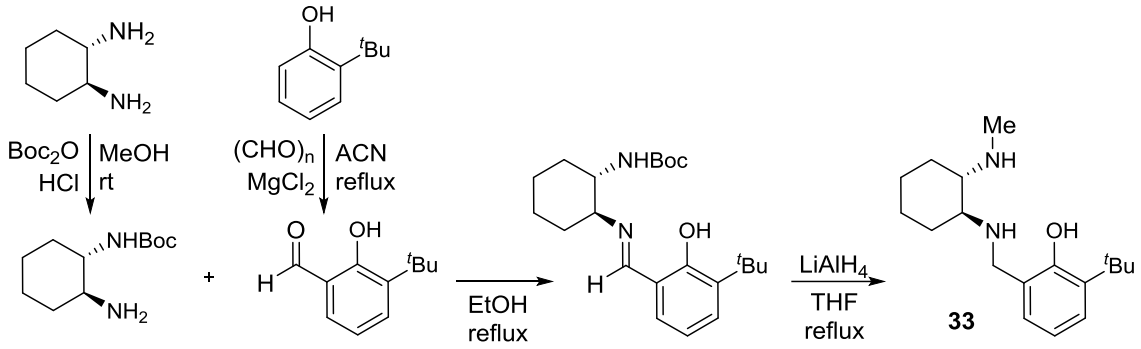
(*Z*)-5-Phenyl-2-pentenal (35)



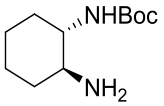
DMSO (145 µL, 2.0 mmol) was added dropwise to a solution of $(COCl)_2$ (90 µL, 1.1 mmol) in DCM (10 mL) at –78 °C. The resultant mixture was stirred for 10 min at –78 °C and a solution of alcohol (*Z*)-5-phenyl-2-pentenol (110 mg, 0.68 mmol) in DCM (4 mL) was added via *cannula* and stirred for 10 min at –60 °C. Et_3N (570 µL, 4.1 mmol) was added to the reaction mixture at –78 °C and the mixture was allowed to warm to rt. The mixture was stirred for 2 h and then it was quenched with H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with hexanes (2 × 10 mL). The combined organic extracts were washed with H_2O (10 mL), 10% acetic acid aqueous solution (10 mL), and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure (H_2O_2 trap!) to afford quantitatively the crude reaction product **35** (119 mg) as a yellowish oil, which was used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.93 (1H, d, *J* = 8.0 Hz, C<u>H</u>O), 7.36–7.15 (5H, m, Ar<u>H</u>), 6.63 (1H, dt, *J* = 11.1, 8.0 Hz, COC<u>H</u>), 5.96 (1H, ddt, *J* = 11.1, 8.0, 1.4 Hz, COCH=C<u>H</u>), 2.97–2.80 (4H, m, (C<u>H</u>$_2$)$_2$).

2-(((1*S*,2*S*)-2-aminocyclohexyl)aminomethyl)-6-*tert*-butylphenol (33)

It was prepared according to the literature.[135]

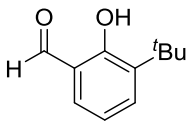


tert-Butyl ((1*S*,2*S*)-2-aminocyclohexyl)carbamate



(*S*,*S*)-diaminocyclohexane (4.00 g, 35 mmol) was added to a solution of conc HCl (2.9 mL, 35 mmol) in MeOH (11 mL) at 0 °C. The mixture was stirred at rt for 15 min and then H_2O (3.7 mL) was added and the mixture was stirred at rt for 30 min. Then, a solution of di-*tert*-butyl dicarbonate (7.64 g, 35 mmol) in MeOH (3.7 mL) was added and the mixture was stirred at rt for 16 h. The reaction crude was concentrated under reduced pressure and the residue was suspended in Et_2O (10 mL), filtered and washed with further Et_2O (3 × 8 mL). The precipitate was treated with 3 M NaOH (25 mL) and extracted with DCM (3 × 15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, the solvent was removed under reduced pressure to afford the title compound (4.18 g, 20 mmol, 55% yield), which was used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.45 (1H, br s, NH), 3.21–3.05 (1H, m, CHNHBoc), 2.32 (1H, td, *J* = 10.4, 4.0 Hz, $CHNH_2$), 2.06–1.91 (2H, m, Cy), 1.75–1.65 (2H, m, Cy), 1.45 (9H, s, $C(CH_3)_3$), 1.41–1.01 (4H, m, Cy).

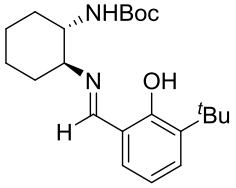
3-(*tert*-Butyl)-2-hydroxybenzaldehyde



Paraformaldehyde (12.16 g, 405 mmol), $MgCl_2$ (8.57 g, 90 mmol) and Et_3N (31 mL, 225 mmol) were added to a solution of 2-*tert*-butylphenol (9.2 mL, 60 mmol) in ACN (120 mL) at rt. The mixture was refluxed for 5 h and quenched with 5% HCl (120 mL). The mixture was extracted with DCM (3 × 100 mL) and the combined organic extracts were concentrated under reduced pressure. The residue was partitioned between Et_2O and H_2O (100 mL each), the organic layer was washed with brine (80 mL) and dried with anhydrous $MgSO_4$, and the solvent was removed

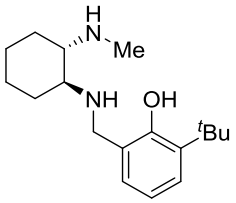
under reduced pressure. The residue was vacuum distilled to afford the title compound (5.06 g, 28 mmol, 47% yield) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.78 (1H, s, OH), 9.88 (1H, s, CHO), 7.53 (1H, dd, *J* = 7.7, 1.7 Hz, ArH), 7.40 (1H, dd, *J* = 7.7, 1.7 Hz, ArH), 6.95 (1H, t, *J* = 7.7 Hz, ArH), 1.42 (9H, s, $C(CH_3)_3$).

1-(3-(*tert*-butyl)-2-hydroxyphenyl)-*N*-((1*S*,2*S*)-2-(*tert*-butyloxycarbonylamino)cyclohexyl)-methanimine



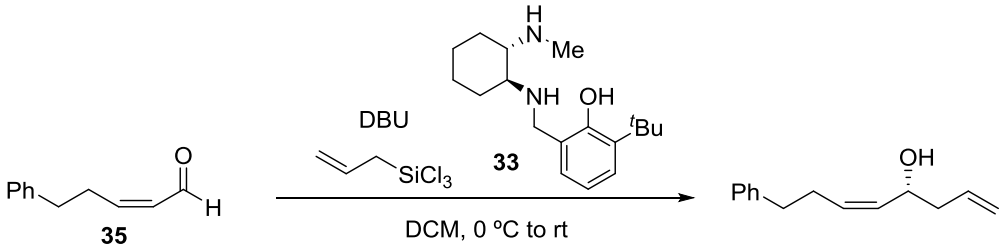
3-(*tert*-Butyl)-2-hydroxybenzaldehyde (3.46 g, 19.4 mmol) was added to a mixture of *tert*-Butyl ((1*S*,2*S*)-2-aminocyclohexyl)carbamate (4.16 g, 19.4 mmol) in EtOH (200 mL). The mixture was refluxed for 3 h and concentrated under reduced pressure. The residue was recrystallized from boiling EtOH to give the title compound (4.87 g, 13 mmol, 67% yield) as long yellow crystals. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.71 (1H, br s, OH), 8.32 (1H, s, CHN), 7.30 (1H, dd, *J* = 7.7, 1.4 Hz, ArH), 7.08 (1H, dd, *J* = 7.6, 1.5 Hz, ArH), 6.79 (1H, t, *J* = 7.6 Hz, ArH), 4.33 (1H, br s, NH), 3.66–3.53 (1H, m, CHN=C), 3.02 (1H, br s, CHNHBoc), 2.13–2.03 (1H, m, Cy), 1.93–1.85 (1H, m, Cy), 1.84–1.62 (3H, m, Cy), 1.45–1.21 (3H, m, Cy), 1.42 (9H, s, $C(CH_3)_3$), 1.28 (9H, s, $C(CH_3)_3$).

2-(((1*S*,2*S*)-2-aminocyclohexyl)aminomethyl)-6-*tert*-butylphenol (**33**)



A solution of the previous imine (4.87 g, 13 mmol) in THF (40 mL) was added dropwise to a mixture of $LiAlH_4$ (1.48 g, 39 mmol) in THF (65 mL) at 0 °C. The mixture was stirred at rt for 2h and then refluxed for 12 h. The mixture was cooled to 0 °C and carefully quenched with H_2O (20 mL). The crude mixture was extracted with Et_2O (5 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, and concentrated. The residue was recrystallized from boiling hexanes to give the title compound (3.14 g, 11 mmol, 84% yield) as white crystals. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.17 (1H, dd, *J* = 7.8, 1.4 Hz, ArH), 6.89–6.83 (1H, m, ArH), 6.70 (1H, t, *J* = 7.6 Hz, ArH), 4.01 (1H, d, *J* = 13.4 Hz, CH_xH_yNH), 3.83 (1H, d, *J* = 13.5 Hz, CH_xH_yNH), 2.39 (3H, s, CH_3), 2.19–2.12 (4H, m, 2 × CHNH, Cy), 1.80–1.67 (2H, m, Cy), 1.42 (9H, s, $C(CH_3)_3$), 1.31–1.13 (3H, m, Cy), 1.06–0.87 (1H, m, Cy).

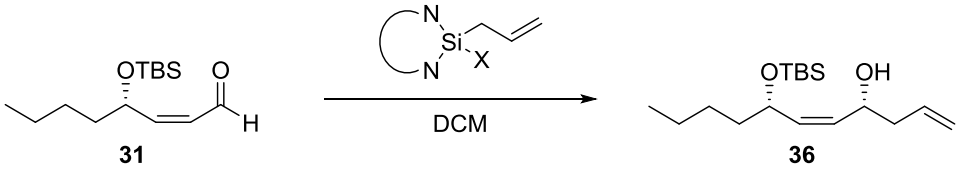
(*R*,*Z*)-5-Phenyl-1,5-octadien-4-ol



DBU (49 µL, 0.33 mmol) and allyltrichlorosilane (18 µL, 0.12 mmol) were added to a solution of diamine (**33**) (32 mg, 0.11 mmol) in DCM (1 mL) at 0 °C. The mixture was stirred at rt for 1 h. A solution of aldehyde **35** (16 mg, 0.10 mmol) in DCM (1 mL) was added via *cannula* and the mixture was stirred for 4 h at 0 °C ad 2.5 h at rt. The volatiles were removed under reduced pressure and the residue was suspended in Et_2O (3 mL) and stirred for 30 min. The mixture was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (80:20 Hexanes/EtOAc) to give impure the tittle allylic alcohol (8 mg) as a colorless oil. **R_f** (80:20 hexanes/EtOAc) 0.4; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44–7.10 (5H, m, ArH), 5.78–5.66 (1H, m, CH=CH_2), 5.57–5.49 (1H, m, CH=CHCHOH), 5.39 (1H, ddt, J = 10.9, 8.8, 1.3 Hz, CH=CHCHOH), 5.11–5.06 (2H, m, CH=CH_2), 4.34–4.25 (1H, m, CHOH), 2.77–2.62 (2H, m, CHOHCH_2), 2.50–2.05 (4H, m, (CH_2)$_2$).

3.3. Allylation reactions

Leighton allylation



With silane **32**

Allylsilane **32** (111 mg, 0.20 mmol) was added to a solution of aldehyde **31** (51 mg, 0.20 mmol) in DCM (1.0 mL) at −10 °C. The reaction mixture was stirred at 0 °C for 16 h. Then, it was quenched with 1M HCl (2 mL), filtered and extracted with EtOAc (2 × 7 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. ^{1}H NMR of the crude showed a complex mixture and probably isomerization of the double bond.

With silane **32** and $Sc(OTf)_3$

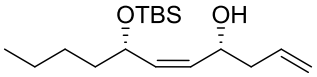
Allylsilane **32** (100 mg, 0.18 mmol) and $Sc(OTf)_3$ (3.7 mg, 0.008 mmol) were added to a solution of aldehyde **31** (38 mg, 0.15 mmol) in DCM (1.5 mL) at −10 °C. The reaction mixture was stirred at −10 °C for 45 minutes and then at rt for 16 h. Then, it was quenched with 1M HCl (2 mL), filtered and extracted with EtOAc (2 × 7 mL). The combined organic extracts were dried with

anhydrous $MgSO_4$ and the solvent evaporated. ^1H NMR of the crude showed a complex mixture and probably isomerization of the double bond.

With silane **34**

DBU (87 µL, 0.58 mmol) and allyltrichlorosilane (31 µL, 0.21 mmol) were added to a solution of diamine **33** (56 mg, 0.19 mmol) in DCM (1 mL) at 0 °C. The mixture was stirred at rt for 1 h. A solution of aldehyde **31** (45 mg, 0.18 mmol) in DCM (1.5 mL) was added via *cannula* and the mixture was stirred for 16 h at –20 °C. The volatiles were removed under reduced pressure and the residue was suspended in Et_2O (3 mL) and stirred for 30 min. The mixture was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (from 99:1 to 95:5 Hexanes/EtOAc) to give allylic alcohol **36** (26 mg, 0.09 mmol, 49% yield) as a colorless oil.

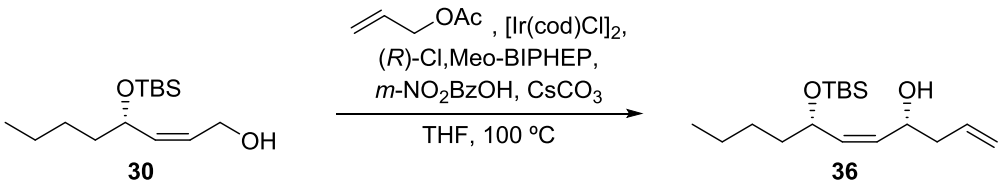
(4*R*,7*S*,*Z*)-7-(*tert*-Butyldimethylsilyloxy)undeca-1,5-dien-4-ol (36)



36

R_f (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ +13.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3369 (br), 2955, 2928, 2856, 1463, 1252, 1049, 1005 cm^{-1}; **^1H NMR** (400 MHz, $CDCl_3$) δ 5.87–5.74 (1H, m, $CH{=}CH_2$), 5.47 (1H, ddd, *J* = 11.4, 8.3, 1.0 Hz, CH=CHCHOH), 5.36 (1H, ddd, *J* = 11.4, 8.3, 0.9 Hz, CH=CHCHOH), 5.18–5.10 (2H, m, $CH{=}CH_2$), 4.50–4.35 (2H, m, CHOTBS, CHOH), 2.34–2.18 (2H, m, $CH_2CH{=}CH_2$), 1.93 (1H, br s, OH), 1.59–1.48 (1H, m, $CH_xH_y(CH_2)_2$), 1.44–1.19 (5H, m, $CH_xH_y(CH_2)_2CH_3$), 0.91–0.87 (12H, m, CH_2CH_3, $C(CH_3)_3$), 0.07 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 135.6 (CH), 134.1 (CH), 130.5 (CH), 118.2 (CH_2), 69.0 (CH), 67.1 (CH), 42.2 (CH_2), 38.2 (CH_2), 27.5 (CH_2), 25.8 (CH_3), 22.6 (CH_2), 18.2 (C), 14.0 (CH_3), –4.3 (CH_3), –4.8 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{17}H_{34}NaO_2Si$ $[M+Na]^+$: 321.2220, found: 321.2217.

Krische allylation

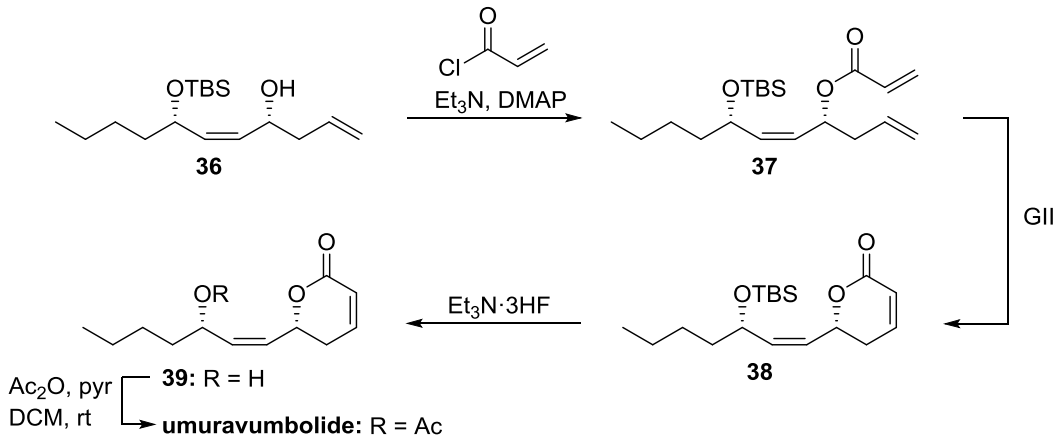


30 **36**

Allyl acetate (2.6 mL, 24 mmol) was added to a mixture of **30** (631 mg, ≈ 2.4 mmol), $[Ir(cod)Cl]_2$ (81 mg, 0.12 mmol, 5 mol%), (*R*)-Cl,MeO-BIPHEP (158 mg, 0.24 mmol, 10 mol%), $CsCO_3$ (313 mg, 0.96 mmol) and 3-nitrobenzoic acid (80 mg, 0.48 mmol) in THF (12 mL) in an oven dried microwave vial (20 ml). The reaction mixture was stirred at 100 °C for 20 h. The resulting mixture

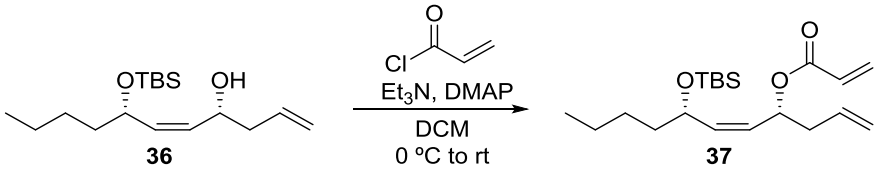
was evaporated in vacuo and purified by flash column chromatography (from 97.5:2.5 to 90:10 Hexanes/EtOAc) to give allylic alcohol **36** (660 mg, 2.2 mmol, 91% yield from **24**, dr >95:5) as a colorless oil.

5. Final steps



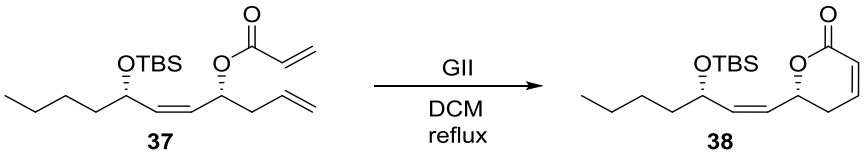
Scheme 144. Final steps towards umuravumbolide

(4*R*,7*S*,*Z*)-7-(*tert*-Butyldimethylsilyloxy)undeca-1,5-dien-4-yl acrylate (37)



DMAP (13 mg, 0.10 mmol), acryloyl chloride (170 µL, 2.1 mmol) and Et_3N (430 µL, 3.1 mmol) were added to a solution of **36** (305 mg, 1.02 mmol) in DCM (13 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 2 h and quenched with sat NH_4Cl (10 mL) and 2 M HCl (1 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 × 15 mL), the combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue through a short pad of silica afforded **37** (344 mg, 0.98 mmol, 96% yield) as a colorless oil. $\mathbf{R_f}$ (95:5 hexanes/EtOAc) 0.7; $[\alpha]_D^{20}$ −9.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2955, 2929, 2856, 1724, 1404, 1255, 1186, 1045, 1005 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.38 (1H, dd, *J* = 17.3, 1.5 Hz, COCH=C$\underline{H}_x$H$_y$), 6.09 (1H, dd, *J* = 17.3, 10.4 Hz, COC$\underline{H}$=CH$_2$), 5.81 (1H, dd, *J* = 10.4, 1.5 Hz, COCH=CH$_x\underline{H}_y$), 5.78–5.62 (2H, m, CH$_2$C$\underline{H}$=CH$_2$, OC$\underline{H}$CH$_2$CH=CH$_2$), 5.55 (1H, ddd, *J* = 11.2, 8.5, 0.9 Hz, C$\underline{H}$=CHCHOCO), 5.34 (1H, ddd, *J* = 11.2, 9.6, 1.1 Hz, CH=C$\underline{H}$CHOCO), 5.13–5.05 (2H, m, CH$_2$CH=C$\underline{H}_2$), 4.58–4.48 (1H, m, C$\underline{H}$OTBS), 2.47–2.30 (2H, m, C$\underline{H}_2$CH=CH$_2$), 1.56–1.45 (1H, m, C$\underline{H}_x$H$_y$CHOTBS), 1.39–1.24 (5H, m, CH$_x\underline{H}_y$CHOTBS, (C$\underline{H}_2$)$_2$CH$_3$), 0.92–0.87 (3H, m, CH$_2$C$\underline{H}_3$), 0.85 (9H, s, C(C$\underline{H}_3$)$_3$), 0.04 (3H, s, SiC$\underline{H}_3$), −0.01 (3H, s, SiC$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 165.1 (C), 138.5 (CH), 132.9 (CH), 130.6 (CH$_2$), 128.6 (CH), 125.4 (CH), 118.3 (CH$_2$), 69.2 (CH), 68.7 (CH), 39.5 (CH$_2$), 38.3 (CH$_2$), 27.4 (CH$_2$), 25.8 (CH$_3$), 22.6 (CH$_2$), 18.1 (C), 14.1 (CH$_3$), −4.6 (CH$_3$), −5.0 (CH$_3$); **HRMS** (+ESI): *m/z* calcd. for $C_{20}H_{36}NaO_3Si$ $[M+Na]^+$: 375.2326, found: 375.2330.

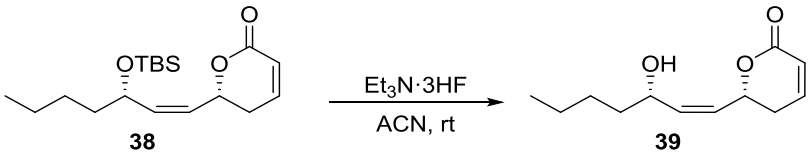
(*R*)-6-[(*S,Z*)-3-(*tert*-Butyldimethylsilyloxy)hept-1-enyl]-5,6-dihydro-2H-pyran-2-one (38)



37 38

A solution of Grubbs II® (20 mg, 2.5 mol%) in DCM (20 mL) was added dropwise (for 40 min aprox) to a refluxing solution of **37** (332 mg, 0.94 mmol) in DCM (95 mL). The mixture was stirred for 1 h and the solvent evaporated. The residue was purified by flash column chromatography (90:10 hexanes/EtOAc) to afford **38** (267 mg, 0.82 mmol, 87% yield). yellowish oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.1; $[\alpha]_D^{20}$ +5.1 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2955, 2929, 2857, 1725, 1380, 1247, 1050, 1023 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.88 (1H, ddd, *J* = 9.8, 5.8, 2.6 Hz, COCH=C<u>H</u>), 6.06 (1H, ddd, *J* = 9.8, 2.6, 1.0 Hz, COC<u>H</u>), 5.62 (1H, ddd, *J* = 11.3, 8.3, 0.7 Hz, TBSOCHC<u>H</u>=CH), 5.53 (1H, ddd, *J* = 11.3, 8.7, 0.8 Hz, TBSOCHCH=C<u>H</u>), 5.28–5.21 (1H, m, CH=CHC<u>H</u>OCO), 4.39–4.34 (1H, m, TBSOC<u>H</u>), 2.42 (1H, ddt, *J* = 18.4, 11.2, 2.6 Hz, CH=CHC<u>H</u>$_x$H$_y$), 2.28 (1H, dddd, *J* = 18.4, 5.8, 4.2, 1.0 Hz, CH=CHCH$_x$<u>H</u>$_y$), 1.60–1.49 (1H, m, TBSOCHC<u>H</u>$_x$H$_y$), 1.42–1.22 (5H, m, TBSOCHCH$_x$<u>H</u>$_y$(C<u>H</u>$_2$)$_2$), 0.91–0.87 (12H, m, CH$_2$C<u>H</u>$_3$, C(C<u>H</u>$_3$)$_3$), 0.06 (3H, s, SiC<u>H</u>$_3$), 0.05 (3H, s, SiC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 163.7 (C), 144.4 (CH), 138.5 (CH), 125.2 (CH), 121.6 (CH), 73.8 (CH), 68.7 (CH), 38.3 (CH_2), 30.1 (CH_2), 27.4 (CH_2), 25.8 (CH_3), 22.6 (CH_2), 18.1 (C), 14.0 (CH_3), −4.3 (CH_3), −4.9 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{18}H_{32}NaO_3Si$ $[M+Na]^+$: 347.2013, found: 347.2011.

(*R*)-6-[(*S,Z*)-3-hydroxyhept-1-enyl]-5,6-dihydro-2H-pyran-2-one (39)

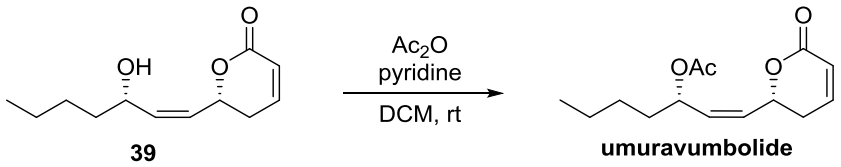


38 39

$Et_3N{\cdot}3HF$ (930 µL, 5.7 mmol) was added to a solution of **38** (236 mg, 0.71 mmol) in ACN (3 mL) at rt and stirred for 16 h. The reaction mixture was partitioned between H_2O (7 mL) and EtOAc (7 mL), the aqueous layer was extracted with further EtOAc (2 × 7 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The residue was purified by flash column chromatography (from 70:30 to 60:40 hexanes/EtOAc) to afford **39** (128 mg, 0.61 mmol, 86% yield) as a white solid. **Mp** 45–46 °C; $\mathbf{R_f}$ (70:30 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ −6.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3421 (br), 2958, 2857, 1682, 1417, 1250, 1157, 1052, 1018 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.90 (1H, ddd, *J* = 9.8, 5.6, 2.8 Hz, COCH=C<u>H</u>), 6.08–6.00 (1H, m, COC<u>H</u>=CH), 5.75–5.58 (2H, m, C<u>H</u>=C<u>H</u>CHOH), 5.34 (1H, ddd, *J* = 11.6, 7.3, 4.6 Hz, C<u>H</u>OCO), 4.43 (1H, q, *J* = 6.8 Hz, C<u>H</u>OH), 2.50–2.32 (2H, m, C<u>H</u>$_2$CH=CHCO), 2.05 (1H, br s, O<u>H</u>), 1.72–1.55 (1H, m, C<u>H</u>$_x$H$_y$CHOH), 1.48–1.39 (1H, m, CH$_x$<u>H</u>$_y$CHOH), 1.39–1.13 (4H,

m, (C<u>H</u>$_2$)$_2$CH$_3$), 0.91 (3H, t, *J* = 6.8 Hz, CH$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 163.7 (C), 144.7 (CH), 137.8 (CH), 127.5 (CH), 121.5 (CH), 73.7 (CH), 67.8 (CH), 36.8 (CH_2), 29.9 (CH_2), 27.4 (CH_2), 22.6 (CH_2), 14.0 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{12}H_{22}NO_3$ $[M+NH_4]^+$: 228.1594, found: 228.1593.

Umuravumbolide



39 **umuravumbolide**

Ac_2O (110 µL, 1.2 mmol) and pyridine (95 µL, 1.2 mmol) were added to a solution of **39** (123 mg, 0.58 mmol) in DCM (1.2 mL) at rt. The reaction mixture was stirred at room temperature for 16 h and evaporated under reduced pressure. The residue was purified by flash column chromatography (80:20 H/EtOAc) to afford **umuravumbolide** (146 mg, 0.58 mmol, quantitative yield) as a colorless oil. **R_f** (80:20 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ +31.4 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2956, 2932, 2862, 1717, 1371, 1230, 1149, 1019 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.88 (1H, ddd, *J* = 9.8, 6.0, 2.5 Hz, COCH=C<u>H</u>), 6.09–6.03 (1H, m, COC<u>H</u>=CH), 5.73 (1H, ddd, *J* = 11.1, 8.2, 0.9, AcOCHCH=C<u>H</u>), 5.55 (1H, ddd, *J* = 11.1, 9.4, 1.1 Hz, AcOCHC<u>H</u>=CH), 5.45–5.39 (2H, m, C<u>H</u>OAc, C<u>H</u>OCO), 2.47 (1H, ddt, *J* = 18.3, 11.7, 2.6 Hz, CH=CHC<u>H$_x$</u>H$_y$), 2.29 (1H, dddd, *J* = 18.3, 5.9, 4.1, 1.0 Hz, CH=CHCH$_x$<u>H$_y$</u>), 2.04 (3H, s, COC<u>H$_3$</u>), 1.74–1.66 (1H, m, AcOCHC<u>H$_x$</u>H$_y$), 1.57–1.48 (1H, m, AcOCHCH$_x$<u>H$_y$</u>), 1.37–1.20 (4H, m, (C<u>H$_2$</u>)$_2$CH$_3$), 0.90 (3H, t, *J* = 7.2 Hz, CH$_2$C<u>H$_3$</u>); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 170.1 (C), 163.5 (C), 144.2 (CH), 131.7 (CH), 130.1 (CH), 121.7 (CH), 74.0 (CH), 69.4 (CH), 34.3 (CH_2), 30.0 (CH_2), 27.2 (CH_2), 22.4 (CH_2), 21.1 (CH_3), 13.9 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{14}H_{20}NaO_4$ $[M+Na]^+$: 275.1254, found: 275.1253.

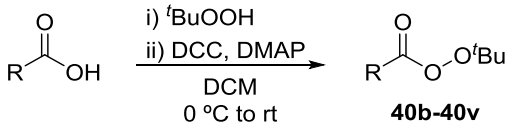
Chapter III

Alkylation of Titanium Enolates with *tert*-Butyl Peresters

1. Preparation of tert-butyl peresters

General Procedure 7

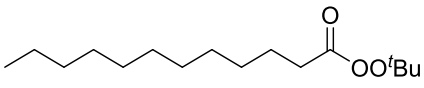
tert-Butyl Peresters were synthesized according to the literature.[86]



40b-40v

70% ^{t}BuOOH in water (4.5–5.0 mmol) was added to a solution of the corresponding carboxylic acid (5.0 mmol) in DCM (10 mL) at 0 °C. The resultant solution was vigorously stirred for 10 min at 0 °C. Then, DMAP (61 mg, 0.5 mmol), DCC (1.13 g, 5.5 mmol) and DCM (5 mL) were added in one portion and the reaction was vigorously stirred at rt for 16 h. After the addition of hexanes (15 mL), the mixture was filtered, dried with anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography to afford the *tert*-butyl perester.

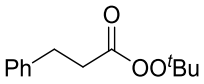
***tert*-Butyl dodecaneperoxoate (40b)**



40b

It was prepared following General Procedure 7 from lauric acid (601 mg, 3.0 mmol), ^{t}BuOOH (390 µL, 3.0 mmol), DMAP (37 mg, 0.3 mmol) and DCC (743 mg, 3.6 mmol). The residue was purified by flash column chromatography (95:5 hexanes/EtOAc) to afford **40b** (726 mg, 2.7 mmol, 89% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; **IR** (ATR) ν 2923, 2853, 1776, 1458, 1365, 1190, 1135, 1090 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.31 (2H, t, *J* = 7.5 Hz, $COC\underline{H}_2$), 1.66 (2H, p, *J* = 7.5 Hz, $COCH_2C\underline{H}_2$), 1.32 (9H, s, $C(C\underline{H}_3)_3$), 1.37–1.26 (16H, m, $(C\underline{H}_2)_8CH_3$), 0.92–0.85 (3H, m, $CH_2C\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.1 (C), 83.2 (C), 31.9 (CH_2), 31.3 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 26.1 (CH_3), 25.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

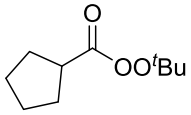
tert-Butyl 3-phenylpropaneperoxoate (40d)



40d

It was prepared following General Procedure 7 from hydrocinnamic acid (300 mg, 2.0 mmol), ^{t}BuOOH (230 µL, 1.8 mmol), DMAP (24 mg, 0.2 mmol) and DCC (454 mg, 2.2 mmol). The residue was purified by flash column chromatography (50:50 hexanes/DCM) to afford **40d** (385 mg, 1.7 mmol, 96% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/DCM) 0.3; **IR** (ATR) ν 3029, 2981, 2933, 1771, 1454, 1366, 1184, 1098, 1072 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.25 (2H, m, ArH), 7.23–7.18 (3H, m, ArH), 2.99 (2H, t, *J* = 7.7 Hz, CH_2Ph), 2.63 (2H, t, *J* = 7.7 Hz, $COCH_2$), 1.25 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.2 (C), 139.8 (C), 128.6 (CH), 128.3 (CH), 126.5 (CH), 83.4 (C), 33.0 (CH_2), 30.9 (CH_2), 26.0 (CH_3).

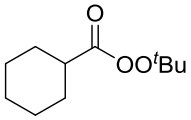
tert-Butyl cyclopentanecarboperoxoate (40i)



40i

It was prepared following General Procedure 7 from cyclopentanecarboxylic acid (360 µL, 3.3 mmol), ^{t}BuOOH (390 µL, 3.0 mmol), DMAP (37 mg, 0.3 mmol) and DCC (743 mg, 3.6 mmol). The residue was purified by flash column chromatography (50:50 hexanes/DCM) to afford **40i** (499 mg, 2.7 mmol, 89% yield) as a colorless oil. $\mathbf{R_f}$ (60:40 hexanes/DCM) 0.2; **IR** (ATR) ν 2976, 2872, 1769, 1365, 1190, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.74 (1H, p, *J* = 8.0 Hz, COCH), 1.99–1.68 (6H, m, 2 × $CHCH_2$, 2 × $CHCH_2CH_xH_y$), 1.65–1.55 (2H, m, 2 × $CHCH_2CH_xH_y$), 1.32 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.9 (C), 83.1 (C), 40.9 (CH), 30.1 (CH_2), 26.0 (CH_3), 25.7 (CH_2).

tert-Butyl cyclohexanecarboperoxoate (40j)

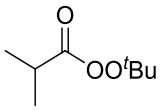


40j

It was prepared following General Procedure 7 from cyclohexanecarboxylic acid (641 mg, 5.0 mmol). The residue was purified by flash column chromatography (50:50 hexanes/DCM) to afford **40j** (843 mg, 4.0 mmol, 88% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/DCM) 0.3; **IR** (ATR) ν 2981, 2932, 2856, 1768, 1451, 1365, 1188, 1146, 1084, 1014 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.37 (1H, tt, *J* = 11.4, 3.7 Hz, COCH), 1.94–1.85 (2H, m, 2 × $CHCH_xH_y$), 1.81–1.75 (2H, m, 2 × $CHCH_2CH_xH_y$), 1.68–1.63 (1H, m, $CHCH_2CH_2CH_xH_y$), 1.59–1.45 (2H, m, 2

× $CHCH_xH_y$), 1.36–1.31 (1H, m, $CHCH_2CH_2CH_xH_y$), 1.32 (9H, s, $C(CH_3)_3$), 1.30–1.24 (2H, m, 2 × $CHCH_2CH_xH_y$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.9 (C), 83.1 (C), 41.0 (CH), 29.0 (CH_2), 26.0 (CH_3), 25.4 (CH_2), 25.2 (CH_2).

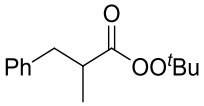
tert-Butyl isobutaneperoxoate (40k)



40k

It was prepared following General Procedure 7 from isobutyric acid (280 µg, 3.0 mmol), ^{t}BuOOH (390 µL, 3.0 mmol), DMAP (37 mg, 0.3 mmol) and DCC (743 mg, 3.6 mmol). The residue was purified by flash column chromatography (95:5 hexanes/EtOAc) to afford **40k** (347 mg, 2.2 mmol, 72% yield) as a colorless oil. **R_f** (90:10 hexanes/EtOAc) 0.5; **IR** (ATR) ν 2979, 2937, 2878, 1772, 1470, 1366, 1191, 1104, 1072, 1030 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.61 (1H, hept, *J* = 7.0 Hz, $COCH$), 1.33 (9H, s, $C(CH_3)_3$), 1.22 (6H, d, *J* = 7.0 Hz, $CH(CH_3)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.2 (C), 83.3 (C), 31.9 (CH), 26.1 (CH_3), 19.0 (CH_3).

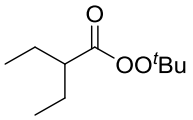
tert-Butyl 2-methyl-3-phenylpropaneperoxoate (40l)



40l

It was prepared following General Procedure 7 from 2-methyl-3-phenylpropanoic acid (542 mg, 3.3 mmol), ^{t}BuOOH (390 µL, 3.0 mmol), DMAP (37 mg, 0.3 mmol) and DCC (743 mg, 3.6 mmol). The residue was purified by flash column chromatography (50:50 hexanes/DCM) to afford **40l** (648 mg, 2.7 mmol, 92% yield) as a white solid. **R_f** (50:50 hexanes/DCM) 0.2; **IR** (ATR) ν 2982, 2933, 1758, 1454, 1366, 1190, 1092 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.15 (5H, m, ArH), 3.06–2.98 (1H, m, $PhCH_xH_y$), 2.82–2.68 (2H, m, $COCH$, $PhCH_xH_y$), 1.23 (3H, d, *J* = 6.7 Hz, $CHCH_3$), 1.19 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.3 (C), 138.7 (C), 129.0 (CH), 128.5 (CH), 126.5 (CH), 83.3 (C), 39.7 (CH_2), 39.4 (CH), 26.0 (CH_3), 17.3 (CH_3).

tert-Butyl 2-ethylbutaneperoxoate (40m)

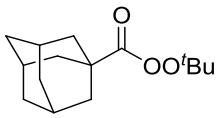


40m

It was prepared following General Procedure 7 from 2-ethylbutyric acid (380 µL, 3.0 mmol), ^{t}BuOOH (390 µL, 3.0 mmol), DMAP (37 mg, 0.3 mmol) and DCC (743 mg, 3.6 mmol). The

residue was purified by flash column chromatography (95:5 hexanes/EtOAc) to afford **40m** (481 mg, 2.6 mmol, 85% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.7; **IR** (ATR) ν 2967, 2934, 2878, 1770, 1460, 1365, 1190, 1071 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.22 (1H, tt, *J* = 8.8, 5.4 Hz, COC<u>H</u>), 1.74–1.61 (2H, m, 2 × COCHC<u>H</u>$_x$H$_y$), 1.61–1.49 (2H, m, 2 × COCHCH$_x$<u>H</u>$_y$), 1.34 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.94 (6H, t, *J* = 7.4 Hz, 2 × CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.4 (C), 82.9 (C), 46.7 (CH), 26.2 (CH_3), 25.2 (CH_2), 11.8 (CH_3).

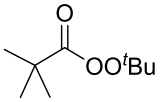
tert-Butyl 1-adamantanecarboperoxoate (40n)



40n

It was prepared following <u>General Procedure 7</u> from 1-adamantanecarboxylic acid (1.98 g, 11.0 mmol), ^{t}BuOOH (1.3 mL, 10.0 mmol), DMAP (134 mg, 1.1 mmol) and DCC (250 g, 12.1 mmol). The residue was purified by flash column chromatography (from 60:40 to 40:60 hexanes/DCM) to afford **40n** (1.63 g, 6.5 mmol, 65% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/DCM) 0.3; **IR** (ATR) ν 2980, 2905, 2852, 1762, 1452, 1365, 1168, 1028 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.03 (3H, br m, 3 × C<u>H</u>(Ad)), 1.97–1.95 (6H, m, 3 × C<u>H</u>$_2$(Ad)), 1.76–1.79 (6H, m, 3 × C<u>H</u>$_2$(Ad)), 1.32 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.2 (C), 83.3 (C), 41.1 (C), 38.8 (CH_2), 36.3 (CH_2), 27.8 (CH), 26.1 (CH_3).

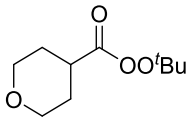
tert-Butyl 2,2-dimethylpropaneperoxoate (40p)



40p

It was prepared following <u>General Procedure 7</u> from pivalic acid (510 mg, 5.0 mmol). The residue was purified by flash column chromatography (95:5 hexanes/EtOAc) to afford **40p** (457 mg, 2.6 mmol, 58% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.5; **IR** (ATR) ν 2979, 2934, 1765, 1479, 1366, 1192, 1091 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.26 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.0 (C), 83.3 (C), 38.8 (C), 27.2 (CH_3), 26.1 (CH_3).

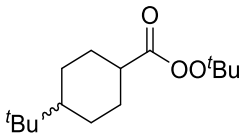
tert-Butyl tetrahydropyrane-4-carboperoxoate (40q)



40q

It was prepared following General Procedure 7 from tetrahydropyrane-4-carboxylic acid (390 mg, 3.0 mmol), ^{t}BuOOH (390 µL, 3.0 mmol), DMAP (37 mg, 0.3 mmol) and DCC (743 mg, 3.6 mmol). The residue was purified by flash column chromatography (90:10 hexanes/EtOAc) to afford **40q** (506 mg, 2.5 mmol, 83% yield) as a colorless oil. **R_f** (90:10 hexanes/EtOAc) 0.2; **IR** (ATR) ν 2979, 2847, 1768, 1446, 1366, 1241, 1189, 1122, 1087, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.98 (2H, dt, *J* = 11.6, 3.5 Hz, 2 × OC$\underline{H}_x$H$_y$), 3.49–3.40 (2H, m, 2 × OCH$_x\underline{H}_y$), 2.64 (1H, tt, *J* = 10.1, 5.2 Hz, COC$\underline{H}$), 1.94–1.79 (4H, m, 2 × OCH$_2$C$\underline{H}_2$), 1.33 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.5 (C), 83.5 (C), 66.8 (CH_2), 38.3 (CH), 28.6 (CH_2), 26.1 (CH_3).

tert-Butyl 4-*tert*-butylcyclohexanecarboperoxoate (40r)



40r

It was prepared following General Procedure 7 from 4-*tert*-butylcyclohexanecarboxylic acid (553 mg, 3.0 mmol), ^{t}BuOOH (390 µL, 3.0 mmol), DMAP (37 mg, 0.3 mmol) and DCC (743 mg, 3.6 mmol). The residue was purified by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) to afford **40r** (704 mg, 2.7 mmol, 92% yield, dr 6:4) as a colorless oil. **R_f** (90:10 hexanes/EtOAc) 0.7; **IR** (ATR) ν 2941, 2862, 1770, 1451, 1365, 1190, 1113, 1082, 1024 cm^{-1};

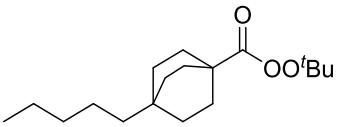
Major:

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (1H, tt, *J* = 12.3, 3.6 Hz, COC$\underline{H}$), 2.06–1.97 (2H, m, 2 × COCHC$\underline{H}_x$H$_y$), 1.89–1.82 (2H, m, 2 × ^{t}BuCHC$\underline{H}_x$H$_y$), 1.56–1.44 (2H, m, 2 × COCHCH$_x\underline{H}_y$), 1.32 (9H, s, OC(C$\underline{H}_3$)$_3$), 1.28–1.15 (1H, m, ^{t}BuC$\underline{H}$), 1.05–0.93 (2H, m, 2 × ^{t}BuCHCH$_x\underline{H}_y$), 0.85 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.2 (C), 83.2 (C), 47.8 (CH), 41.4 (CH), 32.4 (C), 29.6 (CH_2), 27.4 (CH_3), 26.4 (CH_2), 26.1 (CH_3).

Minor:

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74–2.70 (1H, m, COC$\underline{H}$), 2.22–2.16 (2H, m, 2 × COCHC$\underline{H}_x$H$_y$), 1.70–1.64 (2H, m, 2 × ^{t}BuCHC$\underline{H}_x$H$_y$), 1.55–1.44 (2H, m, 2 × COCHCH$_x\underline{H}_y$), 1.34 (9H, s, OC(C$\underline{H}_3$)$_3$), 1.32–1.23 (2H, m, 2 × ^{t}BuCHCH$_x\underline{H}_y$), 1.08–0.99 (1H, m, ^{t}BuC$\underline{H}$), 0.83 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.2 (C), 83.1 (C), 47.1 (CH), 37.4 (CH), 32.5 (C), 28.0 (CH_2), 27.4 (CH_3), 26.2 (CH_3), 23.7 (CH_2).

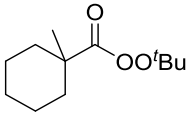
tert-Butyl 4-pentylbicyclo[2.2.2]octane-1-carboperoxoate (40s)



40s

It was prepared following General Procedure 7 from 4-pentylbicyclo[2.2.2]octane-1-carboxylic acid (449 mg, 2.0 mmol), ^{t}BuOOH (260 µL, 2.0 mmol), DMAP (24 mg, 0.2 mmol) and DCC (454 mg, 2.2 mmol). The residue was purified by flash column chromatography (95:5 hexanes/EtOAc) to afford **40s** (423 mg, 1.4 mmol, 71% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.6; **IR** (ATR) ν 2925, 2859, 1765, 1456, 1365, 1184, 1120, 1029 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.86–1.77 (6H, m, 3 × COCC$\underline{H}_2$), 1.45–1.35 (6H, m, 3 × COCCH_2C$\underline{H}_2$), 1.31 (9H, s, C(C$\underline{H}_3$)$_3$), 1.27–1.03 (8H, m, C(C$\underline{H}_2$)$_4$), 0.87 (3H, t, J = 7.2 Hz, C$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.8 (C), 83.3 (C), 41.3 (CH_2), 34.9 (C), 32.7 (CH_2), 30.3 (CH_2), 28.6 (CH_2), 28.1 (C), 26.1 (CH_3), 23.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

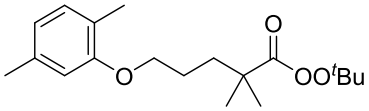
tert-Butyl 1-methylcyclohexaneperoxoate (40t)



40t

n-BuLi 2.5 M in hexanes (1.3 mL, 3.3 mmol) was added to a previously dried (anhydrous $MgSO_4$) solution of ^{t}BuOOH (390 µL, 3.0 mmol) in hexanes (2 mL) at −78 ºC. The solution was stirred at rt for 5 min and cooled to −78 ºC. A solution of 1-methylcyclohexanecarbonyl chloride (530 mg, 3.3 mmol) in toluene (3 mL) was added via *cannula*. The final mixture was stirred at rt for 30 min and quenched with sat $NaHCO_3$. The aqueous phase was extracted with hexanes (2 × 10 mL). The combined organic phases were dried (anhydrous $MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (50:50 hexanes/DCM) to afford **40t** (464 mg, 2.2 mmol, 66% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/DCM) 0.5; **IR** (ATR) ν 2980, 2932, 2857, 1763, 1451, 1365, 1188, 1149, 1081 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.09–2.00 (2H, m, Cy), 1.63–1.48 (3H, m, Cy), 1.48–1.35 (2H, m, Cy), 1.32 (9H, s, C(C$\underline{H}_3$)$_3$), 1.31–1.22 (3H, m, Cy), 1.22 (3H, s, C$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.4 (C), 83.2 (C), 43.5 (C), 35.6 (CH_2), 26.7 (CH_3), 26.2 (CH_3), 25.5 (CH_2), 23.1 (CH_2).

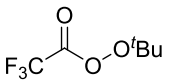
***tert*-Butyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentaneperoxoate (40u)**

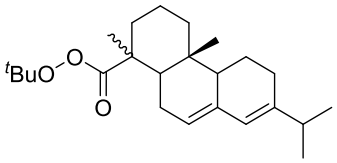


40u

It was prepared following General Procedure 7 from 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid (501 mg, 2.0 mmol), ^{t}BuOOH (260 µL, 2.0 mmol), DMAP (24 mg, 0.2 mmol) and DCC (454 mg, 2.2 mmol). The residue was purified by flash column chromatography (from 80:20 to 50:50 hexanes/DCM) to afford **40u** (185 mg, 0.57 mmol, 29% yield) as a white solid. **R_f** (70:30 hexanes/DCM) 0.2; **IR** (ATR) ν 2981, 2924, 1758, 1510, 1471, 1366, 1259, 1103, 1038 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.00 (1H, br d, *J* = 7.5 Hz, ArH), 6.65 (1H, br d, *J* = 7.5 Hz, ArH), 6.61 (1H, br s, ArH), 3.93 (2H, t, *J* = 5.7 Hz, OCH_2), 2.30 (3H, s, $PhCH_3$), 2.17 (3H, s, $PhCH_3$), 1.85–1.72 (4H, m, $OCH_2(CH_2)_2$), 1.33 (9H, s, $C(CH_3)_3$), 1.28 (6H, s, $C(CH_3)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.3 (C), 156.9 (C), 136.4 (C), 130.3 (CH), 123.5 (C), 120.7 (CH), 111.9 (CH), 83.3 (C), 67.7 (CH_2), 42.3 (C), 37.3 (CH_2), 26.2 (CH_3), 25.2 (CH_3), 25.1 (CH_2), 21.4 (CH_3), 15.7 (CH_3).

Unsuccessful preparation of *tert*-butyl peresters

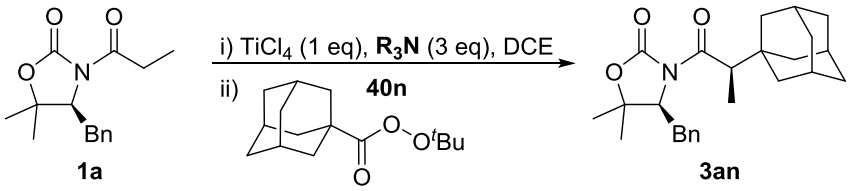




2. Optimization

2.1. Optimization with perester 40n

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone **1a** (0.50 mmol) in DCE (2 mL) at 0 °C. After 5 min, *R_3N* (*n eq*) was added dropwise and the resultant deep purple mixture was stirred at 0 °C for 40 min. A solution of the *tert*-butyl perester **40n** (*n eq*) in DCE (1 mL) was added via cannula. The reaction was stirred at *Temperature* for 2 h. Then, it was quenched with sat NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the volatiles evaporated. The resulting crude mixtures were analyzed by ^1H NMR and purified by flash column chromatography to afford **3an**. Results are summarized in *Table 44*.

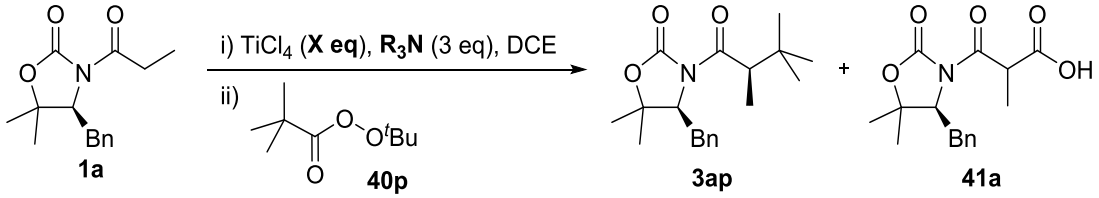


Entry	R_3N	40n	Temperature	Yield
1	Et_3N	2.0 eq	rt	72%
2	Et_3N	1.5 eq	rt	74%
3	Et_3N	2.0 eq	0 °C	60%
4	Et_3N	1.5 eq	0 °C	58%
5	*i*-Pr_2NEt	1.5 eq	rt	66%

Table 44. Optimization of the reaction conditions

2.2. Attempts to suppress the formation of byproduct 41a

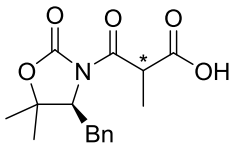
Neat $TiCl_4$ (*n eq*) was added dropwise to a solution of *N*-acyl oxazolidinone **1a** (0.50 mmol) in DCE (2 mL) at 0 °C. After 5 min, *R_3N* (*n eq*) was added dropwise and the resultant deep purple mixture was stirred at 0 °C for 40 min. A solution of the *tert*-butyl perester **40p** (*n eq*) in DCE (1 mL) was added via cannula. The reaction was stirred at *Temperature* for 2 h. Then, it was quenched with sat NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the volatiles evaporated. The resulting crude mixtures were analyzed by ^1H NMR and purified by flash column chromatography to afford **3ap**. Results are summarized in *Table 45*.



Entry	Item	Change from standard conditions	^{1}H NMR crude			Yield
			3ap	1a	41a	
1	-	-	46	17	37	48%
2	time	3h	46	14	40	
3		O/N	50	0	50	42%
4	Amount of perester	1.1 eq perester	38	23	39	
5		3 eq perester	38	42	20	
6	Amount of $TiCl_4$	0.95 eq Ti	37	22	41	
7		1.5 eq Ti	40	5	55	
8	Base	5 eq Et_3N, O/N	56	0	44	40%
9		5 eq *i*-Pr_2NEt, O/N	41	35	24	
10		5 eq TMA, O/N	50	17	33	35%
11	Temperature	35 ºC	26	58	16	
12		40 ºC	40	25	35	
13		45 ºC	27	73	0	
14	Atmosphere	vacuum	0	100	0	
15		Bubbling N_2	44	30	26	
16	Chemical trap	DCC additive	48	16	36	
17		DIC additive	48	12	40	

Table 45. Attempts to suppress the formation of byproduct **41a**

(*S*)-4-Benzyl-*N*-(2-carboxypropanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (41a)

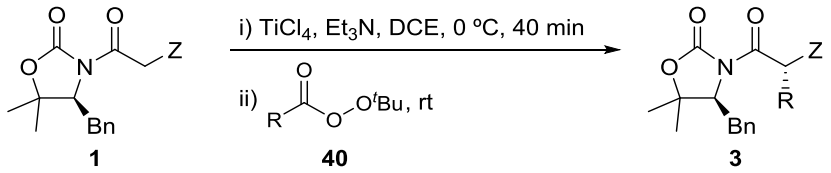


41a

Characterization of one diastereomer. White solid; $\mathbf{R_f}$ (50:50 hexanes/EtOAc) 0.2; **IR** (ATR) ν br 3500–2400, 2931, 1772, 1698, 1455, 1362, 1276, 1237, 1208, 1182 1160, 1080 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.13 (5H, m), 4.59 (1H, q, *J* = 7.2 Hz), 4.53 (1H, dd, *J* = 10.3, 2.9 Hz), 3.27 (1H, dd, *J* = 14.7, 2.9 Hz), 2.90 (1H, dd, *J* = 14.7, 10.3 Hz), 1.52 (3H, d, *J* = 7.2 Hz), 1.37 (6H, s); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.2 (C), 169.4 (C), 152.6 (C), 137.0 (C), 129.0 (CH), 128.7 (CH), 126.7 (CH), 82.9 (C), 64.0 (CH), 45.5 (CH), 34.6 (CH_2), 28.7 (CH_3), 22.4 (CH_3), 13.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{16}H_{20}NO_5$ $[M+H]^+$: 306.1336, found: 306.1345.

3. Scope of the alkylation

General Procedure 8

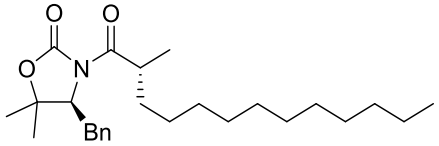


1 **40** **3**

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone (0.50 mmol) in DCE (2 mL) at 0 °C. After 5 min, Et_3N (210 to 350 µL, 1.5 to 2.5 mmol) was added dropwise and the resultant deep purple mixture was stirred at 0 °C for 40 min. A solution of the *tert*-butyl perester (0.75 mmol) in DCE (1 mL) was added via *cannula*. The reaction was allowed to warm to rt and stirred for 1 to 12 h. Then, it was quenched with sat NH_4Cl (3 mL). The layers were separated (2 M HCl could be added to facilitate the separation) and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The residue was purified by flash column chromatography to afford the corresponding alkylated products as a single diastereomer.

3.1. Scope of tert-butyl peresters

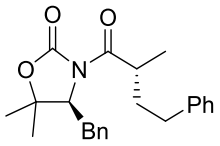
(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methyltridecanoyl]-1,3-oxazolidin-2-one (3ab)



3ab

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (78 mg, 0.30 mmol), $TiCl_4$ (36 µL, 0.33 mmol), Et_3N (125 µL, 0.90 mmol) and *tert*-butyl perester **40b** (123 mg, 0.45 mmol) for 5 h. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3ab** (31 mg, 0.075 mmol, 25% yield). See characterization in page 194.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methyl-4-phenylbutanoyl]-1,3-oxazolidin-2-one (3ad)

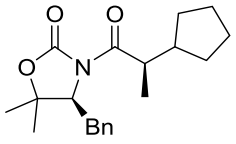


3ad

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (78 mg, 0.30 mmol), $TiCl_4$ (36 µL, 0.33 mmol), Et_3N (125 µL, 0.90 mmol) and *tert*-butyl perester **40d** (100

mg, 0.45 mmol) for 3 h. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3ad** (21 mg, 0.057 mmol, 19% yield). See characterization in page 195.

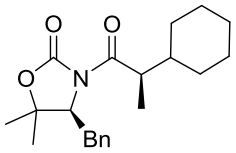
(*S*)-4-Benzyl-*N*-[(*R*)-2-cyclopentylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3ai)



3ai

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol), $TiCl_4$ (61 μL, 0.55 mmol), Et_3N (210 μL, 0.75 mmol) and *tert*-butyl perester **40i** (140 mg, 0.75 mmol) for 1 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3ai** (86 mg, 0.26 mmol, 52% yield). See characterization in page 198.

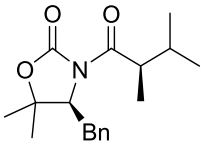
(*S*)-4-Benzyl-*N*-[(*R*)-2-cyclohexylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3aj)



3aj

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol), $TiCl_4$ (61 μL, 0.55 mmol), Et_3N (210 μL, 0.75 mmol) and *tert*-butyl perester **40j** (150 mg, 0.75 mmol) for 1 h. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3aj** (104 mg, 0.30 mmol, 60% yield). See characterization in page 199.

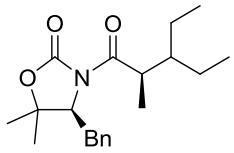
(*S*)-4-Benzyl-*N*-[(*R*)-2,3-dimethylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3ak)



3ak

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol), $TiCl_4$ (61 μL, 0.55 mmol), Et_3N (210 μL, 0.75 mmol) and *tert*-butyl perester **40k** (120 mg, 0.75 mmol) for 2.5 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3ak** (97 mg, 0.35 mmol, 64% yield). See characterization in page 199.

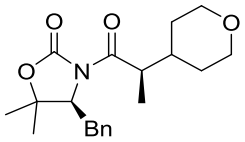
(*S*)-4-Benzyl-*N*-[(*R*)-3-ethyl-2-methylpentanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3am)



3am

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (210 µL, 0.75 mmol) and *tert*-butyl perester **40m** (141 mg, 0.75 mmol) for 2.5 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3am** (96 mg, 0.29 mmol, 58% yield). See characterization in page 201.

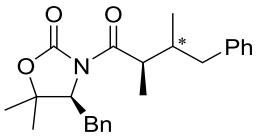
(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-(tetrahydro-4-pyranyl)propanoyl]-1,3-oxazolidin-2-one (3aq)



3aq

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.5 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (210 µL, 1.5 mmol) and *tert*-butyl perester **40q** (152 mg, 0.75 mmol) for 2 h. Purification of the residue by flash column chromatography (from 90:10 to 85:15 hexanes/EtOAc) afforded **3aq** (74 mg, 0.21 mmol, 43% yield) as a colorless oil. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −66.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2936, 2842, 1769, 1692, 1375, 1351, 1275, 1207, 1089 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.19 (5H, m, ArH), 4.57 (1H, dd, *J* = 9.5, 4.1 Hz, NCH), 4.02–3.95 (1H, m, OCH_xH_y), 3.91 (1H, dt, *J* = 11.3, 3.0 Hz, OCH_xH_y), 3.70 (1H, p, *J* = 6.9 Hz, COCH), 3.42–3.29 (2H, m, 2 × OCH_xH_y), 3.11 (1H, dd, *J* = 14.3, 4.1 Hz, $NCHCH_xH_y$), 2.89 (1H, dd, *J* = 14.3, 9.5 Hz, $NCHCH_xH_y$), 1.96–1.80 (1H, m, COCHCH), 1.52–1.38 (4H, m, 2 × OCH_2CH_2), 1.38 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 1.13 (3H, d, *J* = 6.9 Hz, $CHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.6 (C), 152.4 (C), 136.7 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 81.9 (C), 68.0 (CH_2), 67.9 (CH_2), 63.5 (CH), 42.2 (CH), 37.9 (CH), 35.5 (CH_2), 30.9 (CH_2), 28.9 (CH_2), 28.5 (CH_3), 22.2 (CH_3), 13.5 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{20}H_{27}NNaO_4$ $[M+Na]^+$: 368.1832, found: 368.1837.

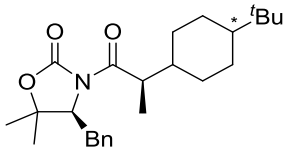
(4*S*)-4-Benzyl-*N*-[(2*R*)-2,3-dimethyl-4-phenylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3al)



3al

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.50 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (210 µL, 0.75 mmol) and *tert*-butyl perester **40l** (177 mg, 0.75 mmol) for 1 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3al** as a mixture of diastereomers (147 mg, 0.39 mmol, 77% yield, dr 2:1). See characterization in page 200.

(*S*)-4-Benzyl-*N*-[(*R*)-2-(4-*tert*-butylcyclohexyl)propanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3ar)



3ar

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.5 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (210 µL, 1.5 mmol) and *tert*-butyl perester **40r** (192 mg, 0.75 mmol) for 2 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3ar** as a mixture of diastereomers (92 mg, 0.23 mmol, 46% yield, dr 1:3) as a white solid. $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.5; **IR** (ATR) ν 2936, 2860, 1774, 1696, 1365, 1351, 1276, 1234, 1207, 1178, 1098; **HRMS** (+ESI): *m/z* calcd. for $C_{25}H_{38}NO_3$ $[M+H]^+$: 400.2833, found: 400.2833.

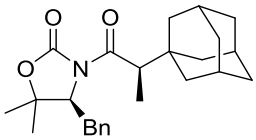
Major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (4H, m, ArH), 7.27–7.18 (1H, m, ArH), 4.56 (1H, dd, *J* = 9.9, 3.5 Hz, NCH), 3.66 (1H, p, *J* = 6.9 Hz, COCH), 3.15 (1H, dd, *J* = 14.3, 3.5 Hz, NCHCH$_x$H$_y$), 2.86 (1H, dd, *J* = 14.3, 9.9 Hz, NCHCH$_x$H$_y$), 1.80–1.66 (4H, m, Cy), 1.64–1.54 (1H, m, COCHCH), 1.35 (3H, s, CCH$_3$), 1.33 (3H, s, CCH$_3$), 1.17–1.07 (1H, m, Cy), 1.11 (3H, d, *J* = 6.9 Hz, COCHCH$_3$), 1.05–0.91 (4H, m, CHC(CH$_3$)$_3$, Cy), 0.83 (9H, s, C(CH$_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.6 (C), 152.4 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.7 (C), 63.7 (CH), 47.8 (CH), 42.5 (CH), 40.9 (CH), 35.4 (CH_2), 32.4 (C), 31.5 (CH_2), 29.0 (CH_2), 28.6 (CH_3), 27.5 (CH_3), 27.2 (CH_2), 27.2 (CH_2), 22.4 (CH_3), 13.6 (CH_3)

Minor diastereomer, main peaks:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (1H, dd, *J* = 9.9, 3.5 Hz, NC<u>H</u>), 4.23 (1H, dq, *J* = 11.0, 6.8 Hz, COC<u>H</u>), 3.18 (1H, dd, *J* = 14.3, 3.5 Hz, NCHC<u>H</u>$_x$H$_y$), 2.92–2.84 (1H, dd, *J* = 14.3, 9.9 Hz, NCHCH$_x$<u>H</u>$_y$), 2.08–1.97 (1H, m, COCHC<u>H</u>), 1.91–1.80 (1H, m, <u>Cy</u>), 1.36 (3H, s, CC<u>H</u>$_3$), 1.33 (3H, s, CC<u>H</u>$_3$), 1.14 (3H, d, *J* = 6.8 Hz, COCHC<u>H</u>$_3$), 0. 86 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 178.6 (C), 152.4 (C), 137.0 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.6 (C), 63.8 (CH), 48.2 (CH), 36.1 (CH), 36.0 (CH), 35.4 (CH_2), 32.6 (C), 29.8 (CH_2), 28.6 (CH_3), 27.4 (CH_2), 22.3 (CH_3), 22.1 (CH_2), 21.6 (CH_2), 16.6 (CH_3).

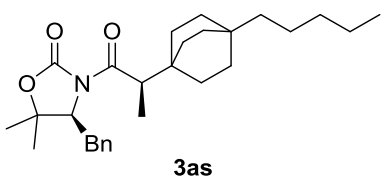
(*S*)-*N*-[(*R*)-2-Adamantylpropanoyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3an)



3an

It was prepared following <u>General Procedure 8</u> from *N*-acyl oxazolidinone **1a** (261 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (420 µL, 3.0 mmol) and *tert*-butyl perester **40n** (379 mg, 1.5 mmol) for 90 min. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3an** (295 mg, 0.74 mmol, 74% yield) as a white solid. **Mp** 132–134 °C; **R$_f$** (90:10 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ –56.9 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2906, 2846, 1773, 1685, 1454 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.17 (5H, m, Ar<u>H</u>), 4.57 (1H, dd, *J* = 10.3, 3.2 Hz, NC<u>H</u>), 3.80 (1H, q, *J* = 7.0 Hz, COC<u>H</u>), 3.27 (1H, dd, *J* = 14.4, 3.2 Hz, C<u>H</u>$_x$H$_y$Ph), 2.84 (1H, dd, *J* = 14.4, 10.3 Hz, CH$_x$<u>H</u>$_y$Ph), 1.98–1.93 (3H, m, 3 × C<u>H</u>(Ad)), 1.82–1.77 (3H, m, 3 × C<u>H</u>$_x$H$_y$(Ad)), 1.70–1.57 (6H, m, 3 × C<u>H</u>$_2$(Ad)), 1.54–1.51 (3H, m, 3 × CH$_x$<u>H</u>$_y$(Ad)), 1.34 (3H, s, CC<u>H</u>$_3$), 1.30 (3H, s, CC<u>H</u>$_3$), 1.10 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.8 (C), 152.7 (C), 137.1 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.3 (C), 64.0 (CH), 45.5 (CH), 39.3 (CH_2), 36.9 (CH_2), 35.9 (C), 35.3 (CH_2), 28.6 (CH), 28.5 (CH_3), 22.5 (CH_3), 11.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{25}H_{34}NO_3$ $[M+H]^+$: 396.2533, found: 396.2534.

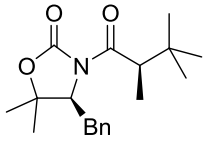
(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-(4-pentylbicyclo[2.2.2]octan-1-yl)propanoyl]-1,3-oxazolidin-2-one (3as)



3as

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.5 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (210 µL, 1.50 mmol) and *tert*-butyl perester **40s** (222 mg, 0.75 mmol) for 4 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3as** (86 mg, 0.19 mmol, 39% yield) as a colorless oil. $\mathbf{R_f}$(90:10 hexanes/EtOAc) 0.4; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ −63.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2925, 2856, 1771, 1691, 1455, 1376, 1351, 1274, 1207, 1178, 1095 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.20 (5H, m, ArH), 4.55 (1H, dd, *J* = 10.3, 3.3 Hz, NCH), 3.82 (1H, q, *J* = 7.0 Hz, COCH), 3.22 (1H, dd, *J* = 14.4, 3.3 Hz, NCHCH$_x$H$_y$), 2.83 (1H, dd, *J* = 14.4, 10.3 Hz, NCHCH$_x$H$_y$), 1.68–1.56 (3H, m, bicyclo), 1.44–1.24 (11H, m, bicyclo, CH_2CH_3), 1.33 (3H, s, CCH_3), 1.30 (3H, s, CCH_3), 1.23–1.10 (4H, m, $(CH_2)_2CH_2CH_3$), 1.07 (3H, d, *J* = 7.0 Hz, $CHCH_3$), 1.04–0.99 (2H, m, CCH_2), 0.86 (3H, t, *J* = 7.2 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.1 (C), 152.6 (C), 137.1 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.3 (C), 63.9 (CH), 43.5 (CH), 41.6 (CH_2), 35.3 (CH_2), 34.6 (C), 32.8 (CH_2), 31.0 (CH_2), 30.2 (C), 28.5 (CH_3), 28.4 (CH_2), 23.3 (CH_2), 22.7 (CH_2), 22.4 (CH_3), 14.1 (CH_3), 12.5 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{28}H_{42}NO_3$ $[M+H]^+$: 440.3159, found: 440.3152.

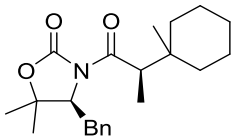
(*S*)-4-Benzyl-*N*-[(*R*)-2-*tert*-butylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3ap)



3ap

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.5 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (210 µL, 1.5 mmol) and *tert*-butyl perester **40p** (131 mg, 0.75 mmol) for 90 min. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3ap** (77 mg, 0.24 mmol, 48% yield) as a white solid. **Mp** 95–97 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.5; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ −52.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2967, 1770, 1692, 1376, 1231, 1275, 1231, 1175, 1103, 1082 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.18 (5H, m, ArH), 4.56 (1H, dd, *J* = 10.5, 3.0 Hz, NCH), 3.93 (1H, q, *J* = 7.0 Hz, COCH), 3.25 (1H, dd, *J* = 14.3, 3.0 Hz, CH$_x$H$_y$Ph), 2.82 (1H, dd, *J* = 14.3, 10.5 Hz, CH$_x$H$_y$Ph), 1.33 (3H, s, CCH_3), 1.30 (3H, s, CCH_3), 1.14 (3H, d, *J* = 7.0 Hz, $CHCH_3$), 1.00 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.3 (C), 152.6 (C), 137.1 (C), 128.9 (CH), 128.7 (CH), 126.7 (CH), 81.3 (C), 64.0 (CH), 44.7 (CH), 35.1 (CH_2), 33.9 (C), 28.6 (CH_3), 27.4 (CH_3), 22.5 (CH_3), 13.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{19}H_{28}NO_3$ $[M+H]^+$: 318.2064, found: 318.2067.

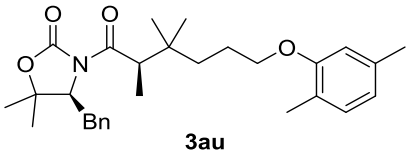
(*S*)-4-Benzyl-*N*-[(*R*)-2-ciclohexyl-2-methylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3at)



3at

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.5 mmol), $TiCl_4$ (61 μL, 0.55 mmol), Et_3N (350 μL, 2.50 mmol) and *tert*-butyl perester **40t** (214 mg, 1.0 mmol) for 16 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3at** (30 mg, 0.08 mmol, 17% yield) as a white solid. **Mp** 91–95 °C; $\mathbf{R_f}$(90:10hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ –48.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2920, 2850, 1774, 1683, 1383, 1351, 1233, 1183, 1104 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH), 4.56 (1H, dd, *J* = 10.4, 3.2 Hz, NCH), 3.98 (1H, q, *J* = 7.0 Hz, COCH), 3.25 (1H, dd, *J* = 14.3, 3.2 Hz, $NCHCH_xH_y$), 2.81 (1H, dd, *J* = 14.3, 10.4 Hz, $NCHCH_xH_y$), 1.59–1.36 (7H, m, Cy), 1.34 (3H, s, CCH_3), 1.29 (3H, s, CCH_3), 1.30–1.16 (3H, m, Cy), 1.12 (3H, d, *J* = 7.0 Hz, $CHCH_3$), 1.03 (3H, s, $CyCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.4 (C), 152.7 (C), 137.1 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.3 (C), 64.0 (CH), 45.2 (CH), 36.6 (C), 35.6 (CH_2), 35.2 (CH_2), 35.0 (CH_2), 28.5 (CH_3), 26.2 (CH_2), 22.5 (CH_3), 21.8 (CH_2), 21.7 (CH_2), 19.5 (CH_3), 12.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{22}H_{32}NO_3$ $[M+H]^+$: 358.2377, found: 358.2376.

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-6-(2,5-dimethylphenoxy)-2,3,3-trimethylhexanoyl]-1,3-oxazolidin-2-one (3au)



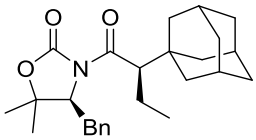
3au

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1a** (131 mg, 0.5 mmol), $TiCl_4$ (61 μL, 0.55 mmol), Et_3N (210 μL, 1.50 mmol) and *tert*-butyl perester **40u** (242 mg, 0.75 mmol) for 2.5 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3au** (54 mg, 0.12 mmol, 23% yield) as a colorless oil. $\mathbf{R_f}$(95:5 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ –52.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2962, 1770, 1693, 1508, 1376, 1350, 1265, 1234, 1207, 1177, 1129, 1103 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.17 (5H, m, ArH), 6.98 (1H, d, *J* = 7.5 Hz, ArH), 6.65 (1H, d, *J* = 7.5 Hz, ArH), 6.62 (1H, s, ArH), 4.56 (1H, dd, *J* = 10.5, 3.0 Hz, NCH), 4.06 (1H, q, *J* = 7.0 Hz, COCH), 3.92 (2H, t, *J* = 6.3 Hz, OCH_2), 3.24 (1H, dd, *J* = 14.4, 3.0 Hz, $NCHCH_xH_y$), 2.77 (1H, dd, *J* = 14.4, 10.5 Hz, $NCHCH_xH_y$), 2.30 (3H, s, $PhCH_3$), 2.15 (3H, s, $PhCH_3$), 1.85–1.76 (2H, m, OCH_2CH_2), 1.60–1.48 (2H, m, $O(CH_2)_2CH_2$), 1.31 (3H, s, CCH_3), 1.30 (3H, s, CCH_3), 1.16 (3H, d, *J* = 7.0 Hz, $CHCH_3$), 1.03 (3H, s, CCH_3), 1.01 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.2 (C),

157.1 (C), 152.6 (C), 137.1 (C), 136.4 (C), 130.2 (C), 128.9 (CH), 128.6 (CH), 126.7 (CH), 123.6 (CH), 120.6 (CH), 112.0 (CH), 81.4 (C), 68.4 (CH_2), 64.0 (CH), 43.4 (CH), 36.6 (CH_2), 36.2 (CH_2), 35.1 (CH_2), 28.6 (CH_3), 24.2 (CH_3), 24.2 (CH_3), 24.0 (CH_2), 22.5 (CH_3), 21.4 (CH_3), 15.8 (CH_3), 12.8 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{29}H_{39}NNaO_4$ $[M+Na]^+$: 488.2771, found: 488.2762.

3.2. Scope of N-acyl oxazolidinones

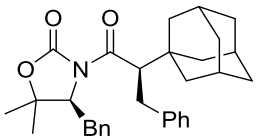
(*S*)-*N*-[(*R*)-2-Adamantylbutanoyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3bn)



3bn

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1b** (275 mg, 1.0 mmol), $TiCl_4$ (121 µL, 1.1 mmol), Et_3N (700 µL, 5.0 mmol) and *tert*-butyl perester **40n** (379 mg, 1.5 mmol) for 3 h. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3bn** (217 mg, 0.53 mmol, 53% yield) as a white solid. **Mp** 155–157 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ –41.0 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2964, 2901, 2888, 2846, 1771, 1682, 1347, 1226, 1174 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.20 (5H, m, ArH), 4.62 (1H, dd, *J* = 10.3, 3.2 Hz, NCH), 3.73 (1H, dd, *J* = 11.8, 3.2 Hz, COCH), 3.24 (1H, dd, *J* = 14.4, 3.2 Hz, CH_xH_yPh), 2.89 (1H, dd, *J* = 14.4, 10.3 Hz, CH_xH_yPh), 1.97–1.91 (3H, m, 3 × CH(Ad)), 1.85–1.79 (3H, m, 3 × CH_xH_y(Ad)), 1.70–1.57 (8H, m, 3 × CH_2(Ad), CH_2CH_3), 1.54–1.48 (3H, m, 3 × CH_xH_y(Ad)), 1.33 (3H, s, CCH_3), 1.32 (3H, s, CCH_3), 0.85 (3H, t, *J* = 7.4 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.3 (C), 152.7 (C), 137.3 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.2 (C), 64.0 (CH), 53.6 (CH), 39.7 (CH_2), 37.0 (CH_2), 36.2 (C), 35.6 (CH_2), 28.6 (CH_3), 28.4 (CH_3), 22.3 (CH_3), 19.7 (CH_2), 12.7 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{26}H_{35}NNaO_3$ $[M+Na]^+$: 432.2509, found: 432.2512.

(*S*)-*N*-[(*R*)-2-Adamantyl-3-phenylpropanoyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3dn)

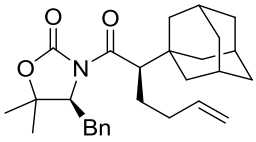


3dn

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1d** (169 mg, 0.5 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (350 µL, 2.5 mmol) and *tert*-butyl perester **40n** (189 mg, 0.75 mmol) for 2 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3dn** (103 mg, 0.22 mmol, 44% yield) as a white solid. **Mp** 150–

155 °C; **R_f** (90:10 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −41.4 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2922, 2902, 1766, 1687, 1387, 1352, 1244, 1229, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30–7.07 (10H, m, ArH), 4.24 (1H, dd, *J* = 10.0, 3.6 Hz, NCH), 4.19 (1H, dd, *J* = 11.9, 4.1 Hz, COCH), 3.06 (1H, dd, *J* = 14.5, 3.6 Hz, CH_xH_yPh), 2.96–2.85 (2H, m, $COCHCH_2Ph$), 2.80 (1H, dd, *J* = 14.5, 10.0 Hz, CH_xH_yPh), 2.01–1.97 (3H, m, 3 × CH(Ad)), 1.95–1.90 (3H, m, 3 × CH_xH_y(Ad)), 1.74–1.63 (6H, m, 3 × CH_2(Ad)), 1.62–1.55 (3H, m, 3 × CH_xH_y(Ad)), 1.15 (3H, s, CCH_3), 0.57 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.7 (C), 152.4 (C), 140.1 (C), 137.2 (C), 129.1 (CH), 129.0 (CH), 128.5 (CH), 128.4 (CH), 126.7 (CH), 126.1 (CH), 81.3 (C), 63.5 (CH), 53.7 (CH), 39.7 (CH_2), 36.9 (CH_2), 36.1 (C), 35.7 (CH_2), 32.9 (CH_2), 28.6 (CH), 27.1 (CH_3), 22.0 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{31}H_{38}NO_3$ $[M+H]^+$: 472.2846, found: 472.2850.

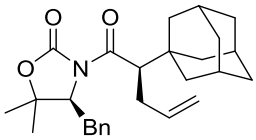
(*S*)-*N*-[(*R*)-2-Adamantyl-5-hexenoyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3en)



3en

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1e** (151 mg, 0.5 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (350 µL, 2.5 mmol) and *tert*-butyl perester **40n** (189 mg, 0.75 mmol) for 2 h. Purification of the residue by flash column chromatography (from 99.5:0.5 to 97.5:2.5 hexanes/EtOAc) afforded **3en** (133 mg, 0.21 mmol, 41% yield) as a colorless oil. **R_f** (60:40 hexanes/DCM) 0.4; $[\alpha]_D^{20}$ −28.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2901, 2847, 1770, 1686, 1348, 1274, 1227, 1205, 1173, 1095 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.19 (5H, m, ArH), 5.78 (1H, ddt, *J* = 16.8, 10.2, 6.5 Hz, $CH=CH_2$), 5.04–4.98 (1H, m, $CH=CH_xH_y$), 4.98–4.93 (1H, m, $CH=CH_xH_y$), 4.61 (1H, dd, *J* = 10.4, 3.0 Hz, CHN), 3.83 (1H, dd, *J* = 11.4, 2.7 Hz, COCH), 3.25 (1H, dd, *J* = 14.4, 3.0 Hz, CH_xH_yPh), 2.87 (1H, dd, *J* = 14.4, 10.4 Hz, CH_xH_yPh), 2.01–1.79 (9H, m, $CH_2CH=CH_2$, 3 × CH(Ad), $COCHCH_xH_y$, 3 × CH_xH_y(Ad)), 1.70–1.57 (7H, m, 3 × CH_2(Ad), $COCHCH_xH_y$), 1.54–1.77 (3H, d, *J* = 12.0 Hz, 3 × CH_xH_y(Ad)), 1.33 (3H, s, CCH_3), 1.32 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 176.0 (C), 152.5 (C), 138.0 (C), 137.2 (CH), 129.0 (CH), 128.6 (CH), 126.7 (CH), 115.0 (CH_2), 81.2 (C), 64.1 (CH), 51.3 (CH), 39.6 (CH_2), 36.9 (CH_2), 36.3 (C), 35.4 (CH_2), 32.5 (CH_2), 28.6 (CH_3), 28.6 (CH), 26.1 (CH_2), 22.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{28}H_{38}NO_3$ $[M+H]^+$: 436.2846, found: 436.2848.

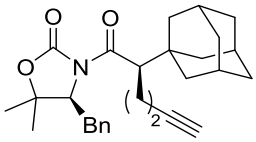
(*S*)-*N*-[(*R*)-2-Adamantyl-4-pentenoyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3sn)



3sn

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1s** (144 mg, 0.5 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (350 µL, 2.5 mmol) and *tert*-butyl perester **40n** (189 mg, 0.75 mmol) for 2.5 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3sn** (50 mg, 0.12 mmol, 24% yield) as a white solid. **Mp** 100–106 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ –40.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2900, 2846, 1770, 1688, 1350, 1275, 1229, 1205, 1174, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.20 (5H, m, ArH), 5.74 (1H, ddt, *J* = 17.1, 10.1, 8.7, 5.3 Hz, CH=CH_2), 5.08–5.02 (1H, m, CH=CH_xH_y), 4.97–4.93 (1H, m, CH=CH_xH_y), 4.56 (1H, dd, *J* = 10.2, 3.4 Hz, CHN), 3.92 (1H, dd, *J* = 11.6, 3.5 Hz, COCH), 3.18 (1H, dd, *J* = 14.4, 3.4 Hz, CH_xH_yPh), 2.89 (1H, dd, *J* = 14.4, 10.2 Hz, CH_xH_yPh), 2.45–2.27 (2H, m, CH_2CH=CH_2), 1.98–1.93 (3H, m, 3 × CH(Ad)), 1.88–1.80 (3H, m, 3 × CH_xH_y(Ad)), 1.70–1.59 (6H, m, 3 × CH_2(Ad)), 1.54–1.47 (3H, m, 3 × CH_xH_y(Ad)), 1.30 (3H, s, CCH_3), 1.30 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.1 (C), 152.7 (C), 137.2 (C), 136.6 (CH), 129.0 (CH), 128.6 (CH), 126.7 (CH), 116.6 (CH_2), 81.4 (C), 63.7 (CH), 51.5 (CH), 39.6 (CH_2), 36.9 (CH_2), 36.0 (C), 35.7 (CH_2), 31.2 (CH_2), 28.6 (CH), 28.3 (CH_3), 22.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{27}H_{35}NNaO_3$ $[M+Na]^+$: 444.2509, found: 444.2507.

(*S*)-*N*-[(*R*)-2-Adamantyl-5-hexynoyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3fn)

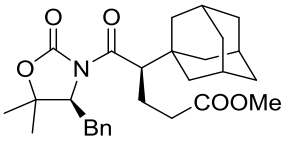


3fn

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1f** (150 mg, 0.5 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (350 µL, 2.5 mmol) and *tert*-butyl perester **40n** (189 mg, 0.75 mmol) for 2.5 h. Purification of the residue by flash column chromatography (from 99.5:0.5 to 97.5:2.5 hexanes/EtOAc) afforded **3fn** (107 mg, 0.25 mmol, 49% yield) as a white solid. **Mp** 137–140 °C; $\mathbf{R_f}$ (95:5 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ –16.9 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3265, 2900, 2888, 2847, 1760, 1694, 1342, 1277, 1203, 1148, 1093 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.19 (5H, m, ArH), 4.59 (1H, dd, *J* = 10.3, 3.1 Hz, NCH), 3.96 (1H, dd, *J* = 11.6, 3.0 Hz, COCH), 3.24 (1H, dd, *J* = 14.4, 3.1 Hz, CH_xH_yPh), 2.88 (1H, dd, *J* = 14.4, 10.3 Hz, CH_xH_yPh),

2.25–2.12 (1H, m, C<u>H</u>$_x$H$_y$C≡CH), 2.14–2.00 (1H, m, CH$_x$<u>H</u>$_y$C≡CH), 2.04–1.96 (1H, m, COCHC<u>H</u>$_x$H$_y$), 1.98 (1H, t, *J* = 2.6 Hz, C≡C<u>H</u>), 1.97–1.93 (3H, m, 3 × C<u>H</u>(Ad)), 1.87–1.74 (4H, m, 3 × C<u>H</u>$_x$H$_y$(Ad), COCHCH$_x$<u>H</u>$_y$), 1.70–1.58 (6H, m, 3 × C<u>H</u>$_2$(Ad)), 1.55–1.49 (3H, m, 3 × CH$_x$<u>H</u>$_y$(Ad)), 1.35 (3H, s, CC<u>H</u>$_3$), 1.32 (3H, s, CC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.3 (C), 152.4 (C), 137.2 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 83.2 (C), 81.3 (C), 69.5 (CH), 64.2 (CH), 50.6 (CH), 39.5 (CH_2), 36.9 (CH_2), 36.3 (C), 35.5 (CH_2), 28.6 (CH), 28.5 (CH_3), 25.5 (CH_2), 22.4 (CH_3), 17.2 (CH_2); **HRMS** (+ESI): *m/z* calcd. for $C_{28}H_{36}NO_3$ $[M+H]^+$: 434.2690, found: 434.2688.

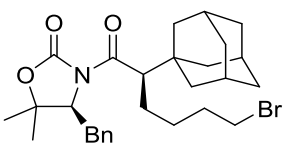
(*S*)-*N*-[(*R*)-2-Adamantyl-5-methoxy-5-oxopentanoyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3gn)



3gn

It was prepared following <u>General Procedure 8</u> from *N*-acyl oxazolidinone **1g** (333 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (700 µL, 5.0 mmol) and *tert*-butyl perester **40n** (379 mg, 1.5 mmol) for 12 h. Purification of the residue by flash column chromatography (85:15 hexanes/EtOAc) afforded **3gn** (312 mg, 0.67 mmol, 67% yield) as a white solid. **Mp** 100–104 °C; **R$_f$** (90:10 hexanes/EtOAc) 0.2; $[\alpha]_D^{20}$ –28.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2900, 1761, 1734, 1698, 1353, 1272, 1205, 1166, 1105, 1093 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.20 (5H, m, Ar<u>H</u>), 4.62 (1H, dd, *J* = 10.5, 3.0 Hz, NC<u>H</u>), 3.79 (1H, dd, *J* = 11.2, 3.4 Hz, COC<u>H</u>), 3.66 (3H, s, OC<u>H</u>$_3$), 3.25 (1H, dd, *J* = 14.4, 2.9 Hz, C<u>H</u>$_x$H$_y$Ph), 2.87 (1H, dd, *J* = 14.4, 10.5 Hz, CH$_x$<u>H</u>$_y$Ph), 2.32–2.13 (2H, m, CHC<u>H</u>$_2$CH$_2$), 2.07–1.92 (5H, m, C<u>H</u>$_2$COOCH$_3$, 3 × C<u>H</u>(Ad)), 1.84–1.78 (3H, m, 3 × C<u>H</u>$_x$H$_y$(Ad)), 1.70–1.57 (6H, m, 3 × C<u>H</u>$_2$(Ad)), 1.55–1.48 (3H, m, 3 × CH$_x$<u>H</u>$_y$(Ad)), 1.37 (3H, s, CC<u>H</u>$_3$), 1.32 (3H, s, CC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.5 (C), 173.3 (C), 152.5 (C), 137.2 (C), 129.0 (CH), 128.6 (CH), 126.8 (CH), 81.3 (C), 64.0 (CH), 51.6 (CH_3), 50.8 (CH), 39.5 (CH_2), 36.8 (CH_2), 36.4 (C), 35.4 (CH_2), 32.8 (CH_2), 28.6 (CH), 28.4 (CH_3), 22.4 (CH_3), 22.2 (CH_2); **HRMS** (+ESI): *m/z* calcd. for $C_{28}H_{38}NO_5$ $[M+H]^+$: 468.2744, found: 486.2745.

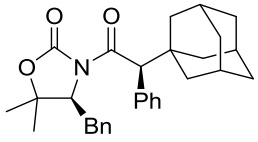
(*S*)-*N*-[(*R*)-2-Adamantyl-5-bromopentanoyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3yn)



3yn

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1y** (191 mg, 0.5 mmol) and *tert*-butyl perester **40n** (189 mg, 0.75 mmol) for 3 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3yn** (89 mg, 0.17 mmol, 34% yield) as a white sticky solid. $\mathbf{R_f}$ (95:5 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ −17.0 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2902, 2848, 1770, 1688, 1350, 1274, 1228, 1206, 1175, 1098 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44–7.14 (5H, m, ArH), 4.62 (1H, dd, *J* = 10.4, 3.0 Hz, NCH), 3.81 (1H, dd, *J* = 11.9, 2.7 Hz, COCH), 3.38 (2H, td, *J* = 6.6, 1.2 Hz, CH_2Br), 3.24 (1H, dd, *J* = 14.5, 3.0 Hz, CH_xH_yPh), 2.88 (1H, dd, *J* = 14.5, 10.4 Hz, CH_xH_yPh), 1.98–1.91 (3H, m, 3 × CH(Ad)), 1.90–1.72 (6H, m, CH_2CH_2Br, $COCHCH_xH_y$, 3 × CH_xH_y(Ad)), 1.70–1.58 (6H, m, 3 × CH_2(Ad)), 1.58–1.53 (1H, m, $COCHCH_xH_y$), 1.53–1.45 (3H, m, 3 × CH_xH_y(Ad)), 1.37–1.31 (2H, m, $CH_2(CH_2)_2Br$), 1.34 (3H, s, CCH_3), 1.32 (3H, s, CCH_3); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 176.0 (C), 152.6 (C), 137.2 (C), 129.0 (CH), 128.6 (CH), 126.7 (CH), 81.4 (C), 64.0 (CH), 51.5 (CH), 39.6 (CH_2), 36.9 (CH_2), 36.2 (C), 35.5 (CH_2), 33.7 (CH_2), 32.6 (CH_2), 28.6 (CH), 28.6 (CH_3), 27.0 (CH_2), 25.8 (CH_2), 22.3 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{28}H_{38}BrNNaO_3$ $[M+Na]^+$: 538.1927, found: 538.1929.

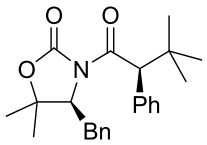
(*S*)-*N*-[(*R*)-2-Adamantyl-2-phenylacetyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3zn)



3zn

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1z** (323 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (700 µL, 5.0 mmol) and *tert*-butyl perester **40n** (379 mg, 1.5 mmol) for 3 h. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3zn** (276 mg, 0.61 mmol, 61% yield) as a white solid. **Mp** 206–208 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ +47.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2903, 1760, 1699, 1348, 1293, 1279, 1213, 1165, 1093 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (10H, m, ArH), 4.94 (1H, s, COCH), 4.48 (1H, dd, *J* = 9.7, 3.9 Hz, NCH), 3.24 (1H, dd, *J* = 14.3, 3.9 Hz, CH_xH_yPh), 2.90 (1H, dd, *J* = 14.3, 9.7 Hz, CH_xH_yPh), 1.95–1.90 (3H, m, 3 × CH(Ad)), 1.81–1.74 (3H, m, 3 × CH_xH_y(Ad)), 1.66–1.52 (9H, m, 3 × CH_2(Ad), 3 × CH_xH_y(Ad)), 1.28 (3H, s, CCH_3), 1.01 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.0 (C), 152.5 (C), 137.0 (C), 134.4 (C), 130.9 (CH), 129.1 (CH), 128.6 (CH), 127.6 (CH), 127.1 (CH), 126.7 (CH), 81.5 (C), 63.8 (CH), 58.4 (CH), 39.9 (CH_2), 37.2 (C), 36.8 (CH_2), 35.6 (CH_2), 28.6 (CH), 28.1 (CH_3), 22.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{30}H_{36}NO_3$ $[M+H]^+$: 458.2690, found: 458.2704.

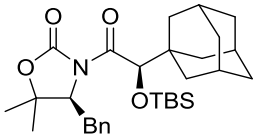
(*S*)-4-Benzyl-*N*-[(*R*)-2-*tert*-butyl-2-phenylacetyl]-5,5-dimethyl-1,3-oxazolidin-2-one (3zp)



3zp

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1z** (162 mg, 0.5 mmol), $TiCl_4$ (61 µL, 0.55 mmol), Et_3N (350 µL, 2.5 mmol) and *tert*-butyl perester **40p** (131 mg, 0.75 mmol) for 12 h. Purification of the residue by flash column chromatography (95:5 hexanes/EtOAc) afforded **3zp** (50 mg, 0.13 mmol, 26% yield) as a white solid. **Mp** 164–165 °C; **R_f** (90:10 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ +77.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2953, 1759, 1704, 1367, 1293, 1233, 1159, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.20 (10H, m, ArH), 5.03 (1H, s, COCH), 4.46 (1H, dd, *J* = 9.7, 3.9 Hz, NCH), 3.22 (1H, dd, *J* = 14.3, 3.9 Hz, CH_xH_yPh), 2.90 (1H, dd, *J* = 14.3, 9.7 Hz, CH_xH_yPh), 1.27 (3H, s, CCH_3), 1.01 (9H, s, $C(CH_3)_3$), 1.00 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C), 152.3 (C), 137.0 (C), 135.7 (C), 130.7 (CH), 129.0 (CH), 128.6 (CH), 127.7 (CH), 127.1 (CH), 126.7 (CH), 81.6 (C), 63.9 (CH), 57.2 (CH), 35.5 (CH_2), 35.0 (C), 28.0 (CH_3), 28.0 (CH_3), 22.1 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{24}H_{29}NNaO_3$ $[M+Na]^+$: 402.2040, found: 402.2040.

(*S*)-*N*-[(*R*)-2-Adamantyl-2-*tert*-butyldimethylsilyloxyacetyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3hn)

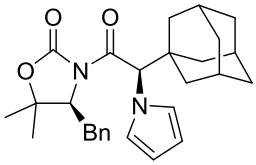


3hn

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1h** (2.45 g, 6.5 mmol), $TiCl_4$ (790 µL, 7.1 mmol), Et_3N (4.5 mL, 32 mmol) and *tert*-butyl perester **40n** (2.46 g, 9.8 mmol) for 3 h. Purification of the residue by flash column chromatography (from 99:1 to 95:5 hexanes/EtOAc) afforded **3hn** (2.32 mg, 4.5 mmol, 69% yield) as a white solid. **Mp** 60–64 °C; **R_f** (90:10 hexanes/EtOAc) 0.5; $[\alpha]_D^{20}$ –35.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2902, 2850, 1771, 1703, 1349, 1252, 1129, 1099 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38-7.20 (5H, m, ArH), 5.37 (1H, s, COCH), 4.65 (1H, dd, *J* = 10.8, 2.9 Hz, NCH), 3.25 (1H, dd, *J* = 14.3, 2.6 Hz, CH_xH_yPh), 2.83 (1H, dd, *J* = 14.3, 10.8 Hz, CH_xH_yPh), 1.99–1.93 (3H, m, 3 × CH(Ad)), 1.81–1.75 (3H, m, 3 × CH_xH_y(Ad)), 1.70–1.54 (9H, m, 3 × CH_2(Ad), 3 × CH_xH_y(Ad)), 1.33 (3H, s, CCH_3), 1.31 (3H, s, CCH_3), 0.93 (9H, s, $SiC(CH_3)_3$), 0.08 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.1 (C), 152.5 (C), 136.9 (C), 129.0 (CH), 128.7 (CH), 126.8 (CH), 81.9 (C), 75.4 (CH), 63.9 (CH), 38.4 (C), 37.7 (CH_2), 37.0 (CH_2), 35.3 (CH_2), 28.9 (CH_3), 28.3 (CH), 25.8

(CH_3), 22.6 (CH_3), 18.2 (C), −4.8 (CH_3), −5.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{30}H_{46}NO_4Si$ $[M+H]^+$: 512.3191, found: 512.3191.

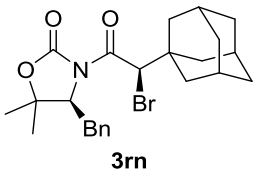
(*S*)-*N*-[(*R*)-2-Adamantyl-2-(1-*H*-*N*-pyrrolyl)acetyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3vn)



3vn

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1v** (2.00 g, 6.4 mmol), $TiCl_4$ (770 µL, 7.0 mmol), Et_3N (4.5 mL, 32 mmol) (enolization was carried out at −20 °C) and *tert*-butyl perester **40n** (2.42 g, 9.6 mmol) for 3 h. Purification of the residue by flash column chromatography (from 95:5 to 90:10 hexanes/EtOAc) afforded **3vn** (1.77 g, 4.0 mmol, 62% yield) as a white solid. **Mp** 210–212 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −22.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2904, 2846, 1760, 1699, 1348, 1293, 1213, 1166, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.14 (5H, m, ArH), 6.88 (2H, t, *J* = 2.2 Hz, NCH=CH), 6.12 (2H, m, *J* = 2.2 Hz, NCH=CH), 5.99 (1H, s, COCH), 4.53 (1H, dd, *J* = 10.0, 3.8 Hz, CHN), 3.28 (1H, dd, *J* = 14.3, 3.8 Hz, CH_xH_yPh), 2.89 (1H, dd, *J* = 14.3, 10.0 Hz, CH_xH_yPh), 2.00–1.93 (3H, m, 3 × CH(Ad)), 1.74–1.56 (12H, m, 6 × CH_2(Ad)), 1.34 (3H, s, CCH_3), 1.18 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.4 (C), 152.4 (C), 136.6 (C), 129.0 (CH), 128.7 (CH), 126.9 (CH), 122.7 (CH), 107.4 (CH), 82.1 (C), 66.3 (CH), 63.9 (CH), 38.8 (CH_2), 38.3 (C), 36.6 (CH_2), 35.2 (CH_2), 28.3 (CH_3), 28.3 (CH), 22.4 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{28}H_{35}N_2O_3$ $[M+H]^+$: 447.2642, found: 447.2646.

(*S*)-*N*-[(*R*)-2-Adamantyl-2-bromoacetyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (3rn)

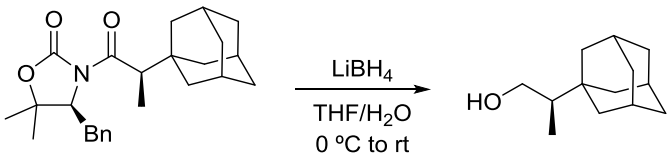


3rn

It was prepared following General Procedure 8 from *N*-acyl oxazolidinone **1r** (323 mg, 1.0 mmol), $TiCl_4$ (122 µL, 1.1 mmol), Et_3N (700 µL, 5.0 mmol) and *tert*-butyl perester **40n** (379 mg, 1.5 mmol) for 3 h. The product was not detected by ^{1}H NMR of the crude mixture.

4. Removal of the chiral auxiliary

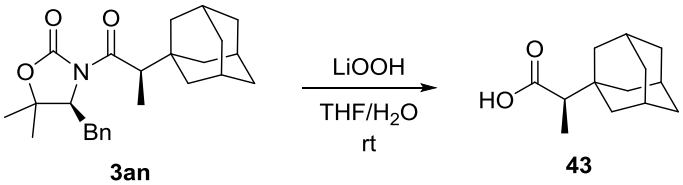
(*R*)-2-Adamantyl-1-propanol (42)



3an **42**

A 2 M solution of $LiBH_4$ in THF (600 µL, 1.2 mmol) was added to a solution of **3an** (158 mg, 0.40 mmol) in THF (3 mL) and H_2O (1 mL) at 0 °C. The reaction mixture was stirred for 3 h at rt. Two batches of $LiBH_4$ 2 M in THF (300 µL, 0.60 mmol) were added after 2.5 h and then 1.5 h. The reaction mixture was quenched with MeOH (500 uL) and partitioned between EtOAc and H_2O (6 mL each). The aqueous layer was extracted with further EtOAc (2 × 6 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. Purification of the residue by flash column chromatography (from 90:10 to 85:15 hexanes:EtOAc) afforded ***SuperQuat*** (55 mg, 0.27 mmol, 67% yield) and **42** (50 mg, 0.26 mmol, 64% yield) as a white solid. **Mp** 74–75 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −22.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) br 3304, 2895, 2846, 1447, 1361, 1344, 1030, 1015 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.84 (1H, dd, *J* = 10.4, 3.9 Hz, C<u>H</u>$_x$H$_y$OH), 3.36 (1H, dd, *J* = 10.4, 8.4 Hz, CH$_x$<u>H</u>$_y$OH), 1.98–1.93 (3H, m, 3 × C<u>H</u>(Ad)), 1.73–1.60 (6H, m, 3 × C<u>H</u>$_2$(Ad)), 1.60–1.48 (6H, m, 3 × C<u>H</u>$_2$(Ad)), 1.28–1.18 (2H, m, C<u>H</u>CH$_3$, O<u>H</u>), 0.92 (3H, d, *J* = 7 Hz, C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 64.4 (CH_2), 46.0 (CH), 39.9 (CH_2), 37.3 (CH_2), 34.1 (C), 28.7 (CH), 10.9 (CH_3); **HRMS** (–ESI): *m/z* calcd. for $C_{13}H_{21}O$ $[M-H]^-$: 193.1598, found: 193.1600.

(*R*)-2-Adamantyl-propionic acid (43)



3an **43**

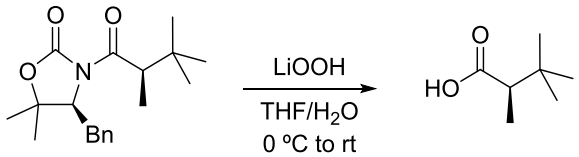
A 30% solution of H_2O_2 (590 µL, 5.9 mmol) and LiOH (164 mg, 3.9 mmol) were added to a solution of **3an** (154 mg, 0.39 mmol) in THF (3.5 mL) and H_2O (1.5 mL) at rt. The reaction mixture was stirred for 3 days at rt and quenched by dropwise addition of 1.5 M Na_2SO_3 (12 mL) and 1 M HCl (12 mL). The mixture was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were extracted with 1 M NaOH (3 × 5 mL) and the organic extracts were set apart. The combined aqueous extracts were acidified with 2 M HCl (pH ~1) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **43** (18 mg, 0.09 mmol, 22% yield) as

a white solid. **Mp** 147–151 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.6; $[\alpha]_D^{20}$ –21.4 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν br 3200–2450, 2898, 2850, 2657, 1696, 1447, 1415, 1288, 1220 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.38 (1H, br s, COOH), 2.15 (1H, q, *J* = 7.1 Hz, COCH), 2.02–1.96 (3H, m, 3 × CH(Ad)), 1.75–1.61 (9H, m, 3 × CH_2(Ad), 3 × CH_xH_y(Ad)), 1.59–1.51 (3H, m, 3 × CH_xH_y(Ad)), 1.10 (3H, d, *J* = 7.1 Hz, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 181.9 (C), 50.5 (CH), 39.6 (CH_2), 36.9 (CH_2), 34.3 (C), 28.6 (CH), 10.8 (CH_3); **HRMS** (–ESI): *m/z* calcd. for $C_{13}H_{19}O_2$ $[M-H]^-$: 207.1391, found: 207.1393.

Recovery of the chiral auxiliary

The organic extracts set apart were treated with 1 M HCl (10 mL) and brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a mixture of oxazolidinone ***SuperQuat*** and **3an**.

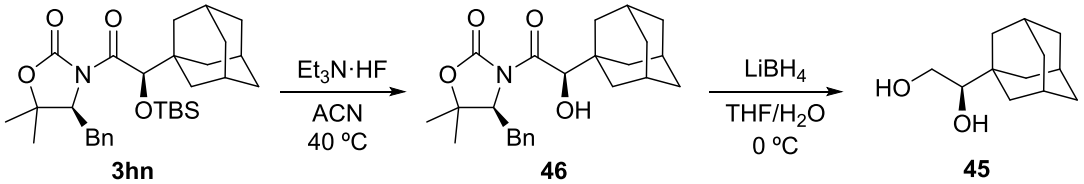
(*R*)-2-Adamantyl-propionic acid (44)



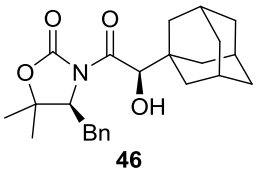
3ap **44**

A 30% solution of H_2O_2 (300 µL, 3.0 mmol) and $LiOH{\cdot}H_2O$ (25 mg, 0.60 mmol) were added to a solution of **3ap** (95 mg, 0.30 mmol) in THF (1.2 mL) and H_2O (0.3 mL) at 0 °C. The reaction mixture was stirred for 24 h at rt and further 30% H_2O_2 (600 µL, 6.0 mmol) and $LiOH{\cdot}H_2O$ (63 mg, 1.5 mmol) were added. The mixture was stirred for 24 h at rt and quenched by dropwise addition of 1.5 M Na_2SO_3 (7 mL) and 1 M HCl (7 mL). The mixture was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were extracted with 1 M NaOH (3 × 5 mL) and the organic extracts were set apart. The combined aqueous extracts were acidified with 2 M HCl (pH ~1) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford **44** (28 mg, 0.21 mmol, 72% yield) as a colorless oil. $\mathbf{R_f}$ (50:50 hexanes/EtOAc) 0.3; $[\alpha]_D^{20}$ –28.1 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν br 3500–2500, 2962, 1701, 1463, 1415, 1368, 1287, 1240, 1184 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 2.30 (1H, q, *J* = 7.1 Hz, COCH), 1.14 (3H, d, *J* = 7.1 Hz, $CHCH_3$), 0.99 (9H, s, CCH_3); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 182.1 (C), 49.4 (CH), 32.5 (C), 27.5 (CH_3), 12.5 (CH_3); **HRMS** (–ESI): *m/z* calcd. for $C_7H_{13}O_2$ $[M-H]^-$: 129.0921, found: 129.0917.

(*R*)-1-Adamantyl-1,2-etandiol (45)

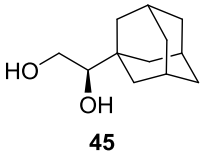


(*S*)-*N*-[(*R*)-2-(1-adamantanyl)-2-hydroxyacetyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (**46**)



Neat $Et_3N{\cdot}3HF$ (650 µL, 4.0 mmol) was added to a solution of **3hn** (256 mg, 0.50 mmol) in ACN (4 mL). The reaction mixture was stirred at 40 °C for 18 h and allowed to cool to rt. The mixture was partitioned between EtOAc and H_2O (7 mL each). The aqueous layer was extracted with further EtOAc (2 × 7 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the volatiles evaporated. Purification of the residue by flash column chromatography (from 99:1 to 90:10 hexanes:EtOAc) afforded **46** (124 mg, 0.31 mmol, 62% yield) as a caramel white solid. **R_f** (80:20 hexanes/EtOAc) 0.4; **$[\alpha]_D^{20}$** −61.6 (c 1.0, $CHCl_3$); **IR** (ATR) ν br 3500, 2903, 2849, 1776, 1731, 1684, 1353, 1275, 1232, 1209, 1102 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.22 (5H, m, ArH), 5.11 (1H, d, J = 10.0 Hz, COCH), 4.65 (1H, dd, J = 10.2, 3.7 Hz, CHN), 3.26 (1H, dd, J = 14.3, 3.7 Hz, CH_xH_yPh), 2.93 (1H, br d, J = 10.5 Hz, OH), 2.87 (1H, dd, J = 14.3, 10.2 Hz, CH_xH_yPh), 2.03–1.95 (3H, m, 3 × CH(Ad)), 1.80–1.75 (3H, m, 3 × CH_xH_y(Ad)), 1.73–1.60 (6H, m, 3 × CH_2(Ad)), 1.56 (3H, m, 3 × CH_xH_y(Ad)), 1.38 (3H, s, CCH_3), 1.33 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.9 (C), 152.1 (C), 136.5 (C), 128.9 (CH), 128.8 (CH), 127.0 (CH), 82.4 (C), 76.1 (CH), 63.8 (CH), 38.3 (C), 37.5 (CH_2), 36.8 (CH_2), 35.3 (CH_2), 28.8 (CH_3), 28.2 (CH), 22.7 (CH_3); **HRMS** (+ESI): m/z calcd. for $C_{24}H_{32}NO_4$ $[M+H]^+$: 398.2326, found: 398.2329.

(*R*)-1-Adamantyl-1,2-etandiol (**45**)

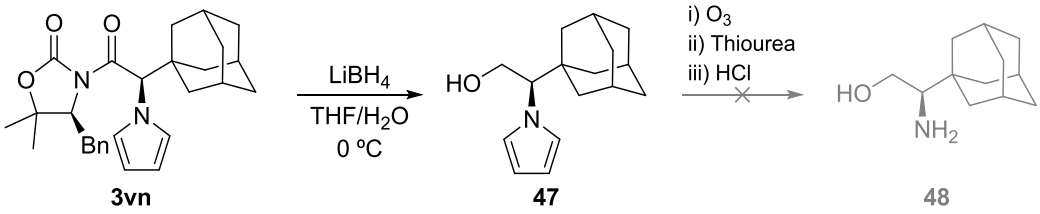


A 2M solution of $LiBH_4$ in THF (450 µL, 0.90 mmol) was added to a solution of **46** (115 mg, 0.29 mmol) in THF (2.4 mL) and H_2O (0.6 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with MeOH (400 uL) and partitioned between EtOAc and H_2O (6 mL each). The aqueous layer was extracted with further EtOAc (2 × 6 mL). The combined

organic extracts were dried with anhydrous $MgSO_4$ and the volatiles evaporated. Purification of the residue by flash column chromatography (from 99.75:0.25 to 98:2 DCM:MeOH) afforded ***SuperQuat*** (59 mg, 0.29 mmol, 97% yield) and **45** (44 mg, 0.22 mmol, 77% yield; 48% over two steps) as a white solid. **Mp** 113–114 °C; $\mathbf{R_f}$ (98:2 DCM/MeOH) 0.3; $[\alpha]_D^{20}$ −10.7 (c 1.0, $CHCl_3$); **IR** (ATR) ν br 3270, 2899, 2848, 1449, 1343, 1077, 1051, 1028 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.74 (1H, dd, J = 11.0, 2.9 Hz, C<u>H</u>$_x$H$_y$OH), 3.55 (1H, dd, J = 11.0, 9.4 Hz, CH$_x$<u>H</u>$_y$OH), 3.22 (1H, dd, J = 9.4, 2.9 Hz, C<u>H</u>OH), 2.47 (2H, br s, 2 × O<u>H</u>), 2.03–1.92 (3H, m, 3 × C<u>H</u>(Ad)), 1.78–1.49 (12H, m, 6 × C<u>H</u>$_2$(Ad)); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 80.0 (CH), 62.2 (CH_2), 38.2 (CH_2), 37.1 (CH_2), 35.6 (C), 28.2 (CH); **HRMS** (+ESI): m/z calcd. for $C_{12}H_{19}O_2$ $[M-H]^-$: 195.1391, found: 195.1393.

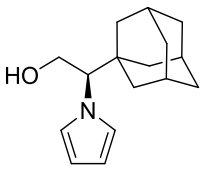
(R)-2-Adamantyl-2-aminoetanol (48)

<u>Initial route</u>



3vn 47 48

<u>(*R*)-2-(1-adamantanyl)-2-(1*H*-1-pyrrolyl)-1-ethanol (**47**)</u>

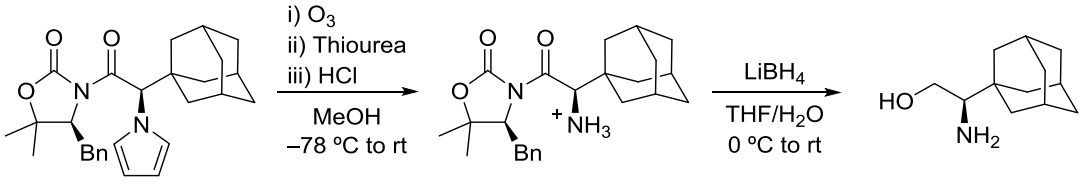


47

A 2M solution of $LiBH_4$ in THF (2.3 mL, 4.6 mmol) was added to a solution of **3vn** (690 mg, 1.55 mmol) in THF (12 mL) and H_2O (4 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with MeOH (1 mL) and partitioned between EtOAc and H_2O (15 mL each). The aqueous layer was extracted with further EtOAc (2 × 15 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the volatiles evaporated. Purification of the residue by flash column chromatography (from 80:20 to 50:50 hexanes/EtOAc) afforded ***SuperQuat*** (307 mg, 1.5 mmol, 97% yield) and **47** (355 mg, 1.45 mmol, 94% yield) as a white solid. **Mp** 131–133 °C; $\mathbf{R_f}$ (80:20 hexanes/EtOAc) 0.4; $[\alpha]_D^{20}$ −1.4 (c 1.0, $CHCl_3$); **IR** (ATR) ν br 3269, 2902, 2847, 1260, 1082, 1058, 1050, 1025 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.67 (2H, t, J = 2.1 Hz, NC<u>H</u>=CH), 6.18 (2H, t, J = 2.1 Hz, NCH=C<u>H</u>), 4.05–3.97 (2H, m, C<u>H</u>$_2$OH), 3.59 (1H, dd, J = 9.2, 5.2 Hz, NC<u>H</u>), 1.98–1.93 (3H, m, 3 × C<u>H</u>(Ad)), 1.71–1.53 (9H, m, 6 × C<u>H</u>$_x$H$_y$ (Ad), 3 × CH$_x$<u>H</u>$_y$(Ad)), 1.44–1.37 (3H, m, 3 × CH$_x$<u>H</u>$_y$(Ad)), 1.34 (1H, br s, O<u>H</u>); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 120.9 (CH), 107.8 (CH), 72.6 (CH), 60.6 (CH_2), 39.5 (CH_2), 36.7 (CH_2),

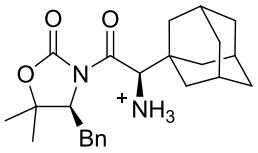
36.2 (C), 28.3 (CH); **HRMS** (+ESI): m/z calcd. for $C_{16}H_{24}NO$ $[M+H]^+$: 246.1852, found: 246.1850.

Final route



3vn **49** **48**

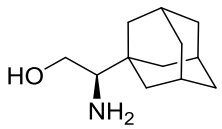
(*S*)-*N*-[(*R*)-2-(1-adamantanyl)-2-amoniumacetyl]-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (**49**)



49

Ozone was bubbled through a solution of **3vn** (179 mg, 0.4 mmol) in methanol (18 mL) and DCM (9 mL) at −78 °C for 50 min. Nitrogen was then bubbled through the mixture at −78 °C for 15 min and then a solution of thiourea (64 mg, 0.8 mmol) in methanol (3 mL) was added via cannula. The resultant mixture was stirred at −78 °C for 15 min, allowed to warm to rt and stirred for 45 min. Then, the mixture was filtered through a short pad of Celite® and concentrated under reduced pressure. The residue was redissolved in methanol (6 mL) and 4 M HCl in dioxane (5.5 mL, 32 mmol) was added. The mixture was stirred at rt for 16 h and concentrated under reduced pressure (2 M NaOH trap!). The residue was partitioned between EtOAc and H_2O (10 mL each). The aqueous layer was extracted with further EtOAc (10 mL). The combined organic extracts were washed with brine and dried with anhydrous $MgSO_4$ and the volatiles evaporated. The resultant amine **49** was used in the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (3H, br s, NH_3), 7.50–7.12 (5H, m, ArH), 5.17 (1H, s, COCH), 4.84 (1H, d, J = 9.4 Hz, NCH), 3.20 (1H, d, J = 14.1 Hz, CH_xH_yPh), 2.93–2.87 (1H, m, CH_xH_yPh), 2.14–1.86 (6H, m, Ad), 1.68 (9H, s, Ad), 1.45 (3H, s, CCH_3), 1.31 (3H, s, CCH_3).

(R)-2-Adamantyl-2-aminoetanol (**48**)



48

A 2 M solution of $LiBH_4$ in THF (600 µL, 1.2 mmol) was added to a solution of non-pure **49** (247 mg, ≈0.5 mmol) in THF (3.2 mL) and H_2O (0.8 mL) at 0 °C and the resultant mixture was stirred

for 45 min at rt. The reaction mixture was quenched with MeOH (500 uL) and partitioned between DCM and H_2O (10 mL each). The aqueous layer was extracted with further DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the volatiles evaporated. Purification of the residue by flash column chromatography (from 95:5 to 70:30 DCM/MeOH) afforded **48** (33 mg, 0.17 mmol, 42% yield over two steps) as a white-off solid. **Mp** 94–99 °C; $\mathbf{R_f}$ (9:1 DCM/MeOH) 0.2; $[\alpha]_D^{20}$ −17.2 (c 1.0, $CHCl_3$), [lit.[175] enant. $[\alpha]_D^{20}$ +17.6 (c 1.0, $CHCl_3$)]; **IR** (ATR) ν br 3343, 2901, 2848, 1593, 1449, 1057 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (1H, dd, J = 10.3, 3.9 Hz, C$\underline{H}_x$H$_y$OH), 3.29 (1H, t, J = 10.3 Hz, CH$_x\underline{H}_y$OH), 2.46–2.26 (4H, m, C$\underline{H}$N$\underline{H}_2$, O$\underline{H}$), 2.03–1.95 (3H, m, 3 × C$\underline{H}$(Ad)), 1.76–1.69 (3H, m, 3 × C$\underline{H}_x$H$_y$(Ad)), 1.69–1.59 (3H, m, 3 × CH$_x\underline{H}_y$(Ad)), 1.60–1.49 (6H, m, 3 × C$\underline{H}_2$(Ad)); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 62.2 (CH), 61.0 (CH_2), 38.6 (CH_2), 37.1 (CH_2), 35.1 (C), 28.3 (CH); **HRMS** (+ESI): m/z calcd. for $C_{12}H_{22}NO$ $[M+H]^+$: 196.1696, found: 196.1699.

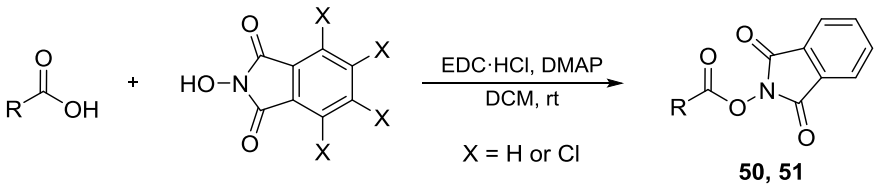
Chapter IV.I

1. Preparation of redox active species

1.1. *N*-Acyloxy phthalimides and *N*-phthalimidoyl oxalates

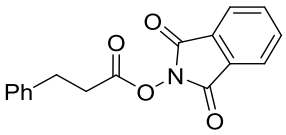
General Procedure 9

N-Acyloxy phthalimides were prepared according to the literature.[155]



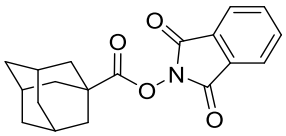
EDC·HCl (2.01 g, 10.5 mmol) was added to a solution of the corresponding carboxylic acid (7.0 mmol), *N*-hydroxyphthalimide (1.71 g, 10.5 mmol) and DMAP (43 mg, 0.35 mmol) in DCM (15 mL) at rt. The mixture was stirred a rt for 16 h. The crude was washed with 1M HCl (10 mL), sat $NaHCO_3$ (10 mL) and brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the corresponding *N*-acyloxy-phthalimide (**50d, 50n, 51d, 51n**).

***N*-(3-Phenylpropanoyloxy)-phthalimide (50d)**



It was prepared following General Procedure 9 from hydrocinnamic acid (1.05 g, 7.0 mmol). Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded **50d** (1.91 g, 6.5 mmol, 92% yield) as a white solid. **Mp** 84–85 °C; **R_f** (80:20 hexanes/EtOAc) 0.4; **IR** (ATR) ν 3134, 2932, 1788, 1705, 1699, 1463, 1453, 1185, 1134 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92–7.87 (2H, m, Phth), 7.83–7.77 (2H, m, Phth), 7.36–7.23 (5H, m, ArH), 3.11 (2H, t, J = 8.2 Hz, CH_2Ph), 2.99 (2H, t, J = 8.2 Hz, $COCH_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.9 (C), 161.9 (C), 139.2 (C), 134.8 (CH), 128.9 (C), 128.7 (CH), 128.3 (CH), 126.7 (CH), 123.9 (CH), 32.7 (CH_2), 30.6 (CH_2).

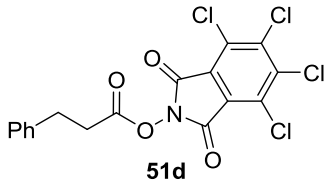
N-(1-Adamantanecarboxyl)-phthalimide (50n)



50n

It was prepared following General Procedure 9 from 1-adamantane carboxylic acid (901 mg, 5.0 mmol), phthalimide (1.22 g, 7.5 mmol), DMAP (30 mg, 0.25 mmol) and EDC·HCl (1.44 g, 7.5 mmol). Purification of the residue by flash column chromatography (90:10 hexanes/EtOAc) afforded **50n** (1.56 g, 4.8 mmol, 96% yield) as a white solid. **Mp** 144–145 °C; $\mathbf{R_f}$ (90:10 hexanes/EtOAc) 0.3; **IR** (ATR) ν 3066, 3050, 2926, 2907, 2849, 1774, 1747, 1590, 1486, 1456, 1204, 1184, 1169, 1009 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92–7.83 (2H, m, Phth), 7.82–7.73 (2H, m, Phth), 2.16–2.08 (9H, m, 3 × C<u>H</u>(Ad), 3 × C<u>H</u>$_2$(Ad)), 1.80–1.77 (6H, m, 3 × C<u>H</u>$_2$(Ad)); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.2 (C), 162.1 (C), 134.6 (CH), 129.1 (C), 123.8 (CH), 40.5 (C), 38.4 (CH_2), 36.2 (CH_2), 27.6 (CH).

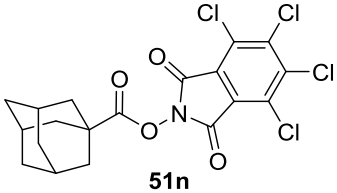
N-(3-Phenylpropanoyloxy)-3,4,5,6-tetrachlorophthalimide (51d)



51d

It was prepared following General Procedure 9 from hydrocinnamic acid (150 mg, 1.0 mmol), 3,4,5,6-tetrachlorophthalimide (451 mg, 1.5 mmol), DMAP (6.0 mg, 0.05 mmol) and EDC·HCl (288 mg, 1.5 mmol). The crude product (399 mg, 0.92 mmol, 92% yield) was used without further purification. **Mp** decomposes at ~180 °C; $\mathbf{R_f}$ (60:40 hexanes/EtOAc) 0.3; **IR** (ATR) ν 3065, 3050, 2899, 2850, 1775, 1716, 1590, 1487, 1197, 1160 cm^{-1}; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.27–7.13 (5H, m, Ar<u>H</u>), 2.90 (2H, t, *J* = 7.7 Hz, C<u>H</u>$_2$Ph), 2.59 (2H, t, *J* = 7.7 Hz, COC<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, CD_3OD) δ 176.8 (C), 161.3 (C), 142.1 (C), 140.5 (C), 130.3 (C), 129.4 (CH), 129.3 (CH), 127.1 (CH), 126.9 (C), 36.7 (CH_2), 32.0 (CH_2).

N-(1-Adamantanecarboxyl)-3,4,5,6-tetrachlorophthalimide phthalimide (51n)



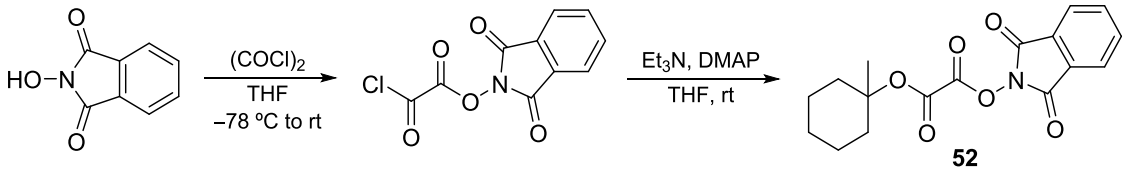
51n

It was prepared following General Procedure 9 from 1-adamantane carboxylic acid (270 mg, 1.0 mmol), 3,4,5,6-tetrachlorophthalimide (541 mg, 1.8 mmol), DMAP (9 mg, 0.075 mmol) and EDC·HCl (431 mg, 2.3 mmol). Purification of the residue by flash column chromatography (95:5

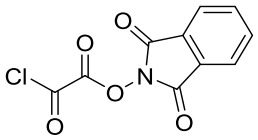
hexanes/EtOAc) afforded **51n** (656 mg, 1.4 mmol, 94% yield) as a white solid. **Mp** 191–198 °C; **R_f** (90:10 hexanes/EtOAc) 0.6; **IR** (ATR) ν 3066, 3050, 2912, 2854, 1780, 1744, 1590, 1487, 1456, 1193, 1167, 1131, 1031, 1003 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.13–2.07 (9H, m, 3 × C<u>H</u>(Ad), 3 × C<u>H$_2$</u>(Ad)), 1.83–1.73 (6H, m, 3 × C<u>H$_2$</u>(Ad)); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.7 (C), 157.8 (C), 140.9 (C), 130.3 (C), 124.8 (C), 40.6 (C), 38.4 (CH_2), 36.1 (CH_2), 27.6 (CH).

1-Methyl-1-cyclohexyl *N*-phthalimidoyl oxalate (52)

It was prepared according to literature.[156]

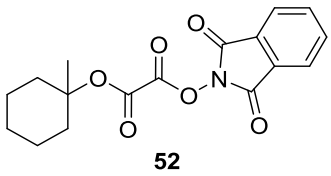


<u>Chloro *N*-phthalimidoyl oxalate</u>



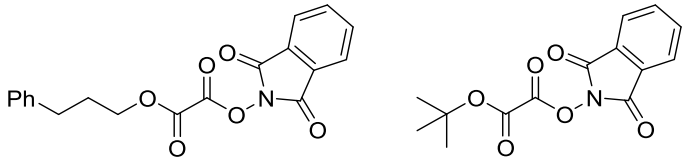
$(COCl)_2$ (400 µL, 4.6 mmol) was added dropwise to a solution of *N*-hydroxyphthalimide (150 mg, 0.92 mmol) in THF (15 mL) at –78 °C. The mixture was stirred at rt for 16 h and the volatiles were removed under reduced pressure ($NaHCO_3$ trap!) to afford the title compound which was used in the next step without further purification.

<u>1-methyl-1-cyclohexyl *N*-phthalimidoyl oxalate</u>



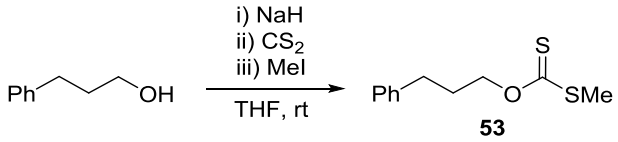
A solution of chloro *N*-phthalimidoyl oxalate (231 mg, 0.91 mmol) in THF (15 mL) was added to a mixture of 1-methylciclohexanol (52 mg, 0.46 mmol), DMAP (6.0 mg, 0.05 mmol) and Et_3N (130 µL, 0.91 mmol) at rt. The mixture was stirred at rt for 1 h. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM (3 mL) and poured into hexanes (75 mL). The mixture was filtered and concentrated under reduced pressure. The product was used without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00–7.89 (2H, m, Phth), 7.89–7.81 (2H, m, Phth), 2.32–2.19 (2H, m, Cy), 1.65 (3H, s, C<u>H$_3$</u>), 1.63–1.51 (7H, m, Cy), 1.37–1.26 (1H, m, Cy).

Unsuccessful substrates



1.2. Thiocarbonyl derivatives

S-methyl *O*-(3-phenylpropyl) carbonodithioate (53)

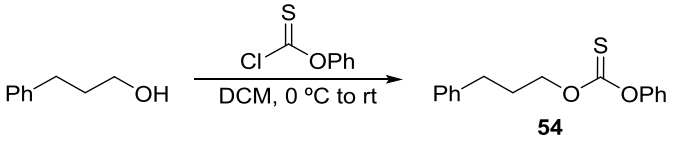


53

It was prepared according to the literature.[176]

3-Phenyl-1-propanol (1.4 mL, 10 mmol) was added to a mixture of NaH 60% dispersion in mineral oil (800 mg, 20 mmol) in THF (40 mL) and stirred for 20 min at rt. Then, carbon disulfide (3.0 mL, 50 mmol) was added and the mixture was stirred for 20 min at rt. Finally, methyl iodide (3.1 mL, 50 mmol) was added and the mixture was stirred for further 20 min at rt. The reaction mixture was quenched with sat NH_4Cl (20 mL) and extracted with DCM (3 × 70 mL). The organic phases combined were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure (H_2O_2 trap!). Purification of the residue by flash column chromatography (95:5 Hexanes/EtOAc) afforded **53** (2.24 g, 9.9 mmol, 99% yield) as a yellow oil. $\mathbf{R_f}$ (95:5 hexanes/EtOAc) 0.4; **IR** (ATR) ν 3024, 2918, 1496, 1453, 1424, 1211, 1171, 1051 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.16 (5H, m, ArH), 4.61 (2H, t, J = 6.4 Hz, CH_2O), 2.79–2.72 (2H, m, CH_2Ph), 2.56 (3H, s, CH_3), 2.18–2.09 (2H, m, CH_2CH_2Ph); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 215.8 (C), 140.8 (C), 128.5 (CH), 128.4 (CH), 126.1 (CH), 73.2 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 18.9 (CH_3).

O-Phenyl *O*-(3-phenylpropyl) carbonothioate (54)



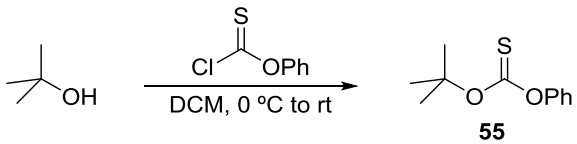
54

It was prepared according to the literature.[177]

Pyridine (240 µL, 3.0 mmol) and chlorothioformate (360 µL, 2.6 mmol) were added to a solution of 3-phenyl-1-propanol (270 µL, 2.0 mmol) in DCM (5 mL) at 0 °C. The mixture was stirred at rt for 16 h and quenched with methanol (100 µL) and stirred for further 15 min. The mixture was diluted with DCM (50 mL) and washed with 1M HCl (30 mL) and brine (30 mL). The organic extract was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash column chromatography (from 99:1 to 95:5 Hexanes/EtOAc) afforded **54** (543 mg, 2.0 mmol, quantitative yield) as a colourless oil. $\mathbf{R_f}$ (95:5 hexanes/EtOAc) 0.2; **IR**

(ATR) ν 3026, 2951, 1590, 1489, 1453, 1388, 1269, 1191, 1018 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48–7.39 (2H, m, Ar<u>H</u>), 7.34–7.27 (3H, m, Ar<u>H</u>), 7.24–7.19 (3H, m, Ar<u>H</u>), 7.15–7.09 (2H, m, Ar<u>H</u>), 4.54 (2H, t, *J* = 6.5 Hz, C<u>H</u>$_2$O), 2.83–2.74 (2H, m, C<u>H</u>$_2$Ph), 2.20–2.12 (2H, m, C<u>H</u>$_2$CH$_2$Ph); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 195.1 (C), 153.4 (C), 140.7 (C), 129.5 (CH), 128.5 (CH), 128.4 (CH), 126.5 (CH), 126.1 (CH), 121.9 (CH), 73.6 (CH_2), 32.0 (CH_2), 29.8 (CH_2).

O-(*tert*-butyl) *O*-Phenyl carbonothioate (55)



55

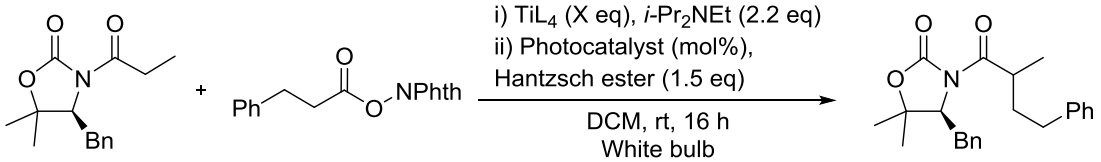
It was prepared according to the literature.[177]

Pyridine (240 µL, 2.0 mmol) and chlorothioformate (290 µL, 2.1 mmol) were added to a solution of *tert*-butanol (190 µL, 2.0 mmol) in DCM (5 mL) at 0 °C. The mixture was stirred at rt for 16 h and quenched with methanol (100 µL) and stirred for further 15 min. The mixture was diluted with DCM (50 mL) and washed with 10% citric acid (30 mL) and brine (30 mL). The organic extract was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash column chromatography (from 80:20 to 70:30 Hexanes/DCM) afforded **55** (81 mg, 0.39 mmol, 19% yield) as a yellow solid. **R_f** (70:30 hexanes/DCM) 0.5; **IR** (ATR) ν 2923, 2854, 1775, 1746, 1591, 1490, 1235, 1180, 1159 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50– 7.09 (5H, m, Ar<u>H</u>), 1.56 (9H, s, C(CH_3)$_3$).

2. Photochemical scission of redox active species

2.1. Screening conditions with 50d

Neat TiL_4 (0.33 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone **1a** (78 mg, 0.30 mmol) in DCM (1.5–15 mL) at 0 °C. After 5 min, *i*-Pr_2NEt (170 µL, 0.99 mmol) was added dropwise and the resultant deep purple mixture was stirred at 0 °C for 40 min. This solution was added via *cannula* to a solution of **50d** (62–275 mg, 0.21–0.93 mmol), Hantzsch ester (114 mg, 0.45 mmol) and the photocatalyst (0.003–0.45 mmol) in DCM (2 mL) at rt. The reaction stirred at rt for 16 h under a 20 W cold fluorescent lightbulb. The reaction mixture was quenched with sat NH_4Cl (3 mL) and filtered through Celite®. The aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The residue was analyzed by ^1H NMR, results are summarized in *Table 46*.



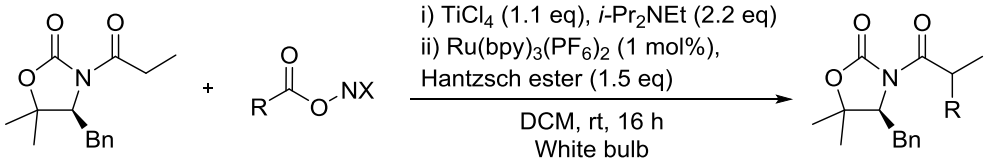
1a **50d** **3ad**

Entry	TiL_4	Conc.	50d	Photocatalyst	^1H NMR
1	$TiCl_4$ (1.1 eq)	0.2 M	0.7 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%	Starting materials recovered. No signals of the product
2	$TiCl_4$ (1.1 eq)	0.2 M	2.1 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%	
3	$TiCl_4$ (1.1 eq)	0.2 M	3.1 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%	
4	$TiCl_3$*i*-PrO (1.1 eq)	0.2 M	1.0 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%	
5	$TiCl_4$ (0.5 eq)	0.2 M	1.5 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%	
6	$TiCl_4$ (1.1 eq)	0.02 M	1.0 eq	$Ru(bpy)_3(PF_6)_2$ 1 mol%	
7	$TiCl_4$ (1.1 eq)	0.2 M	1.5 eq	EOSIN Y 15 mol%	
8	$TiCl_4$ (1.1 eq)	0.2 M	1.5 eq	EOSIN Y 150 mol%	

Table 46. Photochemical activation of **50d**

2.2. Other *N*-acyloxy phthalimides

Neat $TiCl_4$ (36 µL, 0.33 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone **1a** (78 mg, 0.30 mmol) in DCM (1.5 mL) at 0 °C. After 5 min, *i*-Pr_2NEt (180 µL, 1.1 mmol) was added dropwise and the resultant deep purple mixture was stirred at 0 °C for 40 min. This solution was added via *cannula* to a solution of the corresponding *N*-Acyloxyl phthalimide (0.45 mmol), Hantzsch ester (114 mg, 0.45 mmol) and the $Ru(bpy)_3(PF_6)_2$ (2.6 mg, 0.003 mmol) in DCM (2 mL) at rt. The reaction stirred at rt for 16 h under a 20 W cold fluorescent lightbulb. The reaction mixture was quenched with sat NH_4Cl (3 mL) and filtered through Celite®. The aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The residue was analyzed by ^1H NMR, results are summarized in *Table 47*.



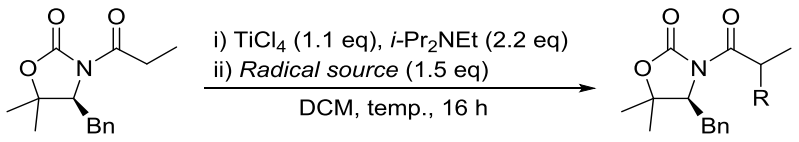
1a **50, 51** **3**

Entry	*N*-Acyloxy phthalimide	R	X	^{1}H NMR
1	**51d**	2-phenylethyl	3,4,5,6-tetrachlorophthalimide	Starting materials recovered. No signals of the product
2	**50n**	1-adamantyl	phthalimide	
3	**51n**	1-adamantyl	3,4,5,6-tetrachlorophthalimide	

Table 47. Photochemical activation of other NHP esters

3. Non-photochemical scission of redox active species

Neat $TiCl_4$ (36 µL, 0.33 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone **1a** (78 mg, 0.30 mmol) and the *additive* (0.45 mmol) in DCM (1.5 mL) at 0 °C. After 5 min, *i*-Pr_2NEt (57 µL, 0.33 mmol) was added dropwise and the resultant deep purple mixture was stirred at 0 °C for 40 min. A solution of the corresponding *radical source* (0.45 mmol) in DCM (1 mL) was added via *cannula* and the reaction stirred at *temperature* for 16. The reaction mixture was quenched with sat NH_4Cl (3 mL) and the aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. The residue was analyzed by ^1H NMR, results are summarized in *Table 48* and *Table 49*.

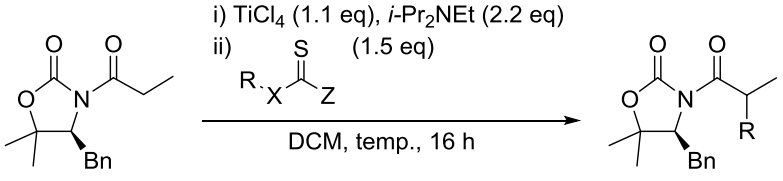


1a **3**

Entry	Radical source	R	Additive	Temp.	^1H NMR
1	**50d**	2-phenylethyl	-	rt	Starting materials recovered. No signals of the product
2[a]	**50d**	2-phenylethyl	-	70 °C	
3	**51d**	2-phenylethyl	-	rt	
4	**52**	1-methylciclohexyl	-	rt	
5	**50d**	2-phenylethyl	$Zn^{(0)}$ 1.5 eq	rt	
6	**50n**	1-adamantyl	$Zn^{(0)}$ 1.5 eq	rt	
7	**50n**	1-adamantyl	$Mn^{(0)}$ 2.5 eq	rt	

[a]in DCE

Table 48. Addition of redox active esters and oxalates to titanium enolates



1a **3**

Entry	Radical source	Z	X	R	T	^1H NMR
1	**53**	SMe	O	3-phenylpropyl	rt	Starting materials recovered. No signals of the product
2[a]	**53**	SMe	O	3-phenylpropyl	70 °C	
3	**54**	OPh	O	3-phenylpropyl	rt	
4	**55**	OPh	O	*tert*-butyl	rt	
5	**56**	Ph	S	benzyl	rt	

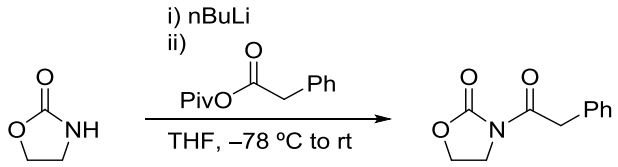
[a]in DCE

Table 49. Addition of thiocarbonyl compounds to titanium enol

Chapter IV.II

1. Preparation of starting materials and standards

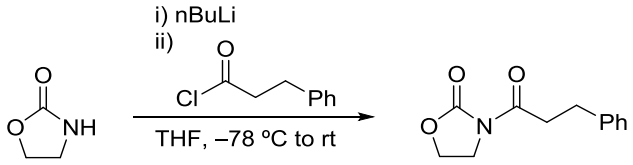
***N*-(2-phenylacetyl)-1,3-oxazolidin-2-one (57)**



57

Et_3N (1.8 mL, 13 mmol) and PivCl (1.6 mL, 13 mmol) were added to a solution of 2-phenylacetic acid (1.77 g, 13 mmol) in THF (65 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 90 min and afterwards it was cooled to −78 °C. Meanwhile, a 2.5 M solution of *n*-BuLi in hexanes (4.4 mL, 11 mmol) was added dropwise to a solution of 1,3-oxazolidinone (871 mg, 10 mmol) in THF (25 mL) at −78 °C and stirred for 15 min. The resulting solution was added to the first mixture via cannula. The reaction mixture was stirred at −78 °C for 20 min and it was allowed to warm to rt and stirred for 2 h. The mixture was quenched with sat NH_4Cl (40 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with sat $NaHCO_3$ (70 mL), brine (70 mL) and dried with anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure. Purification of the crude by flash column chromatography (from 70:30 to 50:50 hexanes/EtOAc) afforded **57** (1.32 g, 6.4 mmol, 64% yield) as a white solid. **Mp** 67–69 °C; $\mathbf{R_f}$ (60:40 hexanes/EtOAc) 0.4; **IR** (ATR) ν 3029, 2922, 1767, 1691, 1385, 1363, 1264, 1219, 1175, 1032, 1015 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35–7.24 (5H, m, Ar<u>H</u>), 4.41–4.35 (2H, m, OC<u>H</u>$_2$), 4.28 (2H, s, COC<u>H</u>$_2$), 4.03–4.99 (2H, m, NC<u>H</u>$_2$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 171.2 (C), 153.4 (C), 133.5 (C), 129.7 (CH), 128.5 (CH), 127.1 (CH), 61.9 (CH_2), 42.6 (CH_2), 41.0 (CH_2); **HRMS** (+ESI): *m/z* calcd. for $C_{11}H_{11}NNaO_3$ $[M+Na]^+$: 228.0631, found: 228.0630; **HPLC-MS** (XTerra® MS C18 3.5 μm, 4.6 × 50 mm column, from 95:5 to 0:100 0.1% formic in water/0.1% formic in ACN, flow rate 1.5 mL/min): Rt 2.92 min , MS (+ESI): $[M+Na]^+$: 228.05.

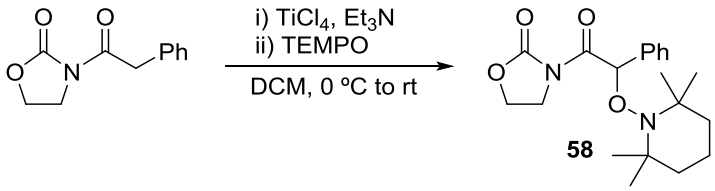
N-(3-phenylpropanonyl)-1,3-oxazolidin-2-one (59)



59

A 2.5 M solution of *n*-BuLi in hexanes (1.3 mL, 3.0 mmol) was added dropwise to a solution of 1,3-oxazolidinone (261 mg, 3.0 mmol) in THF (15 mL) at −78 °C under nitrogen. The solution was stirred for 15 min and 3-phenylpropanoyl chloride (658 mg, 3.0 mmol) was added dropwise. The final mixture was stirred at −78 °C for 20 min, allowed to warm to rt and stirred for 2 h. The reaction mixture was quenched with sat NH_4Cl (10 mL) and concentrated. The residue was partitioned between water and EtOAc (20 mL each). The aqueous layer was extracted with further EtOAc (2 × 20 mL). The combined organic extracts were washed with sat $NaHCO_3$ (50 mL), brine (50 mL), and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Purification of the crude by flash column chromatography (70:30 hexanes/EtOAc) afforded **59** (411 mg, 1.87 mmol, 62% yield) as a white solid. **Mp** 98–101 °C; $\mathbf{R_f}$ (60:40 hexanes/EtOAc) 0.4; **IR** (ATR) ν 3027, 2919, 1778, 1694, 1389, 1315, 1225, 1120, 1042 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31–7.17 (5H, m, ArH), 4.37 (2H, t, *J* = 8.1 Hz, OCH_2), 3.99 (2H, t, *J* = 8.1 Hz, NCH_2), 3.25 (2H, t, *J* = 7.7 Hz, $COCH_2$), 2.99 (2H, t, *J* = 7.7 Hz, CH_2Ph); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 172.5 (C), 153.4 (C), 140.4 (C), 128.5 (CH), 128.4 (CH), 126.2 (CH), 62.0 (CH_2), 42.4 (CH_2), 36.7 (CH_2), 30.2 (CH_2); **HRMS** (+ESI): *m/z* calcd. for $C_{12}H_{13}NNaO_3$ $[M+Na]^+$: 242.0788, found: 242.0789.

N-(2-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetyl)-1,3-oxazolidin-2-one (58)



58

Neat $TiCl_4$ (36 µL, 0.33 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone **57** (62 mg, 0.30 mmol) in DCM (1.5 mL) at 0 °C. After 5 min, Et_3N (46 µL, 0.33 mmol) was added dropwise and the resultant deep purple mixture was stirred at 0 °C for 40 min. A solution of TEMPO (94 mg, 0.6 mmol) in DCM (0.5 mL) was added via *cannula*. The reaction was stirred for 2 h while allowed to warm to rt. Then, it was quenched with sat NH_4Cl (2 mL). The layers were separated and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. Purification of the crude by flash column chromatography (80:20 hexanes/EtOAc) afforded **58** (108 mg, 0.3 mmol,

quantitative yield) as a white solid. **Mp** 42–46 °C; **R_f** (80:20 hexanes/EtOAc) 0.2; **IR** (ATR) ν 2971, 2930, 1775, 1703, 1385, 1361, 1218, 1182, 1108, 1041 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60–7.53 (2H, m, ArH), 7.34–7.25 (3H, m, ArH), 6.63 (1H, s, COCH), 4.42–4.37 (1H, m, OCH_xH_y), 4.32–4.27 (1H, m, OCH_xH_y), 4.04 (1H, ddd, *J* = 11.0, 9.5, 7.6 Hz, NCH_xH_y), 3.86 (1H, ddd, *J* = 11.0, 9.3, 6.0 Hz, NCH_xH_y), 1.68–1.24 (6H, m, 3 × CH_2), 1.22 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.02 (3H, s, CH_3), 0.67 (3H, s, CH_3); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ 172.4 (C), 153.0 (C), 137.8 (C), 128.2 (CH), 128.1 (CH), 128.1 (CH), 85.2 (CH), 62.0 (CH_2), 59.8 (C), 59.4 (C), 42.4 (CH_2), 40.0 (CH_2), 39.9 (CH_2), 33.7 (CH_3), 32.8 (CH_3), 20.0 (CH_3), 20.0 (CH_3), 17.0 (CH_2); **HRMS** (+ESI): *m/z* calcd. for $C_{20}H_{29}N_2O_4$ $[M+H]^+$: 361.2122, found: 361.2123; **HPLC-MS** (XTerra® MS C18 3.5 µm, 4.6 × 50 mm column, from 95:5 to 0:100 0.1% formic in water/0.1% formic in ACN, flow rate 1.5 mL/min): Rt 4.58 min, MS (+ESI): $[M+H]^+$: 361.28.

2. HPLC-MS Calibration

A 0.01 M solution of starting material **57** and a 0.01 M solution of aminoxylated product **58** were mixed in different proportions and analyzed by HPLC-MS. Proportions of the integrations for each compound were used to calculate the following calibration line.

Mixture	µl 57	µl 58	Abs 57	Abs 58	mmol 57/ mmol 58	Int 57/ Int 58
A	900	100	67.92	27.43	9	2.48
B	500	500	30.44	69.56	1	0.44
C	100	900	9.87	90.13	0.1	0.11

Table 50. Calibration data

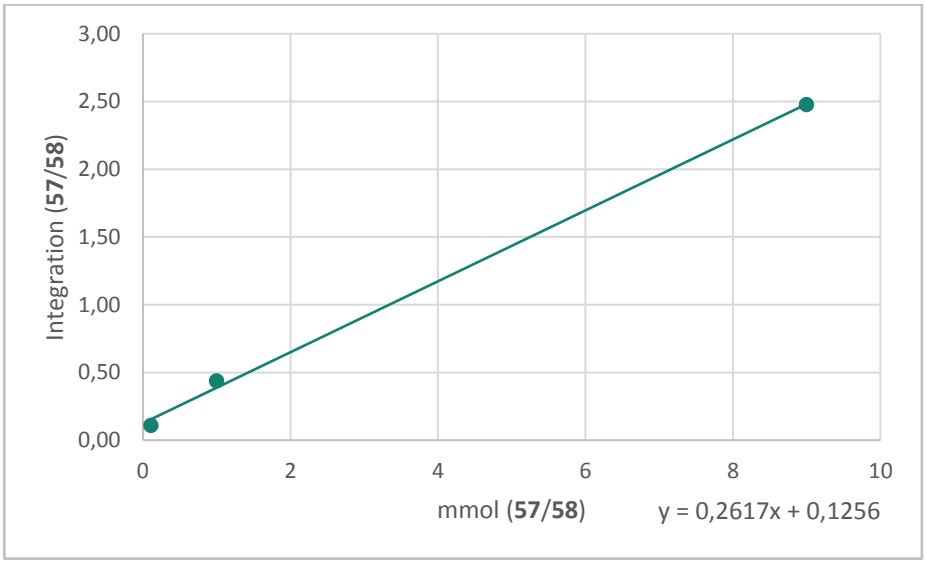


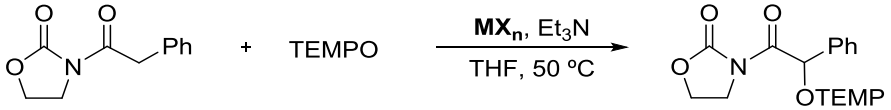
Figure 32. Calibration Line

3. Optimization

All HPLC-MS results obtained during the optimization of the aminoxylation reaction were treated with the previously described calibration line.

3.1. Screening of metals and salts

A microwave vial charged with metal complex (0.05 mmol, 50 mol%), oxazolidinone **57** (20 mg, 0.10 mmol) and TEMPO (31 mg, 0.20 mmol). Then, a 0.2 M solution of NEt_3 in THF (0.5 mL, 0.10 mmol) was added and the mixture was stirred at 50 °C for 16 h. The crude mixture was analyzed by ^1H NMR and HPLC-MS, results are summarized in *Table 51*.



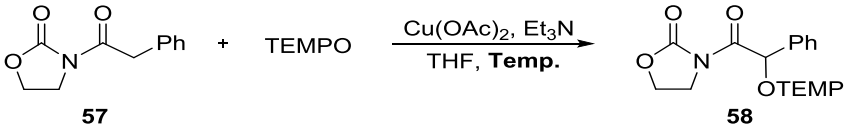
57 **58**

Entry	M	MX_n	Solubility	Conversion (HPLC-MS)
1	Cu^{II}	$Cu(OAc)_2$	✓	41%
2		$CuCl_2$	×	-
3		$CuBr_2$	✓	-
4		$Cu(acac)_2$	×	<10%
5	Cu^{I}	CuOAc	×	35%
6		CuCl	×	-
7		CuBr	~	-
8		CuOTf[a]	✓	-
9	Co^{II}	$CoCl_2$	~	-
10		$Co(OAc)_2$	×	-
11	Fe^{II}	$Fe(OAc)_2$	×	-
12	Fe^{III}	$FeCl_3$	×	-
13		$Fe(acac)_3$	✓	-

Table 51. Screening of metal salts and complexes

3.2. Screening of temperature

A microwave vial charged with $Cu(OAc)_2$ (9.0 mg, 0.05 mmol, 50 mol%), oxazolidinone **57** (20 mg, 0.10 mmol) and TEMPO (31 mg, 0.20 mmol). Then, a 0.2 M solution of NEt_3 in THF (0.5 mL, 0.10 mmol) was added and the mixture was stirred at *temperature* for 16 h. The crude mixture was analyzed by HPLC-MS, results are summarized in *Table 52*.



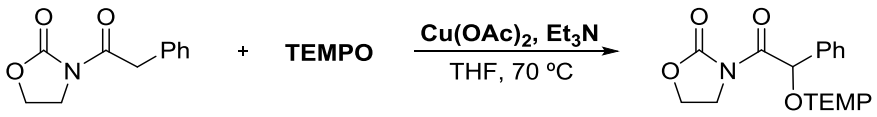
57 **58**

Entry	Temperature	Conversion (HPLC-MS)
1	70 °C	>90%
2	50 °C	41%
3	rt	<10%
4	0 °C	<10%

Table 52. Temperature screening

3.3. Blanks

A microwave vial charged with $Cu(OAc)_2$ (0–9.0 mg, 0–0.05 mmol, 0–50 mol%), oxazolidinone **57** (20 mg, 0.10 mmol) and TEMPO (16–47 mg, 0.10–0.30 mmol). Then, NEt_3 (0–28 µL, 0–0.20 mmol) and THF (0.5 mL) were added and the mixture was stirred at 70 °C for 16 h. The crude mixture was analyzed by HPLC-MS, results are summarized in *Table 53*.



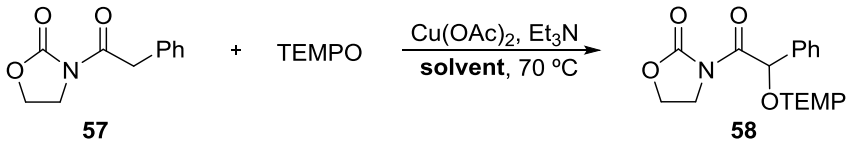
57 **58**

Entry	Item	$Cu(OAc)_2$	Et_3N	TEMPO	Conversion (HPLC-MS)
1		×			<10%
2	$Cu(OAc)_2$	10%	1.0 eq	2.0 eq	23%
3		50%			>90%
4				1.0 eq	24%
5	TEMPO	10%	1.0 eq	2.0 eq	23%
6				3.0 eq	25%
7	TEMPO	50%	1.0 eq	1.0 eq	63%
8				2.0 eq	>90%
9			-		<10%
10	Et_3N	10%	1.0 eq	2.0 eq	23%
11			2.0 eq		27%

Table 53. Blank experiments

3.4. Screening of solvents

A microwave vial charged with $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 10 mol%), oxazolidinone **57** (20 mg, 0.10 mmol) and TEMPO (31–47 mg, 0.20–0.30 mmol). Then, NEt_3 (14 µL, 0.10 mmol) and *solvent* (0.5 mL) were added and the mixture was stirred at 70 °C for 16 h. The crude mixture was analyzed by HPLC-MS, results are summarized in *Table 54*.



57 **58**

Entry	Solvent	Conversion (HPLC-MS)
1	THF	23%
2	ACN	57%
3	DCE	25%
4	DMF	35%
5	DMSO	39%
6	EtOAc	41%
7	IPA	<10%
8[a]	ACN	>90%

[a]3.0 eq of TEMPO were used.

Table 54. Solvent screening

3.5. Reassessment of other salts in acetonitrile

A microwave vial charged with metal complex (50 mol%), oxazolidinone **57** (20 mg, 0.10 mmol) and TEMPO (31 mg, 0.20 mmol). Then, a 0.2 M solution of NEt_3 in ACN (0.5 mL, 0.10 mmol) was added and the mixture was stirred at 70 °C for 16 h. The crude mixture was analyzed by HPLC-MS, results are summarized in *Table 55*.

57 **58**

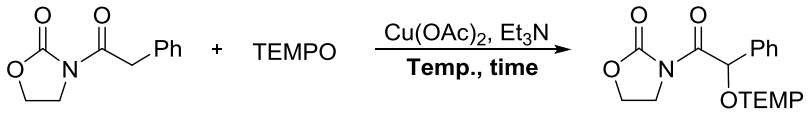
Entry	M	MX_n	Soluble	Conversion (HPLC-MS)	in THF
1	Cu^{II}	$CuCl_2$	~	14%	-
2		$Cu(acac)_2$	✓	83%	<10%
3	Co^{II}	$Co(OAc)_2$	×	<10%	-

Table 55. Reassessment of other compounds in acetonitrile

3.6. Reassasment of temperature and time

A microwave vial charged with $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 10 mol%), oxazolidinone **57** (20 mg, 0.10 mmol) and TEMPO (47 mg, 0.30 mmol). Then, a 0.2 M solution of NEt_3 in ACN (0.5

mL, 0.1 mmol) was added and the mixture was stirred at *temperature* for *time*. The crude mixture was analyzed by HPLC-MS, results are summarized in *Table 56*.



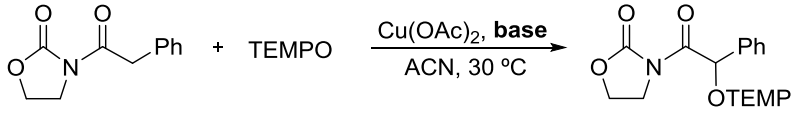
57 58

Entry	T	time	Conversion (HPLC-MS)
1	70 °C	16 h	>90%
2	50 °C	16 h	>90%
3	40 °C	16 h	>90%
4	30 °C	16 h	83%
5	rt	16 h	29%
6	rt	72 h	82%

Table 56. Reassessment of temperature and time

3.7. Screening of bases

A microwave vial charged with $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 10 mol%), oxazolidinone **57** (20 mg, 0.10 mmol) and TEMPO (47 mg, 0.30 mmol). Then, *the base* (0.10 mmol) and ACN (0.5 mL) were added and the mixture was stirred at 30 °C for 16 h. The crude mixture was analyzed by HPLC-MS, results are summarized in *Table 57*.



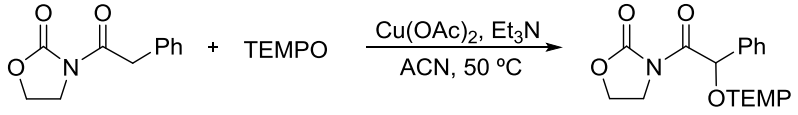
57 58

Entry	base	Conversion (HPLC-MS)
1	Et_3N	83%
2	*i*-Pr_2NEt	18%
3	2,6-lutidine	<10%

Table 57. Base screening

3.8. Scale-up

_N_-(2-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetyl)-1,3-oxazolidin-2-one (58)



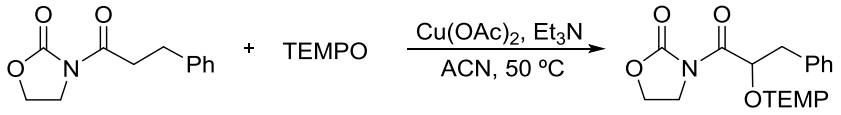
57 58

A microwave vial charged with $Cu(OAc)_2$ (5.4 mg, 0.03 mmol, 10 mol%), oxazolidinone **57** (62 mg, 0.30 mmol) and TEMPO (140 mg, 0.90 mmol). Then, a 0.2 M solution of NEt_3 in ACN (1.65 mL, 0.33 mmol) was added and the mixture was stirred at 50 °C for 16 h. The crude mixture was

quenched with sat NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted with DCM (2 × 5 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the solvent evaporated. Purification of the crude by flash column chromatography (80:20 hexanes/EtOAc) afforded **58** (96 mg, 0.27 mmol, 89% yield) as a white solid. Spectroscopic data matches the product obtained in page 195.

3.9. Another *N*-acyl oxazolidinone

_N_-(2-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetyl)-1,3-oxazolidin-2-one (60)

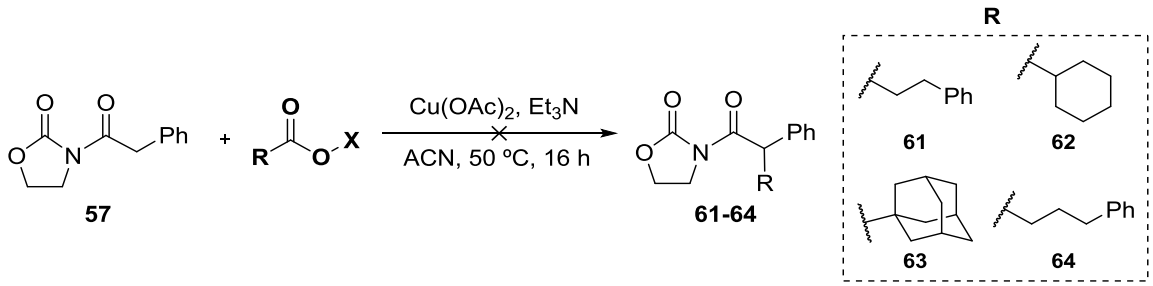


59 **60**

A microwave vial charged with $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 10 mol%), oxazolidinone **59** (22 mg, 0.10 mmol) and TEMPO (47 mg, 0.30 mmol). Then, a 0.2 M solution of NEt_3 in ACN (0.5 mL, 0.10 mmol) was added and the mixture was stirred at 50 °C for 16 h. The crude mixture was analyzed by HPLC-MS and no product was detected.

4. Other radical sources

A microwave vial charged with $Cu(OAc)_2$ (9.0 mg, 0.05 mmol, 50 mol%), oxazolidinone **57** (20 mg, 0.10 mmol) and *the radical source* (0.15 mmol). Then, a 0.2 M solution of NEt_3 in ACN (0.5 mL, 0.10 mmol) was added and the mixture was stirred at 50 °C for 16 h. The crude mixture was analyzed by HPLC-MS, results are summarized in *Table 58*.



Entry	Radical source	RCOOX	R	X	Product	HPLC-MS
1	peroxide	**2d**	2-phenylethyl	OCOR	**61**	Product was not detected
2	perester	**40j**	ciclohexyl	O^{t}Bu	**62**	
3		**40n**	adamantyl		**63**	
4	NHP ester	**50d**	2-phenylethyl	NPhth	**61**	
5	NHP ester (Cl_4)	**51d**	2-phenylethyl	NPhth(Cl_4)	**61**	
6		**51n**	adamantyl		**63**	
7	thiocarbonate	**54**	3-phenylpropyl	different structure	**64**	

Table 58. Screening of other radical sources

ACRONYMS AND ABBREVIATIONS

acac	acetylacetonate
ACN	Acetonitrile
AIBN	Azobisisobutyronitrile
BDE	Bond dissociation energy
BINOL	1,1'-Bi-2-naphtol
BIPHEP	2,2'-Bis(diphenylphosphino)biphenyl
BNAH	1-Benzyl-1,4-dihydronicotinamide
Boc	*tert*-Butyloxycarbonyl
BPO	Benzoyl peroxide
Bpy	2,2'-bipyridine
CAN	Cerium ammonium nitrate
cat	catalyst or catalytic amount
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
DIC	*N,N*-Diisopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dr	diastereomeric ratio
EDA	Electron donor-acceptor
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EPR	Electron paramagnetic resonance
eq	equivalent
ESI	Electrospray ionization
glyme	1,2-dimethoxyethane
h	hour(s)
HG-II	Hoveyda-Grubbs catalyst 2nd generation
HKR	Hydrolytic kinetic resolution
HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HPLC-MS	High-performance liquid chromatography – Mass spectrometry
HWE	Horner-Wadsworth-Emmons
IPA	Isopropanol
IR	Infrared
LDA	Lithium diisopropyl amide
LPO	Lauroyl peroxide
min	minute(s)
Mp	Melting point
NHP	*N*-hydroxyphtalimide
NMR	Nuclear magnetic ressonance
PC	Photocatalyst
Piv	Pivaloyl
PTC	Phase-transfer catalyst
RAFT	Reversible addition-fragmentation chain transfer
RCM	Ring-closing-metathesis
R_f	Retention factor
RSE	Radical stabilization energy
rt	room temperature
sat	saturated
SET	Single electron transfer
SOMO	Single occupied molecular orbital
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TCE	1,1,2,2-tetrachloroethane

TEMPO	2,2,6,6-Tetramethylpiperidine-1-yloxyl
TES	Triethylsilyl
TfO	Triflate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TM	Transition metal
TMPO	2,2,6,6-Tetramethylpiperidine-1-yloxyl
UV	Ultraviolet

BIBLIOGRAPHY

(1) *Award ceremony speech*. NobelPrize.org. https://www.nobelprize.org/prizes/chemistry/1965/ceremony-speech/ (accessed 2021-12-28).

(2) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.* **2000**, *39*, 44–122.

(3) Maier, M. E. *Org. Biomol. Chem.* **2015**, *13*, 5302–5343.

(4) Gomberg, M. *J. Am. Chem. Soc.* **1990**, *22*, 757–771.

(5) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1976**, *9*, 13–19.

(6) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press, **1986**; Vol. Volume 5.

(7) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.

(8) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*, 1st Edition.; Academic Press, **1992**.

(9) Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 12692–12714.

(10) Romero, K. J.; Galliher, M. S.; Pratt, D. A.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2018**, *47*, 7851–7866.

(11) Kerk, G. J. M. van der; Noltes, J. G.; Luijten, J. G. A. *J. App. Chem.* **1957**, *7*, 356–365.

(12) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Transactions 1* **1975**, No. 16, 1574–1585.

(13) Crespi, S.; Fagnoni, M. *Chem. Rev.* **2020**, *120*, 9790–9833.

(14) Baguley, P. A.; Walton, J. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3072–3082.

(15) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, No. 17, 939–941.

(16) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402.

(17) Nicewicz, D. A.; MacMillan, D. W. C. *Science,* **2008**, *332*, 77–80.

(18) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604–14605.

(19) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757.

(20) Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2016**, *55*, 58–102.

(21) Leifert, D.; Studer, A. *Angew. Chem. Int. Ed.* **2020**, *59*, 74–108.

(22) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163–171.

(23) Proctor, R. S. J.; Colgan, A. C.; Phipps, R. J. *Nat. Chem.* **2020**, *12*.

(24) Fu, G. C. *ACS Cent. Sci.* **2017**, *3*, 692–700.

(25) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.

(26) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446–447.

(27) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Kvaerno, L., Ed.; Wiley-VCH: Weinheim; Germany, **2009**.

(28) Kohler, M. C.; Wengryniuk, S. E.; Coltart, D. M. Asymmetric A-Alktlation of Aldehydes, Ketones, and Carboxylic Acids. In *Stereoselective Synthesis of Drugs and Natural Products, Vol. 2*; Andrushko, V., Andrushko, N., Eds.; John Wiley & Sons, **2013**; p 183.

(29) Wright, T. B.; Evans, P. A. *Chem. Rev.* **2021**, *121*, 9196–9242.

(30) Cano, R.; Zakarian, A.; Mcglacken, G. P. *Angew. Chem. Int. Ed.* **2017**, *56*, 9278–9290.

(31) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233–4236.

(32) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137–3139.

(33) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(34) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

(35) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603–5606.

(36) Larcheveque, M.; Ignatova, E.; Cuvigny, T. *J. Organomet. Chem.* **1979**, *177*, 5–15.

(37) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362.

(38) Enders, D.; Eichenauer, H. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 549–551.

(39) Lim, D.; Coltart, D. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 5207–5210.

(40) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2011**, *133*, 11936–11939.

(41) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

(42) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847.

(43) Trost, B. M.; Michaelis, D. J.; Charpentier, J.; Xu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 204–208.

(44) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

(45) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

(46) Maruoka, K. *Prod. Jpn. Acad. Ser. B, Phys. Biol. Sci.* **2019**, *95*, 1–16.

(47) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266.

(48) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.

(49) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520.

(50) Gualandi, A.; Mengozzi, L.; Cozzi, P. G. *Synthesis (Stuttg)* **2017**, *49*, 3433–3443.

(51) Evans, D. A.; Urpi, F.; Somers, T. C.; Stephen Clark, J.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.

(52) Shim, E.; Zakarian, A. *Synlett* **2020**, *31*, 683–686.

(53) Kennington, S. C. D.; Ferré, M.; Romo, J. M.; Romea, P.; Urpí, F.; Font-Bardia, M. *J. Org. Chem.* **2017**, *82*, 6426–6433.

(54) Kennington, S. C. D.; Taylor, A. J.; Romea, P.; Urpí, F.; Aullón, G.; Font-Bardia, M.; Ferré, L.; Rodrigalvarez, J. *Org. Lett.* **2019**, *21*, 305–309.

(55) Vesely, J.; Rios, R. *ChemCatChem* **2012**, *4*, 942–953.

(56) Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 1313–1316.

(57) Sibi, M. P.; Ji, J. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 190–192.

(58) Bennett, C. H.; Brassard, G.; Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; C MacMillan, D. W. *Science* **2007**, *316*, 582–585.

(59) Mastracchio, A.; Warkentin, A. A.; Walji, A. M.; Macmillan, D. W. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *2010*, 5–8.

(60) Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L. A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100–103.

(61) Lauberteaux, J.; Pichon, D.; Baslé, O.; Mauduit, M.; Marcia de Figueiredo, R.; Campagne, J. M. *ChemCatChem* **2019**, *11*, 5705–5722.

(62) Melchiorre, P.; Spinnato, D.; Schweitzer-Chaput, B.; Goti, G.; Ošeka, M. *Angew. Chem. Int. Ed.* **2020**, 2–8.

(63) Arceo, E.; Jurberg, I. D.; Álvarez-Fernández, A.; Melchiorre, P. *Nat. Chem.* **2013**, *5*, 750–756.

(64) Arceo, E.; Bahamonde, A.; Bergonzini, G.; Melchiorre, P. *Chem. Sci.* **2014**, *5*, 2438–2442.

(65) Silvi, M.; Arceo, E.; Jurberg, I. D.; Cassani, C.; Melchiorre, P. *J. Am. Chem. Soc.* **2015**, *137*, 6120–6123.

(66) Braun, M. *Modern Enolate Chemistry: From Preparation to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, **2015**.

(67) Ciez, D.; Pałasz, A.; Trzewik, B. *Eur. J. Org. Chem.* **2016**, *2016*, 1476–1493.

(68) Lehnert, W. *Tetrahedron Lett.* **1970**, *54*, 4723–4724.

(69) Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4135–4138.

(70) Moreira, I. D. P. R.; Bofill, J. M.; Anglada, J. M.; Solsona, J. G.; Nebot, J.; Romea, P.; Urpî, F. *J. Am. Chem. Soc.* **2008**, *130*, 3242–3243.

(71) Heras, C.; Gómez-Palomino, A.; Romea, P.; Urpí, F.; Bofill, J. M.; Moreira, I. D. P. R. *J. Org. Chem.* **2017**, *82*, 8909–8916.

(72) Beaumont, S.; Ilardi, E. A.; Monroe, L. R.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 1482–1483.

(73) Gu, Z.; Herrmann, A. T.; Zakarian, A. *Angew. Chem. In. Ed.* **2011**, *50*, 7136–7139.

(74) Mabe, P. J.; Zakarian, A. *Org. Lett.* **2014**, *16*, 516–519.

(75) Gómez-Palomino, A.; Pellicena, M.; Romo, J. M.; Solà, R.; Romea, P.; Urpí, F.; Font-Bardia, M. *Chem. Eur. J.* **2014**, *20*, 10153–10159.

(76) Kennington, S. C. D.; Gómez-Palomino, A.; Salomó, E.; Romea, P.; Urpí, F.; Font-Bardia, M. *Org. Biomol. Chem.* **2018**, *16*, 4807–4815.

(77) Gómez-Palomino, A.; Romea, P.; Urpí, F. *Synthesis (Germany)* **2018**, *50*, 2721–2726.

(78) Palomino, A. G. Titanium(IV) Enolate Chemistry Applied to the Stereoselective Construction of C–C and C–O Bonds. New Ionic and Radical Processes., Universitat de Barcelona, **2018**.

(79) Davies, S. G.; Sanganee, H. J. *Tetrahedron: Asymmetry* **1995**, *6*, 671–674.

(80) Li, Y.; Ge, L.; Muhammad, M. T.; Bao, H. *Synthesis (Stuttg)* **2017**, *49*, 5263–5284.

(81) Liu, H.; Yu, J. T.; Pan, C. *Chem. Comm.* **2021**, *57*, 6707–6724.

(82) Spantulescu, M. D.; Jain, R. P.; Derksen, D. J.; Vederas, J. C. *Org. Lett.* **2003**, *5*, 2963–2965.

(83) Pan, C.; Fu, Y.; Ni, Q.; Yu, J. T. *J. Org. Chem.* **2017**, *82*, 5005–5010.

(84) Li, Y.; Han, Y.; Xiong, H.; Zhu, N.; Qian, B.; Ye, C.; Kantchev, E. A. B.; Bao, H. *Org. Lett.* **2016**, *18*, 392–395.

(85) Ye, C.; Li, Y.; Bao, H. *Adv. Synth. Catal.* **2017**, 2–7.

(86) Babu, K. R.; Zhu, N.; Bao, H. *Org. Lett.* **2017**, *19*, 46–49.

(87) Jian, W.; Ge, L.; Jiao, Y.; Qian, B.; Bao, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 3650–3654.

(88) Qian, B.; Chen, S.; Wang, T.; Zhang, X.; Bao, H. *J. Am. Chem. Soc.* **2017**, jacs.7b06590.

(89) Ge, L.; Li, Y.; Jian, W.; Bao, H. *Chem. Eur. J.* **2017**, *23*, 11767–11770.

(90) Šakić, D.; Zipse, H. *Adv. Synth. Catal.* **2016**, *358*, 3983–3991.

(91) del Olmo Garcia, M. Studies on Stereoselective Radical Reactions from Titanium(IV) Enolates. Master Thesis, Universitat de Barcelona, **2019**.

(92) Fernandes, R. A.; Ingle, A. B. *Curr. Med. Chem.* **2013**, *20*, 2315–2329.

(93) Kishimoto, K.; Nakai, H. *Chem. Abstr.* **1997**, *126*, 74487; Japan Patent 7-98328, 1995.

(94) Gualandi, A.; Emer, E.; Capdevila, M. G.; Cozzi, P. G. *Angew. Chem. Int. Ed.* **2011**, *50*, 7842–7846.

(95) Afewerki, S.; Ibrahem, I.; Rydfjord, J.; Breistein, P.; Cõrdova, A. *Chem. Eur. J.* **2012**, *18*, 2972–2977.

(96) Pérez, M.; Fañanás-Mastral, M.; Hornillos, V.; Rudolph, A.; Bos, P. H.; Harutyunyan, S. R.; Feringa, B. L. *Chem. Eur. J.* **2012**, *18*, 11880–11883.

(97) Pelotier, B.; Holmes, T.; Piva, O. *Tetrahedron Asymmetry* **2005**, *16*, 1513–1520.

(98) Hasegawa, T.; Kawanaka, Y.; Kasamatsu, E.; Ohta, C.; Nakabayashi, K.; Okamoto, M.; Hamano, M.; Takahashi, K.; Ohuchida, S.; Hamada, Y. *Org. Process Res. Dev.* **2005**, *9*, 774–781.

(99) Goswami, D.; Chattopadhyay, A. *Lett. Org. Chem.* **2007**, *3*, 922–925.

(100) Fernandes, R. A.; Ingle, A. B.; Chaudhari, D. A. *Eur. J. Org. Chem.* **2012**, No. 5, 1047–1055.

(101) Bhosale, V. A.; Waghmode, S. B. *Tetrahedron* **2017**, *73*, 2342–2348.

(102) Xu, S.; Lee, C. T.; Wang, G.; Negishi, E. I. *Chem. Asian J.* **2013**, *8*, 1829–1835.

(103) Kishimoto, K.; Nakai, H. *Chem. Abstr.* **1997**, *126*, 74488; Japan patent 7-102693, 1995.

(104) Hasegawa, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 423–428.

(105) Hasegawa, T.; Yamamoto, H. *Synthesis (Stuttg)* **2003**, No. 8, 1181–1186.

(106) García, J. M.; Odriozola, J. M.; Lecumberri, A.; Razkin, J.; González, A. *Tetrahedron* **2008**, *64*, 10664–10669.

(107) Lu, C.; Zhang, L.; Su, H.; Yang, G.; Chen, Z. *J. Chem. Res.* **2012**, *36*, 678–679.

(108) Hesse, T. Stereoselective Decarboxylative Akylation of N-Acylated Oxazolidinones. Erasmus Project, Universitat de Barcelona, **2019**.

(109) Fleckenstein, S. Total Synthesis of (R)-Arundic Acid by Stereoselective Alkylation of Titanium(IV) Enolates with Peroxides. Erasmus Project, Universitat de Barcelona, **2018**.

(110) Van Puyvelde, L.; Dube, S.; Uwimana, E.; Uwera, C.; Dommisse, R. A.; Esmans, E. L.; Van Schoor, O.; Vlietinck, A. J. *Phytochemistry* **1979**, *18*, 1215–1218.

(111) Davies-Coleman, M. T.; Rivett, D. E. A. *Phytochemistry* **1995**, *38*, 791–792.

(112) Davies-Coleman, M. T.; Rivett, D. E. A. Naturally Occurring 6-Substituted 5,6-Dihydro-α-Pyrones. *Fortschr. Chem. Org. Naturst.* 1989, pp 1–35.

(113) Venkat Ram Reddy, M.; Rearick, J. P.; Hoch, N.; Veeraraghavan Ramachandran, P. *Org. Lett.* **2001**, *3*, 19–20.

(114) Shekhar, V.; Reddy, D. K.; Reddy, S. P.; Prabhakar, P.; Venkateswarlu, Y. *Eur. J. Org. Chem.* **2011**, No. 23, 4460–4464.

(115) Sabitha, G.; Reddy, D. V.; Reddy, S. S. S.; Yadav, J. S.; Kumar, C. G.; Sujitha, P. *RSC Adv.* **2012**, *2*, 7241–7247.

(116) Shekhar, V.; Reddy, D. K.; Venkateswarlu, Y. *Helv. Chim. Acta.* **2012**, *95*, 1593–1599.

(117) Chowdhury, P. S.; Kumar, P. *Eur. J. Org. Chem.* **2013**, No. 21, 4586–4593.

(118) Kumar, T. V.; Reddy, G. V.; Babu, K. S.; Rao, J. M. *Tetrahedron Asymmetry* **2013**, *24*, 594–598.

(119) Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 348–359.

(120) Bach, J.; Blachère, C.; Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Price, P. D.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2001–2010.

(121) Roman, D.; Sauer, M.; Beemelmanns, C. *Synthesis (Germany)* **2021**, *53*, 2713–2739.

(122) Janicki, I.; Kiełbasiński, P. *Adv. Synth. Catal.* **2020**, *362*, 2552–2596.

(123) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.

(124) Larrosa Guerrero, I. Reacciones de C-Glicosidación Estereoselectivas Con Enolatos de Titanio Quirales. Síntesis Del Fragmento C1-C9 de La Salinomicina, Universitat de Barcelona, **2004**.

(125) Balaguer Garcia, E. An Approach to the Total Synthesis of Umuravumbolide, **2021**.

(126) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105–4108.

(127) Olpp, T.; Brückner, R. *Synthesis (Stuttg)* **2004**, *2004*, 2135–2152.

(128) Pihko, P. M.; Salo, T. M. *Tetrahedron Lett.* **2003**, *44*, 4361–4364.

(129) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406–8408.

(130) Yus, M.; Gonza, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595–5698.

(131) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920–7921.

(132) Zhang, X.; Houk, K. N.; Leighton, J. L. *Angew. Chem.* **2005**, *117*, 960–963.

(133) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946–948.

(134) Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 6517–6520.

(135) Suen, L. M.; Steigerwald, M. L.; Leighton, J. L. *Chem. Sci.* **2013**, *4*, 2413–2417.

(136) Kim, I. S.; Ngai, M. Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891–14899.

(137) Han, S. B.; Kim, I. S.; Krische, M. J. *Chem. Comm.* **2009**, No. 47, 7278–7287.

(138) Locklear, M.; Dussault, P. H. *Eur. J. Org. Chem.* **2020**, *2020*, 4814–4840.

(139) Kurose, A.; Ishida, Y.; Hirata, G.; Nishikata, T. *Angew. Chem.* **2021**, *133*, 10714–10719.

(140) Recupero, F.; Bravo, A.; Bjørsvik, H. R.; Fontana, F.; Minisci, F.; Piredda, M. *J. Chem. Soc. Perkin Transactions 2* **1997**, No. 11, 2399–2405.

(141) Aresta, M.; Dibenedetto, A.; Fracchiolla, E.; Giannoccaro, P.; Pastore, C.; Pápai, I.; Schubert, G. *J. Org. Chem.* **2005**, *70*, 6177–6186.

(142) Sanosa i Ferro, N. Stereoselective Decarboxylative Alkylation of Titanium(IV) Enolates with Tert-Butyl Peresters, **2020**.

(143) Agnew-Francis, K. A.; Williams, C. M. *Adv. Synth. Catal.* **2016**, *358*, 675–700.

(144) Wanka, L.; Iqbal, K.; Schreiner, P. R. *Chem. Rev.* **2013**, *113*, 3516–3604.

(145) Lamoureux, G.; Artavia, G. *Curr. Med. Chem.* **2010**, *17*, 2967–2978.

(146) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651.

(147) Wolf, C.; Xu, H. *Chem. Comm.* **2011**, *47*, 3339–3350.

(148) Heravi, M. M.; Zadsirjan, V.; Farajpour, B. *RSC Adv.* **2016**, *6*, 30498–30551.

(149) Reddy, U. V. S.; Chennapuram, M.; Seki, C.; Kwon, E.; Okuyama, Y.; Nakano, H. *Eur. J. Org. Chem.* **2016**, *2016*, 4124–4143.

(150) Ye, C. X.; Melcamu, Y. Y.; Li, H. H.; Cheng, J. T.; Zhang, T. T.; Ruan, Y. P.; Zheng, X.; Lu, X.; Huang, P. Q. *Nat. Commun.* **2018**, *9*, 1–9.

(151) Saito, A.; Yoshioka, S.; Naruto, M.; Saito, S. *Adv. Synth. Catal.* **2020**, *362*, 424–429.

(152) Clariana, J.; García-Granda, S.; Gotor, V.; Gutiérrez-Fernández, A.; Luna, A.; Moreno-Maas, M.; Vallribera, A. *Tetrahedron Asymmetry* **2000**, *11*, 4549–4557.

(153) Okada, K.; Okamoto, K.; Oda, M. *J. Am. Chem. Soc.* **1988**, *110*, 8736–8738.

(154) Schnermann, M. J.; Overman, L. E. *Angew. Chem. Int. Ed.* **2012**, *51*, 9576–9580.

(155) Pratsch, G.; Lackner, G. L.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 6025–6036.

(156) Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345.

(157) Lackner, G. L.; Quasdorf, K. W.; Pratsch, G.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 6012–6024.

(158) Schwarz, J.; König, B. *Green Chem.* **2016**, *18*, 4743–4749.

(159) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C. M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177.

(160) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science.* **2016**, *352*, 801–805.

(161) Toriyama, F.; Cornella, J.; Wimmer, L.; Chen, T. G.; Dixon, D. D.; Creech, G.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 11132–11135.

(162) Wang, J.; Shang, M.; Lundberg, H.; Feu, K. S.; Hecker, S. J.; Qin, T.; Blackmond, D. G.; Baran, P. S. *ACS Catal.* **2018**, *8*, 9537–9542.

(163) Jiang, W. T.; Yang, S.; Xu, M. Y.; Xie, X. Y.; Xiao, B. *Chem. Sci.* **2020**, *11*, 488–493.

(164) Giese, B.; Gonzalez-Gomez, J. A.; Witzel, T. *Angew. Chem. Int. Ed.* **1984**, *23*, 69–70.

(165) McCombie, S. W.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron* **2018**, *74*, 4969–4979.

(166) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559–5562.

(167) Taninokuchi, S.; Yazaki, R.; Ohshima, T. *Org. Lett.* **2017**, *19*, 3187–3190.

(168) Tanaka, T.; Yazaki, R.; Ohshima, T. *J. Am. Chem. Soc.* **2020**, *142*, 4517–4524.

(169) Bull, S. D.; Davies, S. G.; Jones, S.; Polywka, M. E. C.; Shyam Prasad, R.; Sanganee, H. J. *Synlett* **1998**, *1998*, 519–521.

(170) Davies, I. R.; Cheeseman, M.; Green, R.; Mahon, M. F.; Merritt, A.; Bull, S. D. *Org. Lett.* **2009**, *11*, 2896–2899.

(171) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2886–2899.

(172) Peed, J.; Periñán Domínguez, I.; Davies, I. R.; Cheeseman, M.; Taylor, J. E.; Kociok-Köhn, G.; Bull, S. D. *Org. Lett.* **2011**, *13*, 3592–3595.

(173) Davies, S. G.; Hunter, I. A.; Nicholson, R. L.; Roberts, P. M.; Savory, E. D.; Smith, A. D. *Tetrahedron* **2004**, *60*, 7553–7577.

(174) Mukund P, S.; Soeta, T.; Jasperse, C. P. *Org. Lett.* **2009**, *11*, 5366–5369.

(175) Poh, J. S.; Makai, S.; von Keutz, T.; Tran, D. N.; Battilocchio, C.; Pasau, P.; Ley, S. v. *Angew. Chem. Int. Ed.* **2017**, *56*, 1864–1868.

(176) Thorsheim, K.; Manner, S.; Ellervik, U. *Tetrahedron* **2017**, *73*, 6329–6333.

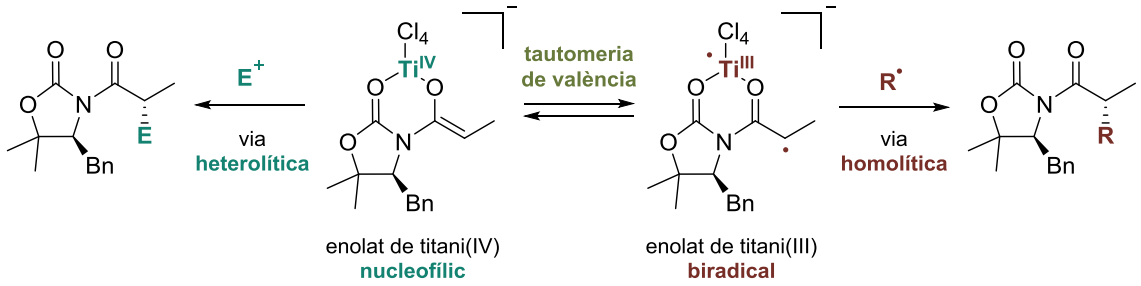
(177) Tormo, J.; Fu, G. C. *Org. Synth.* **2002**, *78*, 239.

RESUM

Històricament s'ha establert que els radicals són espècies que reaccionen de manera caòtica i descontrolada i que, per tant, són poc útils per a formar part en reaccions pràctiques dins la síntesi orgànica. No obstant, els estudis sobre la seva estabilitat i modes de reacció duts a terme a finals del segle passat han permès, avui en dia, l'ús d'aquestes espècies en transformacions importants de manera controlada. Els radicals segueixen patrons de reactivitat diferents als que exhibeixen les molècules neutres o iòniques. Aquest fet els ha posat en el punt de mira durant aquesta última dècada, ja que gràcies a aquests, s'han pogut dur a terme transformacions que eren impossibles usant mètodes heterolítics.

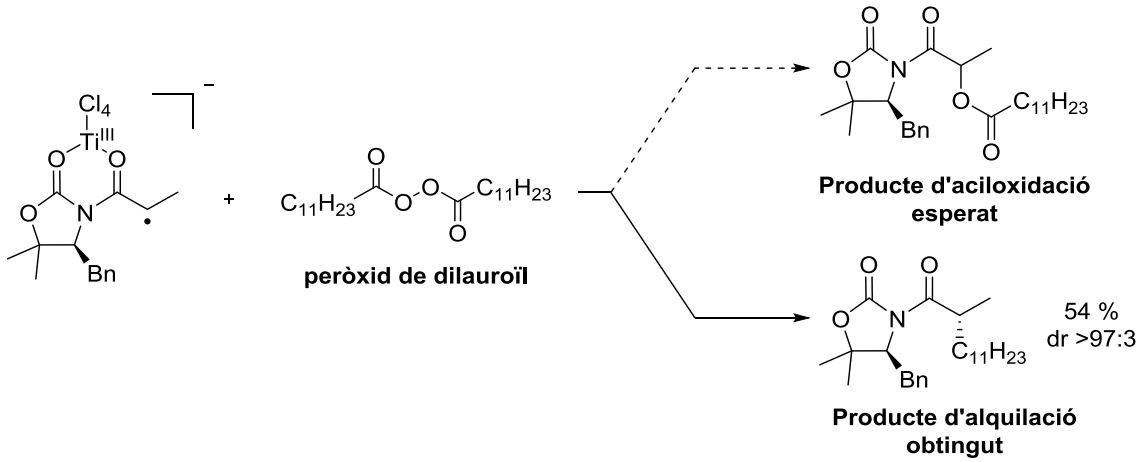
Per exemple, els radicals han demostrat ser una alternativa útil en processos heterolítics de substitució nucleòfila S_N1 i S_N2. Els electròfils adequats per a aquestes reaccions estan molt restringits a uns quants substrats de naturalesa privilegiada, de manera que la substitució nucleòfila no es pot dur a terme de forma general. Més concretament, aquesta limitació es posa de manifest en les alquilacions en α al grup carbonil. La majoria de mètodes descrits per aconseguir aquesta transformació es basen en la formació d'un enolat nucleofílic i la seva posterior alquilació. Normalment l'alquilació té lloc a través d'un procés S_N2, el qual només permet alquilar l'enolat amb halurs d'al·lil, de benzil o d'alquil primaris poc impedits. Altrament, alguns mètodes permeten l'alquilació de l'enolat mitjançant una S_N1 amb espècies limitades a la formació de carbocations prou estables. Tot i que ja s'han descrit alguns exemples en el camp de l'alquilació radicalària, aquests només permeten, majoritàriament, l'α-alquilació de grups carbonil amb halurs d'alquil primaris activats mitjançant la formació d'enamines.

Dins aquest context, la tesi es centra en l'alquilació radicalària d'enolats de titani emprant derivats d'àcids carboxílics com agents alquilants. Tal transformació és possible gràcies a l'equilibri de tautomeria de valència que presenten els enolats de titani (*Esquema 145*). A una de les cares de l'equilibri s'hi troba l'enolat de titani(IV), de caràcter nucleòfil. I a l'altra, després d'un procés de transferència de càrrega del lligand (l'enolat) al titani, s'hi troba l'enolat de titani(III), de caràcter biradical. Aquest últim és el responsable de la reactivitat radicalària que presenten els enolats de titani, i que ha estat demostrada experimentalment en més d'una ocasió.



Esquema 145. Tautomeria de valència dels enolats de titani

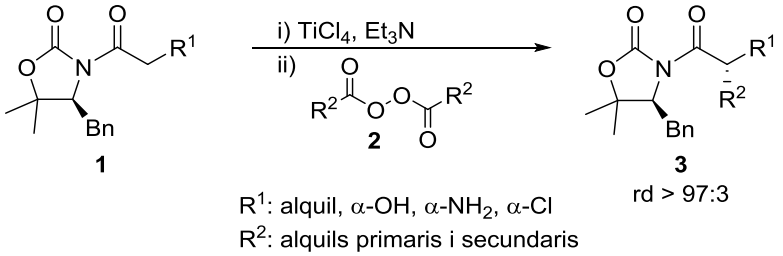
El grup ja havia estudiat l'oxidació radicalària dels enolats de titani derivats *d'N*-acil oxazolidinones quirals amb radicals lliures com el TEMPO o amb molècules paramagnètiques com l'oxigen. Seguidament, es va voler investigar l'addició de peròxids de diacil als enolats de titani, qüestionant si es produiria l'homòlisi de l'enllaç feble O-O per donar lloc al radical aciloxi, de manera que s'esperava un producte d'aciloxidació. No obstant, en els resultats preliminars amb peròxid de dilauroïl es va aïllar el producte d'alquilació resultant de la descarboxilació del radical aciloxi (*Esquema 146*). Tenint en compte la dificultat de dur a terme alquilacions en α al carbonil amb grups alquil poc activats o altament impedits, es va considerar que aquest resultat era molt interessant. Així doncs, va començar l'estudi de l'alquilació d'enolats de titani amb peròxids de diacil. Prèviament a aquesta tesi, ja s'havien optimitzat les condicions de reacció i se n'havia estudiat l'abast de peròxids de diacil, l'alquilació es podia dur a terme amb una diversitat de peròxids amb grups alquil primaris i secundaris tot obtenint bons rendiments i excel·lents diastereoselectivitats.



Esquema 146. Resultats preliminars amb peròxid de dilauroïl

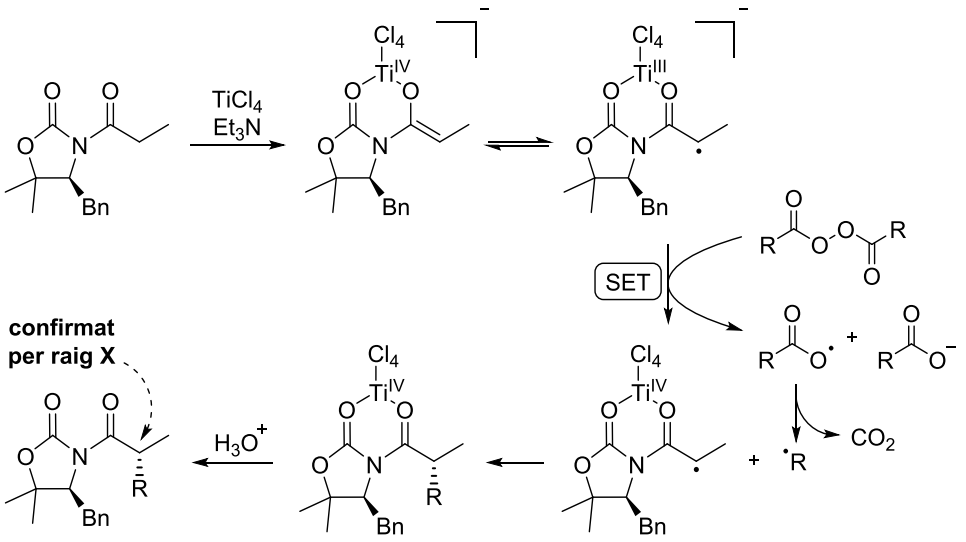
El **capítol I** segueix l'estudi de l'abast de la reacció d'alquilació emprant diferents *N*-acil oxazolidinones. No obstant, tot i que la diastereoselectivitat es manté, els rendiments

obtinguts en els nous exemples no són tant brillants com els anteriors. De fet, durant aquest estudi s'identifiquen diferents subproductes que són responsables de la disminució del rendiment d'alquilació, fet que porta a una reavaluació de les condicions de reacció. Durant aquesta reoptimització s'identifiquen noves condicions que eviten la formació dels subproductes i que per tant, donen lloc a rendiments més elevats. Tot seguit, es torna a avaluar l'abast de la reacció amb diferents peròxids de diacil, que permeten l'addició de grups alquil primaris i secundaris amb millors rendiments que anteriorment. Després es repeteix l'alquilació de diferents enolats de titani, i s'observa un augment dels rendiments en tots els casos. Amb aquests estudis es conclou que tant en l'estructura dels peròxids de diacil com en la dels enolats de titani s'hi poden incloure diferents grups funcionals tals com dobles i triples enllaços, fenils i esters. En el cas dels enolats, fins i tot permeten la incorporació d'oxigen i nitrogen en la posició α degudament protegits (*Esquema 147*).



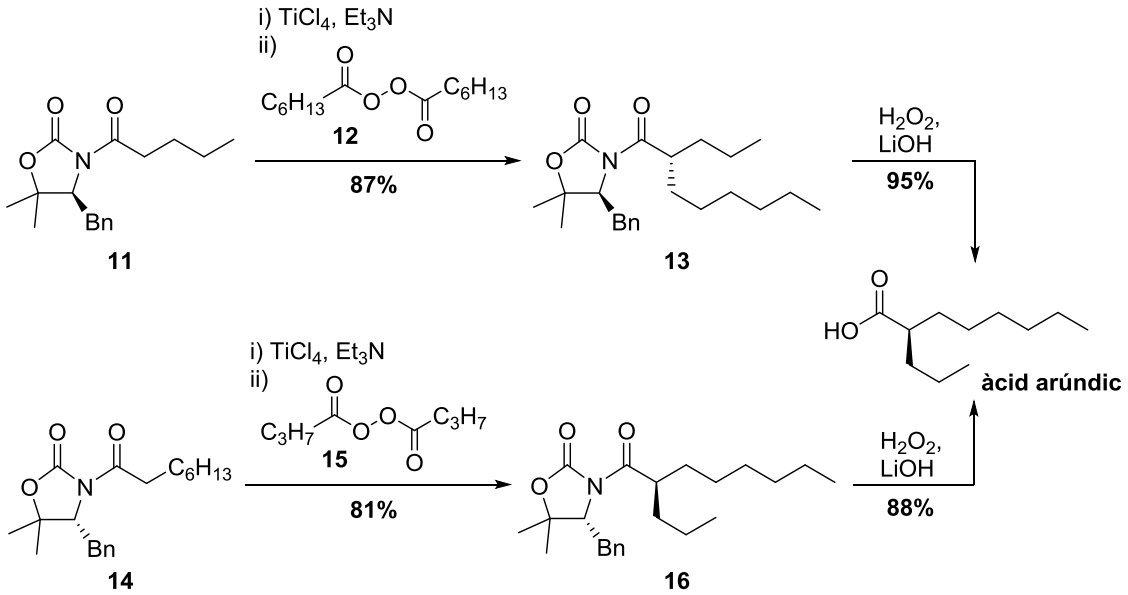
Esquema 147. Alquilació d'enolats de titani amb peròxids de diacil

L'exploració d'aquesta reacció s'acompanya de càlculs computacionals per proposar un mecanisme, el qual atribueix el trencament dels peròxids de diacil a un procés de transferència d'un sol electró "SET" de l'enolat de titani al peròxid de diacil (*Esquema 148*). Aquest, un cop reduït es trenca formant un anió carboxilat i un radical aciloxi. La descarboxilació de l'últim dona lloc a un radical alquil que es recombina amb l'enolat per formar el producte de manera estereoselectiva gràcies a l'auxiliar quiral. La configuració absoluta dels productes es confirma per raig X d'un dels productes cristal·litzat.



Esquema 148. Mecanisme proposat per l'alquilació d'enolats de titani amb peròxids de diacil

Finalment es demostra l'aplicabilitat de la metodologia mitjançant la síntesis de l'àcid arúndic per dues vies diferents, ja que l'alquilació permet la incorporació de qualsevol de les cadenes alquíliques que formen part de l'àcid independentment de la seva llargària (*Esquema 149*). Ambdues vies forneixen l'àcid arúndic amb rendiments globals alts.

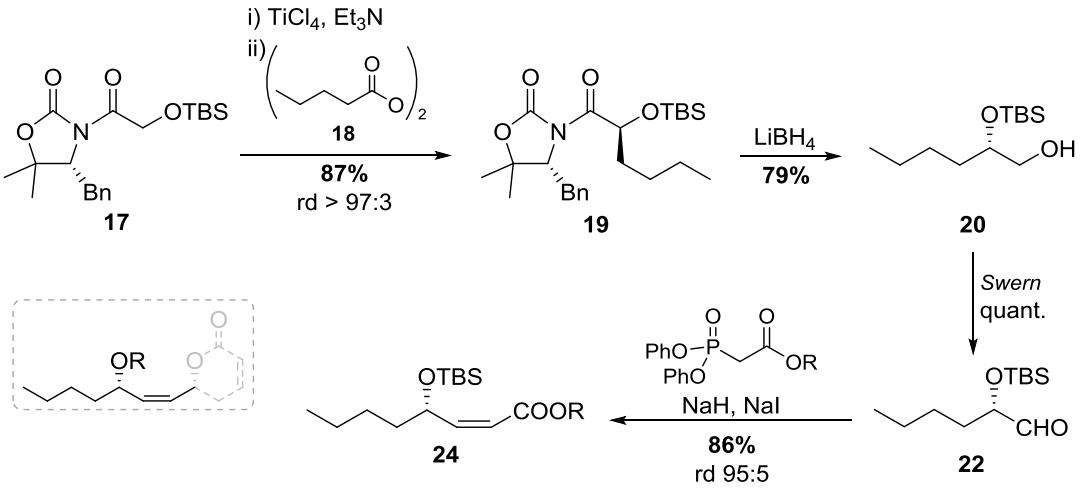


Esquema 149. Síntesis de l'àcid arúndic

En el **capítol II**, la metodologia descrita anteriorment s'aplica a la síntesis total de l'umuravumbolida, una dihidro-α-pirona substituïda descoberta en els extractes de l'*Iboza Riparia*, una planta medicinal emprada a l'Àfrica central.

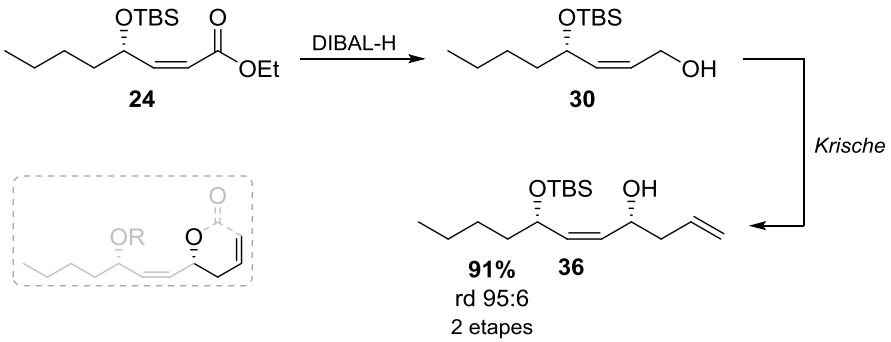
La síntesi comença amb l'alquilació de l'enolat de titani d'un derivat de l'àcid glicòlic amb peròxid de pentanoïl per formar l'estereocentre de la cadena lateral. El producte

d'alquilació **19** s'obté com a un únic diastereòmer amb alts rendiments. L'auxiliar quiral s'elimina amb borohidrur de liti per donar lloc a l'alcohol **20**, que seguidament s'oxida en condicions de Swern per obtenir el corresponent aldehid. Aquest s'empra en una variació Ando de l'olefinació de Horner-Wadsworth-Emmons per obtenir selectivament el doble enllaç *Z* (rd 95:5) de la cadena lateral (*Esquema 150*). Afortunadament, els isòmers *E* i *Z* es poden separar durant la purificació.



Esquema 150. Formació de la cadena lateral de l'umuravumbolida

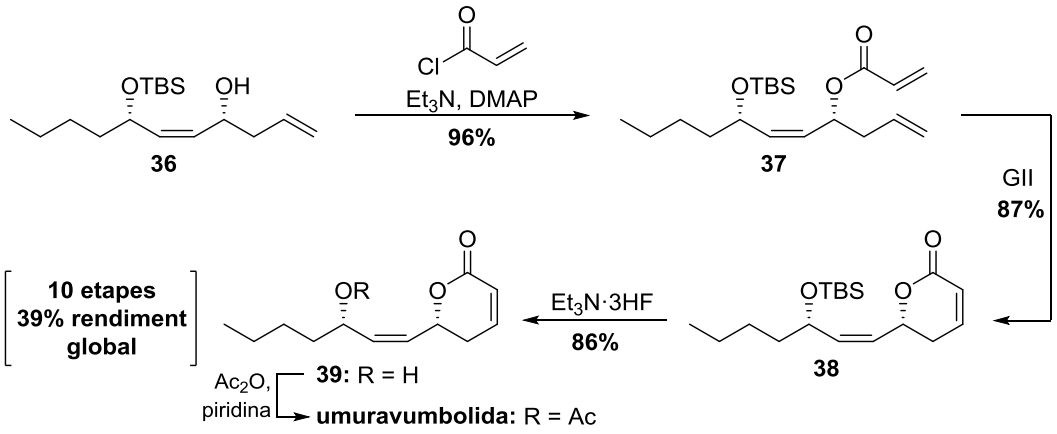
L'èster resultant es redueix amb DIBAL-H per formar l'alcohol **30** en rendiments quantitatius. Aquest es sotmet a una al·lilació asimètrica de Krische, que permet l'obtenció de l'alcohol al·lílic **36** amb bons rendiments i una gran diastereoselectivitat (rd 95:5) en condicions catalítiques. L'anell de pirona s'acaba de formar mitjançant l'acilació de l'alcohol obtingut amb clorur d'acriloïl i una posterior *ring-closing* metàtesis emprant el catalitzador de Grubbs II (*Esquema 151*).



Esquema 151. Formació de l'anell pirona de l'umuravumbolida

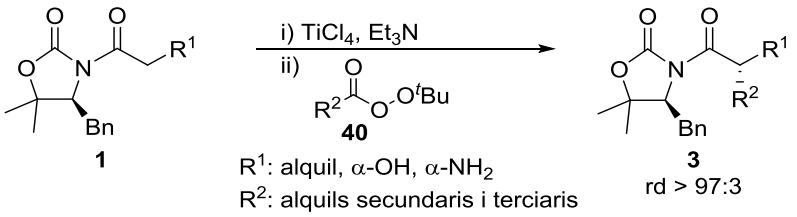
Finalment, la desprotecció de l'hidroxil de la cadena lateral amb un complex de $Et_3N{\cdot}3HF$ forneix la desacetilumuravumbolida (**39**). I, mitjançant una acetilació, s'obté

el producte final, l'umuravumbolida. La síntesis total consta de deu etapes amb tan sols vuit purificacions cromatogràfiques i un rendiment global del 39%. Es tracta d'una de les síntesis més curtes que s'han descrit i, gràcies a la formació dels estereocentres amb alts nivells de selectivitat, una de les que presenten un rendiment més elevat (*Esquema 152*).



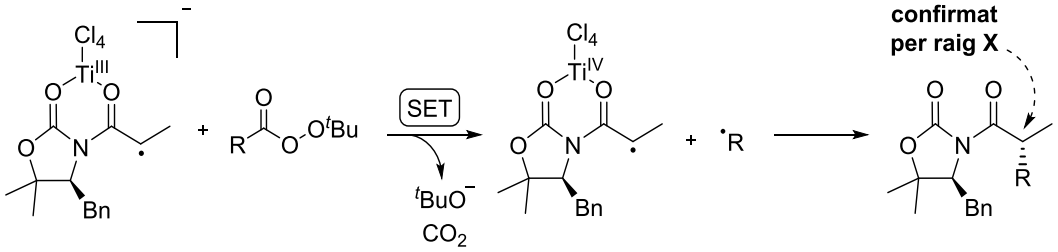
Esquema 152. Passos finals de la síntesis de la umuravumbolida

El **capítol III** torna a centrar-se en el desenvolupament de metodologies. En el capítol I, l'alquilació d'enolats de titani amb peròxids de diacil ha demostrat ser útil i molt versàtil. Tot i això, presenta algunes limitacions, com per exemple la difícil manipulació dels peròxids de diacil secundaris o la impossibilitat de dur a terme alquilacions amb grups terciaris ja que no s'ha aconseguit la formació del peròxid terciari corresponent. Per això, en aquest capítol s'estudia una nova alquilació d'enolats de titani derivats d'*N*-acil oxazolidinones quirals, aquest cop, emprant perèsters de *tert*-butil, d'estructura semblant als peròxids de diacil. El capítol comença amb una breu optimització de les condicions de reacció utilitzant el perèster de *tert*-butil derivat de l'àcid carboxílic d'1-adamantil. Després s'identifica un subproducte resultant de la reacció de l'enolat de titani amb el CO_2 alliberat durant la descarboxilació dels perèsters. Malauradament, els esforços per eliminar aquest producte resulten ineficaços. Seguidament, s'estudia l'abast de la reacció en relació als perèsters de *tert*-butil; s'obtenen bons rendiments per diversos grups d'alquil secundaris i terciaris (*Esquema 153*). Tanmateix, l'alquilació amb grups primaris resulta molt desfavorable. D'altra banda es demostra que els enolats que es poden alquilar amb el grup adamantil permeten incloure grups funcionals com insaturacions, grups èster i un oxigen o nitrogen en posició α degudament protegits.



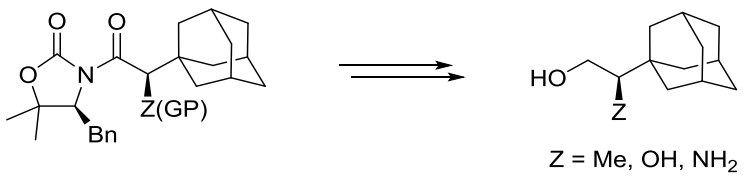
Esquema 153. Alquilació d'enolats de titani amb peresters de *tert*-butil

El mecanisme transcorre de manera similar a la reacció amb peròxids de diacil, és a dir, a través d'un procés de transferència d'un sol electró de l'enolat de titani al perèster de *tert*-butil. Aquesta redox, desencadena el trencament homolític del perèster per donar lloc a un anió *tert*-butòxid i, després de la descarboxilació, un radical alquil. Aquest últim es recombina amb l'enolat de titani per donar lloc al producte d'alquilació de manera altament diastereoselectiva. Altra vegada, la configuració absoluta dels productes d'alquilació es confirma per raig X (*Esquema 154*).



Esquema 154. Breu mecanisme proposat per l'alquilació d'enolats de titani amb perèsters de *tert*-butil

Finalment s'estudien alguns exemples d'eliminació de l'auxiliar quiral en productes d'alquilació que contenen el grup adamantil (*Esquema 155*). En aquests casos l'eliminació esdevé difícil degut a l'alt impediment estèric dels productes obtinguts.

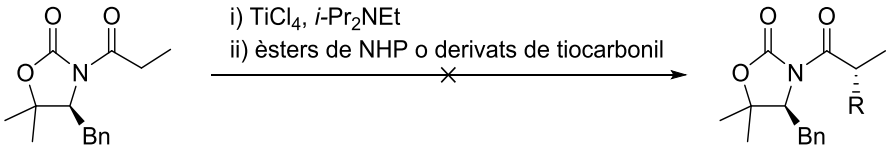


Esquema 155. Eliminació de l'auxiliar quiral

El **capítol IV** es basa en la recerca d'una nova metodologia d'alquilació que superi aquells desavantatges que s'han identificat durant els capítols I i III, per fer-ho, s'aborda el tema des de dos punts de vista diferents.

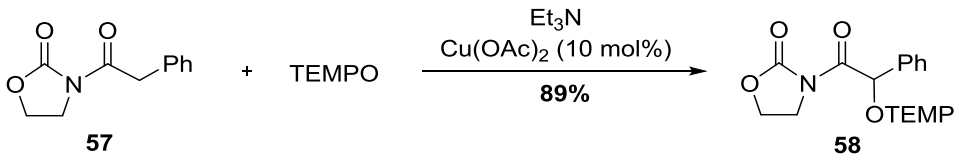
Primerament, es busca un altre substitut dels peròxids de diacil o perèsters que també pugui formar radicals alquil, però que permeti l'incorporació de grups primaris,

secundaris i terciaris sense la formació de subproductes. En aquest cas s'estudien els èsters d'*N*-hidroxiftalimida, que contenen un enllaç O-N sensible a l'homòlisi en comptes d'un enllaç O-O. Aquests èsters s'intenten reduir amb l'enolat de titani mateix i també en condicions fotoquímiques descrites a la literatura, però no se n'aconsegueix la seva escissió, i per tant, tampoc el producte d'alquilació. També s'estudien derivats de compostos tiocarbonílics inspirats en la desoxigenació de Barton-McCombie. Però tampoc se n'assoleix el trencament per formar el radical alquil (*Esquema 156*).



Esquema 156. Intent d'alquilació d'enolats de titani amb altres espècies redox-actives

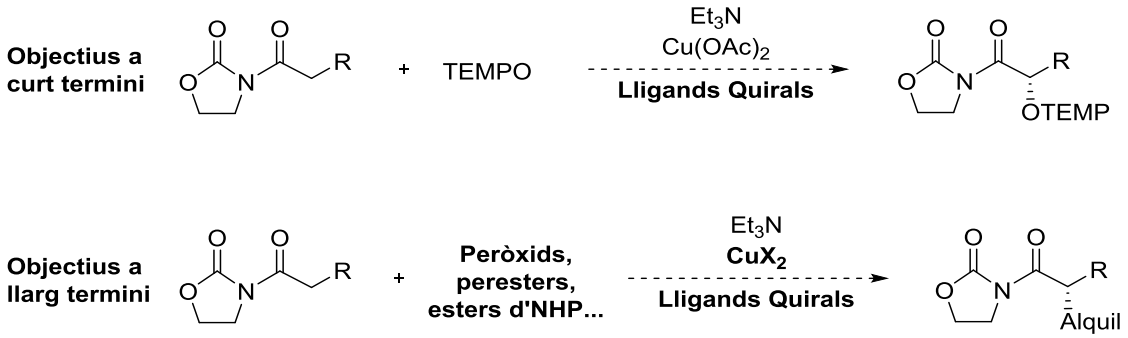
Davant d'aquests resultats negatius es fa un canvi d'estratègia i, en comptes de substituir els peròxids o perèsters, es busca desbancar el titani. Els enolats de titani no es poden formar de manera catalítica perquè el metall es coordina molt fortament a l'*N*-acil oxazolidinona. A més a més, en les reaccions amb enolats de titani cal pre-formar l'enolat i, passats 40 minuts, es pot afegir l'agent alquilant, essent un procediment llarg per disposar la reacció al laboratori. Així doncs, en la segona part del capítol IV es busca un metall que formi enolats amb característiques similars als enolats de titani pel que fa l'activitat radicalària, però que alhora permeti la formació d'aquests de manera catalítica. Per identificar aquest metall suplent, es fa servir el radical lliure TEMPO per atrapar els possibles enolats metàl·lics que exhibeixin reactivitat radicalària. Després de provar diferents salts de metalls com coure, cobalt i ferro en diferents estats d'oxidació, es descobreix que l'acetat de coure(II) forneix el producte aminoxilat amb TEMPO. Seguint amb l'acetat de coure(II) es duu a terme un anàlisis de diferents paràmetres com la temperatura, el dissolvent, i la base, i es troben unes condicions que permeten l'obtenció del producte en grans rendiments i emprant tan sols un 10% d'acetat de coure(II) (*Esquema 157*).



57 58

Esquema 157. α-Aminoxilació catalítica de derivats d'àcids carboxílics

En un futur proper, caldria seguir aquest projecte estudiant diferents lligands quirals per tal de desenvolupar un procés asimètric. I més endavant, es podrien modular aquestes condicions catalítiques per tal d'aconseguir un procediment d'alquilació basat en els mateixos conceptes d'aquesta tesis, però de caràcter catalític (*Esquema 158*).



Esquema 158. Futurs objectius del projecte

ANNEX

Publications

OL | Organic Letters

Letter

Cite This: Org. Lett. 2020, 22, 199−203

pubs.acs.org/OrgLett

Stereoselective Decarboxylative Alkylation of Titanium(IV) Enolates with Diacyl Peroxides

Alejandro Gómez-Palomino,[†,∥,#] Marina Pérez-Palau,[†,#] Pedro Romea,[*,†] Fèlix Urpí,[*,†] Marc Del Olmo,[†] Timo Hesse,[†,¶] Sonja Fleckenstein,[†,⊥] Enrique Gómez-Bengoa,[*,‡] Lia Sotorríos,[‡] and Mercè Font-Bardia[§]

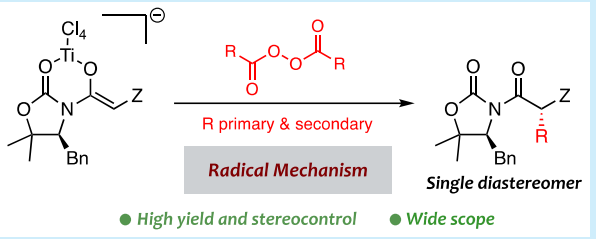
[†]Secció de Química Orgànica, Departament de Química Inorgànica i Orgànica and Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, Carrer Martí i Franqués 1-11, 08028 Barcelona, Catalonia, Spain

[‡]Departamento de Química Orgánica I, Universidad del Pais Vasco, UPV/EHU, Apdo. 1072, 20080 San Sebastián, Spain

[§]Unitat de Difracció de RX. CCiTUB. Universitat de Barcelona. Carrer Solé i Sabarís 1-3, 08028 Barcelona, Catalonia, Spain

Supporting Information

ABSTRACT: Simple treatment of chiral titanium(IV) enolates with diacyl peroxides produces highly diastereoselective decarboxylative alkylations to efficiently deliver the corresponding adducts, most of which are not accessible through any of the current alkylating procedures. Such an unprecedented alkylation proceeds through an SET process that triggers the decomposition of the peroxide into a carbon-centered radical that finally combines with the resulting Cα radical. The procedure has been applied to the enantioselective synthesis of arundic acid.



The stereocontrolled construction of the carbon backbone of chiral molecules is at the core of asymmetric synthesis.[1] One of the simplest approaches to meet such a challenge hinges on the alkylation of the Cα position of carbonyl compounds.[2] Indeed, the alkylation of alkaline enolates of chiral *N*-acyl oxazolidinones[3] and pseudoephedrines[4,5] holds a prominent position among the carbon−carbon bond forming reactions and usually remains the method of choice for the synthesis of natural products.[6,7] These, as well as related methods,[8−10] proceed through an S_N2 mechanism so their scope is restricted to a set of privileged electrophiles (Scheme 1). Furthermore, Evans reported that titanium(IV) enolates of chiral *N*-acyl oxazolidinones may undergo stereoselective S_N1-like alkylations with certain oxocarbenium intermediates (Scheme 1).[11] Therefore, and despite the undeniable success of such approaches, there is still a need for a wide breadth of Cα alkylating methods that enable the stereoselective introduction of any alkyl group without requiring strong bases in the enolization step that may thwart their application to sensitive substrates. A compelling manner to address such a challenge involves the use of radical intermediates that undergo homolytic reactions.[12−14] Unfortunately, carbon-centered radicals are highly reactive species, which can only be produced from a small number of substrates.[15]

Herein, we disclose a *different concept* to overcome the above-mentioned limitations. This calls for the unprecedented stereoselective alkylation of titanium(IV) enolates with diacyl peroxides through a homolytic mechanism. Indeed, a single electron transfer from the enolate to the peroxide triggers a mesolytic cleavage and consequent decarboxylation, which leads to the formation of a carbon-centered radical that combines with the enolate. As represented in Scheme 1, this new approach relies on the diradical character of titanium enolates[16−19] and the weak oxygen−oxygen bond of peroxides. Synthetically, it allows the straightforward and stereoselective alkylation of chiral imides including their α-chloro, α-amino, and α-hydroxy counterpart with a large variety of R groups. Therefore, this method combines simplicity and robustness, which makes possible the highly chemo- and stereoselective introduction of primary and secondary alkyl groups that are not easily amenable to any other current alkylation method.

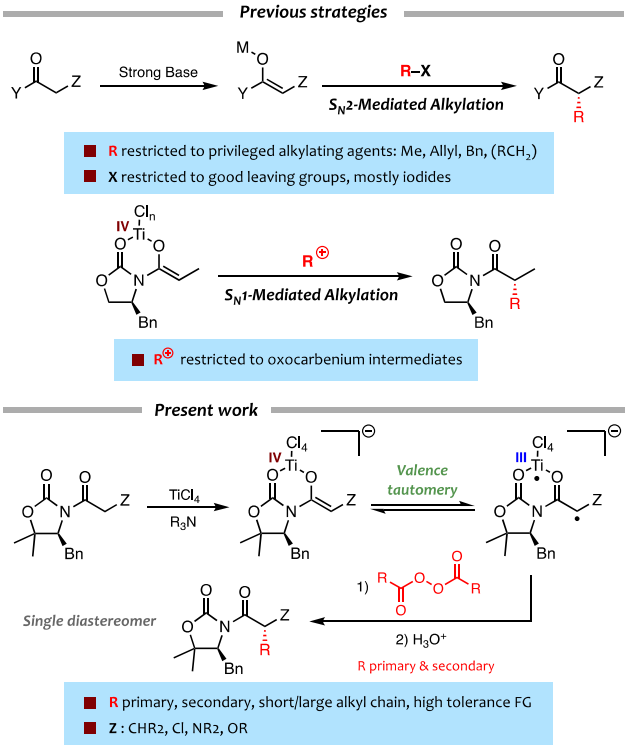
In our search for new reactivity of titanium(IV) enolates based on their diradical character, we envisaged that diacyl peroxides might be a suitable source for carbon-centered radicals.[20,21] Initially, we explored the stereoselective alkylation of titanium(IV) enolates of chiral *N*-propanoyl oxazolidinone **1**[22] with commercially available benzoyl peroxide (BPO) and lauroyl peroxide (LPO) shown in Scheme 2. Benzoyl peroxide did not undergo the desired carbon−carbon bond forming reaction and afforded instead α-benzoyloxy adduct **2** in acceptable yields but moderate diastereoselectivity. Otherwise, lauroyl peroxide (LPO) proceeded as expected and produced a single undecyl-derived diastereomer **3a** (Scheme 2).

A detailed examination of the reaction showed the benefits of working with an excess of LPO. Increasing the amount of peroxide provided higher yields and kinetic rates up to a point

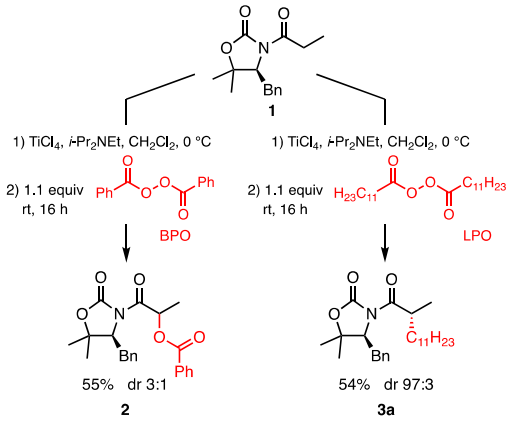
Received: November 20, 2019
Published: December 11, 2019

DOI: 10.1021/acs.orglett.9b04148
Org. Lett. 2020, 22, 199−203

Scheme 1. Stereoselective Alkylations



Scheme 2. Reactions of Titanium(IV) Enolate from 1 with Diacyl Peroxides



in which the alkylation of **1** was completed in less than 2 h and afforded 76% of **3a** with 3 equiv of LPO. Larger quantities of LPO proved superfluous (Table S1). With the optimal amount of peroxide determined, we also established that changes in the temperature or concentration, as well as the use of other titanium(IV) Lewis acids or a less bulky oxazolidinone, did not improve the outcome of the alkylation (Table S2). Interestingly, we observed along these studies the formation of traces of **I** and significant amounts (5−10%) of dichloromethyl derivative **II** (Figure 1), which further suggested the involvement of radicals in the alkylating pathway. Thus, we decided to evaluate the influence of other chlorinated solvents.

Gratifyingly, the solvent had a dramatic impact on the alkylation. Indeed, CCl_4 and $CHCl_3$ proved to be completely unsuitable and 1,1,2,2-tetrachloroethane (TCE) gave similar

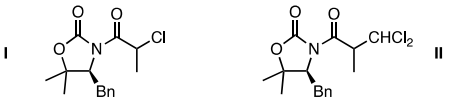
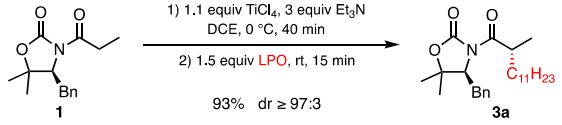


Figure 1. Byproducts of the decarboxylative alkylation.

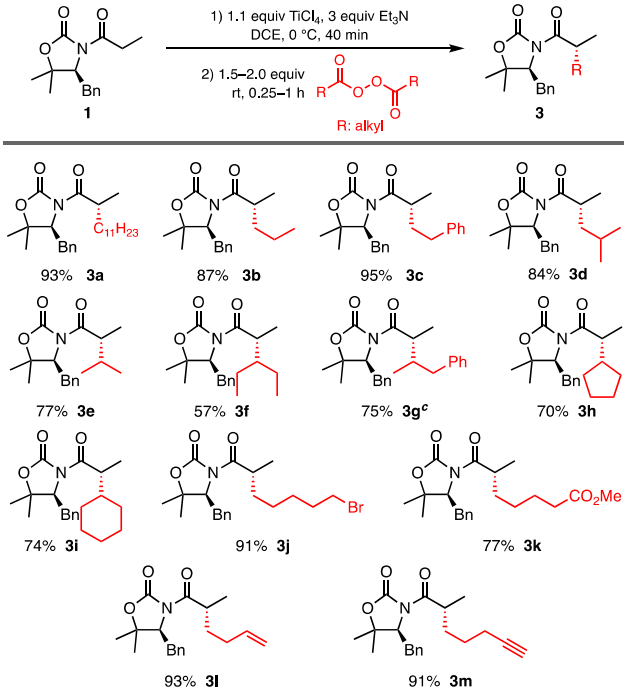
results to CH_2Cl_2, but 1,2-dichloroethane (DCE) afforded **3a** in a higher yield without being contaminated by the corresponding analog of **II** (Table S3). Then, following a comprehensive survey of the alkylation in DCE (Table S4)[16] we established that the use of 3 equiv of Et_3N and just 1.5 equiv of LPO allowed us to isolate diastereomerically pure **3a** with a 93% yield (Scheme 3).

Scheme 3. Optimized Alkylation of 1 with LPO



Having improved the experimental procedure, we assessed the scope of the reaction by applying the optimized conditions to other diacyl peroxides.[23] The results summarized in Scheme 4 show that our protocol affords a single diastereomer (dr

Scheme 4. Scope of the Alkylation of 1[a,b]



[a]Isolated yield. [b]Dr ≥97:3. [c]Dr 2:1 at Cβ.

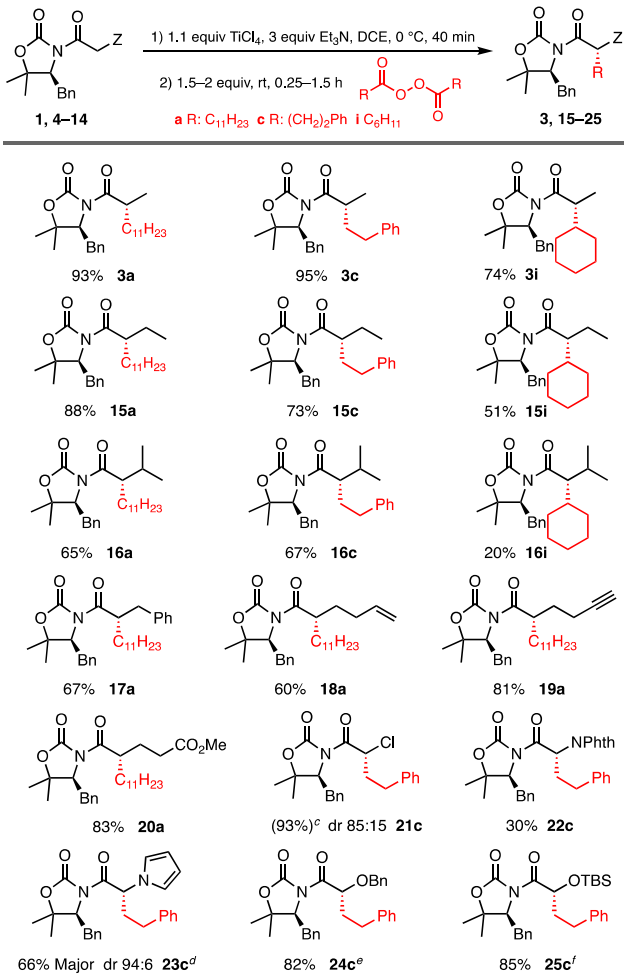
≥97:3) in yields of up to 95%. Noteworthily, this is not limited to primary alkyl groups **3a**−**3d** but may also be applied to secondary alkyl groups **3e**−**3i**. Indeed, the method permits the introduction of isopropyl (**3e**), 3-pentyl (**3f**), 1-phenyl-2-propyl (**3g**), cyclopentyl (**3h**), or cyclohexyl (**3i**) groups in high yields, a range of substrates that had proven elusive to other alkylation procedures. Finally, we were delighted to observe that the alkylation with diacyl peroxides containing halides, esters, and double and triple bonds also led to the

DOI: 10.1021/acs.orglett.9b04148
Org. Lett. 2020, 22, 199−203

isolation of a single diastereomer of adducts **3j**−**3m** in high to excellent yields. Furthermore, the tolerance of these functional groups is remarkable and highlights the outstanding chemoselectivity of the process.

In view of such results, we next examined the robustness of the acyl group. As summarized in Scheme 5, the alkylation of

Scheme 5. Scope of the Alkylation of *N*-Acyl Oxazolidinones[a,b]

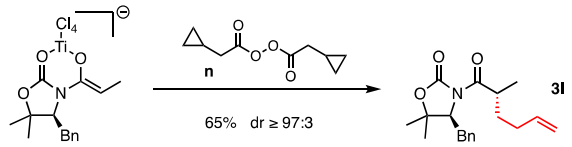


[a]Isolated yield. [b]Dr ≥97:3. [c]Overall yield. [d]Reaction at −20 °C. [e]Reaction at 0 °C. [f]Reaction at −10 °C

increasingly sterically hindered substrates at both the Cα acyl group (Z) and the radical (R) is possible. Indeed, substrates **1** and **4** containing unhindered acyl groups (Z: Me, Et) react with diacyl peroxides **a** and **c** to give **3a**, **3c**, **15a**, and **15c** as a single diastereomer (dr ≥97:3) in excellent yields (73−95%), whereas parallel reactions with the more bulky diacyl peroxide **i** provided adducts **3i** and **15i** in good yields (51−74%). Likewise, alkylation of a more hindered substrate **5** (Z: *i*-Pr) with diacyl peroxides **a**, **c**, and **i** also gave adducts **16a**, **16c**, and **16i** with notable efficiency (20−67%). At this point, configuration of the Cα chiral center was firmly established by X-ray analysis of **16c** (CCDC 1939369). Importantly, substrates containing phenyl, alkene, alkyne, or ester groups proved suitable and gave adducts **17a**−**20a** with a 60−83% yield. Furthermore, the alkylation resulted in being compatible with Cα heteroatoms. Thereby, alkylation of *N*-chloroacetyl oxazolidinone (Z: Cl) with diacyl peroxide **c** produced the α-chlorinated adduct **21c** as an 85:15 diastereomeric mixture with a 92% overall yield. Even the alkylation of α-nitrogenated substrates resulted in being feasible, and pyrrole-derived oxazolidinone (Z: pyrrole) afforded a 94:6 diastereomeric mixture from which **23c** was isolated in a 66% yield. Eventually, α-hydroxy substrates (Z: OBn, OTBS) were also found to be appropriate and produced adducts **24c** and **25c** in an 82−85% yield. All together, these results show that the appropriate choice of Z group may give a straightforward access to a remarkable range of enantiomerically pure α-halo, α-amino, and α-hydroxy acids.[24]

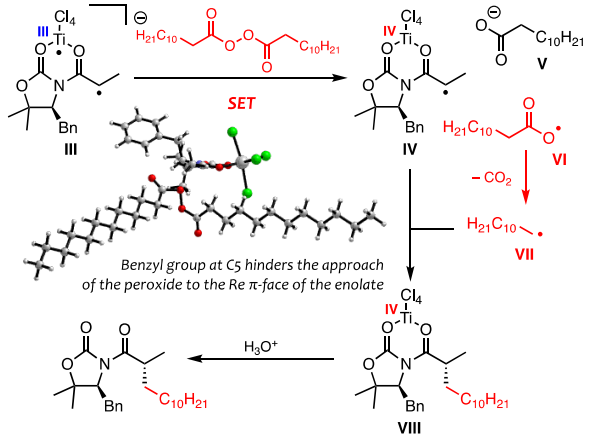
Having demonstrated the wide scope and the robustness of the alkylation, we focused our attention on its mechanism. Our working hypothesis revolved around the diradical character of the titanium(IV) enolates[16,17] of **1**. The isolation of small quantities of dichloromethyl derivative **II** (Figure 1) supported such a hypothesis, but further proof was required. In this context, the alkylation with the diacyl peroxide from 2-cyclopropylacetic acid (**n**) was crucial. Importantly, we only observed the formation of the open-chain adduct **3l** (Scheme 6), which is strong evidence that the decarboxylative alkylation proceeds through the addition of radicals to the titanium(IV) enolates.[25]

Scheme 6. Mechanistic Studies



In parallel, we carried out a computational analysis to gain insight into the mechanistic details of the process.[26] Keeping in mind the diradical character of the titanium(IV) enolates,[16,17] we thoroughly examined the addition of the titanium(IV) enolate from **1** to the model dilauroyl peroxide (Scheme 7).

Scheme 7. Mechanistic Hypothesis



Thereby, it was found that the reaction proceeds through an electron transfer from the α-carbon in **III** to the σ^* orbital of the O−O bond in a Single Electron Transfer (SET) *redox reaction*, which gives radical **IV**, causing the cleavage of the O−O bond into a carboxylate anion and a radical (**V** and **VI** respectively). Then, the spontaneous decarboxylation of **VI** produces a carbon-centered radical **VII** that may combine with

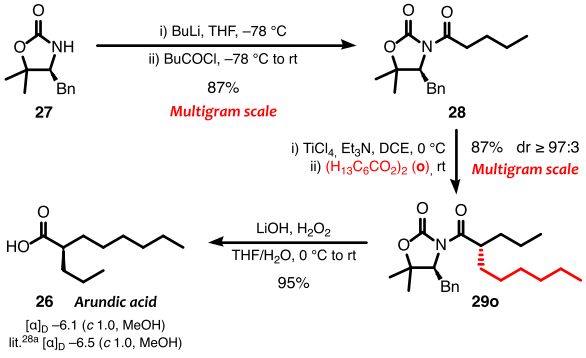
DOI: 10.1021/acs.orglett.9b04148
Org. Lett. 2020, 22, 199−203

IV to form the C−C bond. At this point, we cannot rule out the possibility that the key C−C bond can be formed by reaction of the alkyl radical **VII** with **III** (instead of **IV**) in a radical chain reaction, more complex than the depicted in Scheme 7 (for further details, see the Supporting Information).

In any case, an SET mechanism may account for the experimental results. Indeed, this involves alkyl radical intermediates, which explains the occurrence of compounds such as **3l** and byproduct **II**. Remarkably, the overall transformation is energetically feasible (ΔG = −16.6 kcal mol^{-1}). Furthermore, the reagents must approach to within a short distance for the electron transfer to occur, and due to the bulkiness of **III** and the diacyl peroxides good diastereoselectivity is ensured (Scheme 7). Thereby, a remarkable minimum energy difference of at least 3.5 kcal mol^{-1} for the approach to both π-faces in the electron transfer structure at C−O distances ranging from 1.8 to 4 Å in distinct conformations was calculated, which corresponds to a dr >99:1. Therefore, the proposal depicted in Scheme 7 accounts for both the observed reactivity and stereoselectivity, since carbon-centered alkyl radicals are involved in the reaction and the stereochemical outcome of the alkylation depends on the approach of the entire diacyl peroxide to the less sterically shielded *Si* face of the enolate.

Finally, we considered the opportunity to apply the new method to the synthesis of arundic acid (**26** in Scheme 8), a

Scheme 8. Enantioselective Synthesis of Arundic Acid



chiral carboxylic acid with potential neuroprotective activity.[27] The synthesis commenced with a standard acylation of **27** to produce *N*-pentanoyl oxazolidinone **28**.[28] Then, treatment of the titanium(IV) enolate of **28** with diheptanoyl peroxide (**o**) provided a single diastereomer of the alkylated adduct **29o** with an 87% yield at multigram scale. Next, removal of the chiral auxiliary afforded enantiomerically pure arundic acid **26** in 95% yield and complete recovery of **27**.[29] Therefore, arundic acid has been prepared with a 70% overall yield in a three-step sequence that involves the decarboxylative alkylation previously developed.

In summary, a highly stereoselective decarboxylative alkylation of the titanium(IV) enolates from a wide array of chiral *N*-acyl oxazolidinones with diacyl peroxides from primary and secondary aliphatic carboxylic acids is described. Experimental evidence and theoretical calculations indicate that the reaction takes advantage of the diradical character of the titanium(IV) enolate and proceeds through an SET step that triggers the decomposition of the diacyl peroxide. This proves for the first time that titanium(IV) enolates may behave as *reducing agents* and thus take part in radical transformations to afford enantiomerically pure alkylated products. Furthermore, this method has been applied to the enantioselective synthesis of the arundic acid at a multigram scale.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04148.

Experimental details and compound characterization (PDF)
Copies of ^{1}H and ^{13}C NMR spectra (PDF)
Details of theoretical calculations (PDF)

Accession Codes

CCDC 1939369 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: pedro.romea@ub.edu.
*E-mail: felix.urpi@ub.edu.
*E-mail: enrique.gomez@ehu.es.

ORCID

Alejandro Gómez-Palomino: 0000-0001-5127-3445
Marina Pérez-Palau: 0000-0001-9905-3513
Pedro Romea: 0000-0002-0259-9155
Fèlix Urpí: 0000-0003-4289-6506
Enrique Gómez-Bengoa: 0000-0002-8753-3760

Present Addresses

‖A.G.-P: Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany.
⊥S.F.: Institute of Organic Chemistry and Biochemistry. Technical University of Darmstadt, Darmstadt, Germany.
¶T.H.: Institute of Organic Chemistry. Leibniz University, Hannover, Germany.

Author Contributions

#A.G.-P. and M.P.-P. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Professor Paul Knochel (Ludwig-Maximilians-Universität München) for insightful comments on the use of pyrroles as amino protecting groups and David Casanova (DIPC, Donostia International Physics Center, San Sebastián) for helpful mechanistic discussions. Financial support from the Spanish Ministerio de Economía y Competitividad (Grant No. CTQ2015-65759-P), the Spanish Ministerio de Ciencia, Innovación y Universidades (MCIU)/Agencia Estatal de Investigación (AEI)/Fondo Europeo de Desarrollo Regional (FEDER, UE) (Grant No. PGC2018-094311-B-I00), and the Generalitat de Catalunya (2017SGR 271) as well as doctorate studentships to A.G.-P. (APIF, Universitat de Barcelona), M.P.-P. (FPU, MCIU), and L.S. (MINECO, CTQ2016-78083-P) are acknowledged. We also thank IZO/SGI-SGIker of UPV/EHU for human and computational resources.

DOI: 10.1021/acs.orglett.9b04148
Org. Lett. 2020, 22, 199−203

REFERENCES

(1) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, 2009.

(2) Stoltz, B. M.; Bennett, N. B.; Duquette, D. C.; Goldberg, A. F. G.; Liu, Y.; Loewinger, M. M.; Reeves, C. M. *Comprehensive Organic Synthesis*, 2nd ed.; Knochel, P., Molander, G. A., Eds.; Elsevier: 2014; Vol. 3, pp 1−20.

(3) Evans, D. A.; Ennis, M. D.; Mathre, D. J. Asymmetric Alkylation Reactions of Chiral Imide Enolates. A Practical Approach to the Enantioselective Synthesis of α-Substituted Carboxylic Acid Derivatives. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

(4) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. Pseudoephedrine as a Practical Chiral Auxiliary for the Synthesis of Highly Enantiomerically Enriched Carboxylic Acids, Alcohols, Aldehydes, and Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

(5) Morales, M. R.; Mellem, K. T.; Myers, A. G. Pseudoephenamine: A Practical Chiral Auxiliary for Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568−4571.

(6) For a recent example, see: Rohrs, T. M.; Qin, Q.; Floreancig, P. E. Re_2O_7-Mediated Dehydrative Cyclization Reactions: Total Synthesis of Herboxidiene and Its 12-Desmethyl Analogue. *Angew. Chem., Int. Ed.* **2017**, *56*, 10900−10904.

(7) For a recent example, see: Lu, Z.; Zhang, X.; Guo, Z.; Chen, Y.; Mu, T.; Li, A. Total Synthesis of Aplysiasecosterol A. *J. Am. Chem. Soc.* **2018**, *140*, 9211−9218.

(8) Schöllkopf, U. Asymmetric Synthesis of Amino Acids Via Metalated Bis-Lactam Ethers of 2,5-Diketopiperazines. *Pure Appl. Chem.* **1983**, *55*, 1799−1806.

(9) Oppolzer, W. Camphor as a Natural Source of Chirality in Asymmetric Synthesis. *Pure Appl. Chem.* **1990**, *62*, 1241−1250.

(10) Ooi, T.; Maruoka, K. Recent Advances in Asymmetric Phase-Transfer Catalysis. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222−4266.

(11) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. New Procedure for the Direct Generation of Titanium Enolates. Diastereoselective Bond Constructions with Representative Electrophiles. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216.

(12) Sibi, M. P.; Ji, J. Acyclic Stereocontrol in Radical Reactions: ρ-Selectivity with Oxazolidinone Auxiliaries. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190−192.

(13) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. Enantioselective Organocatalysis Using SOMO Activation. *Science* **2007**, *316*, 582−585.

(14) Capacci, A. G.; Malinowski, J. T.; McAlpine, N. J.; Kuhne, J.; MacMillan, D. W. C. Direct, Enantioselective α-Alkylation of Aldehydes Using Simple Olefins. *Nat. Chem.* **2017**, *9*, 1073−1077.

(15) For recent accounts on the importance of radicals in organic synthesis, see: (a) Smith, J. M.; Harwood, S. J.; Baran, P. S. Radical Retrosynthesis. *Acc. Chem. Res.* **2018**, *51*, 1807−1817. (b) Smith, J. M.; Dixon, J. A.; deGruyter, J. N.; Baran, P. S. Alkyl Sulfinates: Radical Precursors Enabling Drug Discovery. *J. Med. Chem.* **2019**, *62*, 2256−2264.

(16) Moreira, I. de P. R.; Bofill, J. M.; Anglada, J. M.; Solsona, J. G.; Nebot, J.; Romea, P.; Urpí, F. Unconventional Biradical Character of Titanium Enolates. *J. Am. Chem. Soc.* **2008**, *130*, 3242−3243.

(17) Heras, C.; Gómez-Palomino, A.; Romea, P.; Urpí, F.; Bofill, J. M.; Moreira, I. de P. R. Experimental and Computational Evidence of the Biradical Structure and Reactivity of Titanium(IV) Enolates. *J. Org. Chem.* **2017**, *82*, 8909−8916.

(18) Beaumont, S.; Ilardi, E. A.; Monroe, L. R.; Zakarian, A. Valence Tautomerism in Titanium Enolates: Catalytic Radical Haloalkylation and Application in the Total Synthesis of Neodysidenin. *J. Am. Chem. Soc.* **2010**, *132*, 1482−1483.

(19) Gu, Z.; Herrmann, A. T.; Zakarian, A. Dual Ti−Ru Catalysis in the Direct Radical Haloalkylation of *N*-Acyl Oxazolidinones. *Angew. Chem., Int. Ed.* **2011**, *50*, 7136−7139.

(20) Li, Y.; Ge, L.; Muhammad, M. T.; Bao, H. Recent Progress on Radical Decarboxylative Alkylation for Csp3−C Bond Formation. *Synthesis* **2017**, *49*, 5263−5284.

(21) For recent reports on the use of decarboxylation of diacyl peroxides as a source of radicals, see: (a) Qian, B.; Chen, S.; Wang, T.; Zhang, X.; Bao, H. Iron-Catalyzed Carboamination of Olefins: Synthesis of Amines and Disubstituted ß-Amino Acids. *J. Am. Chem. Soc.* **2017**, *139*, 13076−13082. (b) Ye, C.; Li, Y.; Zhu, X.; Hu, S.; Yuan, D.; Bao, H. Copper Catalyzed 1,4-Alkylarylation of 1,3-Enynes with Masked Alkyl Electrophiles. *Chem. Sci.* **2019**, *10*, 3632−3636.

(22) Davies, S. G.; Sanganee, H. J. 4-Substituted-5,5-dimethyl Oxazolidin-2-ones as Effective Chiral Auxiliaries for Enolate Alkylations and Michael Additions. *Tetrahedron: Asymmetry* **1995**, *6*, 671−674.

(23) For the synthesis of noncommercially available diacyl peroxides, see the Supporting Information.

(24) For a recent and insightful radical-like approach to the synthesis of α-amino acids, see: Ni, S.; Garrido-Castro, A. F.; Merchant, R. R.; de Gruyter, J. N.; Schmitt, D. C.; Mousseau, J. J.; Gallego, G. M.; Yang, S.; Collins, M. R.; Qiao, J. X.; Yeung, K.-S.; Langley, D. R.; Poss, M. A.; Scola, P. M.; Qin, T.; Baran, P. S. A General Amino Acid Synthesis Enabled by Innate Radical Cross-Coupling. *Angew. Chem., Int. Ed.* **2018**, *57*, 14560−14565.

(25) Nonhebel, D. C. The Chemistry of Cyclopropylmethyl and Related Radicals. *Chem. Soc. Rev.* **1993**, *22*, 347−359.

(26) The calculations were run with the M06 functional, including an implicit solvation model (IEF-PCM, CH_2Cl_2). See Supporting Information for details.

(27) Tateishi, N.; Mori, T.; Kagamiishi, Y.; Satoh, S.; Katsube, N.; Morikawa, E.; Morimoto, T.; Matsui, T.; Asano, T. Astrocytic Activation and Delayed Infarct Expansion after Permanent Focal Ischemia in Rats. Part II: Suppression of Astrocytic Activation by a Novel Agent (*R*)-(−)-2-Propyloctanoic Acid (ONO-2506) Leads to Mitigation of Delayed Infarct Expansion and Early Improvement of Neurologic Deficits. *J. Cereb. Blood Flow Metab.* **2002**, *22*, 723−734.

(28) For previous syntheses, see: (a) García, J. M.; Odriozola, J. M.; Lecumberri, A.; Razkin, J.; González, A. Concise and Efficient Route to the Alzheimer's Therapeutic Agent (*R*)-Arundic Acid. *Tetrahedron* **2008**, *64*, 10664−10669. (b) Gualandi, A.; Emer, E.; Capdevila, M. G.; Cozzi, P. G. Highly Enantioselective α Alkylation of Aldehydes with 1,3-Benzodithiolylium Tetrafluoroborate: A Formal Organocatalytic α Alkylation of Aldehydes by the Carbenium Ion. *Angew. Chem., Int. Ed.* **2011**, *50*, 7842−7846. (c) Pérez, M.; Fañanás-Mastral, M.; Hornillos, V.; Rudolph, A.; Bos, P. H.; Harutyunyan, S. R.; Feringa, B. L. Asymmetric Allylic Alkylation of Acyclic Allylic Ethers with Organolithium Reagents. *Chem. - Eur. J.* **2012**, *18*, 11880−11883.

(29) Beutner, G. L.; Cohen, B. M.; DelMonte, A. J.; Dixon, D. D.; Fraunhoffer, K. J.; Glace, A. W.; Lo, E.; Stevens, J. M.; Vanyo, D.; Wilbert, C. Revisiting the Cleavage of Evans Oxazolidinones with $LiOH/H_2O_2$. *Org. Process Res. Dev.* **2019**, *23*, 1378−1385.

DOI: 10.1021/acs.orglett.9b04148
Org. Lett. 2020, 22, 199−203

OL Organic Letters

pubs.acs.org/OrgLett Letter

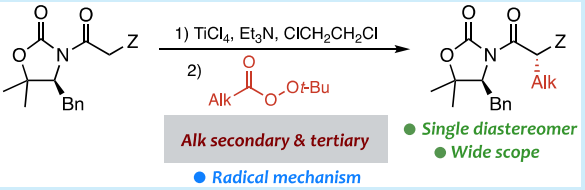
Stereoselective Alkylation of Chiral Titanium(IV) Enolates with *tert*-Butyl Peresters

Marina Pérez-Palau, Nil Sanosa, Pedro Romea,* Fèlix Urpí,* Rosa López, Enrique Gómez-Bengoa,* and Mercè Font-Bardia

Cite This: *Org. Lett.* 2021, 23, 8852–8856 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Here, we present a new stereoselective alkylation of titanium(IV) enolates of chiral *N*-acyl oxazolidinones with *tert*-butyl peresters from Cα-branched aliphatic carboxylic acids, which proceeds through the decarboxylation of the peresters and the subsequent formation of alkyl radicals to produce the alkylated adducts with an excellent diastereoselectivity. Theoretical calculations account for the observed reactivity and the outstanding stereocontrol. Importantly, the resultant compounds can be easily converted into ligands for asymmetric and catalytic transformations.



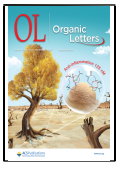
The need for more efficient and broad scope methods for the stereoselective construction of chiral molecular architectures is an endless source of inspiration for the development of new carbon−carbon bond-forming reactions.[1] In this context and despite the advances reported in the last decades, the α-alkylation of carbonyl compounds still remains as a challenging objective.[2] It is certainly true that successful methods based on the alkylation of metal enolates and enamines are widespread, but they are usually restricted to a privileged set of alkylating agents, namely sterically unhindered and active alkyl halides or sulfonates, able to react through an S_N2-like mechanism.[3−5] Alternative methods based on an S_N1-like mechanism have been also reported, but they mostly require stabilized carbenium or oxocarbenium intermediates.[6−8] As a result, the chemo- and stereoselective introduction of any secondary or tertiary alkyl groups continues to be an unresolved issue.[9]

Radical chemistry may offer an appealing way to achieve such an objective. Indeed, the tremendous success of the SOMO activation mode concept coined by MacMillan in the context of the direct and asymmetric alkylation of aldehydes illustrates the synthetic potential of the radical approach.[10] Inspired by these ideas and considering the biradical character of the titanium(IV) enolates,[11] we envisaged that they might undergo highly stereoselective alkylations provided that the required radical intermediates were generated in the reaction mixture. The feasibility of such an approach was clearly demonstrated in the alkylation of chiral *N*-acyl oxazolidinones with diacyl peroxides (Scheme 1).[12−14] Unfortunately, diacyl peroxides from α-branched aliphatic carboxylic acids are difficult to manipulate, which made the reaction with tertiary alkyl groups particularly elusive. In the search for more stable carboxylic acid derivatives to enable the introduction of secondary and tertiary alkyl groups we focused our attention on redox-active esters (Scheme 1).[15] Widely used phthalimide-derived esters[16] containing an O−N bond proved to be unreactive, but peresters containing an O−O bond turned out to be much more satisfactory.[17] Herein, we describe the chemo- and stereoselective Cα alkylation of titanium(IV) enolates from chiral *N*-acyl oxazolidinones with *tert*-butyl peresters from branched aliphatic carboxylic acids, which permits the stereocontrolled introduction of secondary and tertiary alkyl groups with moderate to high yields (Scheme 1). Importantly, this method gives a straightforward access to enantiomerically pure intermediates that can be employed as precursors for ligands in catalytic and asymmetric synthesis.[18]

Taking advantage of our experience, we were pleased to observe that the titanium(IV) enolate of (*S*) 4-benzyl-5,5-dimethyl-*N*-propanoyl-1,3-oxazolidin-2-one (**1** in Table 1) reacted with the *tert*-butyl perester from 1-adamantanecarboxylic acid (**a** in Table 1) under mild conditions similar to those employed for the alkylation with diacyl peroxides.[12] Indeed, the alkylated adduct **1a** was isolated with a high yield and an excellent diastereoselectivity (74% and dr 97:3, see Table 1) through the simple stirring of a mixture of the titanium(IV) enolate of **1** with 1.5 equiv of **a** in 1,2-dichloroethane for 1.5 h at room temperature. Slight variations of such conditions also gave the desired adduct **1a** but in lower yields (Table 1).

The experimental procedure was next applied to a number of *tert*-butyl peresters from Cα branched carboxylic acids.[19]

Received: October 4, 2021
Published: October 26, 2021



Scheme 1. Stereoselective Decarboxylative Alkylation of Titanium(IV) Enolates from Chiral *N*-Acyloxazolidinones

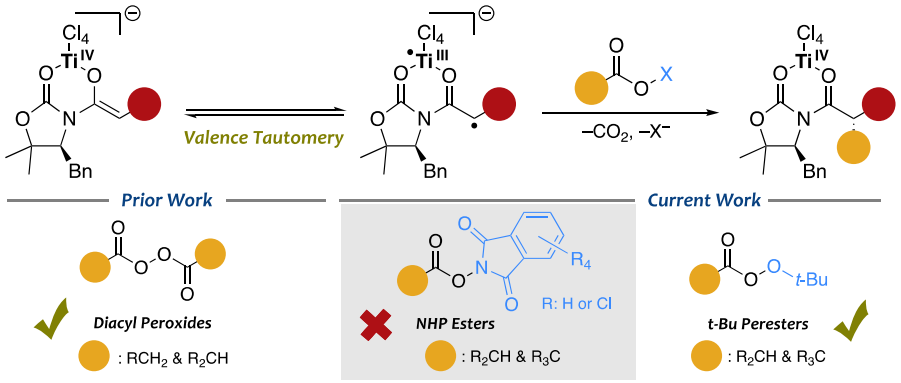
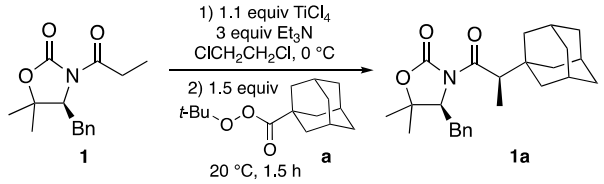


Table 1. Examination of the Alkylation Conditions



entry	changes on the reaction conditions	yield[a] (%)
1	none	74
2	*i*-Pr_2NEt	66
3	2 equiv of **a**	62
4	0 °C for 2 h	58
5	2 equiv of **a** at 0 °C for 2 h	60

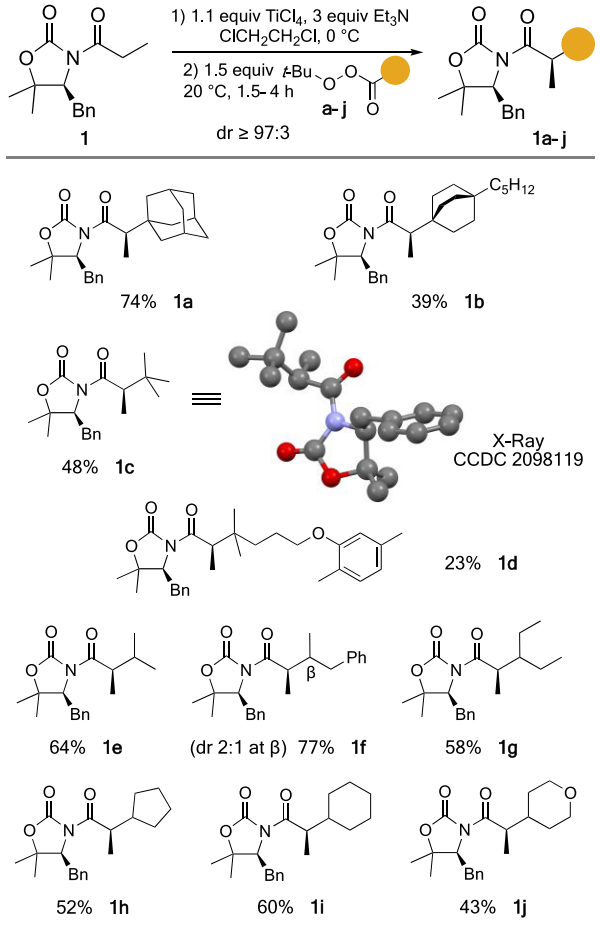
[a]Isolated yield after chromatographic purification of **1a**

The introduction of tertiary alkyl groups proved to be possible in variable yields and heavily dependent on their structure but with outstanding stereocontrol since a single diastereomer (dr ≥97:3) of the alkylated adducts **1a–d** was observed in all cases. Indeed, the results summarized in Scheme 2 show that they range from excellent for **1a** (74%) to low for **1d** in which perester **d** contains a *tert*-butyl-like chain possessing an aryl ether (23%). Importantly, peresters **b–d** react slowly compared to **a**, and we have occasionally observed the formation of the carboxylic acid derived from the reaction of the titanium enolate from **1** with the carbon dioxide released in the perester decarboxylation. Therefore, slow kinetics allow undesired side reactions to emerge and reduce the overall yield. Remarkably, the stereochemical outcome of the alkylation was firmly established through X-ray analysis of *tert*-butyl alkylated adduct **1c**.

The reaction with secondary alkyl groups proved to be much more successful. As summarized in Scheme 2, the reaction with *tert*-butyl peresters **e–j** with Cα acyclic and cyclic aliphatic chains also gave the corresponding adducts **1e–j** as a single diastereomer (dr ≥97:3) in good to high yields. Finally, it is worth pointing out the lack of stereocontrol of the β-stereocenter in the alkylation with perester **f**, so adduct **1f** was isolated as a 2:1 mixture of two diastereomers (Scheme 2).

Having established the scope of the alkylating agent, we next examined the influence of the *N*-acyl group on the outcome of the alkylation with **a**. The reaction turned out to be sensitive to steric hindrance but at the same time chemoselective. Indeed, a variety of functional groups as double or triple bonds, esters, or phenyl rings may be embedded in the acyl chain and produce the corresponding alkylated adducts in yields up to 67%

Scheme 2. Alkylation of 1 with *tert*-Butyl Peresters a–j from Cα-Branched Carboxylic Acids

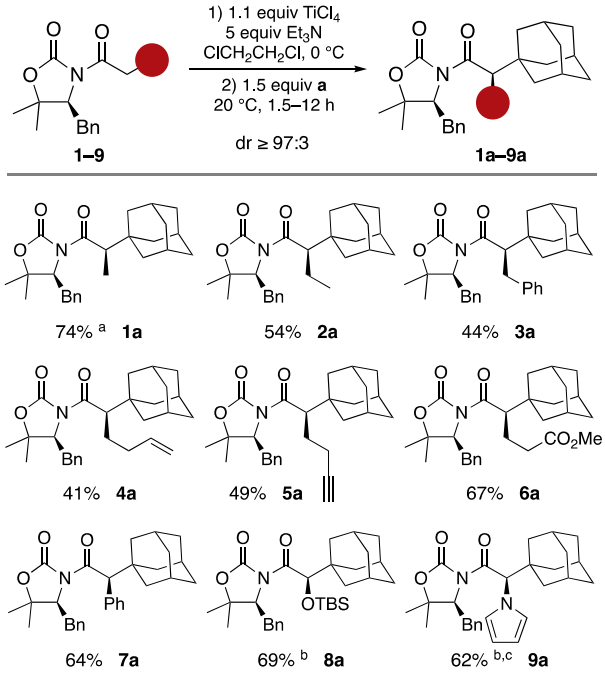


(Scheme 3). Importantly, protected α-hydroxy and α-amino acyl derivatives (α-OTBS and α-pyrrole, **8** and **9**, respectively, in Scheme 3) proved to be successful platforms from which the alkylated adducts **8a** and **9a** were obtained in high yields in a multigram scale, which demonstrates the robustness of the method and represents a straightforward way to get access to enantiomerically pure α-hydroxy and α-amino acids.

At this point, we carried out a comprehensive theoretical study to unveil the origin of the observed reactivity and selectivity. As for the reaction with diacyl peroxides,[12] DFT calculations[20] of the alkylation of **1** with perester **a** indicated that it also may proceed through an electron transfer from **I**

https://doi.org/10.1021/acs.orglett.1c03366
Org. Lett. 2021, 23, 8852–8856

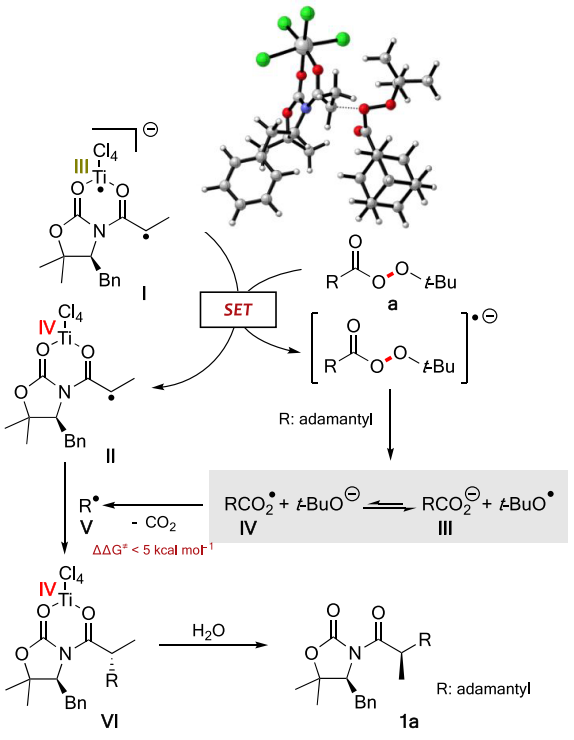
Scheme 3. Alkylation of 1−9 with *tert*-Butyl Perester of 1-Adamantanecarboxylic Acid (a)



[a]3 equiv of Et_3N was employed. [b]Yield at 6.5 mmol scale. [c]The enolization was carried out at −20 °C.

(Scheme 4), the biradical form of titanium enolates,[11] to the σ^* of the O−O bond of **a**. Thus, a single-electron transfer (SET) redox reaction causes the formation of the Ti(IV) radical **II** by a one electron loss and triggers the cleavage of the O−O bond, which produces an oxygen radical and an oxygen anion species. Due to the lack of symmetry of the perester, such a fragmentation may produce up to four different species shown in Scheme 4. These species may be in an equilibrium favoring the carboxylate anion **III**, more stable than the radical counterpart **IV**. However, **IV** is a very unstable intermediate and undergoes a spontaneous decarboxylation to the corresponding tertiary radical **V** in an almost barrierless step ($\Delta\Delta G^{\ddagger} < 5$ kcal mol^{-1}); importantly, a parallel decomposition of anion **III** is precluded by kinetic and thermodynamic reasons ($\Delta G^{\circ} \approx 50$ kcal mol^{-1}). Thus, a Curtin−Hammett model may account for the formation of the adamantly radical **V**, which combines with the highly reactive Ti(IV) radical **II** to lead to the alkylated product **1a** after C−C bond formation and decoordination of the titanium.

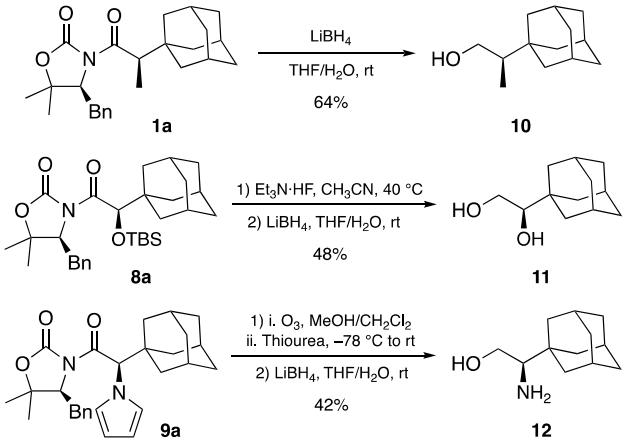
Scheme 4. Mechanistic Proposal



Given the short distance at which the reagents must approach for the occurrence of the electron transfer, and due to the bulkiness of **I** and **a**, a good diastereoselectivity was ensured. Thereby, a remarkable minimum energy difference of at least 5.0 kcal·mol^{-1} corresponding to a dr >99:1 was calculated for the approach of distinct conformations of the perester to both π-faces of the enolate, with C−O distances ranging from 1.8 to 4 Å. This effect can be visualized in the 3D-representation shown in Scheme 4 of the approach between **I** and **a**, where the bulky adamantyl perester and the benzyl directing group are located at opposite faces of the enolate. Therefore, such a proposal accounts for both the observed reactivity and stereoselectivity since carbon-centered alkyl radicals are involved in the alkylation, whose stereochemical outcome hinges on the approach of the entire perester to the less sterically shielded *Si* π-face of the enolate.

Eventually, the easy access to α-adamantyl alkylated adducts **1a−9a** led us to explore their conversion into enantiomerically pure building blocks and derivatives that might be employed as ligands for chiral catalysts. The results matched our expectations (Scheme 5). Indeed, reductive removal of the chiral auxiliary from **1a** with $LiBH_4$ gave the corresponding alcohol **10** in 64% yield. Furthermore, 1,2-dihydroxy and 2-amino-1-hydroxy derivatives **11** and **12**, respectively, were synthesized from adducts **8a** and **9a** in a similar way, which represents a straightforward approach to such interesting ligands.[21]

Scheme 5. Synthesis of Enantiomerically Pure Derivatives

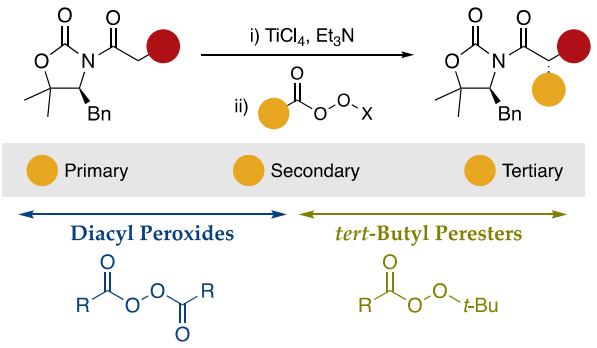


In summary, we have developed a highly stereoselective alkylation of titanium(IV) enolates of a variety of chiral *N*-acyl oxazolidinones with *tert*-butyl peresters from Cα branched aliphatic acids under experimentally mild conditions. The resultant alkylated adducts are isolated in moderate to high

https://doi.org/10.1021/acs.orglett.1c03366
Org. Lett. 2021, 23, 8852−8856

yields as a single diastereomer (dr ≥97:3), which represents an appealing entry to the challenging alkylation of metal enolates with secondary or tertiary alkyl groups. Computational studies have revealed that the success of such an approach is based on the reduction of the *tert*-butyl perester by the enolate, which triggers a radical-like transformation. Finally, it should be noted that this method complements a parallel and previously reported introduction of secondary and primary alkyl groups based on the use of diacyl peroxides. All together, both pieces of reactivity permit the diastereoselective Cα alkylation of titanium enolates with a broad range of alkyl groups (Scheme 6).

Scheme 6. Cα Alkylation



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03366.

Experimental details, compound characterization, and copies of ^{1}H and ^{13}C NMR spectra (PDF)
Crystallographic data for **1c** (PDF)

Accession Codes

CCDC 2098119 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Pedro Romea − *Secció de Química Orgànica, Departament de Química Inorgànica i Orgànica and Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain;* orcid.org/0000-0002-0259-9155; Email: pedro.romea@ub.edu

Fèlix Urpí − *Secció de Química Orgànica, Departament de Química Inorgànica i Orgànica and Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain;* orcid.org/0000-0003-4289-6506; Email: felix.urpi@ub.edu

Enrique Gómez-Bengoa − *Departamento de Química Orgánica I, Universidad del Pais Vasco, 20080 San Sebastián, Spain;* orcid.org/0000-0002-8753-3760; Email: enrique.gomez@ehu.es

Authors

Marina Pérez-Palau − *Secció de Química Orgànica, Departament de Química Inorgànica i Orgànica and Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain;* orcid.org/0000-0001-9905-3513

Nil Sanosa − *Secció de Química Orgànica, Departament de Química Inorgànica i Orgànica and Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain;* Present Address: Departamento de Química, Centro de Investigación en Síntesis Química (CISQ), Universidad de La Rioja (Spain)

Rosa López − *Departamento de Química Orgánica I, Universidad del Pais Vasco, 20080 San Sebastián, Spain*

Mercè Font-Bardia − *Unitat de Difracció de RX. CCiTUB, Universitat de Barcelona, 08028 Barcelona, Catalonia, Spain*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c03366

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Spanish Ministerio de Ciencia, e Innovación (MCIN)/Agencia Estatal de Investigación (AEI)/Fondo Europeo de Desarrollo Regional (FEDER, UE) (Grant No. PGC2018-094311-B-I00 and Grant No. PID2019-110008GB-I00), the Generalitat de Catalunya (2017SGR 271), and SGIker (UPV/EHU) for providing human and computational resources. Furthermore, a doctorate studentship to M.P.-P. (FPU, MINU) is acknowledged.

■ REFERENCES

(1) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, 2009.

(2) (a) MacMillan, D. W. C.; Watson, A. J. B. α-Functionalization of Carbonyl Compounds. In *Science of Synthesis: Stereoselective Synthesis 3*; De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Thieme: Stuttgart, Germany, 2011; Vol. 3, pp 674−715. (b) Stoltz, B. M.; Bennett, N. B.; Duquette, D. C.; Goldberg, A. F. G.; Liu, Y.; Loewinger, M. B.; Reeves, C. M. Alkylation of Enols and Enolates. In *Comprehensive Organic Synthesis II*; Knochel, P.; Molander, G. A., Eds.; Pergamon Press: Oxford, 2014; Vol. 3, Chapter 3.1; pp 1−49.

(3) For classical approaches based on chiral auxiliaries, see: (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. Asymmetric Alkylation Reactions of Chiral Imide Enolates. A Practical Approach to the Enantioselective Synthesis of α-Substituted Carboxylic Acid Derivatives. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. Pseudoephedrine as a Practical Chiral Auxiliary for the Synthesis of Highly Enantiomerically Enriched Carboxylic Acids, Alcohols, Aldehydes, and Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511.

(4) For a method based on the use of a traceless chiral auxiliary, see: Stivala, C. E.; Zakarian, A. Highly Enantioselective Direct Alkylation of Arylacetic Acids with Chiral Lithium Amides as Traceless Auxiliaries. *J. Am. Chem. Soc.* **2011**, *133*, 11936−11939.

(5) For a recent review, see: Wright, T. B.; Evans, P. A. Catalytic Enantioselective Alkylation of Prochiral Enolates. *Chem. Rev.* **2021**, *121*, 9196−9242.

(6) (a) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. Direct Nucleophilic S_N1-Type Reactions of Alcohols. *Eur. J. Org. Chem.* **2011**, *2011*, 647−666. (b) Gualandi, A.; Mengozzi, L.; Cozzi, P. G. Stereoselective S_N1-Type Reaction of Enols and Enolates. *Synthesis* **2017**, *49*, 3433−3443.

(7) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. New Procedure for the Direct Generation of Titanium Enolates. Diastereoselective Bond Construction with Representative Electrophiles. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216.
(8) For recent contributions to the stereoselective catalytic alkylations of metal enolates, see: (a) Fernández-Valparís, J.; Romo, J. M.; Romea, P.; Urpí, F.; Kowalski, H.; Font-Bardia, M. Stereoselective Alkylation of (*S*)-*N*-Acyl-4-isopropyl-1,3-thiazolidine-2-thiones catalyzed by $(Me_3P)_2NiCl_2$. *Org. Lett.* **2015**, *17*, 3540−3543. (b) Kennington, S. C. D.; Ferré, M.; Romo, J. M.; Romea, P.; Urpí, F.; Font-Bardia, M. Diastereoselective and Catalytic *α*-Alkylation of Chiral *N*-Acyl Thiazolidinethiones with Stable Carbocationic Salts. *J. Org. Chem.* **2017**, *82*, 6426−6433. (c) Kennington, S. C. D.; Taylor, A. J.; Romea, P.; Urpí, F.; Aullón, G.; Font-Bardia, M.; Ferré, L.; Rodrigalvarez, J. Direct and Asymmetric Nickel(II)-Catalyzed Construction of Carbon−Carbon Bonds from *N*-Acyl Thiazinanethiones. *Org. Lett.* **2019**, *21*, 305−309.
(9) For a recent report on a successful Lewis acid mediated alkylation of zirconium enolates from *N*-arylacetyl oxazolidinones with tertiary alkyl electrophiles, see: Shim, E.; Zakarian, A. Stereoselective *α*-Tertiary Alkylation of *N*-(Arylacetyl)oxazolidinones. *Synlett* **2020**, *31*, 683−686.
(10) (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. Enantioselective Catalysis Using SOMO Activation. *Science* **2007**, *316*, 582−585. (b) Nicewicz, D. A.; MacMillan, D. W. C. Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes. *Science* **2008**, *322*, 77−80.
(11) (a) Moreira, I. de P. R.; de, P. R.; Bofill, J. M.; Anglada, J. M.; Solsona, J. G.; Nebot, J.; Romea, P.; Urpí, F. Unconventional Biradical Character of Titanium Enolates. *J. Am. Chem. Soc.* **2008**, *130*, 3242−3243. (b) Heras, C.; Gómez-Palomino, A.; Romea, P.; Urpí, F.; Bofill, J. M.; Moreira, I. de P. R. Experimental and Computational Evidence for Biradical Structure and Reactivity of Titanium(IV) Enolates. *J. Org. Chem.* **2017**, *82*, 8909−8916.
(12) Gómez-Palomino, A.; Pérez-Palau, M.; Romea, P.; Urpí, F.; Del Olmo, M.; Hesse, T.; Fleckenstein, S.; Gómez-Bengoa, E.; Sotorríos, L.; Font-Bardia, M. *Org. Lett.* **2020**, *22*, 199−203.
(13) For other radical alkylation of titanium enolates, see: (a) Beaumont, S.; Ilardi, E. A.; Monoe, L. R.; Zakarian, A. Valence Tautomerismin Titanium Enolates: Catalytic Radical Haloalkylation and Application in the Total Synthesis of Neodysidenin. *J. Am. Chem. Soc.* **2010**, *132*, 1482−1483. (b) Gu, Z.; Herrmann, A. T.; Zakarian, A. Dual Ti−Ru Catalysis in the Direct Radical Haloalkylation of *N*-Acyl Oxazolidinones. *Angew. Chem., Int. Ed.* **2011**, *50*, 7136−7139.
(14) For a radical alkylation of zirconium enolates, see: Herrmann, A. T.; Smith, L. L.; Zakarian, A. A Simple Method for Asymmetric Trifluoromethylation of *N*-Acyl Oxazolidinones via Ru-Catalyzed Radical Addition to Zirconium Enolates. *J. Am. Chem. Soc.* **2012**, *134*, 6976−6979.
(15) Li, Y.; Ge, L.; Muhammad, M. T.; Bao, H. Recent Progress on Radical Decarboxylative Alkylation for Csp^3−C Bond Formation. *Synthesis* **2017**, *49*, 5263−5284.
(16) (a) Murarka, S. *N*-(Acyloxy)phtalimides as Redox-Active Esters in Cross-Coupling Reactions. *Adv. Synth. Catal.* **2018**, *360*, 1735−1753. (b) Niu, P.; Li, J.; Zhang, Y.; Huo, C. One-Electron Reduction of Redox-Active Esters to Generate Carbon-Centered Radicals. *Eur. J. Org. Chem.* **2020**, *2020*, 5801−5814.
(17) Locklear, M.; Dussault, P. H. The Chemistry of Peresters. *Eur. J. Org. Chem.* **2020**, *2020*, 4814−4840.
(18) (a) Yoon, T. P.; Jacobsen, E. N. Privileged Chiral Catalysts. *Science* **2003**, *299*, 1691−1693. (b) Connon, R.; Roche, B.; Rokade, B. V.; Guiry, P. J. Further Developments and Applications of Oxazoline-Containing Ligands in Asymmetric Catalysis. *Chem. Rev.* **2021**, *121*, 6373−6521.
(19) For the synthesis of the peresters, see the Supporting Information.
(20) The calculations were run with the Gaussian 16 set of programs and the M06 functional, including an implicit solvation model (IEF-PCM, $ClCH_2CH_2Cl$). For more details, see the Supporting Information.
(21) (a) Clariana, J.; Garcia-Granda, S.; Gotor, V.; Gutiérrez-Fernández, A.; Luna, A.; Moreno-Mañas, M.; Vallribera, A. Preparation of (*R*)-(1-adamantyl)glycine and (*R*)-2-(1-adamantyl)-2-aminoethanol: a combination of cobalt-mediated *β*-ketoester alkylation and enzyme-based aminoalcohol resolution. *Tetrahedron: Asymmetry* **2000**, *11*, 4549−4557. (b) Clariana, J.; Comelles, J.; Moreno-Mañas, M.; Vallribera, A. 2,2-Isopropylidenebis[(4*R*)-(1-adamantyl)-2-oxazoline] (Adam-Box). A new enantiopure C2-symmetrical ligand: enantioselective cyclopropanations, Diels−Alder reactions, and allylic oxidations. *Tetrahedron: Asymmetry* **2002**, *13*, 1551−1554.

https://doi.org/10.1021/acs.orglett.1c03366
Org. Lett. 2021, 23, 8852−8856