Titanium(IV) enolate chemistry applied to the stereoselective construction of C–C and C–O bonds. New ionic and radical processes

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Organic Chemistry Doctoral Program

TITANIUM(IV) ENOLATE CHEMISTRY APPLIED TO THE STEREOSELECTIVE CONSTRUCTION OF C–C AND C–O BONDS. NEW IONIC AND RADICAL PROCESSES

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Cover Image

Laura Ferré

The experimental work of this Thesis has been entirety carried out in the Department of Organic Chemistry of the University of Barcelona, from September 2014 to December 2017, under the direction of Prof. Dr. Fèlix Urpí and Dr. Pedro Romea. From May of 2015 to April of 2018 I have enjoyed a predoctoral fellowship “Ajuts de Personal Investigador Predoctoral en Formació (APIF) per a Alumnes de Tercer Cicle de la Universitat de Barcelona”

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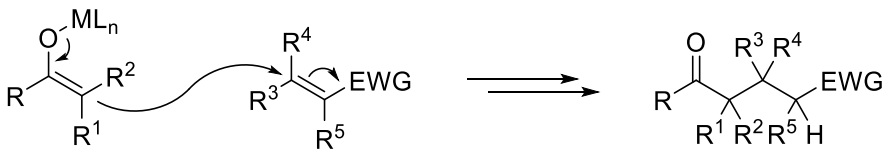
GENERAL INTRODUCTION

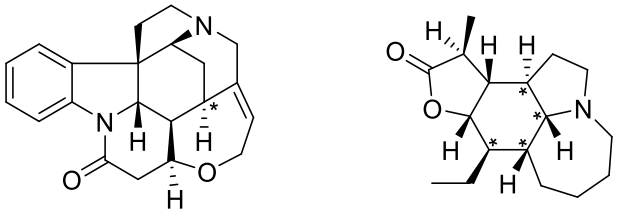
One of the main challenges within organic synthesis is to gain access to enantiomerically pure chiral compounds following short and highly efficient synthetic sequences. This encouraged the development of new synthetic methods that provide the desired products in a straightforward and stereocontrolled manner. In this context, for the last three decades, the outstanding development of a wide range of stereoselective methods has enabled the synthesis of numerous natural products with great structural complexity.[1–5]

In particular, the development of new synthetic methods aimed towards the stereoselective construction of C–C bonds has been a crucial element to achieve these milestones. Among the various key reactions available for organic synthetic chemists, the venerable Michael reaction, which refers to additions of stable carbon nucleophiles such as enolates to conjugated olefins bearing an electron-withdrawing group, is beyond doubt one of the most powerful C–C bond forming reactions (Scheme 1).[6,7]



Scheme 1

In fact, the wide range of available donors and acceptors this transformation can combine sustains a lingering interest in the Michael reaction within synthetic chemistry. Comprehensive studies carried out in the 1980s on the conjugate addition of metallic enolates to α,β-unsaturated compounds provided a reasonably good understanding of the key elements that determine the relative configuration of the resultant adducts.[6–10] Thus, great effort has been dedicated to developing asymmetric procedures to control the configuration of as many stereocentres as possible,[11–16] and a variety of recently reported enantioselective and catalytic Michael reactions have already been employed in the synthesis of a plethora of natural products.[2–4,17] Unfortunately and despite these early achievements and the ensuing exploitation of this transformation in the synthesis of natural products (Figure 1), there is still a shortage of asymmetric Michael methodologies.

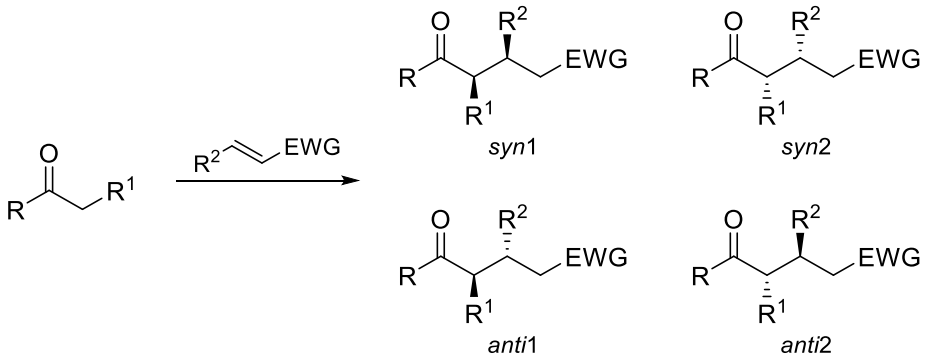


(-)-Strychnine (-)-Stenine

Examples of natural products synthesised using asymmetric Michael reactions (stereogenic centres created by the asymmetric Michael addition are indicated with *).

Figure 1

In order for a Michael reaction to be synthetically useful, the formation of only one of the different possible Michael adduct's stereoisomers is needed. From a synthetic point of view, up to eight possible stereoisomers can be produced when three new stereocentres are introduced. However, the use of less substituted acceptors limits the number up to four. In this case, two of the stereoisomers show a relative *syn* configuration and the other two show a relative *anti* configuration (Scheme 2). If none of the reagents has any chiral element initially, *syn* (or *anti*) adducts become enantiomers, while any *syn* and any *anti* adduct are diastereomers. If, under these conditions, a Michael reaction mainly affords either *syn* or *anti* pair, it is said that there has been relative stereochemical control or diastereoselectivity. In contrast, when adducts *syn*1 and *syn*2 (or *anti*1 and *anti*2) can be formed in different ratios, we talk of absolute stereochemical control or enantioselectivity.



*syn*1 *syn*2 *anti*1 *anti*2

Scheme 2

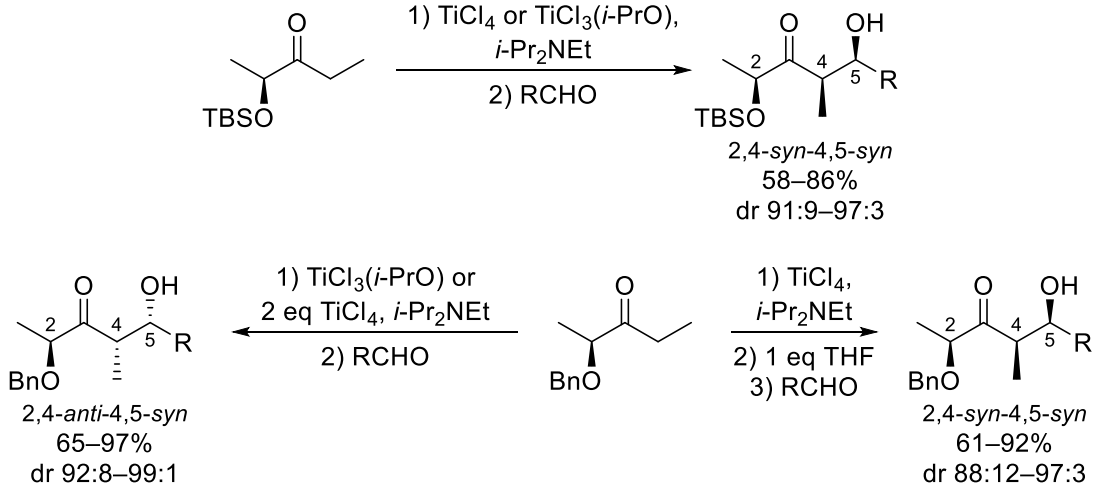
The control of the configuration of the new stereocentres can be achieved by the use of internal chiral auxiliaries,[18,19] external chiral auxiliaries (either stoichiometric or catalytic),[15,18,20] or by means of strategies based on substrate control.[21] Internal chiral auxiliaries and substrate control approaches rely on the presence of a chiral element, usually a chiral centre, in the starting molecule that controls the stereochemical outcome of the reaction; importantly, the relation between adducts *syn*1, *syn*2, *anti*1 and *anti*2 is all diastereomeric, so that all isomers may be differentiated and separated. In turn,

external chiral auxiliaries rely on the formation of diastereomeric transition states or reaction intermediates that evolve following different pathways, which permits the main formation of one of the possible stereoisomers. Unfortunately, in the case of no additional chiral centres in the molecule, adducts *syn*1 and *syn*2 (or *anti*1 and *anti*2) cannot be separated from each other using currently available achiral purification techniques.

The impact of internal chiral auxiliaries on stereoselective reactions has been widely studied, so the choice of the appropriate chiral auxiliary and reaction conditions usually provides excellent stereochemical control. However, the use of internal chiral auxiliaries is often limited to the initial stages of a synthesis, since it involves the lengthening of the synthetic sequence by two steps, introduction and removal, that often require conditions that could damage the synthesised structure. To avoid these disadvantages, many efforts have been made to develop external chiral auxiliaries. Furthermore, the possibility of being used in a catalytic version allows the obtention a similar efficiency with the minimum expense of reagents (atom economy).[22,23]

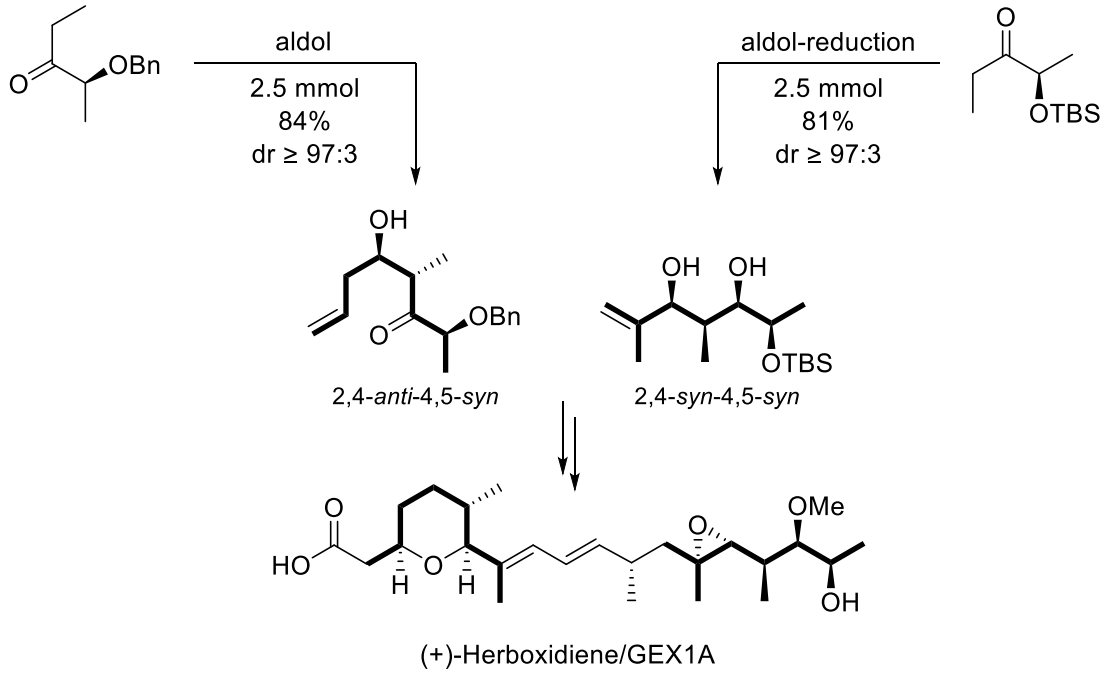
Another option to control the stereochemical outcome of a reaction is so-called *substrate control*. These methodologies take advantage of the functionality and stereochemistry already inherent in a structure to control the configuration of the new stereocentres and also incorporate this structure as part of the growing molecule. These approaches are limited by the nature of the starting structure, but they can be applied both in early and advanced stages and allow the shortening of the number of steps of a sequence (step economy).[24]

In this context, a few years ago our group launched a research project dedicated to the study of the reactivity of titanium(IV) enolates from chiral ketones. Initially, aldol additions of titanium(IV) enolates from chiral α- and β-hydroxy ketones were examined, which finally permitted us to establish highly stereoselective procedures useful for the synthesis of natural products. As shown in Scheme 3, lactate derived ethyl ketones turned out to be excellent platforms from which *syn* aldol adducts were accessible, depending on the hydroxy protecting group and the titanium(IV) Lewis acid. Indeed, enolization of α-sililoxy ketones with $TiCl_4$ or $TiCl_3$(*i*-PrO) led to 2,4-*syn*-4,5-*syn* adducts,[25] whereas α-benzyloxy counterparts produced the same diastereomer with $TiCl_4$ but the opposite 2,4-*anti*-4,5-*syn* if $TiCl_3$(*i*-PrO) or two equivalents of $TiCl_4$ were used instead.[26–28]



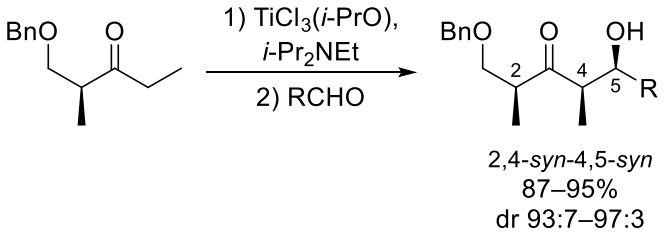
Scheme 3

These procedures were employed for the total synthesis of herboxidiene/GEX1A (Scheme 4).[29] Importantly, the entire set of chiral centres were introduced by means of substrate-controlled reactions from two lactate-derived ketones. Furthermore, the whole carbon framework of the resultant aldol adducts were incorporated into the final molecule.



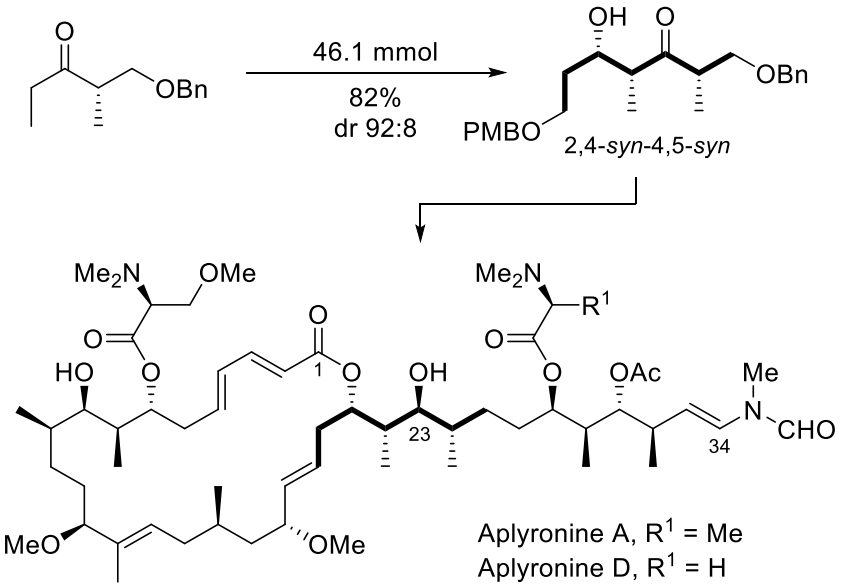
Scheme 4

In turn, Roche ester-derived β-benzyloxy ketones also proved to be suitable starting materials for the obtention of 2,4-*syn*-4,5-*syn* aldol adducts in high yields and diastereoselectivities by simple enolization with $TiCl_3$(*i*-PrO) (Scheme 5).[30]



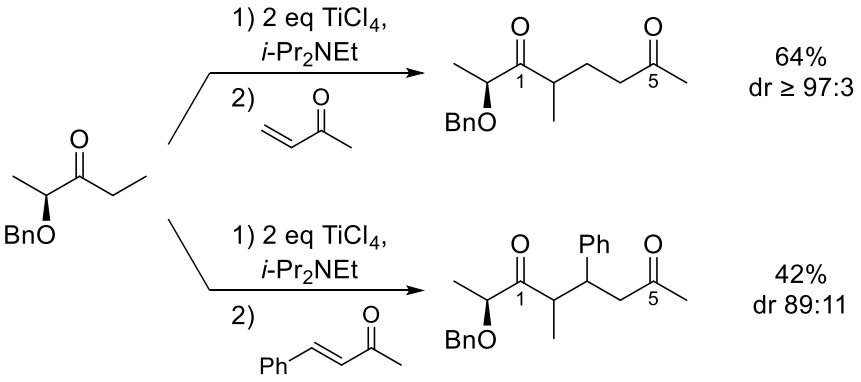
Scheme 5

This procedure has proved highly efficient, much more reliable than parallel methods based on $Sn(OTf)_2$.[31,32] For instance, it has been successfully applied to the synthesis of Aplyronine A and D (Scheme 6).[33]



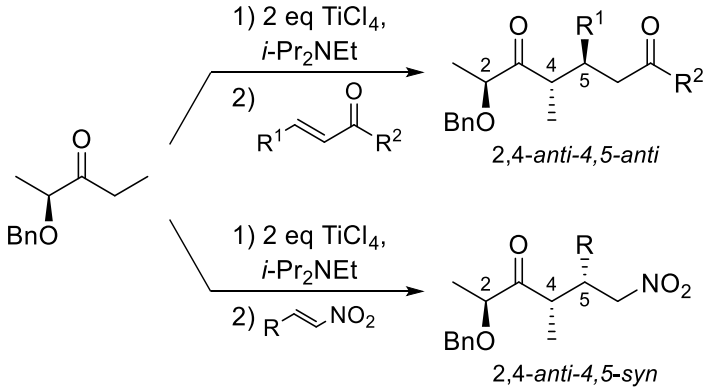
Scheme 6

Taking advantage of this chemistry, Miquel Pellicena in his PhD also explored Michael additions of α-benzyloxy ethyl ketones to α,β-unsaturated carbonyl compounds with the aim of developing new substrate-controlled stereoselective methods for preparing 1,5-dioxygenated structures (Scheme 7).[34] The preliminary results summarised in Scheme 7 indicated that titanium(IV) enolates from lactate-derived α-benzyloxy ethyl ketones might be excellent nucleophiles to carry out highly diastereoselective substrate-controlled Michael additions.



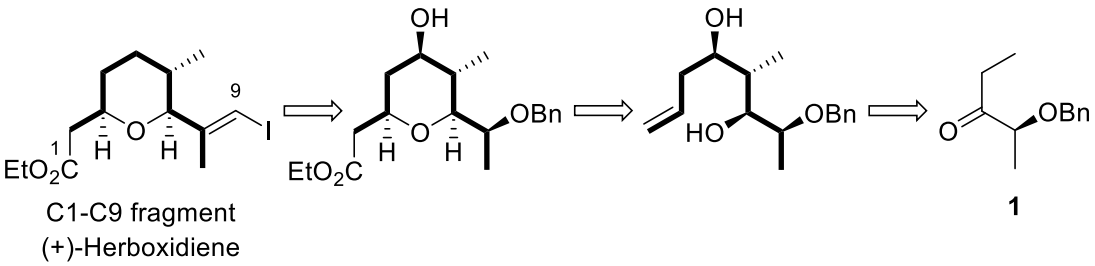
Scheme 7

Therefore, the first objective of this Thesis was to go deeper into the analysis of the nucleophilic character of titanium(IV) enolates. Particularly, we focused our attention on the analysis of substrate-controlled Michael additions to enones and other acceptors. According to these objectives, we evaluated in Chapter 1 the effect of different activating Lewis acids on the Michael addition of chiral α-benzyloxy ketones to α,β-unsaturated ketones which finally gave 2,4-*anti*-4,5-*anti* adducts (Scheme 8). Moreover, it was later expanded to additions to conjugated nitroalkenes to obtain γ-nitrocarbonyl backbones with 2,4-*anti*-4,5-*syn* relative configuration.



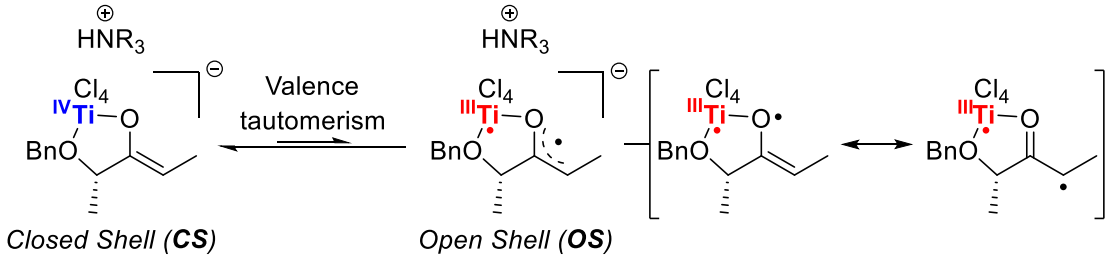
Scheme 8

The success of such an approach led us to re-evaluate the synthesis of the tetrahydropyran ring of the C1-C9 fragment of (+)-herboxidiene/GEX1A (Scheme 9). In Chapter 2, we analysed the initial retrosynthesis of the C1-C9 fragment and studied the oxa-Michael cyclization. Finally, we designed and carried out two parallel sequences to improve the first approach of (+)-herboxidiene/GEX1A.



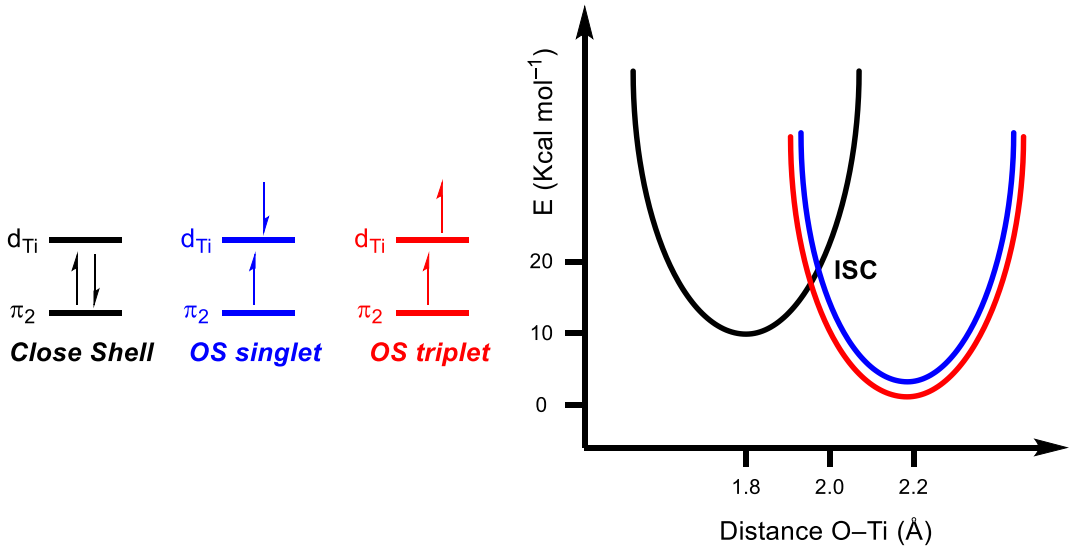
Scheme 9

The second objective of this Thesis is rooted in completely different ground. As the god Janus from the ancient roman times, titanium(IV) enolates possess two opposite faces looking to the past but also to the future. One of these faces refers to their nucleophilic character, in common with other enolates. However, titanium(IV) enolates also have a biradical character, much less reported, that might confer new reacting avenues to them. Theoretical calculations coupled with EPR studies carried out in our group proved that α-benzyloxy titanium enolates ketones derived from lactic acid are an almost planar *ate-complex* with a chelated five membered ring structure (Scheme 10). Such calculations also showed that the electronic distribution in the titanium *ate-complex* of α-hydroxy ketones had to be considered as two utterly unlike but almost degenerated electronic configurations. Indeed, the nature of these electronic configurations is, to a large extent, distinct: one corresponds to a *closed shell* electronic state (***CS***, Scheme 10), whereas the other has a marked *open shell* (***OS***, Scheme 10), delocalised biradical character, which requires an electron transfer from the organic ligand to the titanium metal, in a valence tautomerism process.[35]



Scheme 10

Actually, the calculations identified low energy *singlet* and *triplet* electronic states with a very strong biradical character in which one electron is mainly located over the titanium atom and the other one forms an allylic-like system [O−CR−CH_2]•. Such species may be classified as titanium(III) enolates (Scheme 11). These biradical species are close in energy to the titanium(IV) enolate, and these three species are connected through an *intersystem crossing* (**ISC,** Scheme 11) with a very low energy barrier.

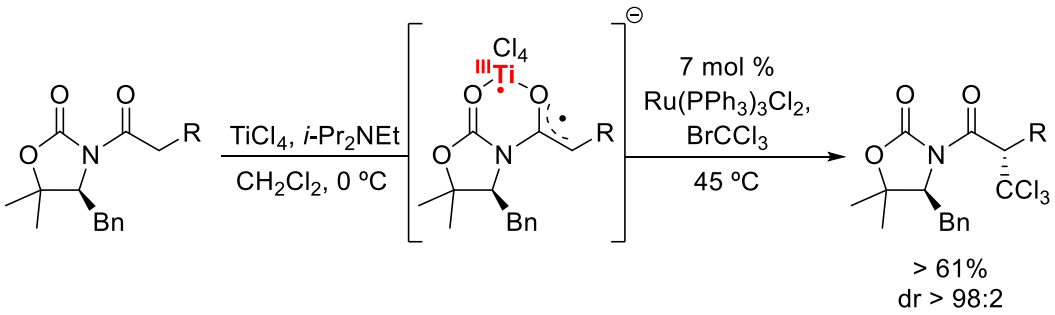


Scheme 11

Therefore, the closed shell electronic configuration would be responsible for the classical nucleophilic reactivity observed for these titanium enolates, like the reactivity studied in the first part of this Thesis, whereas the open shell might be the basis for a new reacting paradigm in which *titanium(IV) enolates can also participate in radical reactions*.

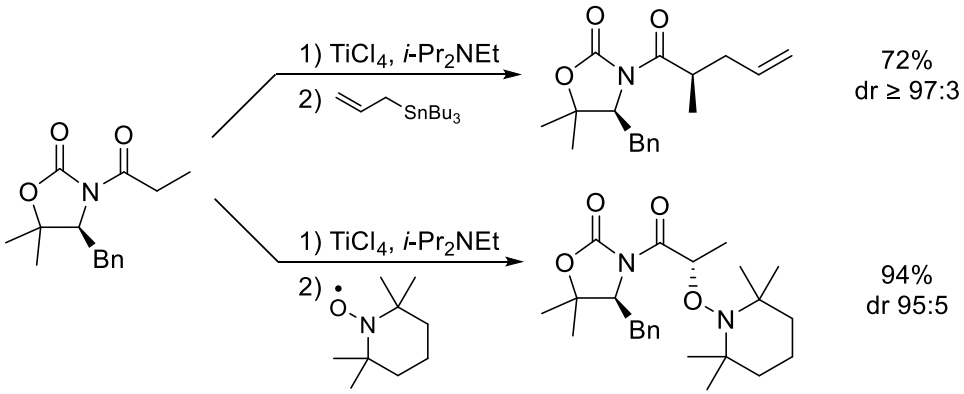
In this context, Miquel Pellicena, in his PhD, tried to exploit this biradical character for the stereoselective allylation of lactate derived α-benzyloxy ketones with allyltributyltin compounds. Unfortunately, the titanium enolate of this ketone was unstable at temperatures close to 0 °C and the allylation failed.

These drawbacks may be overcome by using much more robust titanium(IV) enolates from *N*-acyl oxazolidinones. Indeed, they also displayed a biradical character, due to the planarity exhibited by a chelated six membered ring structure, similar to that from α-hydroxy ketones.[36] Actually, Zakarian proved that titanium(IV) enolates derived from chiral *N*-acyl oxazolidinones could indeed react stereoselectively with carbon-centred radicals in selective haloalkylations, through a homolytic mechanism (Scheme 12).[37]



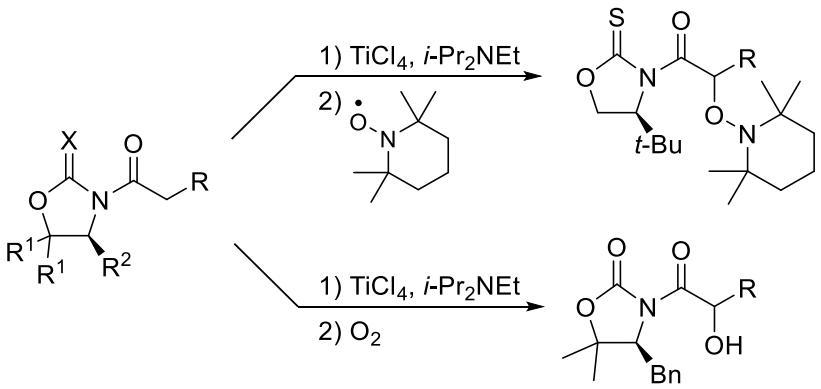
Scheme 12

Inspired by such an approach, Miquel Pellicena developed a stereoselective allylation of chiral *N*-acyl oxazolidinones with allyl stannanes (Scheme 13). Parallel to these C–C bond forming reactions, he also explored the oxidation of such titanium(IV) enolates with TEMPO, a commercially available oxygen-based radical (Scheme 13).



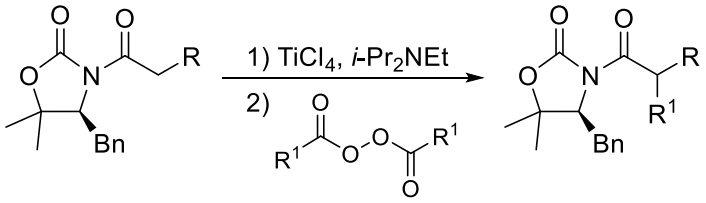
Scheme 13

Hence, in the second part of this Thesis we examined the uncommon biradical reactivity of titanium enolates derived from chiral *N*-acyl oxazolidinones when exposed to radical reagents (Scheme 14). In fact, in Chapter 3, the α-aminoxylation project was continued and the methodology was further expanded to other substrates. Concurrently, additional theoretical calculations and experimental studies were carried out to further understand this transformation. Subsequently, we reported a highly stereoselective oxidation of titanium enolates from chiral *N*-acyl oxazolidinones with molecular oxygen, a novel approach for the synthesis of enantiomerically pure α-hydroxy carboxylic derivatives taking advantage of the biradical character of oxygen (throughout this Thesis we will use the word oxygen for the O_2 molecule, which is properly called dioxygen).



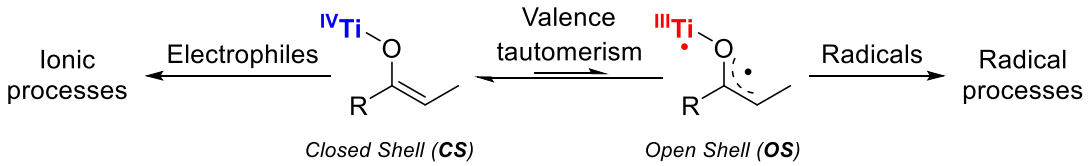
Scheme 14

Then, we describe in Chapter 4 a comprehensive search of compounds able to participate homolytic reactions, which involves a brief exploration in the jungle of photoredox catalysis. Finally, such research led to the discovery of a new and highly stereoselective alkylation reaction with diacyl peroxides. Decarboxylation of the diacyl peroxides from aliphatic acids produces primary and secondary radicals promoted by the titanium enolates, which triggers stereoselective alkylations that were beyond imagination with classic methodologies (Scheme 15).



Scheme 15

In summary, this Thesis studies stereoselective methodologies for constructing C–C and C–O bonds based on chiral titanium(IV) enolates, involving new ionic and radical processes (Scheme 16).



Scheme 16

CHAPTER 1

Michael additions of α-benzyloxy ethyl ketones

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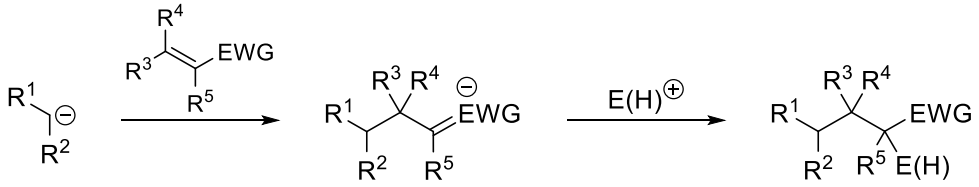
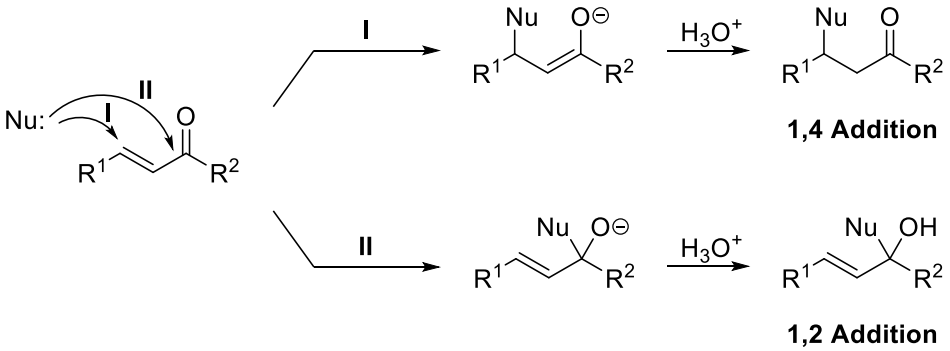
1. Introduction

Originally, the Michael reaction referred to the conjugate addition of a stabilised enolate to an α,β-unsaturated carbonyl compound providing a valuable 1,5-dioxygenated pattern.[6,7] However, nowadays, it is generally accepted that the Michael addition consists in the nucleophilic addition of an enolate or carbanion to an alkene bearing an electron withdrawing group (EWG). Such a conjugate addition leads to an intermediate that, upon treatment with water (H) or another electrophile (E) furnishes the final Michael adduct and overall forming one new C–C bond and up to three new stereocentres (Scheme 17).



Scheme 17

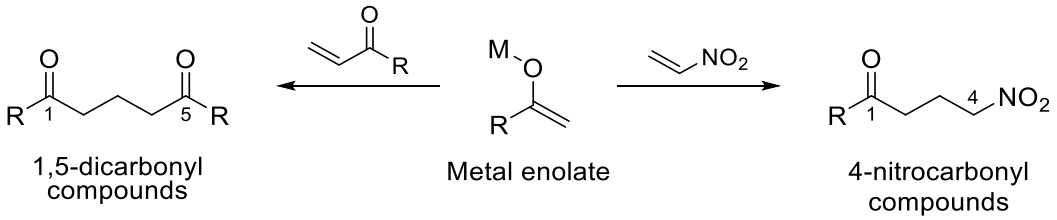
Some of the most well-known Michael acceptors are α,β-unsaturated carbonyl compounds, such as acrylic acid derivatives or enones. Two reaction pathways are possible for this kind of electrophiles. The first one involves a 1,4 addition, in which the nucleophile attacks at the conjugated position and affords the Michael adduct (see route **I** in Scheme 18). The second is based on a 1,2 addition, in which the nucleophile undergoes a direct attack to the carbonyl group to yield an allylic alcohol (see route **II** in Scheme 18).



Scheme 18

Conjugated nitroalkenes are another well-known type of Michael acceptor that do not suffer the abovementioned problems of regioselectivity. The strong electron withdrawing character of the nitro group makes these substrates significant Michael acceptors.[38,39] Thus, Michael additions of enolates to enones and α,β-unsaturated nitroalkenes give access to 1,5-dicarbonyl and 4-nitrocarbonyl compounds respectively

(Scheme 19); both intermediates are useful platforms from which the synthesis of a variety of structurally complex compounds can be attained.



Scheme 19

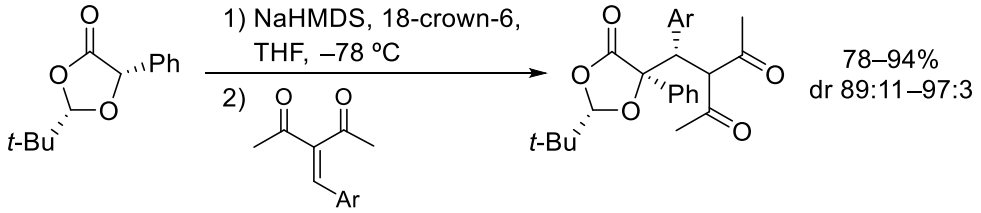
In summary, the wide range of nucleophiles and acceptors makes the Michael addition one of the most relevant C–C bond formation tools,[1–5] and it has stimulated the development of a number of methodologies designed for the selective formation of one of all the possible stereoisomers.

1.1. Michael additions to enones

1.1.1. Stoichiometric addition of metallic enolates to enones

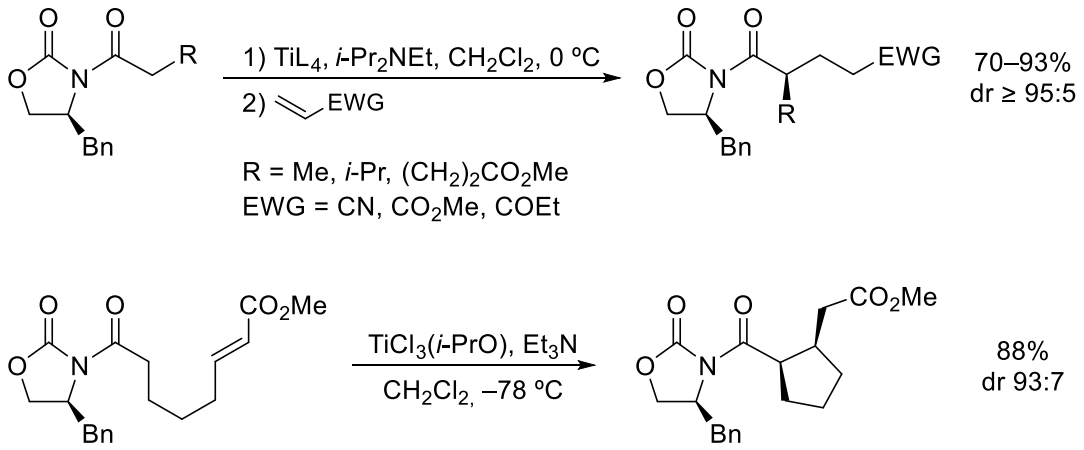
Stereoselective Michael addition of metallic enolates, mostly lithium, sodium and titanium enolates, to enones have been thoroughly studied.

Pedro reported a diastereoselective Michael addition of a chiral enolate prepared from (*S*)-mandelic acid and pivalaldehyde.[40] Lithium and potassium enolates offered moderate selectivity, whereas sodium enolates gave good to excellent yields and diastereoselectivity in the addition to conjugated 1,3-diketones (Scheme 20).



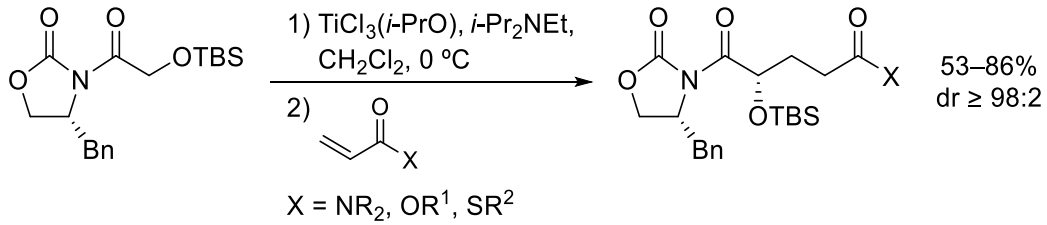
Scheme 20

It was Evans who showed one again the power of the direct formation of titanium enolates from chiral *N*-acyl oxazolidinones in conjugate additions.[41] Indeed, Michael additions of titanium(IV) enolates, prepared by directly treating such substrates with $TiCl_4/R_3N$ or $TiCl_3(i\text{-PrO})/R_3N$, afford the corresponding adducts with excellent yields and stereoselectivities even when two stereocentres were formed (Scheme 21).



Scheme 21

Later on, and following the same research path, Urpí and Vilarrasa expanded the former methodology to chiral *N*-glycolyl oxazolidinones and other acrylate derived compounds using $TiCl_3$(*i*-PrO) with good yields and excellent diastereselectivities (Scheme 22).[42]

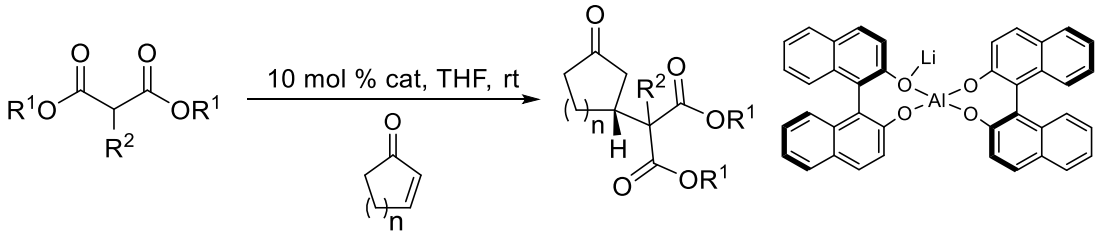


Scheme 22

These examples prove the synthetic power of titanium enolates, mainly due to the simplicity in their preparation and manipulation, which allows them to participate in total synthesis.

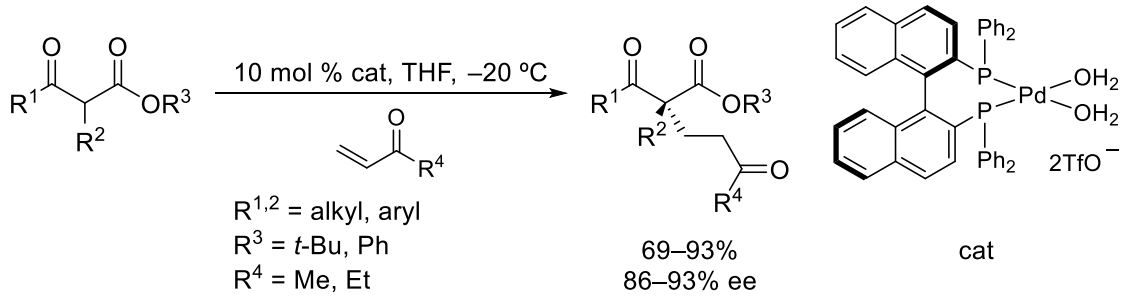
1.1.2. Catalytic additions of metallic enolates to enones

Great efforts had been made to remove the need to preform a stoichiometric enolate. Shibasaki et al., for example, reported a lithium-aluminium heterobimetallic catalyst with a chiral BINOL backbone.[43] This catalyst triggers the addition of stabilised enolates from malonates to cyclic enones with excellent yields and good enantioselectivities (Scheme 23).



Scheme 23

In turn, Sodeoka described the addition of stabilised enolates from 1,3-diketones and 1,3-ketoesters to vinyl ketones catalysed by a palladium complex containing a chiral diphosphine.[44] This catalyst affords the corresponding Michael adducts with good yields although the enantioselectivities range from moderate to good (Scheme 24).

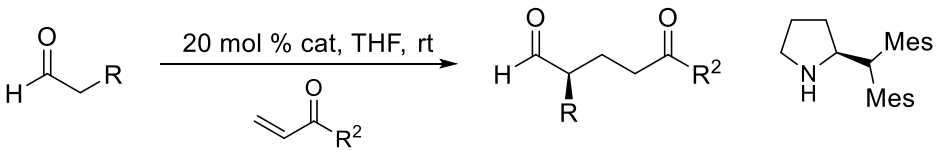


Scheme 24

Despite the success of such catalytic transformations, they are still limited to particularly acidic compounds, like β-ketoesters or 1,3-diketones.

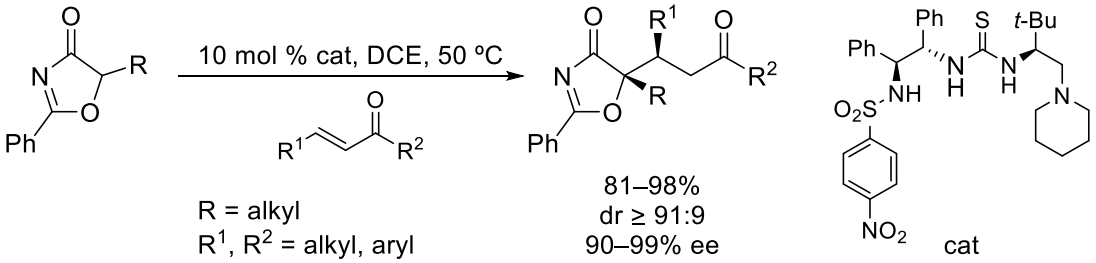
1.1.3. Organocatalytic Michael additions to enones

In the past fifteen years organocatalysis has been one of the most trending areas in organic chemistry.[15] Despite the narrow scope of such reactions, intrinsic to organocatalysis, some examples of organocatalytic Michael additions to enones are really remarkable. In this context, Melchiorre and Jørgensen developed a novel, direct and enantioselective Michael addition of aldehydes to vinyl ketones catalysed by a proline derivative with moderate yields and enantioselectivities (Scheme 25).[45]



Scheme 25

In turn, Ye described Michael additions of oxazolones to α,β-unsaturated ketones using a *tert*-leucine based amine-thiourea bifunctional organocatalyst. The corresponding adducts can be obtained with excellent yield, diastereo and enantioselectivity (Scheme 26).[46]

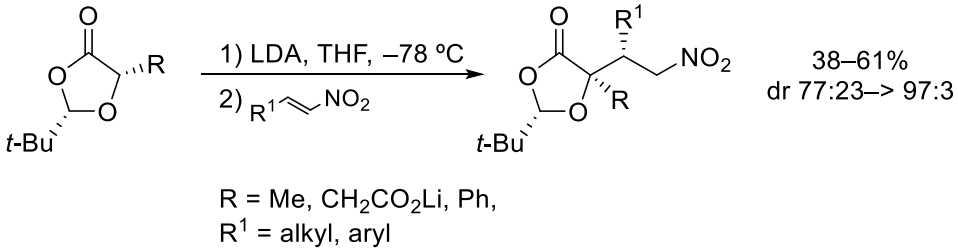


Scheme 26

1.2. Michael additions to nitroalkenes

1.2.1. Stoichiometric addition of metallic enolates to nitroalkenes

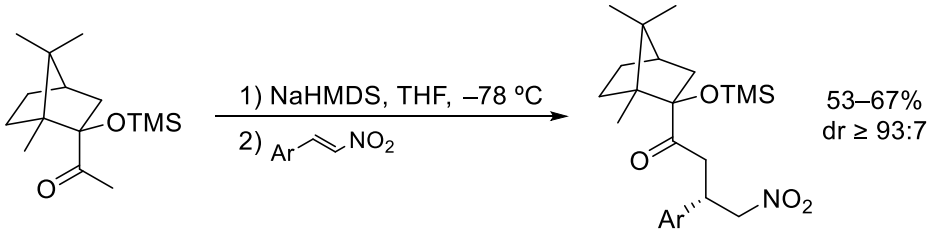
Parallelly to the addition to enones, alkaline metallic enolates, mostly lithium and sodium, and titanium enolates attracted much interest for the addition to nitroalkenes. For example, Seebach el al. reported a diastereoselective Michael addition of chiral lithium enolates, prepared from either mandelic acid, lactic acid or malic acid and pivalaldehyde, to α,β-unsaturated nitroalkenes.[47] Although aromatic nitroalkenes afforded moderate selectivity, their aliphatic counterparts provided good yields and excellent diastereselectivities (Scheme 27)



Scheme 27

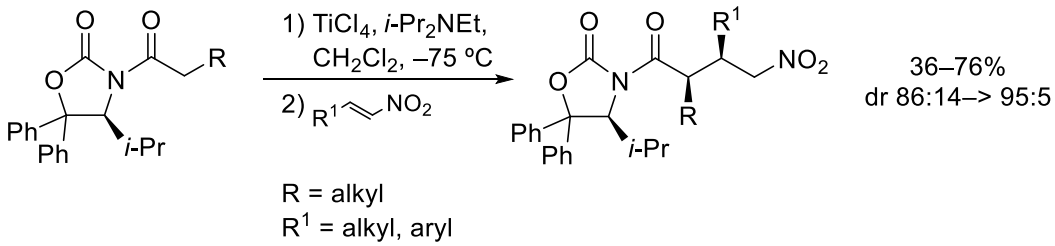
In the same context, Palomo examined the Michael addition of enolates from α-hydroxy ketones derived from camphor to aromatic nitroalkenes.[48] Whereas the lithium

enolate worked without efficiency in terms of diastereoselectivity, and the potassium enolate did not provide the expected adduct, sodium enolates gave the corresponding Michael adducts in good yields and excellent diastereoselectivities for aromatic nitroalkenes (Scheme 28).



Scheme 28

Seebach later described the addition of titanium(IV) enolates from chiral *N*-acyl oxazolidinones to aromatic and aliphatic nitroalkenes.[49] While alkaline-metal enolates afforded moderate results, the titanium counterparts provided the corresponding Michael adducts with better yields and diastereoselectivities (Scheme 29).

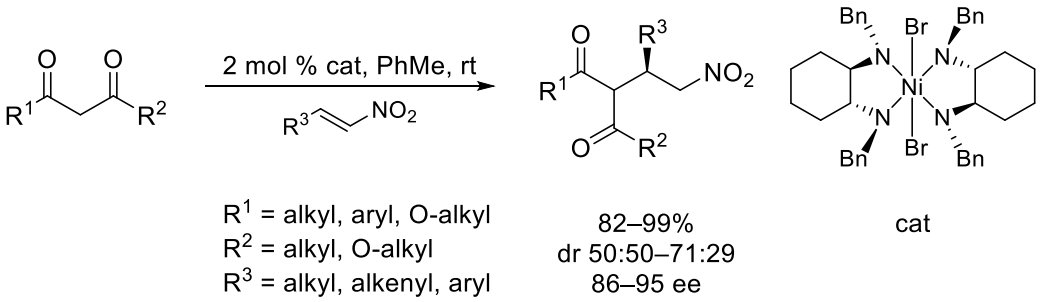


Scheme 29

As for the case of conjugate additions to enones, these examples show the synthetic potential of titanium enolates in Michael additions to α,β-unsaturated nitroalkenes.

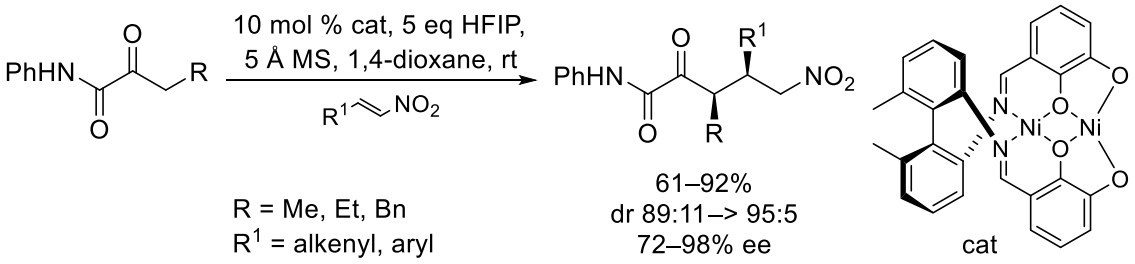
1.2.2. Catalytic additions of metallic enolates to nitroalkenes

Great efforts have also been made in the catalytic area of the addition to nitroalkenes. For example, Evans reported a bimetallic nickel complex with a chiral diamine ligand.[50,51] This catalyst promoted the addition of stabilised enolates from malonates to aromatic nitroalkenes with excellent yields and good enantioselectivities (Scheme 30).



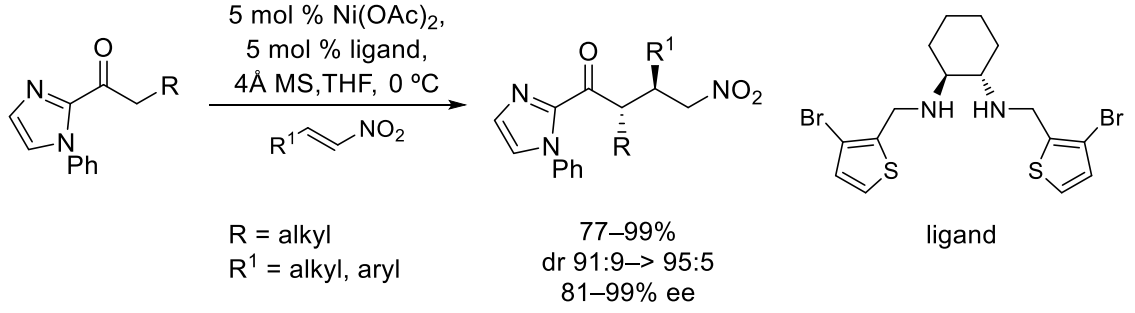
Scheme 30

In turn, Shibasaki described a highly diastereoselective Michael addition of α-keto anilides to nitroalkenes catalysed by a homodinuclear nickel complex to afford *syn* Michael adducts in good yields and remarkable selectivities (Scheme 31).[52]



Scheme 31

Finally, Wang reported the conjugate addition of imidazole-modified ketones to nitroalkenes in the presence of a chiral nickel catalyst which provided the corresponding *anti* adducts with excellent yields and good enantioselectivities (Scheme 32).[53]

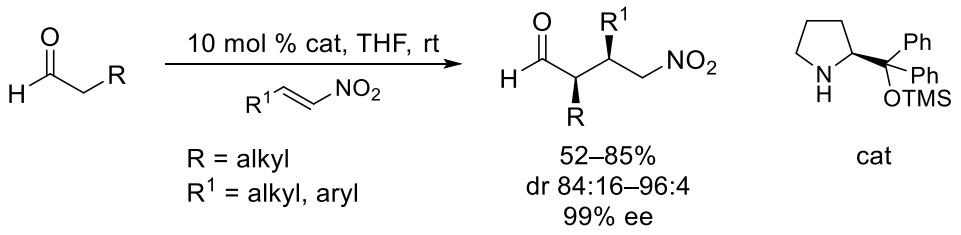


Scheme 32

1.2.3. Organocatalytic Michael additions to nitroalkenes

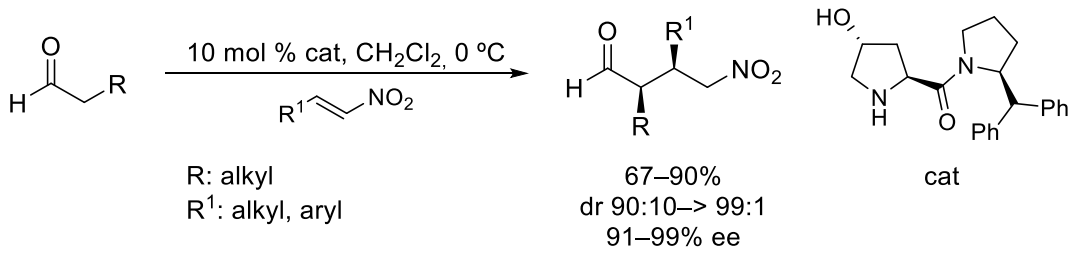
Despite the essentially narrow scope of substrates available for organocatalysis, remarkable steps toward a general method for Michael additions to α,β-unsaturated nitroalkenes have been reported. In this case, the addition is conceptually easier than for enones because the lack of a carbonyl group in the electrophile avoids the regioselective choice of the substrate to be converted into the required nucleophile. For example, Hayashi described a diphenyl prolinol catalysed Michael addition of

aldehydes to nitroalkenes (Scheme 33), which affords the *syn* adducts with good yields and excellent stereoselectivities.[54]



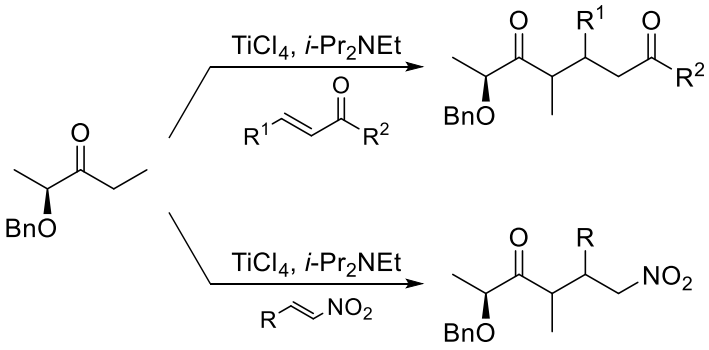
Scheme 33

In parallel, Palomo reported the Michael addition of aldehydes to nitroalkenes catalysed by proline-based derivatives shown in Scheme 34.[55] Finally, hydroxyprolinamide afforded the *syn* adducts with good yields an excellent stereoselectitivies.



Scheme 34

After this brief review of Michael additions to enones and nitroalkenes, one can notice that there is a lack of examples where the control of the stereoselectivity comes from the titanium enolate of a chiral α-hydroxy ketone. Moreover, there is no general procedure, to the best of our knowledge, to carry out additions to nitroalkenes with an aryl or alkyl group equally. In this context and taking advantage of the previous work conducted in the research group on the aldol reaction of titanium enolates from α and β hydroxy ketones, we centred our attention on the assessment of the Michael addition of chiral α-benzyloxy ketones to enones and nitroalkenes (Scheme 35).



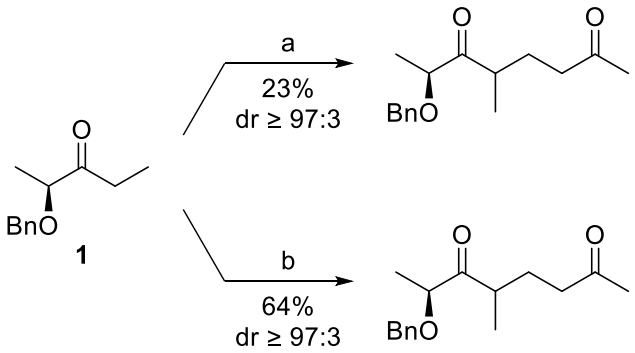
Scheme 35

2. Michael additions to enones

2.1. Introduction

Miquel Pellicena, in his PhD thesis, examined the Michael addition of titanium enolates of (*S*)-2-benzyloxy-3-pentanone (**1**) to α,β-unsaturated nitriles, esters and ketones. Acrylonitrile was found to be unreactive. Thus, a more reactive alkene was necessary; ethyl acrylate proved to be more reactive and afforded the desired Michael adducts but in very low yields. Finally, enones turned out to be suitable acceptor for such reactions.[34]

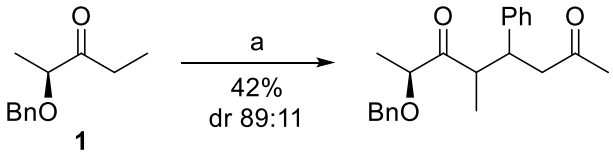
A preliminary screening of reaction conditions revealed that the titanium enolate reacted with methyl vinyl ketone to afford low yields of a single diastereomer. However, the addition of a second equivalent of $TiCl_4$, dramatically increased the yield maintaining an excellent diastereoselectivity (Scheme 36).



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.2 eq CH_2=$CHCOCH_3$, –78 °C, 2 h; b) (i) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.2 eq CH_2=$CHCOCH_3$, –78 °C, 2 h.

Scheme 36

Unfortunately, β-substituted enones afforded the corresponding adducts containing two stereocentres in low yields. The reaction was then carried out at higher temperatures (–40 °C), which improved the yield without eroding diastereoselectivity (Scheme 37).



a) (i) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.2 eq (*E*)-PhCH=$CHCOCH_3$, –40 °C, 2 h.

Scheme 37

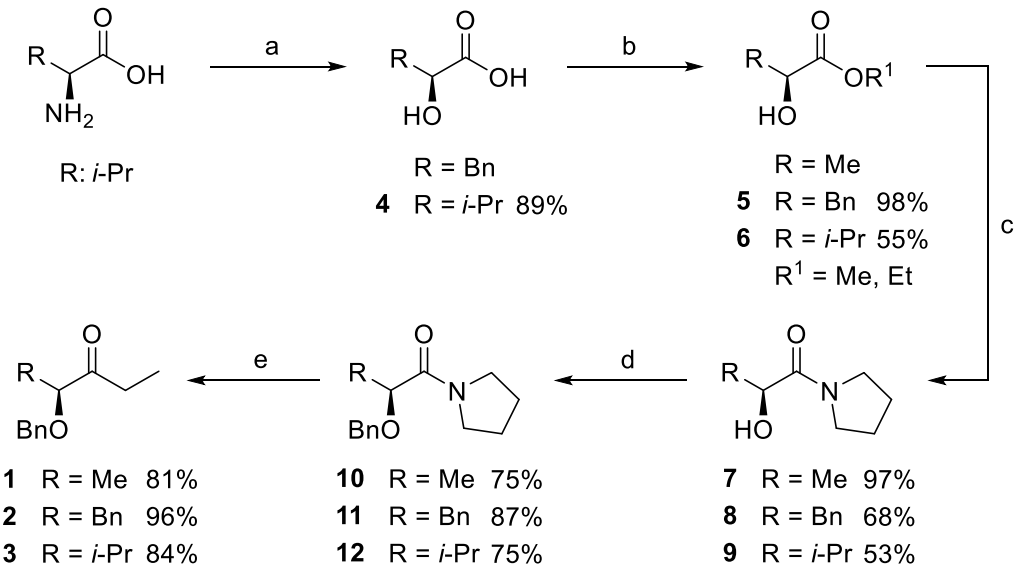
Keeping in mind such precedents, we aimed to examine in detail the substrate-controlled Michael addition of titanium(IV) enolates from chiral ketones to enones. Our

first objective was to study the effect of other Lewis acids added to the titanium enolate and to test more vinyl ketones to expand the scope of the process. The second objective was to test and optimise the Michael addition to β-substituted enones. Furthermore, the configuration of the new stereocentres had to be determined.

2.2. Preparation of α-benzyloxy ethyl ketones

α-Benzyloxy ketones were prepared following a procedure developed in our research group, a straightforward and reliable method that involves the acylation of organomagnesium reagents with the corresponding α-benzyloxy amides.[56,57] This preparation requires the formation of a pyrrolidine amide followed by the protection of the alcohol as a benzyl ether. The chelating ability of the benzyloxy group enables the addition of the organomagnesium reagent, stabilizing the reaction intermediate and avoiding epimerization and multiple additions.

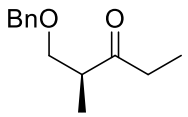
This study was carried out mainly with (*S*)-2-benzyloxy-3-pentanone (**1**), a ketone derived from (*S*)-ethyl lactate. The α-hydroxy ketones **2** and **3** derived from (*S*)-phenylalanine and (*S*)-valine were also prepared following the same procedure (Scheme 38). To be able to form the pyrrolidine amide, the amino acid had to be transformed to the hydroxy acid in a nitrosation-hydrolysis process that keeps the configuration to form hydroxy acid **4**, the hydroxy acid was commercially available for the benzyl derivative and the synthesis starts from this point. This was then followed by a simple esterification to afford hydroxy esters **5**–**6,** the hydroxyester was commercially available for the methyl derivative and again the synthesis starts at this point. Then hydroxy amides **7**–**9** were obtained by simple treatment with pyrrolidine without solvent followed by the protection with benzyl chloride under phase transfer conditions to isolate α-benzyloxy amides **10**–**12**. Finally, treatment with ethyl magnesium chloride provided enantiopure ketones **1**–**3** with very good overall yield in three to five steps.



a) $NaNO_2$, H_2SO_4, H_2O, rt; b) MeOH, $CH(OMe)_3$, cat. TsOH, 65 °C; c) pyrrolidine, rt (R = Me, Bn) o 45 °C (R = *i*-Pr); b) BnCl, NaOH, $[Oct_3NMe]Cl$, toluene, rt; c) EtMgCl, THF, 0 °C.

Scheme 38

Additionally, (*S*)-1-benzyloxy-2-methyl-3-pentanone (**13**) (Figure 2), a Roche ester derived β-benzyloxy ketone was already prepared in our laboratory, we planned to use it also to fully assess the scope of the process and prove the feasibility and robustness of the methodologies developed.



13

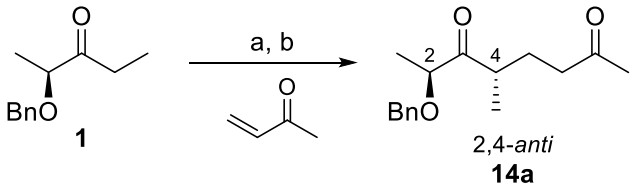
Figure 2

2.3. Michael additions to vinyl ketones

2.3.1. Optimisation of the Michael addition to vinyl ketones

Preliminary experiments by Miquel Pellicena showed that the titanium enolate reacted with methyl vinyl ketone (**Ea**), although with low yields. In turn, enolates prepared with other common metals behaved differently. Test experiments showed that the dibutylboron enolate from (*S*)-2-benzyloxy-3-pentanone (**1**) was unable to undergo conjugate additions to methyl vinyl ketone (**Ea**) and ketone **1** was recovered unchanged even after long reaction times. In turn, the lithium enolate counterpart turned out to be more reactive, but it only afforded trace amounts of the Michael adduct after 16 hours at –78 °C. Then, we focused our attention on the Michael additions from titanium(IV) enolates.

Keeping in mind that the equivalents of $TiCl_4$ used to prepare the titanium(IV) enolates may determine the yield of the Michael reaction, we initially examined the influence of different Lewis acids on the addition of the enolate of **1** to methyl vinyl ketone (**Ea**). The results are summarised in Table 1.



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq LA, –78 °C, 10 min; b) 1.2 eq CH_2=$CHCOCH_3$, –78 °C, 2 h.

Entry	LA	dr[a]	Yield 14a (%)[b]
1	-	≥ 97:3	23
2	$BF_3{\cdot}OEt_2$	-	-
3	$MgBr_2{\cdot}OEt_2$	≥ 97:3	29
4	Et_2AlCl	≥ 97:3	26
5	Ti(*i*-PrO)$_4$	≥ 97:3	13
6	$TiCl_4$	≥ 97:3	62
7	$SnCl_4$	≥ 97:3	60
8[c]	$TiCl_4$	≥ 97:3	80

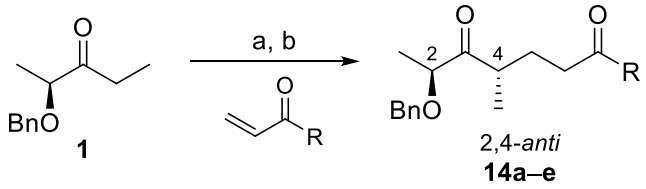
[a] Determined by ^{1}H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Reaction performed for 5 hours.

Table 1

A quick glance at Table 1 reveals that the second equivalent of Lewis acid added to the enolate has no effect on the stereochemical outcome of the conjugate addition since adduct **14a** was obtained as a single diastereomer in all cases. Nevertheless, the second Lewis acid did play a major role in achieving a high yield of **14a**. Soft activators did not largely affect the yield of adduct **14a** (compare entries 1–4, Table 1) while $BF_3{\cdot}OEt_2$ and Ti(*i*-PrO)$_4$ plummeted the performance of the addition (entries 2 and 5, Table 1). Only the addition of $SnCl_4$ and $TiCl_4$ improved significantly the yield and led to **14a** with a 60% yield (entries 6 and 7, Table 1). As both Lewis acids gave similar results, $TiCl_4$ was the chosen to continue since it simplified the method. Additionally, the lengthening in reaction time from 2 to 5 hours increased the yield of adduct **14a** up to 80% (entry 8, Table 1).

2.3.2. General procedure for Michael addition to vinyl ketones

Once a general protocol for the addition was established, a set of vinyl ketones (**Ea–Ee**) with different groups was prepared and tested to fully determine the scope of the reaction. The results are summarised in Table 2.



a) 2.1 eq $TiCl_4$, 1.1 *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq CH_2=CHCOR, –78 °C, t.

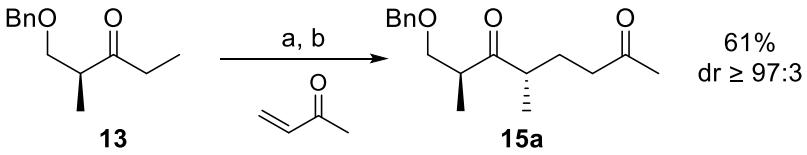
Entry	Enone	R	Time (h)	Product	dr[a]	Yield 14 (%)[b]
1	**Ea**	Me	5	**14a**	≥ 97:3	80
2	**Eb**	Et	5	**14b**	≥ 97:3	79
3	**Ec**	$(CH_2)_2Ph$	5	**14c**	≥ 97:3	75
4	**Ed**	C_6H_{11}	5	**14d**	≥ 97:3	73
5	**Ee**	(*S*)-CH(OTBS)Bn	2	**14e**	≥ 97:3	78

[a] Determined by 1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.

Table 2

As it can be seen in Table 2, all 2,4-*anti* adducts **14a–e** were obtained with similar yields ranging from 73% to 80%. Besides, the R group did not have a significant effect on the stereochemical control since all compounds were isolated as single diastereomers. Moreover, the presence of a chiral centre and a heteroatom at the α position of the enone did not affect the selectivity but matched the yield of the corresponding adduct as the other examples in only 2 h (entry 5, Table 2)

Finally, the excellent results achieved in the Lewis acid mediated Michael addition from lactate-derived chiral ketone **1** to vinyl ketones led us to examine the scope of the method using (*S*)-1-benzyloxy-2-methyl-3-pentanone (**13**), a β-benzyloxy ketone synthesised from Roche ester. The enolate of this ketone was more delicate and a little less reactive, but the Michael addition to methyl vinyl ketone (**Ea**) performed at –78 °C afforded **15a** with 61% yield of a single diastereomer adduct (Scheme 39).



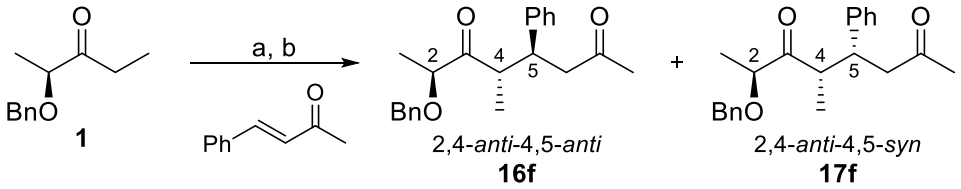
a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (b) 1.2 eq CH_2=$CHCOCH_3$, –78 °C, 4 h.

Scheme 39

2.4. Michael additions to β-substituted enones

2.4.1. Optimisation of the Michael additions to β-substituted enones

As mentioned in the introduction, the preliminary protocol by Miquel Pellicena during his PhD afforded poor yields of the Michael adduct from 4-phenyl-3-buten-2-one (**Ef**). Conventional wisdom predicted that the introduction of any group in the β-position would reduce the reactivity of the Michael acceptor, so we decided to carefully examine the addition to 4-phenyl-3-buten-2-one (**Ef**). Initially, we assessed the influence on the quench method (NH_4Cl or SiO_2) to be sure that a retro-Michael during the purification was not the reason of the low yields. Once we were sure of the suitability of the quench we focused our attention on the influence of the temperature and the second Lewis acid. The results are summarised in Table 3.



a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq (*E*)-PhCH=CHCOCH$_3$, T, t.

Entry	T (°C)	Time (h)	dr (16f:17f)[a]	Yield 16f (%)[b]
1	–78	2	90:10	5
2	–40	2	90:10	35
3	–20	3	90:10	55
4	–20	15	88:12	55
5[c]	–20	3	90:10	83

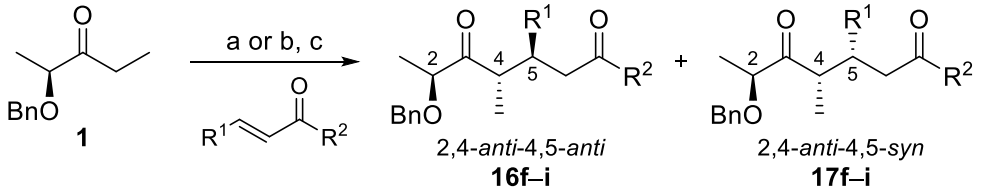
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Reaction performed with 1.1 eq of $TiCl_4$ and 1.1 eq of $SnCl_4$.

Table 3

The general procedure established for vinyl ketones only afforded small amounts of adducts **16f** and **17f** although the stereoselectivity of the addition of the titanium enolate was still very good (dr 90:10), considering that two new chiral centres were formed in a single step (entry 1, Table 3). An increase of the reaction temperature triggered the conjugate addition and dramatically improved the formation of the adducts without producing any loss of stereocontrol (compare entries 1–3, Table 3). Longer reaction times had no effect in the yield (compare entries 3 and 4, Table 3). Finally, we were delighted to observe that the addition of $SnCl_4$ as activating Lewis acid led to a considerable increase up to 83% of the isolated yield of **16f** maintaining the same excellent stereoselectivity (entry 5, Table 3).

2.4.2. General procedure for Michael addition to β-substituted enones

With a general procedure now established, it was applied to a number of β-substituted (*E*)-enones (**Ef–Ei**) with different groups. The Michael additions were carried out using both $TiCl_4$ and $SnCl_4$ to compare the results with each activating Lewis acid. The results are summarised in Table 4.



a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; c) 1.2 eq $R^1CH{=}CHCOR^2$, –20, 3 h.

Entry	Enone	R^1	R^2	LA	Product	dr (16:17)[a]	Yield 16 (%)[b]
1	**Ef**	Ph	Me	$TiCl_4$	**16f**	90:10	55
2	**Ef**	Ph	Me	$SnCl_4$	**16f**	90:10	83
3	**Eg**	Me	Et	$TiCl_4$	**16g**	90:10	(90)
4	**Eg**	Me	Et	$SnCl_4$	**16g**	94:6	(81)
5	**Eh**	$(CH_2)_2Ph$	Me	$TiCl_4$	**16h**	90:10	67
6	**Eh**	$(CH_2)_2Ph$	Me	$SnCl_4$	**16h**	94:6	63
7	**Ei**	$(CH_2)_2OTBS$	Me	$TiCl_4$	**16i**	90:10	68
8	**Ei**	$(CH_2)_2OTBS$	Me	$SnCl_4$	**16i**	-	complex mixture

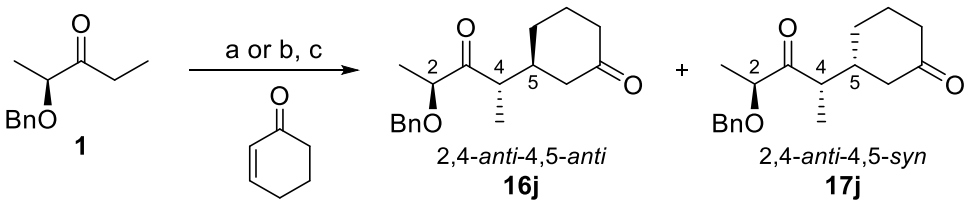
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography. Isolated overall yield into brackets.

Table 4

Results in Table 4 show the excellent stereochemical outcome of these Michael additions. In fact, titanium enolates activated with $TiCl_4$ afforded 2,4-*anti*-4,5-*anti* adducts with diastereoselectivities of 90:10 for all (*E*)-enones and yields from 55% to 90%, proportional to the bulkiness of the β-group (entries 1, 3, 5 and 7, Table 4).

Surprisingly, the use of $SnCl_4$ instead of $TiCl_4$ as a second Lewis acid improved the majority of the abovementioned results. The titanium-tin enolate led to a considerable increase in the isolated yield for adduct **16f**, up to 83% (compare entries 1 and 2, Table 4), maintaining the same excellent stereoselectivity. Michael adducts **16g–h** were obtained in slightly lower yields but with a higher 94:6 diastereomeric ratio (compare entries 3 and 4, and 5 and 6, Table 4) although the addition of $SnCl_4$ was detrimental for adduct **16i** because of the partial removal of the TBS protecting group that was negligible in the case of $TiCl_4$ (compare entries 7 and 8, Table 4).

Unfortunately, the general procedure could not be applied to (*Z*)-enones. Indeed, the addition to cyclohexenone (**Ej**) gave a 66:34 mixture of diastereomers in low overall yield (entry 1, Table 5). As for (*E*)-enones, the addition of $SnCl_4$ was beneficial, but it was not good enough for the addition to cyclohexenone (**Ej**) to be considered synthetically useful (entry 2, Table 5).



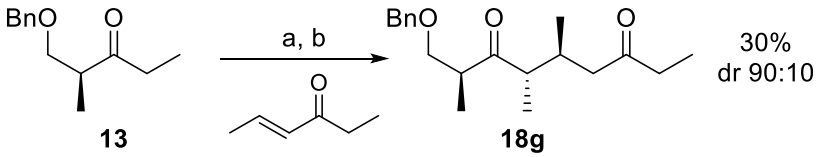
a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; c) 1.2 eq cyclohexenone, –20, 3 h.

Entry	LA	dr[a]	Yield 16j–17j (%)[b]
1	$TiCl_4$	66:34	19
2	$SnCl_4$	75:25	81

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated overall yield.

Table 5

Finally, the general procedure was applied to (*S*)-1-benzyloxy-2-methyl-3-pentanone (**13**), a β-benzyloxy ketone synthesised from Roche ester. Titanium enolates of ketone **13** proved to be slightly less reactive and stable than those from **1**, but the application of the optimised procedure to enone **Eg** at –40 °C led to adduct **18g** in a moderate yield and highly stereocontrolled manner (Scheme 40).

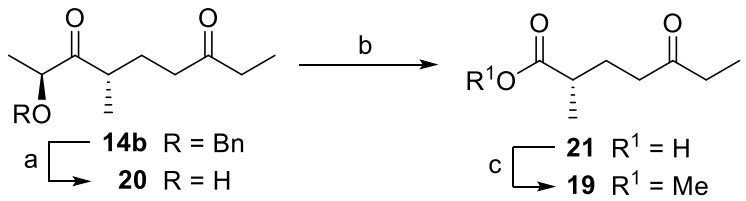


a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; (b) 1.2 eq (*E*)-MeCH=CHCOEt, –40 °C, 3.5 h.

Scheme 40

2.5. Absolute configuration of adducts 14 and 16

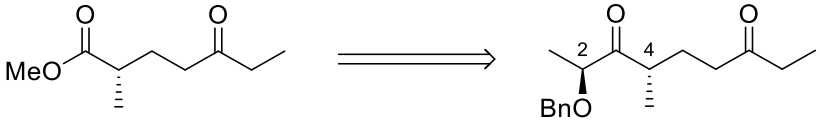
The absolute configuration of the new chiral centre formed in the Michael adducts was determined by conversion of **14b** into methyl (*S*)-2-methyl-5-oxoheptanoate (**19**, Scheme 41), whose physical and spectroscopic data had been described in the literature.[41] The sequence begins with the deprotection of the alcohol by hydrogenolysis followed by oxidation of the α-hydroxyketone **20** to the keto acid **21** and finally esterification gave methyl keto ester **19** with an overall 68% yield in three steps.



a) H2, Pd/C, EtOH, rt, 3 h; b) NaIO4, 2:1 MeOH/H2O, rt, 1.5 h; c) (i) i-Pr2NEt, PivCl, THF, 0 °C, 1 h; (ii) MeOH, DMAP cat, 0 °C to rt, 18 h.

Scheme 41

Physical and spectroscopic data of keto ester **19** matched the data of the enantiomer of the product described in the literature, allowing us to assign the 2,4-*anti* configuration of Michael adduct **14b** (Scheme 42).



19 2,4-*anti* **14b**

19 $[\alpha]_D$ = +21.2 (*c* 1.0, $CHCl_3$)

Evans[41] ***ent*-19** $[\alpha]_D$ = –25.0 (*c* 1.05, $CHCl_3$)

Scheme 42

The configuration of the second chiral centre formed in the Michael adducts was determined by X-ray diffraction analysis of a crystal prepared from pure adduct **16f** (Figure 3).

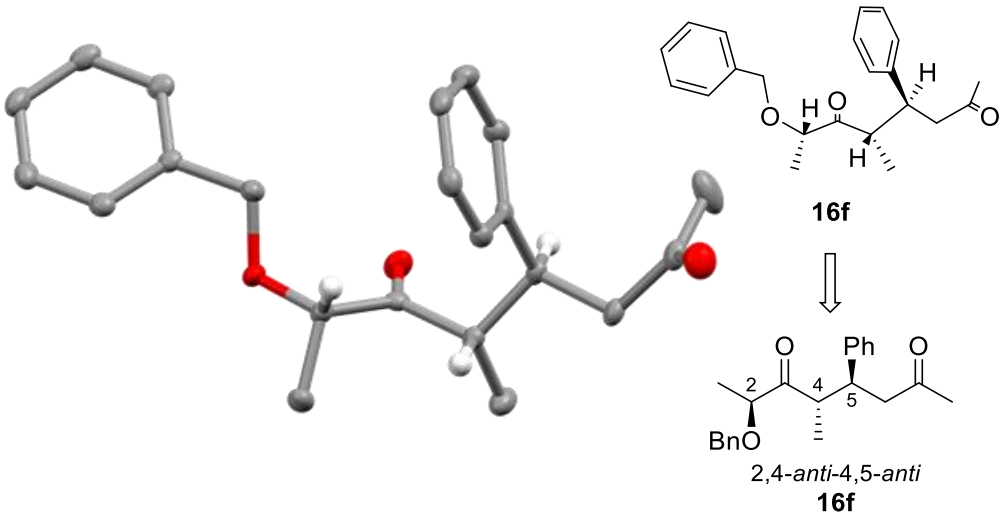


Figure 3

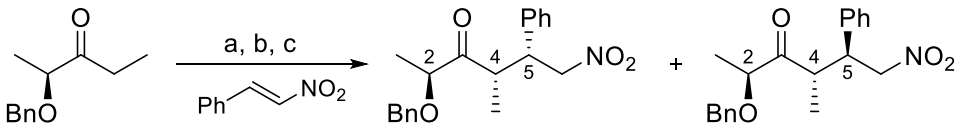
3. Michael additions to nitroalkenes

3.1. Michael additions to aromatic nitroalkenes

3.1.1. Optimisation of the Michael addition to aromatic nitroalkenes

Preliminary experiments showed that despite the strong character of β-nitrostyrene (**Na**) as a Michael acceptor, the reaction with the titanium enolate from (*S*)-2-benzyloxy-3-pentanone (**1**) did not produce any adduct and the starting materials were recovered unchanged. However, full conversion was achieved by adding a second equivalent of $TiCl_4$ to the enolate. The resultant residue contained an 87:13 mixture of two diastereomers (**22a**/**23a**), but the major component **22a** was isolated in a moderate yield (41%) after chromatographic purification (entry 1, Table 6). The use of a stronger Brønsted acid for quenching the reaction only produced a small improvement of the yield (entries 2–4, Table 6).

Then, a careful analysis of the literature unveiled that Seebach had also faced a similar problem. Indeed, he found that the addition of titanium enolates from chiral imides to nitroalkenes gave stable titanium nitronates that were not satisfactorily released by using standard acid treatments. Instead, it was necessary to quench the reaction with NH_4F.[49] The application of such conditions after some optimisation allowed us to obtain a 87:13 diastereomeric mixture, from which diastereomerically pure adduct **22a** was isolated in an 80% yield (entry 7, Table 6).



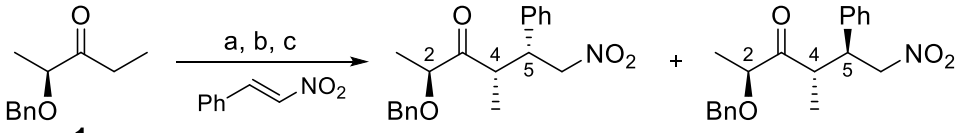
a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq (*E*)-$PhCH=CHNO_2$, –78 °C, $t_{reaction}$; c) quench, t_{quench}.

Entry	$Time_{reaction}$ (h)	$Time_{quench}$	Quench	dr (22a:23a)[a]	Yield 22a (%)[b]
1	1.5	10 min	NH_4Cl	87:13	41
2	1.5	15 min	HCl	87:13	52
3	1.5	1.5 h	HCl	87:13	55
4	1.5	12 h	HCl	87:13	47
5	1.5	1.5 h	NH_4F	87:13	79
6	1	1 h	NH_4F	87:13	77
7	1	0.5	NH_4F	87:13	80

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.

Table 6

As we were aware of the significant impact of the Lewis acid used to trigger the reaction with β-substituted enones, several tests were carried out adding a variety of Lewis acids to the titanium enolate to assess the optimal combination, results are shown in Table 7.



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq LA, –78 °C, 10 min; b) 1.2 eq (*E*)-$PhCH=CHNO_2$, –78 °C, 1 h; c) NH_4F, rt, 30 min.

Entry	LA	dr (22a:23a)[a]	Yield 22a (%)[b]
1	$BF_3{\cdot}OEt_2$	-	-
2	$MgBr_2{\cdot}OEt_2$	-	traces
3	Et_2AlCl	75:25	(60)[c]
4	Ti(*i*-PrO)$_4$	-	traces
5	$TiCl_4$	87:13	80
6	$SnCl_4$	37:47:13:2	31[d]

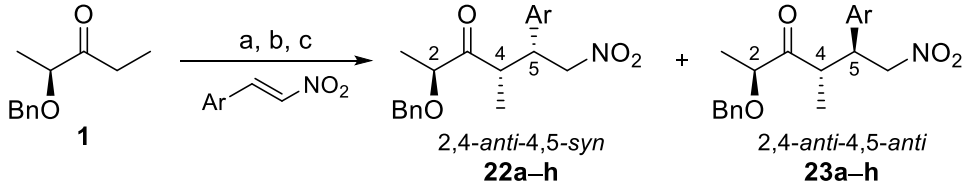
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Overall conversion determined by ^1H NMR analysis of the crude mixture.
[d] Diastereomer **23a** was isolated as major product**.**

Table 7

Unfortunately, and despite efforts to reach a better stereocontrol, the diastereoselectivity was not improved. Soft Lewis acids were unable to trigger the addition (entries 1, 2 and 4, Table 7) while Et_2AlCl offered lower conversion and stereocontrol (entry 3, Table 7). Surprisingly, $SnCl_4$ reversed the selectivity and formed little amounts of other minor diastereomers (compare entries 5 and 6, Table 7). Thereby, $TiCl_4$ remained the most appropriate Lewis acid to perform the Michael addition of **1** to β-nitrostyrene (**Na**).

3.1.2. General procedure for Michael addition to aromatic nitroalkenes

Once a general protocol for the addition was established, a set of aromatic nitroalkenes (**Na–Nh**) with different aryl groups was prepared and tested to complete the study of the scope. The results are summarised in Table 8.



a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq (*E*)-ArCH=$CRNO_2$, –78 °C, 1 h; c) NH_4F, rt, 30 min.

Entry	Nitroalkene	Ar	Product	dr (22:23)[a]	Yield 22 (%)[b]
1	**Na**	Ph	**22a**	87:13	80
2	**Nb**	4-MeC_6H_4	**22b**	88:12	80
3	**Nc**	4-$MeOC_6H_4$	**22c**	93:7	80
4	**Nd**	3,4-$(OCH_2O)C_6H_3$	**22d**	90:10	82
5	**Ne**	4-ClC_6H_4	**22e**	87:13	70
6	**Nf**	4-$NO_2C_6H_4$	**22f**	-	< 5
7	**Ng**	2-furyl	**22g**	93:7	60
8	**Nh**	(*E*)-PhCH=CH	**22h**	-	complex mixture
9[c]	**Nh**	(*E*)-PhCH=CH	**22h**	-	complex mixture

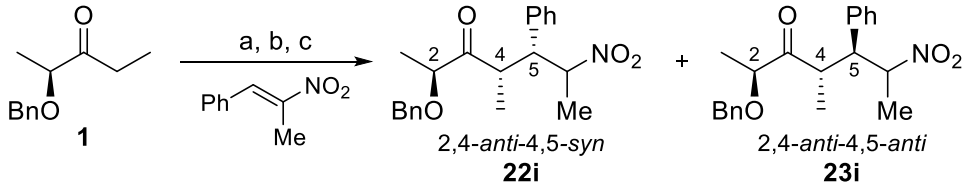
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Reaction performed with 1.1 eq of $TiCl_4$ and 1.1 eq of $SnCl_4$.

Table 8

As shown in Table 8, most of the substrates examined reacted smoothly to afford mixtures from which 2,4-*anti*-4,5-*syn* diastereomers **22a**–**e** were isolated in yields from 70% to 80% (entries 1–5, Table 8), except for 4-nitrophenyl nitroalkene **Nf** that proved to be unreactive (entry 6, Table 8). Remarkably, even the addition of **1** to a Lewis acid sensitive acceptor such as furyl nitroalkene **Ng** proceeded successfully and the adduct **22g** was isolated in a 60% yield (entry 7, Table 8). Interestingly, the

diastereoselectivity of the reaction turned out to be somehow dependent on the electronic character of the aromatic ring, from 87:13 up to 93:7, being slightly higher for those containing electron-donating groups as in **22c**, **22d** or **22g** (entries 3, 4 and 7, Table 8). Moreover, the general procedure was also applied to nitro-4-phenyl-1,3-butadiene (**Nh**), but there was no regioselectivity between the β and the δ electrophilic carbons (entries 8 and 9, Table 8).

Furthermore, the reaction to α-substituted nitroalkenes would provide three new stereocentres. However, addition of **1** to (*E*)-β-methyl-β-nitrostyrene (**Ni**) led to complex mixtures. Conventional wisdom predicted the lack of stereocontrol in the third stereocentre since it is formed during the aqueous quench. Nevertheless, it seems that the presence of the α-methyl also induced a loss in the stereocontrol of the second stereocentre (Table 9).



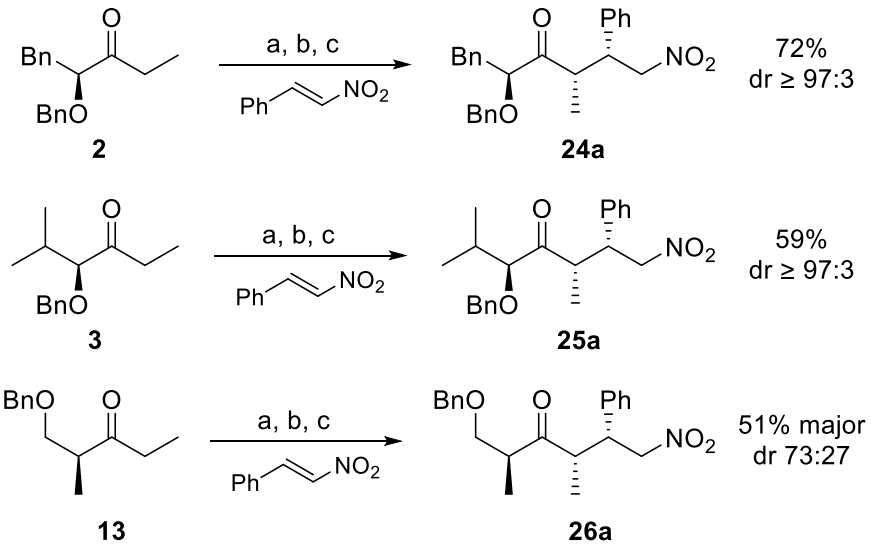
a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq (*E*)-PhCH=C(Me)NO_2, –78 °C, 1 h; c) NH_4F, rt, 30 min.

Entry	dr (22i:23i)[a]	Yield 22i–23i (%)[b]
1	(1:1):(1:1)	81
2[c]	(3:3):(1:1)	23

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated overall yield.
[c] Performed with 1.1 eq of $TiCl_4$ and 1.1 eq of $SnCl_4$.

Table 9

The good yields and diastereoselectivities achieved in Lewis acid-mediated Michael additions of **1** to nitroalkenes **Na**–**Ne** and **Ng** encouraged us to explore similar substrate-controlled reactions with other chiral hydroxy ketones (Scheme 43). Titanium(IV) enolates from α-benzyloxy ketones **2** and **3** as well as β-benzyloxy ketone **13** proved to be slightly less reactive and stable than those from **1.** Nevertheless, we were pleased to observe that α-benzyloxy ketones underwent smooth additions to β-nitrostyrene (**Na**) to afford **24a** and **25a** as single diastereomers (dr ≥ 97:3) in yields up to 72%, whereas β-benzyloxy counterpart provided the corresponding adduct with a poorer diastereoselectivity (dr 73:27).



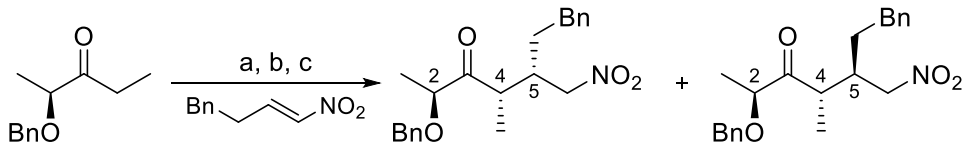
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $TiCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$PhCH{=}CHNO_2$, –40 °C, 1 h; c) NH_4F, rt, 30 min.

Scheme 43

3.2. Michael addition to aliphatic nitroalkenes

3.2.1. Optimisation of the Michael addition to aliphatic nitroalkenes

Aiming to expand the scope of the process, we next examined conjugate additions to β–alkyl nitroalkenes. Unfortunately, the reaction of **1** with (*E*)-1-nitro-4-phenyl-1-butene (**NI**) gave the expected adducts **27l/28l** but with moderate stereocontrol (dr 60:40) and 60% overall yield (entry 3, Table 10). Then, considering the crucial impact of the second Lewis acid on the outcome of these additions, we evaluated the influence of Lewis acids on the addition to (*E*)-1-nitro-4-phenyl-1-butene (**NI**).



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq LA, –78 °C, 10 min; b) 1.2 eq (*E*)-$BnCH_2CH{=}CHNO_2$, –78 °C, 1 h; c) NH_4F, rt, 30 min.

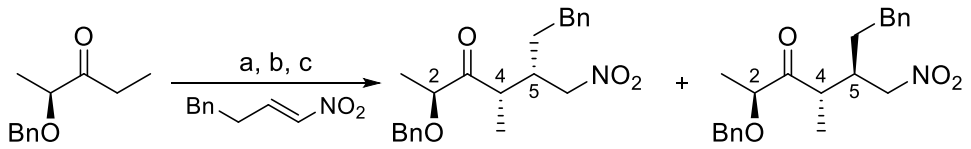
Entry	LA	dr (27l:28l)[a]	Yield 27l (%)[b]
1	Et_2AlCl	62:38	(49)[c]
2	$TiCl_3$(*i*-PrO)	65:35	(25)[c]
3	$TiCl_4$	60:40	(60)
4	$TiBr_4$	-	-
5[d]	$TiBr_4$	-	-
6	$ZrCl_4$	70:30	(38)[c]
7	$SnCl_4$	84:10:6[e]	46 (55)

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography. Isolated overall yield into brackets.
[c] Overall conversion determined by ^1H NMR analysis of the crude mixture.
[d] Performed with 2.1 eq of $TiBr_4$.
[e] Other minor diastereomer.

Table 10

After a careful analysis, we observed that other titanium(IV) as well as zirconium(IV) or aluminium Lewis acids afforded similar or even worse results, but $SnCl_4$ was able to provide a much better diastereoselectivity with a comparable yield (Table 10). Indeed, treatment of the titanium enolate with one equivalent of $SnCl_4$ before the addition of nitroalkene **Nl** gave a mixture of three diastereomers (dr 84:10:6) from which adduct **27l** was isolated in 46% yield (entry 7, Table 10).

The following optimisation of conditions showed that an increase of the temperature to –40 °C improved the yield decreasing slightly the diastereoselectivity; whereas a higher temperature had a deleterious impact on the yield (compare entries 3–5, Table 11). Finally, longer reaction times also improved the yield (compare entries 1 and 2, Table 11), so diastereomerically pure **27l** was finally isolated in 54% yield after 3 h at –78 °C (entry 2, Table 11).



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$BnCH_2CH{=}CHNO_2$, T, t; c) NH_4F, rt, 30 min.

Entry	T (°C)	Time (h)	dr (27l:28l)[a]	Yield 27l (%)[b]
1	−78	1	84:10:6[c]	46 (55)
2	−78	3	84:10:6[c]	54 (66)
3	−78 → −40	1+1	83:12:5[c]	56 (66)
4[d]	−78 → −40	1+1	79:15:6[c]	51 (64)
5	−78 → −20	1+1	nd	(33)[e]

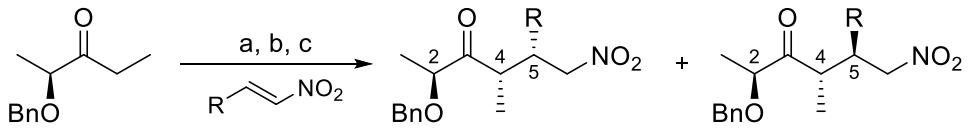
[a] Determined by ^1H NMR and HPLC analysis of the crude mixture.
[b] Isolated yield after column chromatography. Isolated overall yield into brackets.
[c] Other minor diastereomer.
[d] Performed with 1.8 eq of nitroalkene.
[e] Overall conversion determined by ^1H NMR analysis of the crude mixture.

Table 11

3.2.2. General procedure for Michael addition to aliphatic nitroalkenes

Once a general protocol for the addition was already established, a set of aromatic nitroalkenes (**Nj–Nq**) with different alkyl groups was prepared and tested to study of the scope. The results are summarised in Table 12.

The conjugate addition proceeded smoothly with yields up to 80% and diastereoselectivities from 84:16 to 89:11 for the least branched chains (entries 1–3, Table 12) while bulky groups suffer a dramatic loss of yield and stereoselectivity (entries 4, 5 and 10, Table 12). In turn, the reaction with benzyloxy protected nitroalkene **No** gave adduct **27o** with an excellent diastereoselectivity but in a 25% yield (entry 6, Table 12); attempts to increase the yield of adduct **27o** were unsuccessful (entries 6–8, Table 12). In contrast, the use of a bulky and non-chelating TIPS protecting group in **Np** provided the desired adduct **27p** as a single diastereomer with a 64% yield (entry 9, Table 12). In turn, the introduction of a chiral centre and a TBDPS protecting group **Nq** was detrimental for the reaction and no product was found (entry 10, Table 12).



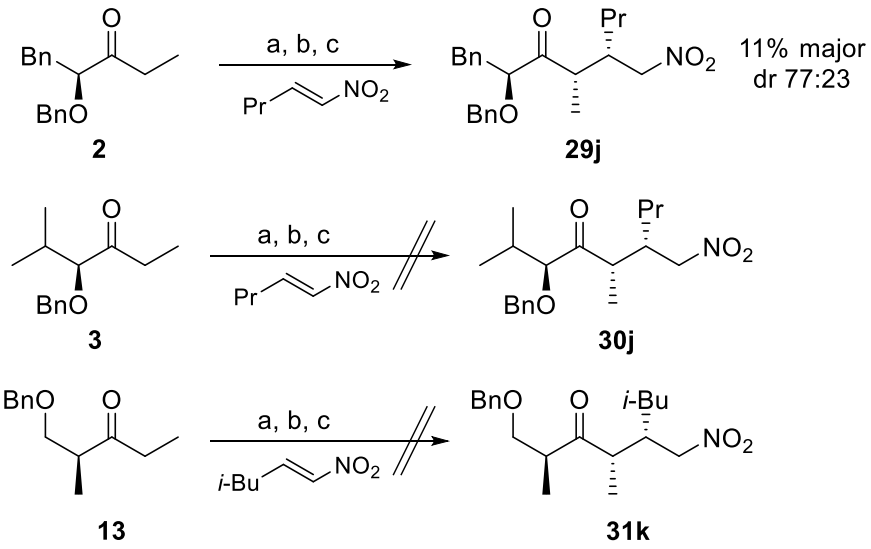
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$RCH=CHNO_2$, –78 °C, 3 h; c) NH_4F, rt, 30 min.

Entry	Nitroalkene	R	Product	dr (27:28)[a]	Yield 27 (%)[b]
1	**Nj**	Pr	**27j**	89:6:5[c]	69 (77)
2	**Nk**	*i*-Bu	**27k**	88:12	80
3	**Nl**	$BnCH_2$	**27l**	84:10:6[c]	54 (66)
4	**Nm**	*i*-Pr	**27m**	72:21:6[c]	28 (38)
5	**Nn**	C_6H_{11}	**27n**	nd	(< 5)[a]
6	**No**	$BnO(CH_2)_2$	**27o**	94:4:2[c]	25 (27)
7[d]	**No**	$BnO(CH_2)_2$	**27o**	94:4:2[c]	(32)[a]
8[e]	**No**	$BnO(CH_2)_2$	**27o**	nd	(< 5)[a]
9	**Np**	$TIPSO(CH_2)_2$	**27p**	≥ 97:3	64
10	**Nq**	(*S*)-CH(OTBDPS)Me	**27q**	-	-

[a] Determined by ^1H NMR and HPLC analysis of the crude mixture.
[b] Isolated yield after column chromatography. Isolated overall yield into brackets.
[c] Other minor diastereomer.
[d] Reaction performed with 2 eq of electrophile.
[e] Reaction performed with 0.5 eq of electrophile.

Table 12

Finally, the excellent results achieved in the abovementioned Lewis acid-mediated Michael additions of **1** to β–alkyl nitroalkenes encouraged us to explore similar substrate-controlled reactions with other chiral hydroxy ketones. Titanium(IV) enolates from α-benzyloxy ketones **2** and **3** as well as β-benzyloxy ketone **13** proved to be less reactive, less stereoselective, and less stable than those from **1**, hence only **29j** could be isolated in a 11% yield as a pure diastereomer (dr 77:23) (Scheme 44).



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-RCH=$CHNO_2$, –78 °C, 3 h; c) NH_4F, rt, 30 min.

Scheme 44

3.3. Absolute configuration of adducts 22 and 23

The absolute configuration of the major and the minor diastereomers were established through X-ray diffraction analyses of crystalline pure adducts **22g** (Figure 4) and **23a** (Figure 5) allowing us to determine the 2,4-*anti*-4,5-*syn* configuration of the Michael adducts.

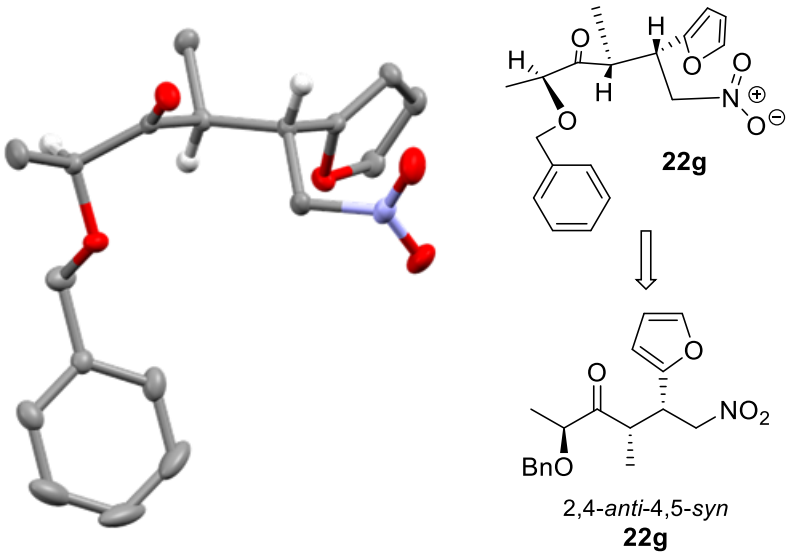


Figure 4

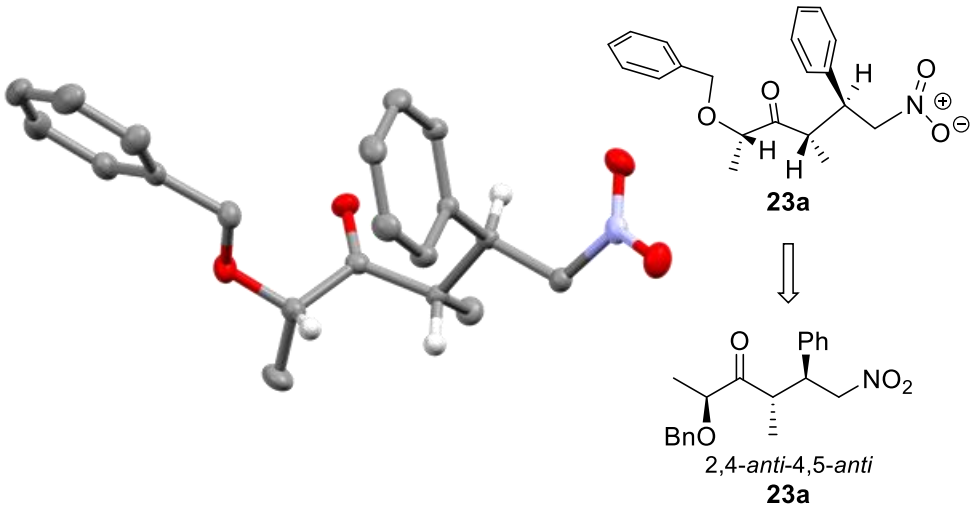
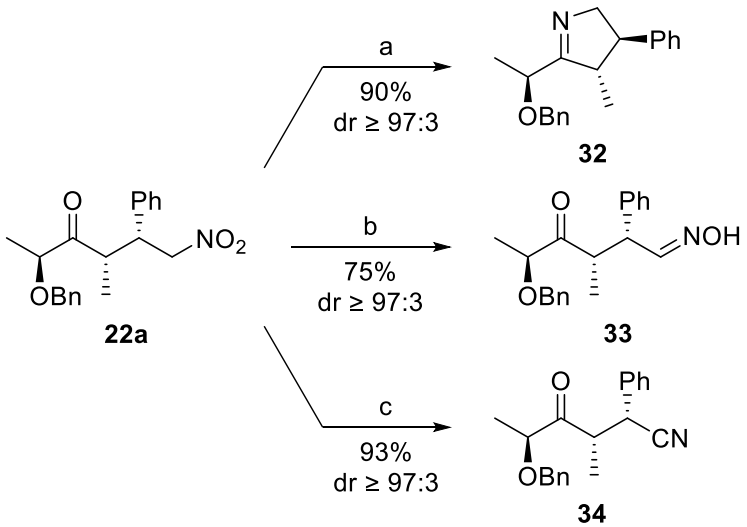


Figure 5

3.4. Nitroalkane transformations of 22a

Finally, we explored the conversion of the nitro group into other nitrogenated functional groups to confirm the synthetic potential of the adducts. Thus, the reduction of the nitro group of adduct **22a** with $NaBH_4$, in the presence of nickel(II) chloride, led to enantiomerically pure and highly functionalised cyclic imine **32**.[51,58] Whereas treatment of **22a** with a 1:3:3 mixture of $SnCl_2$/PhSH/Et_3N afforded oxime **33**.[59] In turn, reductive dehydration of **22a** with tetrakis(thiophenolate)tin(IV) and PMe_3 and DEAD allowed us to isolate β-cyano ketone **34** in an excellent yield (Scheme 45).[60] All these reactions were carried out under mild conditions and the resulting densely functionalised compounds **32**–**34** were easily isolated in high yields and without any loss of the chiral integrity of the starting material.



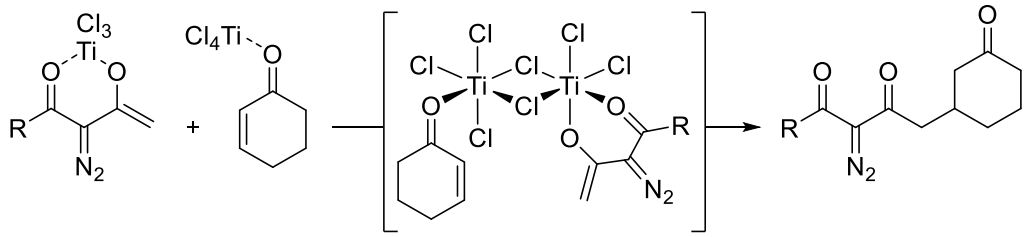
a) $NiCl_2·6H_2O$, $NaBH_4$, CH_2Cl_2, 0 °C, 30 min; b) 1:3:3 $SnCl_2$/PhSH/Et_3N, CH_2Cl_2, rt, 30 min; c) $Sn(SPh)_4$, PMe_3, DEAD, DMAP, CH_2Cl_2, rt, 30 min.

Scheme 45

4. Mechanistic hypothesis

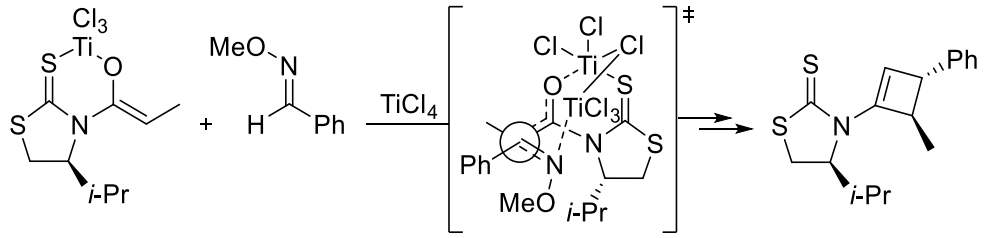
The comprehensive analysis of the Michael additions of titanium(IV) enolates to enones and α,β-unsaturated nitroalkenes has clearly established the need for a second equivalent of a Lewis acid to attain highly diastereoselective and efficient transformations. Unfortunately, the specific function of the excess Lewis acid is still unknown. NMR studies of the chiral enolates from α-benzyloxy ketones suggested that their structure was dramatically affected by the addition of $TiCl_4$ or $SnCl_4$ although they have not allowed us to establish the structure of the resultant aggregate.

There are some examples in the literature in which bimetallic species involving titanium enolates have been suggested. For example, Wang proposed a complex with two titanium atoms or a titanium-tin couple bound through chlorine bridges to account for the high regioselectivity observed for the conjugate addition of a titanium(IV) enolate to an enone (Scheme 46).[61]



Scheme 46

Furthermore, Liotta described a transition state involving a chlorine bridge bond between two titanium atoms to explain the stereocontrolled addition of a titanium enolate to $TiCl_4$ activated *O*-methyl oximes (Scheme 47).[62]



Scheme 47

The models presented by Wang and Liotta agree with the structure of other titanium complexes. For instance, the stoichiometric $TiCl_4$-benzaldehyde complex exists as a dimer with two bridging chlorine atoms granting a pseudo-octahedral geometry to each metal (**I**, Figure 6).[63] In turn, the Sharpless epoxidation is supposed to proceed through catalytic species containing a four membered ring with two titanium atoms

connected by two oxygen bridge bonds granting again a pseudo-octahedral geometry (**II**, Figure 6).[64]

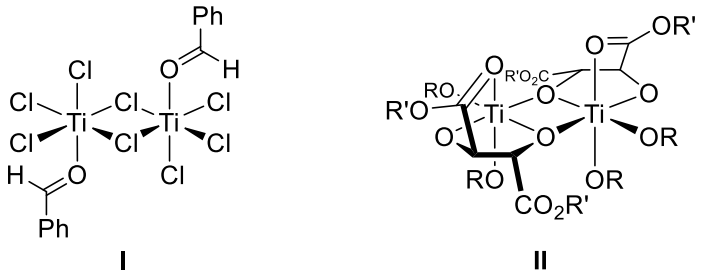
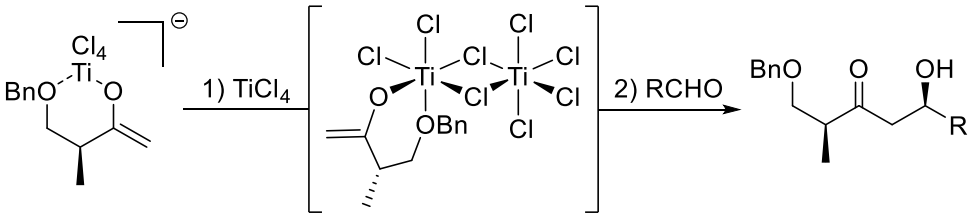


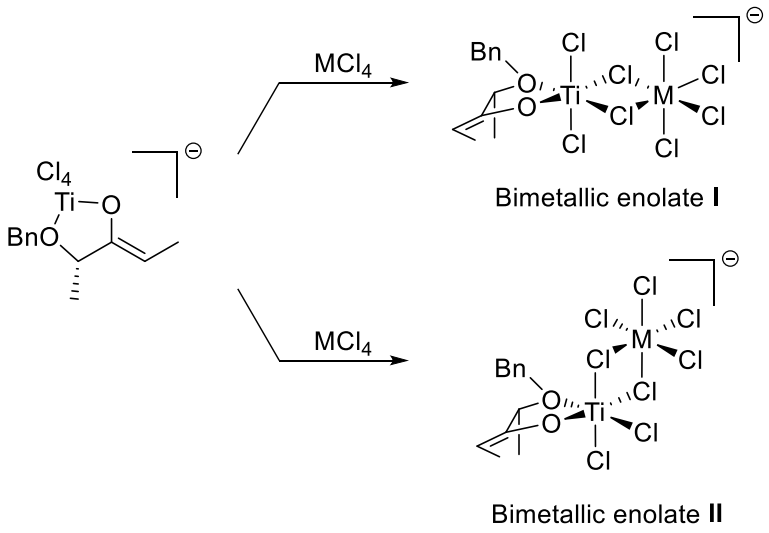
Figure 6

Importantly, unpublished calculations by our group unveiled that the stereochemical outcome of the Lewis acid-mediated substrate-controlled aldol reaction of titanium(IV) enolates from β-benzyloxy methyl ketones could be explained from structurally complex intermediates containing chlorine bridges between both titanium atoms (Scheme 48).



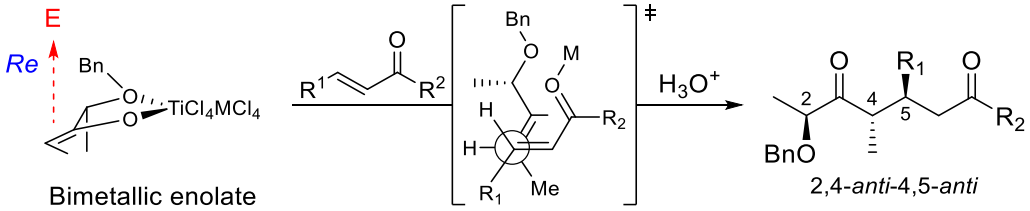
Scheme 48

Therefore, similar bimetallic enolates might undergo the highly stereoselective Michael additions of titanium(IV) enolates from lactate derived ketones to enones and nitroalkenes. The precise structure of such an intermediate is still unknown, so two alternative complexes were envisaged (Scheme 49): if the coordination of the second Lewis acid ($TiCl_4$ or $SnCl_4$) occurs far from the nucleophilic centre it results in a somewhat linear enolate **I**, whereas a more compact bimetallic enolate **II** might also result if the coordination of the second Lewis acid takes place close to the nucleophilic centre. In summary, taking advantage of our own experience and supported by models proposed by other authors, we suggest that a bimetallic enolate from the coordination of the second Lewis acid to the titanium *(Z)*-enolate may be the real nucleophilic species involved in these additions.



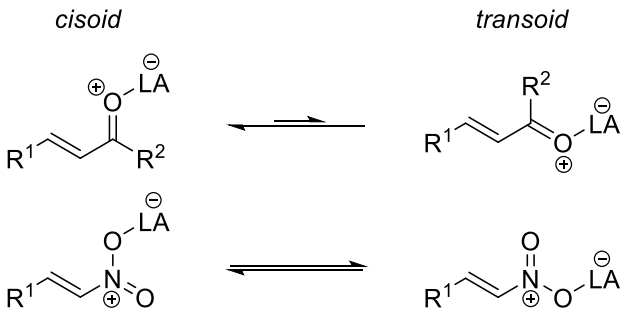
Scheme 49

Hence, coordination of an enone to a metal centre (Ti or Sn) of the bimetallic enolate would trigger the C−C bond formation through a cyclic transition state in which the *Re* face of the enolate attacks the *Si* face of the enone, following Heathcock's model, producing a 4,5-*anti* relative configuration (Scheme 50).[6] This model states that the most favourable pathway for the conjugated addition of a lithium enolate involves attack to the *cis* conformation of the enone and proceeds through a closed transition state with a staggered arrangement about the new C−C bond.



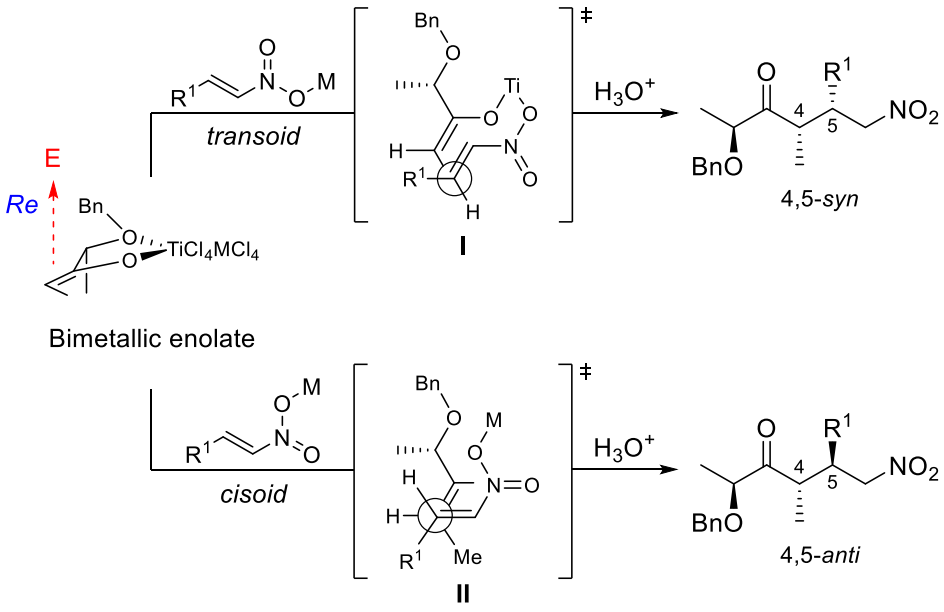
Scheme 50

Alternatively, parallel addition to α,β-unsaturated nitroalkenes produced 4,5-*syn* adducts in which the C4 configuration is the same that that of enones. This means that the configuration of the C4-stereocentre relies on the approach of the electrophile to the same face of the enolate. The reasons for such a discrepancy of the C5 stereocentre may be due to conformational differences in the activation of the double bond by the Lewis acid. Indeed, the equilibrium for enones is shifted towards the *cisoid* conformation to avoid allylic (1,3) interactions, whereas the lack of a R^2 group in nitroalkenes makes the *transoid* conformation much more accessible (Scheme 51).



Scheme 51

Moreover, the essentially flat nitroalkene does not contain any R^2 group to prevent an eclipsed approach (**I**, Scheme 52) that looks like an eight-membered cycle. Our working hypothesis precisely pondered if such approach was responsible for the obtention of 4,5-*syn* diastereomer, whereas the 4,5-*anti* counterpart may arise from a staggered approach (**II**, Scheme 52). Then, little differences in the electronic character of nitroalkenes (aryl or alkyl) and the steric bulk of R^1 can have a dramatic impact on the stereochemical outcome of these additions.

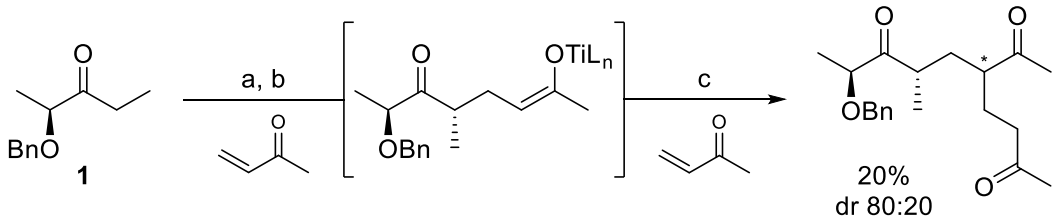


Scheme 52

5. Other Michael additions

5.1. Double Michael additions

Since the Michael addition to an enone produces a new enolate, this can be trapped by an enone in a double Michael addition. Miquel Pellicena, in his PhD, observed the formation of double Michael adducts (Scheme 23). Such an adduct was isolated in a 20% yield and with good diastereoselectivity (dr 80:20) when large amounts of methyl vinyl ketone were used, thus we thought that it might be interesting to explore their formation.



a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq CH_2=CHCOMe, –78 °C, 4 h; c) 0.8 eq CH_2=CHCOMe, –78 °C, 2 h.

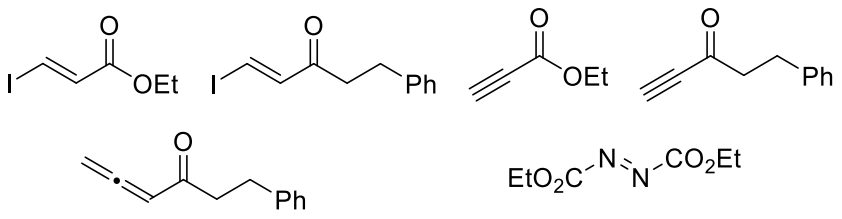
Scheme 53

Unfortunately, all our attempts to force such a reaction were unsuccessful, and the desired double Michael adducts were not found. We also explored the use of β-nitrostyrene to trap the intermediate enolate formed from the first Michael addition with methyl vinyl ketone. Unfortunately, complex crudes were obtained in all cases even with a second Lewis acid activation step. Similar results were obtained when the order of electrophiles was reversed.

5.2. Michael addition to other α,β-unsaturated carbonyl compounds

Encouraged by the excellent results obtained for the addition to enones, we assessed parallel reactions with other α,β-unsaturated carbonyl compounds like iodovinyl ketones and esters, ethynyl ketones and esters, allenyl ketones, DEAD, 3-acetoacrylates and acrylamides.

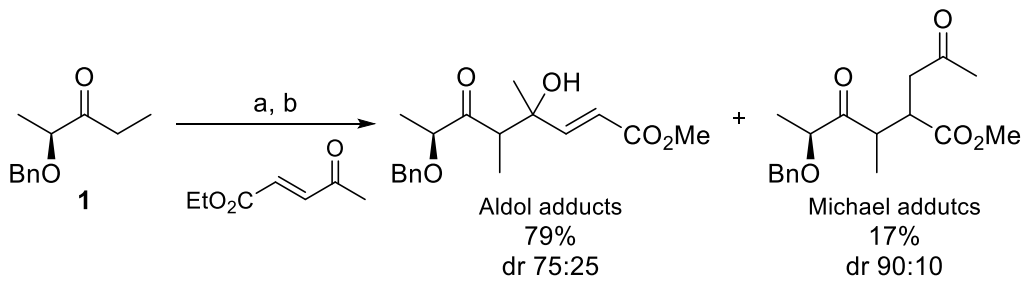
Unfortunately, ethyl iodoacrylate, iodovinyl-phenylpropanoyl ketone, ethyl propiolate, ethynyl-phenylpropanoyl ketone, allenyl-phenylpropanoyl ketone and DEAD were unable to afford any kind of product following the general procedures described in section 2.4.2 (Figure 7).



Unreactive α,β-unsaturated carbonyl compounds

Figure 7

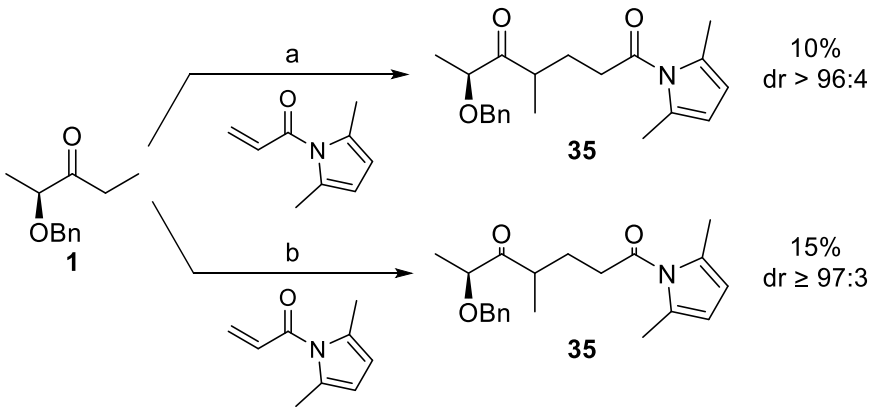
Addition to methyl (*E*)-4-oxopent-2-enoate, a conjugated keto ester, deserved special attention. This activated enone proved to be highly reactive, but the aldol adducts (79%, dr 75:25) were isolated together with the desired Michael adducts (17%, dr 90:10). Lower reaction temperature only decreased the overall conversion leaving the ratios mainly untouched and other attempts to improve the Michael/aldol ratio or the diastereoselectivity of the aldol were unsuccessful.



a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.5 eq (*E*)-$MeO_2CCH{=}CHCOCH_3$, –20 °C, 3 h.

Scheme 54

Finally, *N*-Acryloyl-2,5-dimethylpyrrole was chosen to test further Michael additions. The methyls of the aromatic cycle induced steric stress twisting the C-N bond almost perpendicular and making the molecule non-planar. This loss of planarity prevents the nitrogen of the amide having any kind of electronic resonance thus making the carbonyl electronically similar to a ketone. Thanks to this property, the amide is also easily converted into other acid derivatives. Thereby, this acrylamide was thought to be a good candidate and was tested following the general procedure for vinyl ketones. Preliminary experiments revealed the feasibility of this reaction and despite a low 10% yield of adduct **35** the diastereoselectivity was very good (dr 94:6, Scheme 55). Unfortunately, an increase in the reaction time or temperature did not improve the yields. Other tests carried out with $SnCl_4$ proved promising and the diastereoselectivity was improved (dr ≥ 97:3), but the problem with the yield remained unsolved as only 15% of adduct **35** was isolated (Scheme 55).



a) (i) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (i) 1.2 eq *N*-acryloyl-2,5-dimethylpyrrole, –40 °C, 3 h; b) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) (i) 1.1 eq $SnCl_4$, –78 °C, 10 min; (iii) 1.2 eq *N*-acryloyl-2,5-dimethylpyrrole, –40 °C, 3 h.

Scheme 55

6. Final considerations

In summary, the Michael addition of benzyloxy ketones to vinyl ketones allowed us to obtain the corresponding 2,4-*anti* adducts as single diastereomers with excellent yields. Together, extraordinarily good results were obtained for the Michael addition of benzyloxy ketones to β-substituted enones using both $TiCl_4$ and $SnCl_4$, and the corresponding 2,4-*anti*-4,5-*anti* adducts were obtained with diastereoselectivities above 90:10 in all cases with good yields.

In turn, the Michael addition of benzyloxy ketones to aromatic nitroalkenes provided the corresponding 2,4-*anti*-4,5-*syn* adducts with diastereoselectivities above 87:13 and excellent yields. Additionally, the $SnCl_4$ mediated Michael additions of benzyloxy ketones to aliphatic nitroalkenes afforded the corresponding 2,4-*anti*-4,5-*syn* adducts with good diastereoselectivities and yields. Furthermore, the nitro group was derivatised to other synthetically useful functional groups.

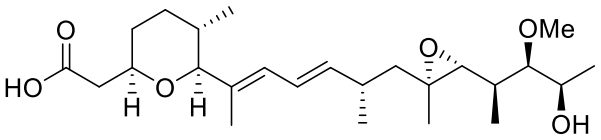
CHAPTER 2

Synthesis of the tetrahydropyran ring of (+)-herboxidiene

CHAPTER 2. TABLE OF CONTENTS

1. Introduction

(+)-Herboxidiene (**36**, Figure 8), is a secondary metabolite isolated from the bacteria *Streptomyces chromofuscus* in 1992 by Stonard at Monsanto Agric. Co.[65] Its exceptional phytotoxic activity toward a wide range of broadleaf weeds[65,66] attracted the attention and interest of researchers. Further studies showed that herboxidiene could also up-regulate the gene expression of the low-density-lipoprotein receptor, which reduces cholesterol in blood,[67] and it was later identified as the major component, named GEX1A, of a family of new antitumor antibiotics derived from *Streptomyces* species.[68–70]



herboxidiene/GEX1A (**36**)

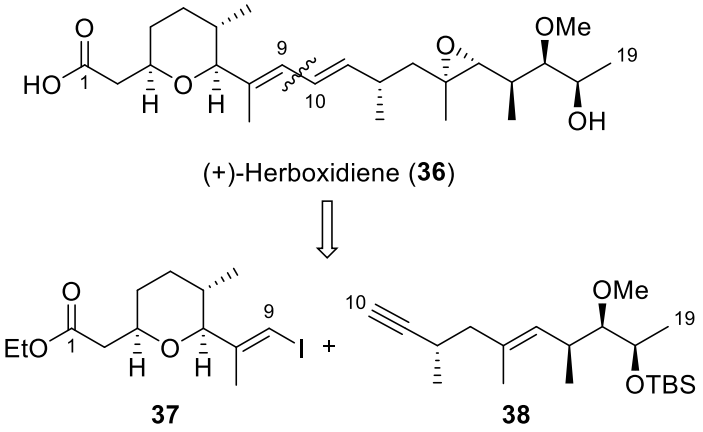
Figure 8

The structure and absolute configuration of (+)-herboxidiene/GEX1A was established in 1997 by a combination of degradation studies and X-ray crystallographic analysis,[71] and was finally confirmed through total synthesis by Kocieński in 1999.[72,73] From a structural point of view, herboxidiene is a medium-size polyketide with nine chiral centres in which a conjugated diene connects a tetrahydropyran core to a polyoxygenated fragment containing an epoxide, a methyl ether, and an alcohol.

The combination of such diverse biological activity, low natural abundance, and tempting structural features has aroused considerable interest and has prompted numerous synthetic studies, which nowadays involve several syntheses.[29,74–80] Thus, it is of little surprise that the structure of (+)-herboxidiene/GEX 1A caught the interest of our research group as the basis of a possible challenge to the efficiency of certain stereoselective transformations.

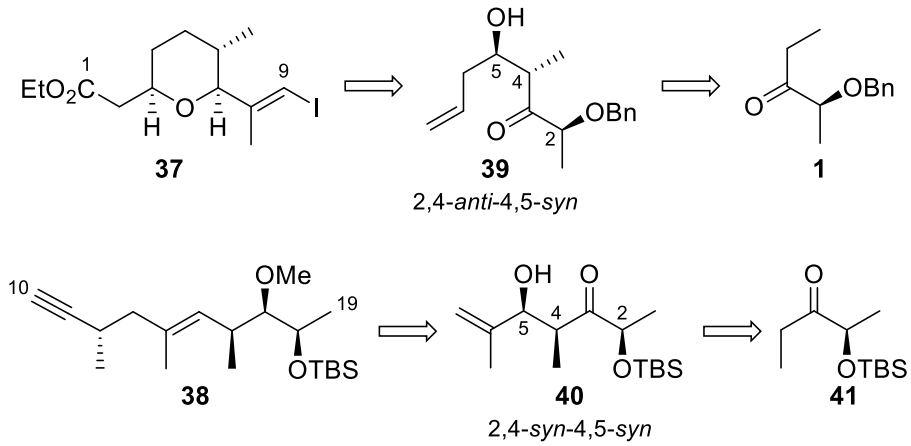
1.1. Previous synthesis in the group

Miquel Pellicena, during his PhD, carried out the challenging synthesis of (+)-herboxidiene (**36**) as a way to demonstrate the synthetic potential of the substrate-controlled titanium-mediated aldol reaction developed in our laboratory.[34] The retrosynthesis was based on the disconnection of C9–C10 bond into vinyl iodide **37** and alkyne **38** that could be assembled by palladium catalysed cross coupling (Scheme 56).[29]



Scheme 56

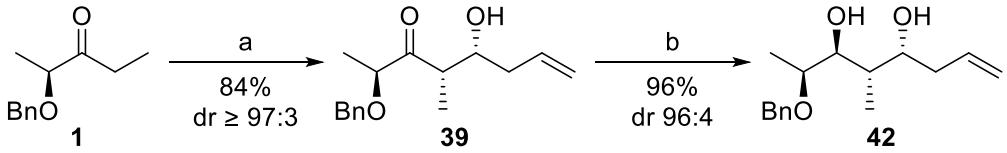
In turn, these advanced intermediates could be obtained through the appropriate manipulation of two aldol adducts, **39** and **40**, synthesised from the lactate-derived ethyl ketones **1** and **41** respectively (Scheme 57). On one side, the aldol reaction from (*S*)-2-benzyloxy-3-pentanone (**1**) provided 2,4-*anti*-4,5-*syn* aldols when two equivalents of $TiCl_4$ were used to prepare the enolate.[28] On the other side, the *O*-TBS protected counterpart **41** led to 2,4-*syn*-4,5-*syn* aldols when the enolate was prepared with only one equivalent of $TiCl_4$.[25] Thus, all the chiral centres would be installed via highly stereoselective substrate-controlled reactions which eventually relied on titanium-mediated aldol reactions developed by our group.



Scheme 57

From now on, we will focus on the synthesis C1-C9 fragment, the vinyl iodide **37**. Particularly, we will pay a special attention to the stereoselective formation of the tetrahydropyran ring. The starting point was the substrate-controlled Lewis acid-mediated aldol addition of the titanium enolate of **1** to 3-butenal.[28] As shown in Scheme 58, the 2,4-*anti*-4,5-*syn* aldol adduct **39** was isolated as a single diastereomer (dr ≥ 97:3) in 84% yield, and was subsequently reduced to the 1,3-*anti* diol **42** using the Evans–

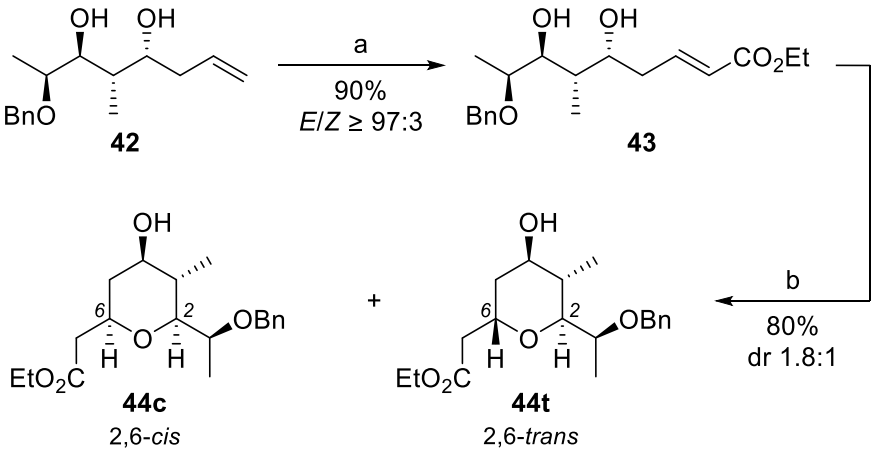
Chapman–Carreira protocol with an excellent yield (96%) and diastereoselectivity (dr 94:6).[81]



a) (i) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.2 eq CH_2=$CHCH_2CHO$, –78 °C, 30 min; b) 8 eq $(Me_4N)HB(OAc)_3$, 1:1 AcOH/CH_3CN, –35 to 0 °C, 20 h.

Scheme 58

The tetrahydropyran ring was prepared through a two-step sequence based on a cross metathesis of diol **42** with ethyl acrylate,[82] followed by an 6-*exo*-*trig* oxa-Michael cyclization of the resultant α,β-unsaturated ester (Scheme 59).[83] This intramolecular reaction was expected to produce the desired 2,6-*cis* pyran ring since all the substituents would lie in equatorial positions. As planned, the initial cross metathesis promoted by the second generation Hoveyda–Grubbs ruthenium complex produced the α,β-unsaturated ethyl ester **43** cleanly,[84,85] with excellent diastereoselectivity and yield (*E*/*Z* ≥ 97:3, 90% yield), but the subsequent intramolecular oxa-Michael addition proved troublesome. Preliminary experiments with *t*-BuOK afforded 2,6-*trans* pyran **44t** as the major diastereomer (dr 1:2). After considerable investigation, it was found that Fuwa's conditions (excess DBU, toluene, 100 °C) provided an inseparable 1.8:1 mixture of **44c** and **44t** diastereomers in 80% yield (Scheme 59).[86–90]

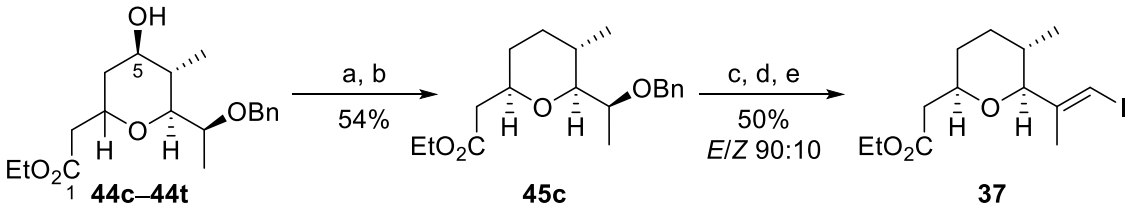


a) 3 eq CH_2=$CHCO_2Et$, 5 mol % HG-II, CH_2Cl_2, rt, 24 h; b) 10 eq DBU, toluene, 100 °C, 5 h.

Scheme 59

Then, Barton-McCombie removal of the C5-hydroxy group under tin-free conditions,[91–93] followed by chromatographic purification of the reaction mixture, furnished the desired diastereomerically pure 2,6-*cis* deoxygenated derivative **45c** with

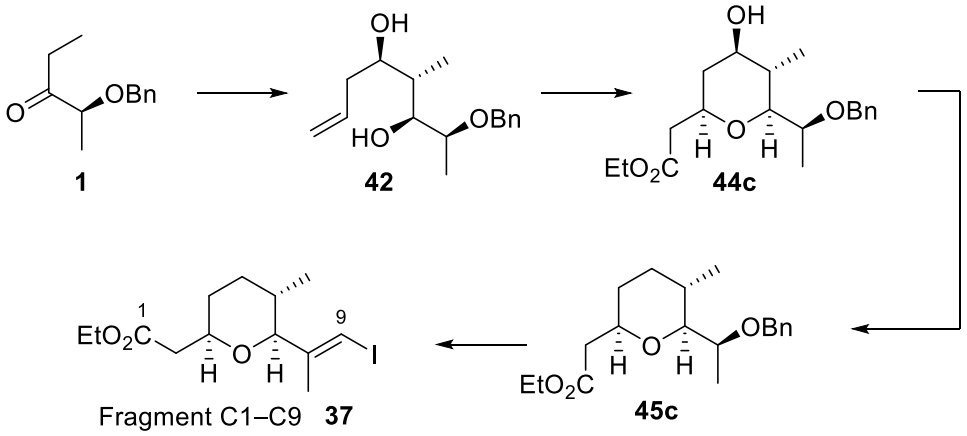
a 54% yield; the 2,6-*trans* counterpart **45t** was isolated in 10% yield (Scheme 60). Finally, hydrogenolysis of the benzyl ether and Swern oxidation of the resultant alcohol afforded a ketone, which was submitted to Takai conditions[94] to deliver the C1–C9 fragment **37** in three steps, as an *E*/*Z* 90:10 mixture in 50% yield (Scheme 60).



a) PhOCSCl, pyr, CH_2Cl_2, 0 °C to rt, 15 h; b) TTMSS, 20 mol % AIBN, toluene, 100 °C, 2 h; c) H_2, Pd/C, EtOAc, rt, 3 h; d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 30 min; (ii) Et_3N, –78 °C to rt, 45 min; e) $CrCl_2$, CHI_3, THF, rt, 2.5 h.

Scheme 60

In summary, vinyl iodide **37** had been synthesised in 10 steps and in an overall 17% yield from lactate-derived ketone **1**. Key steps of the sequence involve a highly diastereoselective titanium-mediated aldol reaction and an oxa-Michael cyclization. Appropriate manipulation of the resultant pyran ring led to advanced intermediate **45c**, which was finally converted into C1–C9 fragment **37**.

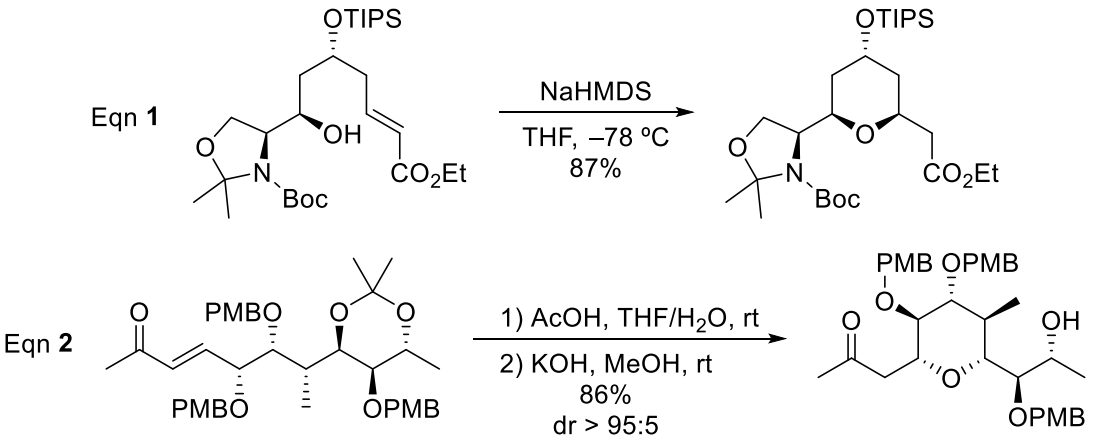


Scheme 61

1.2. Theoretical studies on oxa-Michael cyclizations

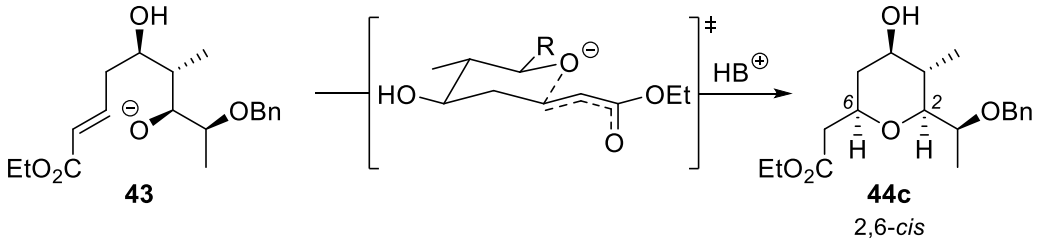
Common procedures for the synthesis of tetrahydropyrans based on an intramolecular oxa-Michael reaction involve the 6-exo-trig cyclization of α,β-unsaturated hydroxy ketones or esters.[83] These transformations are usually carried out in the presence of base under thermodynamic control, which implies that the configuration of the new stereocentre can be predicted from conformational analysis of the resultant heterocycle. Therefore, considering that the most stable conformer of saturated six-membered heterocycles adopts the chair form, it is in general anticipated that these

cyclizations mainly provide 2,6-cis-disubstituted tetrahydropyrans. As represented in Scheme 62, this procedure had been largely applied to the total syntheses of many natural compounds like spongistatin 1 (Eqn **1**, Scheme 62) and phorboxazole A (Eqn **2**, Scheme 62).[95,96]



Scheme 62

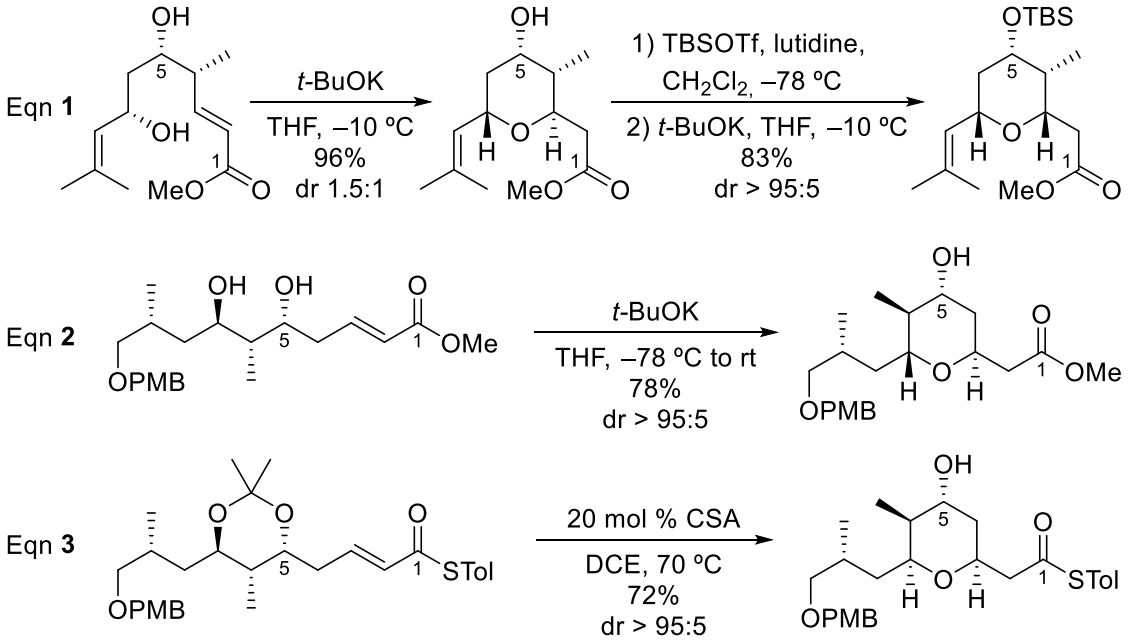
Thus, the equatorial position of all the substituents in the 2,6-*cis* pyran ring **44c** seemed to warrant it being the main diastereomer under thermodynamic conditions. Unfortunately, the results of the base promoted 6-*exo*-*trig* oxa-Michael did not meet these expectations (Scheme 63).



Scheme 63

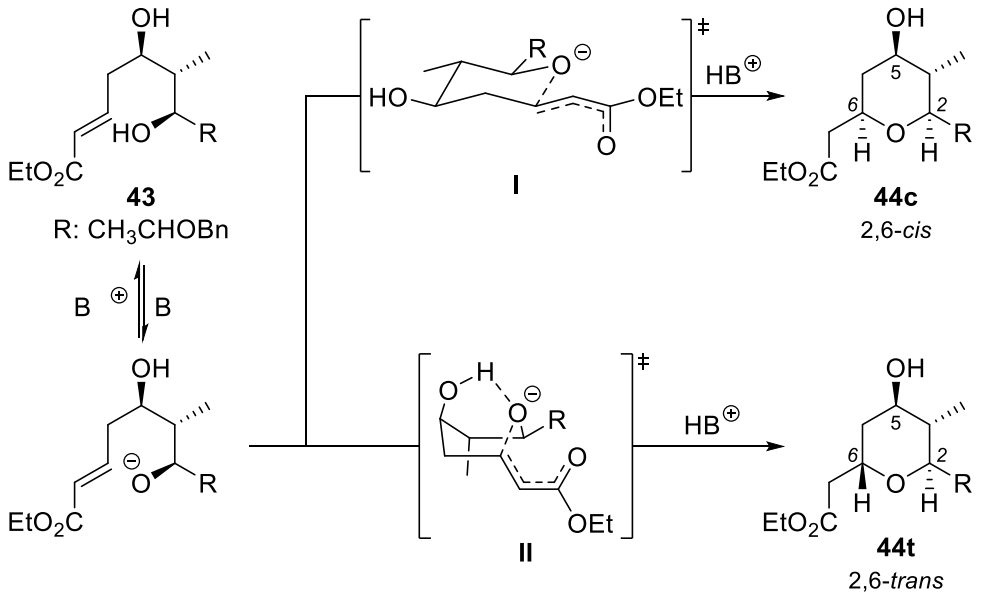
A similar cyclization was examined by Evans in the total synthesis of (+)-miyakolide.[97] Treatment of the conjugated ester with *t*-BuOK gave a 1.5:1 mixture of tetrahydropyrans (Eqn **1**, Scheme 64). Unexpectedly, this cyclization turned out to be non-reversible, but the protection of the secondary alcohol at C5 followed by resubmission of the resultant mixture to the former basic conditions produced the 2,6-*cis* pyran as a single diastereomer (Eqn **1**, Scheme 64). In turn, Paterson reported that the oxa-Michael cyclization of an α,β-unsaturated ester under basic conditions provided almost exclusively the 2,6-*trans* tetrahydropyran (Eqn **2**, Scheme 64).[98] All attempts to generate the desired 2,6-*cis* pyran isomer proved unsuccessful. Instead, an alternative cyclization of a conjugated thioester under acidic conditions led to the selective formation of the targeted 2,6-*cis*-tetrahydropyran (Eqn **3**, Scheme 64). Interestingly, the apparent

low *cis* selectivity achieved in the cyclizations described in Eqn **1** and Eqn **2** might be due to the presence of a non-protected alcohol at C5.



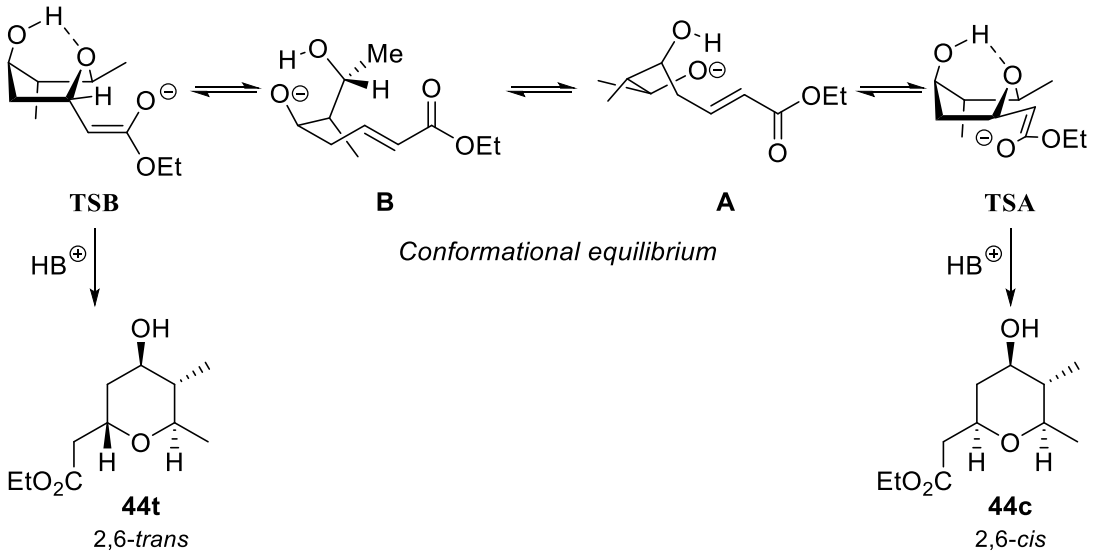
Scheme 64

Assuming that the cyclization leading to tetrahydropyran **44c** from ester **43** takes places through transition state like **I** (Scheme 65) where all substituents were located into equatorial positions, it was suggested that the poor stereochemical control was due to the formation of an intramolecular hydrogen bond that stabilised a boat like transition state like **II** leading to tetrahydropyran **44t** (Scheme 65).



Scheme 65

Indeed, theoretical studies indicated that the oxa-Michael cyclization of **43** mainly proceeds through a boat-like transition state.[99] As represented in Scheme 66, the acyclic alkoxide **A** yields the desired 2,6-*cis* pyran through a boat transition state **TSA**; whereas a related but more stable transition state **TSB** available from alkoxide **B** is responsible for the 2,6-*trans* pyran counterpart.[99] Once again, the strong interaction between the C5–OH and the anionic oxygen determines the boat-like geometry of both transition states. Indeed, the 2,6-*trans* pyran is obtained via a transition state lower in energy than that leading to the more stable 2,6-*cis* pyran. Therefore, the experimental conditions govern the stereochemical outcome of the oxa-Michael cyclization of such dihydroxy α,β-unsaturated esters: low temperatures and catalytic amounts of base favours the formation of the 2,6-*trans* pyran (kinetic control); whereas the 2,6-*cis* pyran may be favoured by high temperatures and an excess of base (thermodynamic control).[99]

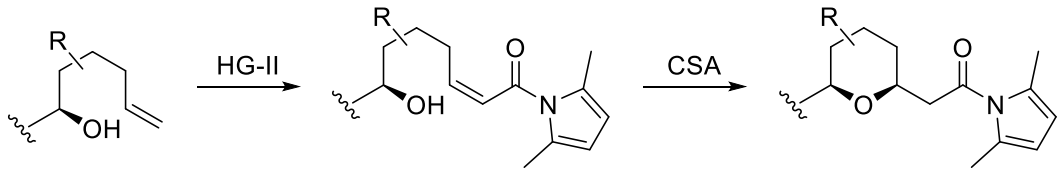


Scheme 66

Despite the successful synthesis of the iodovinyl intermediate **37** and the total synthesis of herboxidiene achieved by Miquel Pellicena, the modest selectivity of the base-mediated oxa-Michael cyclization of α,β-unsaturated ester **43** led us to explore an alternative procedure for the preparation of the 2,6-*cis* pyran ring **44c** in order to improve the overall herboxidiene/GEX1A synthesis.

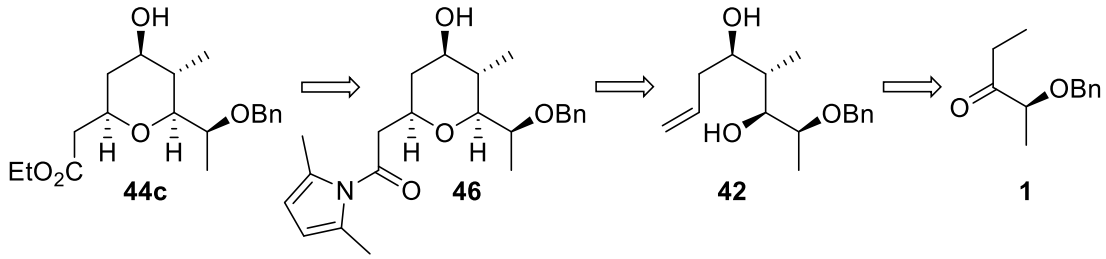
2. Approach 1: oxa-Michael cyclization of an α,β-unsaturated amide

A thorough search for other *cis* selective methods uncovered the cyclization of conjugated thioesters or amides under acidic conditions developed by Fuwa et al.[100–102] Specifically, we were attracted by the concise synthesis of 2,6-*cis*-disubstituted tetrahydropyrans by means of a domino olefin metathesis and oxa-Michael cyclization from 2,5-dimethylpyrrole amides catalysed by Brønsted acids, which might yield the desired substrate in a rapid, efficient, and selective sequence (Scheme 67).



Scheme 67

The new tactical approach towards the tetrahydropyran was close to the previous approach (Scheme 68). First, the substrate-controlled Lewis acid-mediated aldol addition of the titanium enolate of **1** to 3-butenal followed by Evans–Chapman–Carreira protocol reduction would provide diol **42**. Then, the tetrahydropyran ring would be finally prepared through the two-step sequence based on a cross metathesis of diol **42** with *N*-acryloyl-2,5-dimethylpyrrole followed by an oxa-Michael cyclization under Fuwa's acidic conditions. Finally, the transformation of the amide **46** to ethyl ester **44c** under basic conditions would deliver the previously synthesised ester.[101]

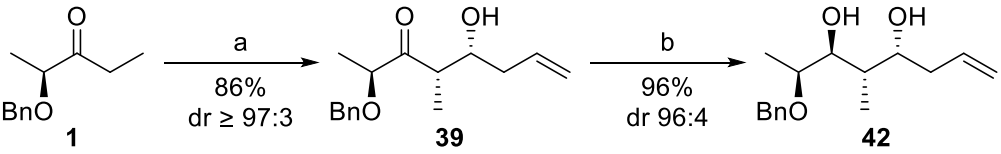


Scheme 68

2.1. Synthesis of diol 42

Substrate-controlled Lewis acid-mediated aldol addition of the titanium enolate of (*S*)-2-benzyloxy-3-pentanone (**1**) and 3-butenal was carried out as reported. The aldol reaction of titanium enolate from ketone **1** to 3-butenal with two equivalents of $TiCl_4$ provided aldol **39** as a single diastereomer with an 86% yield (Scheme 69).[28] The next step towards the construction of the tetrahydropyran ring was the stereoselective

reduction to form diol **42**. Indeed, the substrate-controlled *anti* reduction of the ketone could be directed by the hydroxy group of the aldol through a methodology developed by Evans et al.[81] This reduction hinges on the utilization of $(Me_4N)HB(OAc)_3$, that transfers a hydride from the boron to the carbonyl in an intramolecular way through a cyclic transition state. Thus, treatment of aldol **39** with excess of $(Me_4N)HB(OAc)_3$ afforded 3,5-*anti* diol **42** with excellent results, 96% yield and dr of 96:4 (Scheme 69).



a) (i) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.2 eq $CH_2{=}CHCH_2CHO$, –78 °C, 30 min; b) 8 eq $(Me_4N)HB(OAc)_3$, 1:1 AcOH/CH_3CN, –35 to 0 °C, 20 h.

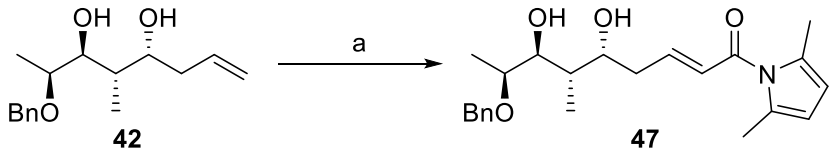
Scheme 69

2.2. Construction of the tetrahydropyran ring

As mentioned at the beginning of this section, Fuwa had reported that cyclization of conjugated amides under acidic conditions led to 2,6-*cis*-disubstituted tetrahydropyrans by means of a domino olefin metathesis and oxa-Michael cyclization from 2,5-dimethylpyrrole amides.[101,102] Therefore, our aim was to achieve the ring formation in a two-step cross-metathesis/intramolecular oxa-conjugate cyclization that would allow us to obtain the corresponding 2,6-*cis*-tetrahydropyran amide in a very selective manner.

2.2.1. Cross metathesis with *N*-acryloyl-2,5-dimethylpyrrole

In our case, metathesis between alkenediol **42** and *N*-acryloyl-2,5-dimethylpyrrole catalysed by second generation Hoveyda-Grubbs ruthenium complex afforded only low quantities of conjugated amide **47** even with very long reaction times and several catalyst additions (compare entries 1–3, Table 13)



42 **47**

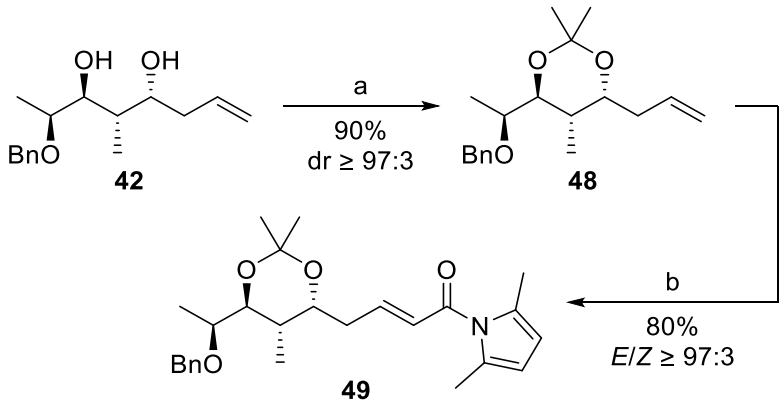
a) 3 eq *N*-acryloyl-2,5-dimethylpyrrole, cat HG-II, CH_2Cl_2, T, t.

Entry	% HG-II	T (°C)	Time (h)	Yield 47 (%)[a]
1	5 + 5	rt	24+24	26 (50)
2	5 + 5	35	24+24	30 (16)
3	5 +5 +5	35	24+24+24	15 (25)

[a] Isolated overall yield after column chromatography. Recovered starting material into brackets.

Table 13

Presumably, the lower reactivity of the acrylamide slowed the cross metathesis giving the diol time to poison the ruthenium complex. Protection of the diol was necessary to avoid the presumed catalyst poisoning. Transformation of diol **42** into acetonide **48** turned out to be doubly beneficial. First, the acetonide was isolated in a 90% yield as the pure *anti* diastereomer; and second, cross metathesis with *N*-acryloyl-2,5-dimethylpyrrole gave smoothly the pure conjugated amide **49** with an 80% yield (E/Z ≥ 97:3) under standard conditions as a single diastereomer (Scheme 70).



42 **48** **49**

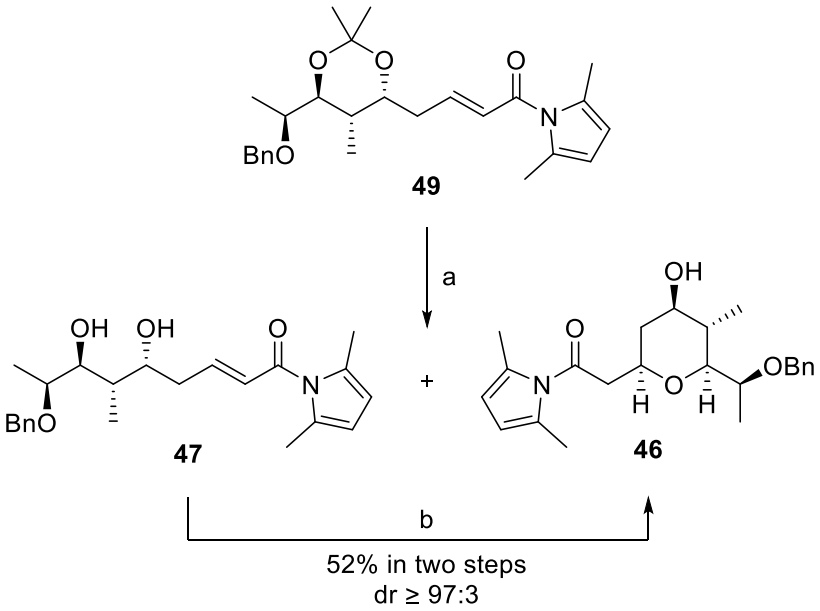
a) 10 mol % CSA, $CH_2Cl_2/Me_2C(OMe)_2$, rt, 16 h; b) 3 eq acrylamide, 5 + 5 mol % HG-II, CH_2Cl_2, rt, 21 h.

Scheme 70

2.2.2. Oxa-Michael cyclization

Conversion of the conjugated amide **49** into the 2,6-*cis*-tetrahydropyran ring **46** involved the removal of the acetonide protecting group and the stereocontrolled oxa-Michael cyclization. First, elimination of the acetonide under PPTS catalysis in DCE/MeOH resulted in a fully deprotected open amide **47** and cyclic amide **46** in a 60:40 ratio (Scheme 71). The crude was treated further under Fuwa's cyclization conditions

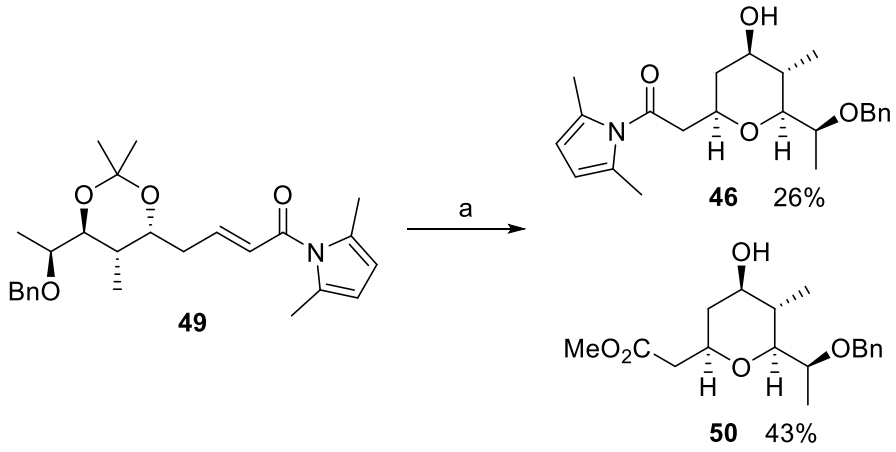
with CSA at 60 °C until complete consumption of the open amide to obtain a 52% yield of pure 2,6-*cis*-tetrahydropyran amide **46** as a single diastereomer (Scheme 71).



a) cat PPTS, MeOH, CH_2Cl_2, rt, 72 h; b) 20 mol % CSA, DCE, 60 °C, 48 h.

Scheme 71

Encouraged by this result, we designed a tandem deprotection/oxa-Michael with MeOH and CSA. Removal of the acetonide was fast at rt and cyclization was pushed by heating at 60 °C until complete consumption of the open amide **47**. Surprisingly, besides 2,6-*cis*-tetrahydropyran amide **46**, 2,6-*cis*-tetrahydropyran ester **50** was also found and isolated, with yields of 26% and 43% respectively (69% overall) (Scheme 72).

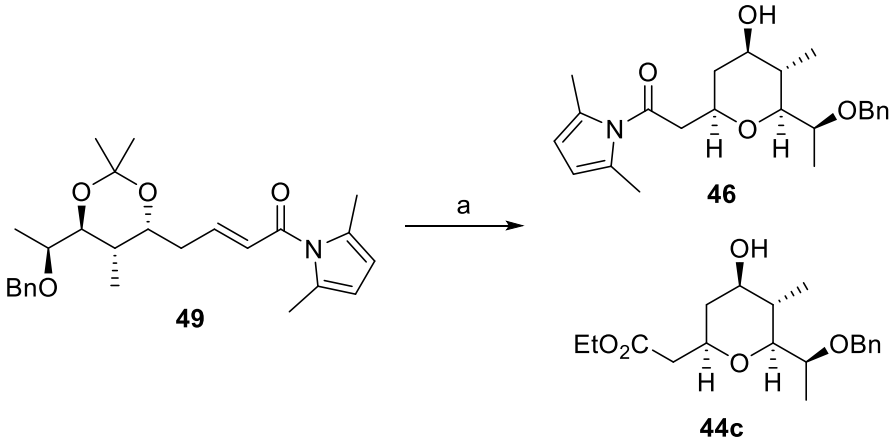


a) 20 mol % CSA, MeOH, DCE, 60 °C, 48 h.

Scheme 72

The particular electronics of the dimethylpyrrole amide granted it good reactivity not only to bases as described, but also towards acidic conditions. This finding encouraged us to assess a triple tandem deprotection/oxa-Michael/ester-transformation.

Removal of acetonide and cyclization to the cyclic amide **46** was carried out as before, but in this case, the lower nucleophilicity of ethanol versus methanol required an increase in the temperature to 70 °C and also in the amount of CSA. Finally, tetrahydropyran ester **44c** was isolated as a single 2,6-*cis* diastereomer in 43% yield as well as 8% of tetrahydropyran amide **46** with an overall 51% yield (entry 2, Table 14).



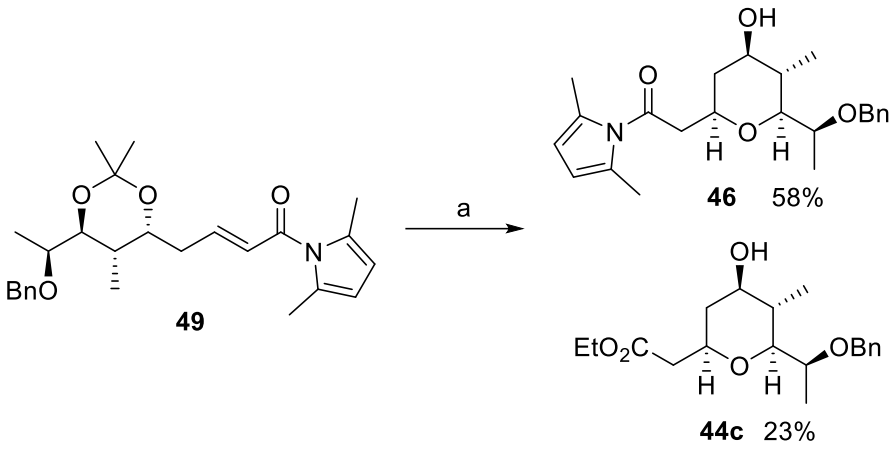
a) n mol % CSA, EtOH, DCE, rt to 70 °C, 48 h.

Entry	% CSA	Yield Amide 46 (%)[a]	Yield Ester 44c (%)[a]	Overall (%)[a]
1	10 + 10	20	30	50
2	20 +20	8	43	51

[a] Isolated overall yield after column chromatography.

Table 14

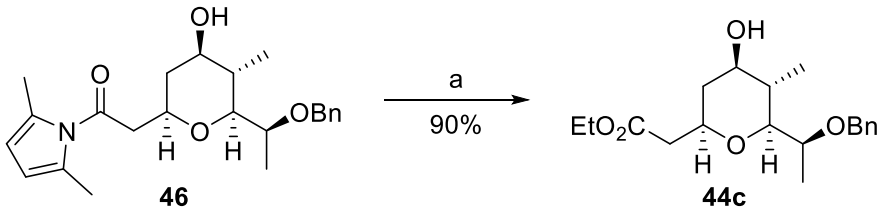
Such a triple tandem sequence proved to be less promising than expected: although tetrahydropyran ester **44c** was obtained as a single product, the harsh conditions required to force the formation of the ester proved detrimental to the overall yield. So, a more conservative approach was designed in which the removal of the acetonide and cyclization would be performed in milder acidic conditions aiming for the maximum overall yield instead of a shorter sequence to the final ester. These milder conditions involved short reaction times and reduced amounts of CSA. After 16 hours, 58% of 2,6-*cis*-tetrahydropyran amide **46** and 23% of 2,6-*cis*-tetrahydropyran ester **44c** were isolated separately with an overall 81% yield (Scheme 73).



a) 10 mol % CSA, EtOH, DCE, rt to 60 °C, 22 h.

Scheme 73

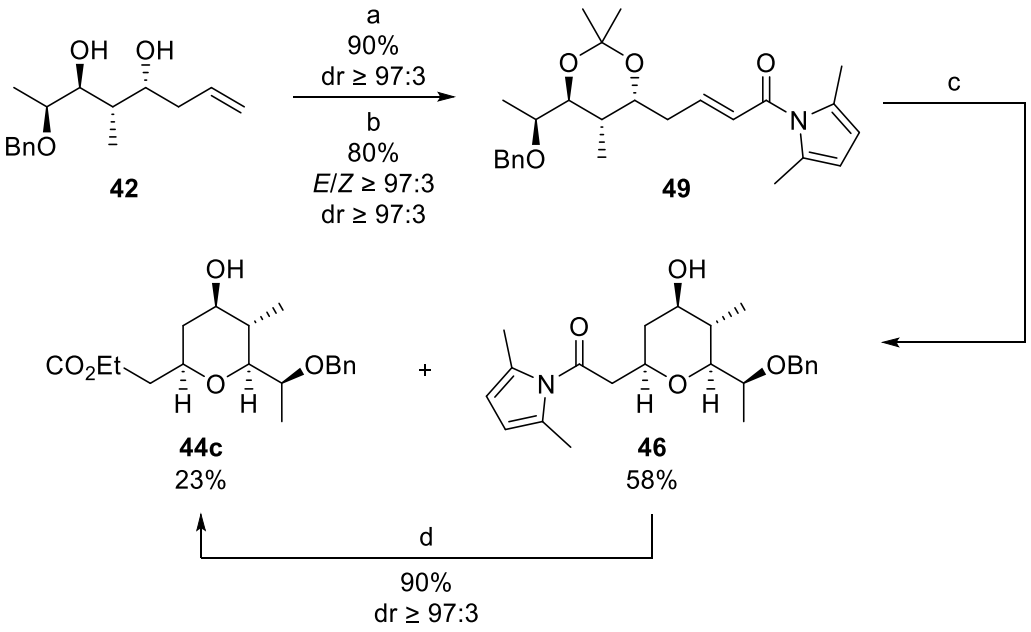
Finally, transformation of the dimethylpyrrole amide of tetrahydropyran **46** into ethyl ester **44c** was carried out smoothly by simple treatment with freshly prepared NaOEt with a 90% yield (Scheme 74).[101]



a) 1.2 eq EtONa, EtOH, CH_2Cl_2, –25 °C to 0 °C, 16 h.

Scheme 74

In summary, the stereocontrolled synthesis of 2,6-*cis* ethyl ester **44c** from alkenediol **42** had been completed in four steps and a 54% overall yield while the original approach yielded 46% of the ester **44c** (72% overall yield of **44c** and **44t**, in a dr 1.8:1) (Scheme 75).

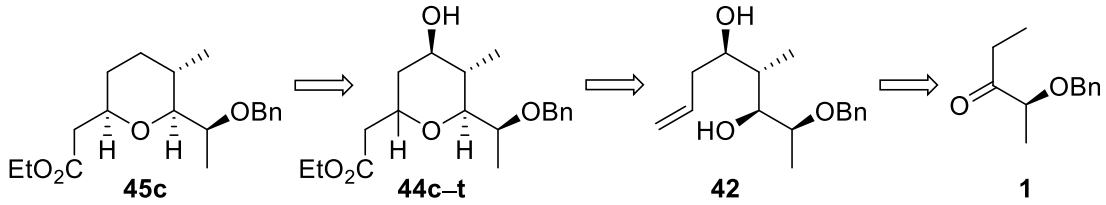


a) 10 mol % CSA, CH_2Cl_2/$Me_2C(OMe)_2$, rt, 16 h; b) 3 eq acrylamide, 5 + 5 mol % HG-II, CH_2Cl_2, rt, 21 h; b) 10 mol % CSA, EtOH, DCE, rt to 60 °C, 22 h; d) 1.2 eq EtONa, EtOH, CH_2Cl_2, –25 °C to 0 °C, 16 h.

Scheme 75

3. Approach 2: oxa-Michael cyclization of an α,β-unsaturated ester, deoxygenation of the resultant pyrans, and re-equilibration

While approach 1 afforded the 2,6-*cis* tetrahydropyran stereoselectively, the need for the acetonide protecting group increased the number of steps, which pushed us to re-examine the original approach. Since the theoretical calculations and our own experience had identified the C5 alcohol as the reason for the lack of stereocontrol of the oxa-Michael cyclization, we envisioned that the re-equilibration of the 2,6-*trans* pyran isomer could be attempted once that C5–OH was removed. Thus, we envisioned a modification of the original approach (Scheme 76), in which the cyclization would be performed with *t*-BuOK and once the C5 hydroxyl was removed, the 2,6-*trans* isomer would be re-equilibrated into the 2,6-*cis* one.



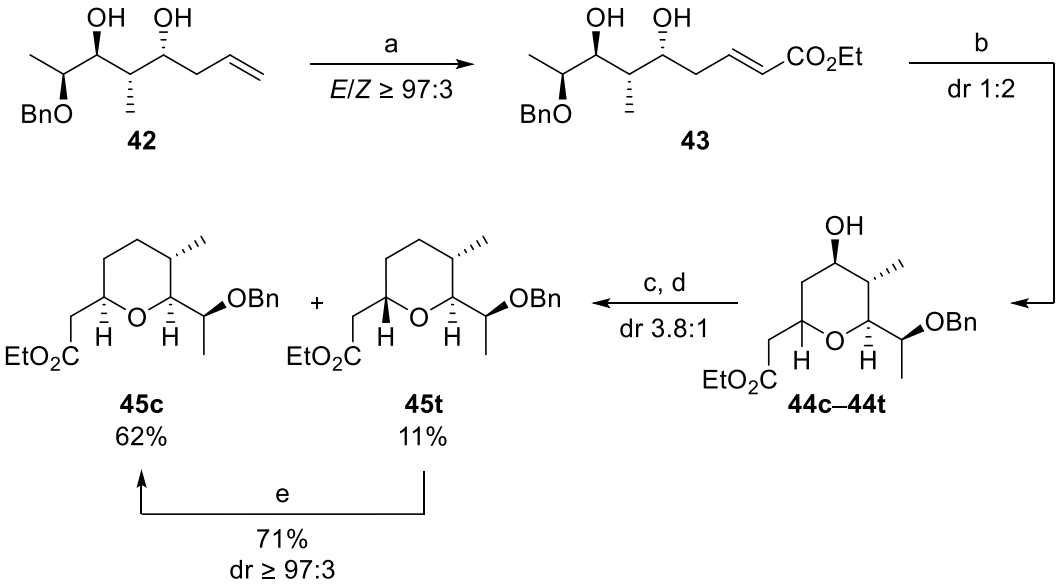
Scheme 76

3.1. Construction of the tetrahydropyran ring

3.1.1. Cross metathesis with ethyl acrylate

Cross metathesis between alkene **42** and ethyl acrylate catalysed by the second generation Hoveyda-Grubbs ruthenium complex afforded the α,β-unsaturated ethyl ester **43**, with excellent diastereoselectivity (E/Z ≥ 97:3). Furthermore, since the spectroscopic analysis of the crude mixtures were clean and showed almost complete conversion of the starting alkene, we decided to continue the synthesis without further purification, thus minimising the number of chromatographic purifications (Scheme 77).

The crude of unsaturated ethyl ester **43** was then submitted to cyclization in the presence of 20 mol % of *t*-BuOK. The reaction provided a *cis/trans* 1:2 mixture of pyrans **44c** and **44t** that was not purified by column chromatography and was directly submitted to the deoxygenation procedure (Scheme 77). This started with the preparation of the corresponding thionocarbonates with *O*-phenyl chlorothionoformate and pyridine. After complete conversion of the alcohols, a tin-free Barton–McCombie reduction provided diastereomerically pure 2,6-*cis* deoxygenated derivative **45c** with a 62% yield and the 2,6-*trans* counterpart **45t** in 11% yield, which could be separated by column chromatography (Scheme 77). Interestingly, the **45c**/**45t** diastereomeric ratio (dr 3.8:1) was higher than that of the starting hydroxy pyrans **44c**/**44t** (dr 1:2), which indicated that the reaction conditions caused a certain resolution (Scheme 77).



a) 3 eq CH_2=$CHCO_2Et$, 5 mol % HG-II, CH_2Cl_2, rt, 24 h; b) 20 mol % *t*-BuOK, THF, rt, 2 h. c) PhOCSCl, pyr, CH_2Cl_2, 0 °C to rt, 15 h; d) TTMSS, 20 mol % AIBN, toluene, 100 °C, 2 h; e) 40 mol % *t*-BuOK, THF, rt, 24 h.

Scheme 77

Finally, the 2,6-*trans* pyran **45t** was easily isomerised by treatment with 40 mol % of *t*-BuOK affording 71% of 2,6-*cis* ethyl ester **45c**, which highlights the crucial role of the C5–OH in the stereochemical outcome of the oxa-Michael cyclization (Scheme 77).

In summary, the stereocontrolled synthesis of 2,6-*cis* ethyl ester **45c** from alkenediol **42** has been completed in three steps and a 58% overall yield, much better than the 39% of the first original approach (Scheme 77). Furthermore, the new approach involved less chromatographic purifications which conferred a major simplicity and efficiency to the new sequence.

4. Final considerations

The stereoselective synthesis of the tetrahydropyran ring was successfully accomplished following two different approaches. In approach 1, although the number of steps was increased, the sequence reactions pursued a fully stereoselective pathway taking advantage of the great selectivity offered by a dimethylpyrrole amide under acidic conditions attaining a 54% yield of 2,6-*cis* ethyl ester **44c** (46% for the original approach). In approach 2, the original sequence of reactions was followed, but the removal of unnecessary purification steps and a final isomerization managed to increase notably the yield up to 58% of 2,6-*cis* ethyl ester **45c** (39% for the original approach).

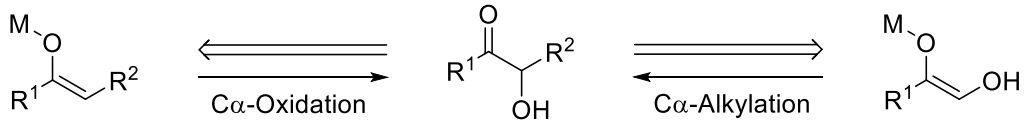
CHAPTER 3

Oxidations with TEMPO and Oxygen

CHAPTER 3. TABLE OF CONTENTS

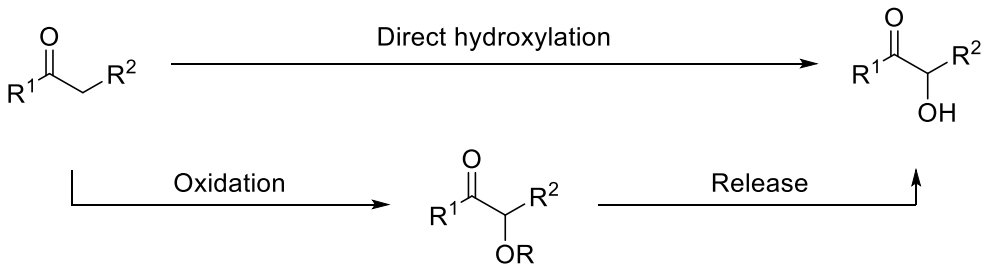
1. Introduction

The widespread presence of α-hydroxy carbonylic and carboxylic structures in biologically active natural products has fostered the development of increasingly efficient transformations involving the asymmetric construction of C–C and C–O bonds (Scheme 78). Particularly, the chemo and stereoselective oxidation of the carbon backbone of organic molecules is a formidable challenge that has attracted increasing interest in recent years.[103,104] In that context, stereoselective Cα-oxidation of carbonyl bonds has received lasting attention, resulting in a number of procedures based on the treatment of enolates with a variety of oxidizing agents.



Scheme 78

The asymmetric synthesis of α-hydroxy carbonyl compounds follows two main pathways (Scheme 79). One of them involves the *direct* installation of an OH group at the Cα position. The second one, namely a *two-step* approach, refers to the stereoselective construction of a C–O bond leading to an intermediate, which can be subsequently converted into the desired α-hydroxy carbonyl compounds. The first approach is usually carried out under harsh reaction conditions or with expensive or delicate reagents, whereas the second approach relies on mild reaction conditions but requires a second step to finally obtain the free alcohol.



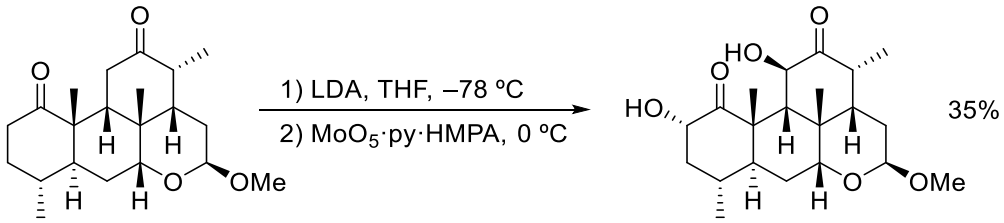
Scheme 79

1.1. Direct hydroxylations

1.1.1. Hydroxylations with MoO_5·py·HMPA

The combination of oxodiperoxymolybdenium with pyridine and HMPA (MoO_5·py·HMPA) was first developed by Vedejs as a general electrophilic reagent for the α-hydroxylation of enolates.[105,106] Due to steric bulk of the reagent, the oxidation of enolates proceeds preferentially from the less hindered face, as shown in Scheme 80

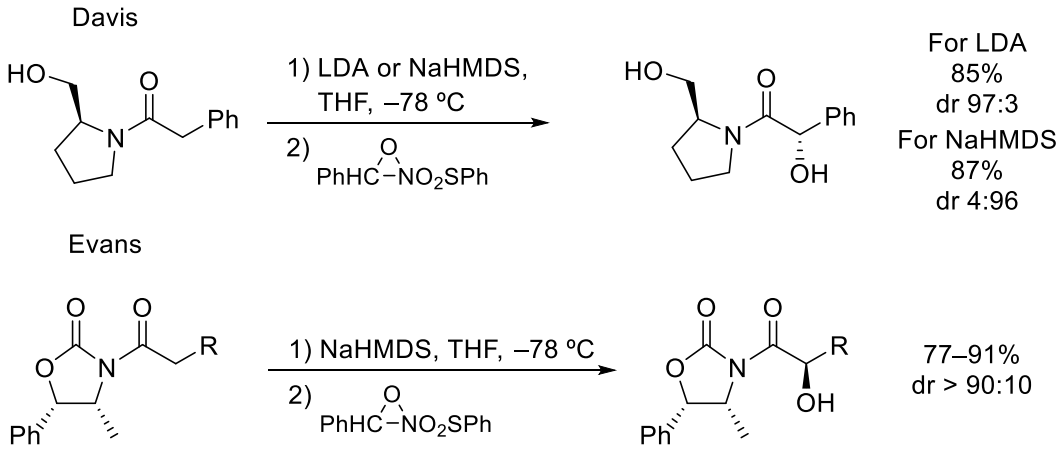
from Grieco's stereoselective double hydroxylation of a tetracyclic diketone for the total synthesis of quassin.[107,108]



Scheme 80

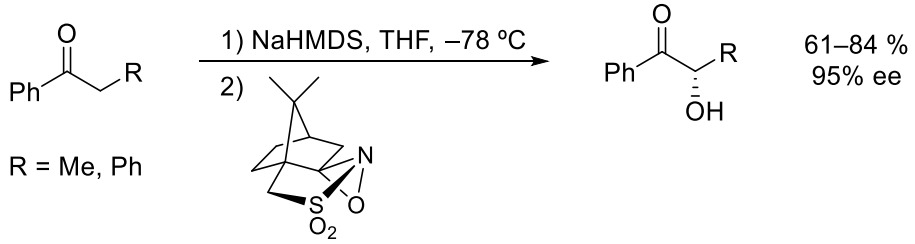
1.1.2. Hydroxylations with *N*-sulfonyloxaziridines

Traditionally, the stereoselective Cα-hydroxylation of metallic enolates has been carried out with *N*-sulfonyloxaziridines. For instance, the diastereoselective hydroxylation of lithium or sodium enolates of chiral imides with oxaziridines reported by Davis et al.[109], and Evans et al.,[110] proved to be a convenient approach to the asymmetric synthesis of α-hydroxy acid synthons (Scheme 81). In this strategy, the chirality of the alcohol was determined by the chiral auxiliary.



Scheme 81

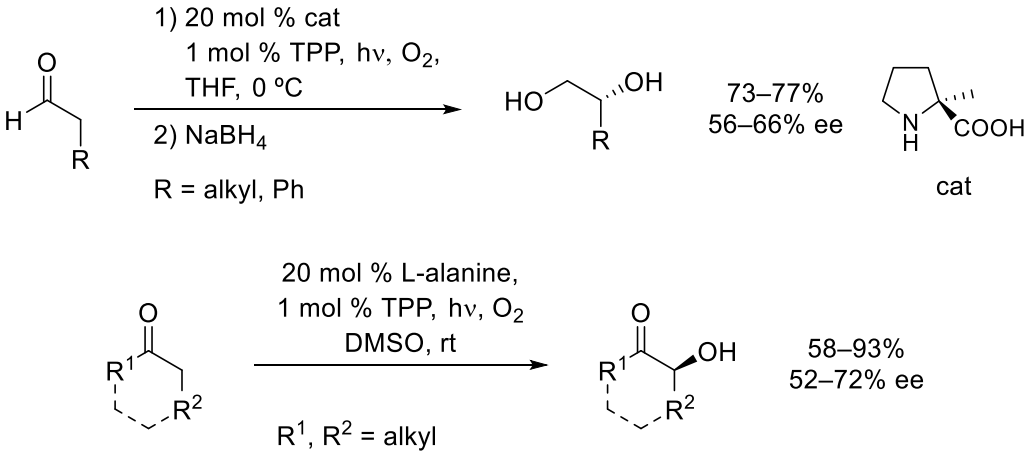
Furthermore, Davis also described a procedure involving the asymmetric oxidation of enolates using a chiral sulfonyloxaziridine derived from camphorsulfonic acid (Scheme 82).[111,112]



Scheme 82

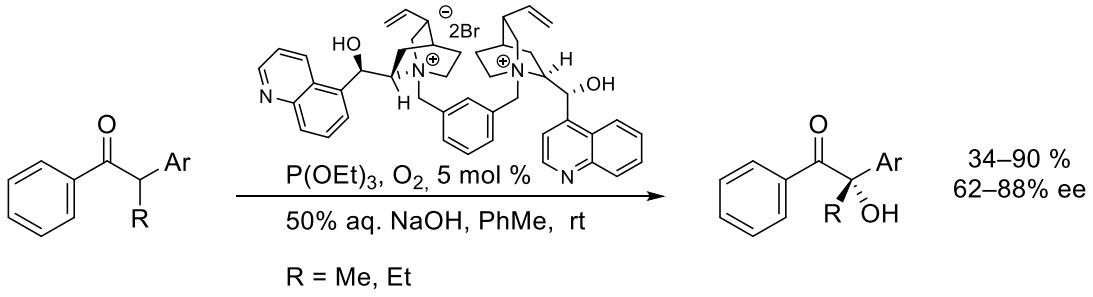
1.1.3. Hydroxylations with oxygen

Molecular oxygen is an ideal oxidant because it is readily available, inexpensive, and environmentally benign. Surprisingly and despite such appealing properties, there are not many hydroxylation examples using oxygen. In pioneering studies, Córdova described the organocatalytic and photosensitised α-hydroxylation of aldehydes and cyclohexanones with molecular singlet oxygen (Scheme 83).[113,114] In this novel strategy, singlet oxygen is formed via photoactivation and reacts with enamines in a non-radical manner to give a hydroperoxide that is then reduced to the desired alcohol.



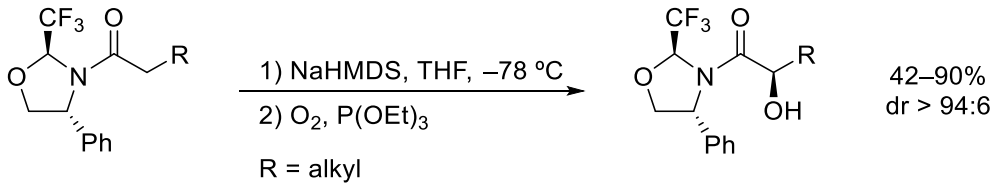
Scheme 83

More recently, Zhao reported a highly efficient, enantioselective, phase transfer catalysed α-hydroxylation of ketones leading to tertiary hydroperoxides that are then reduced with triethyl phosphite to obtain the desired alcohols. (Scheme 84).[115]



Scheme 84

In turn, Brigaud established that treatment of sodium enolates from chiral *N*-acyl trifluoromethylated oxazolidines (Fox) with molecular oxygen produced α-hydroxy adducts with excellent diastereoselectivities upon reduction of the initially formed hydroperoxide (Scheme 85).[116] The ionic mechanism postulated agrees with the results obtained by Córdova as in both cases a hydroperoxide is the true product of the reaction.



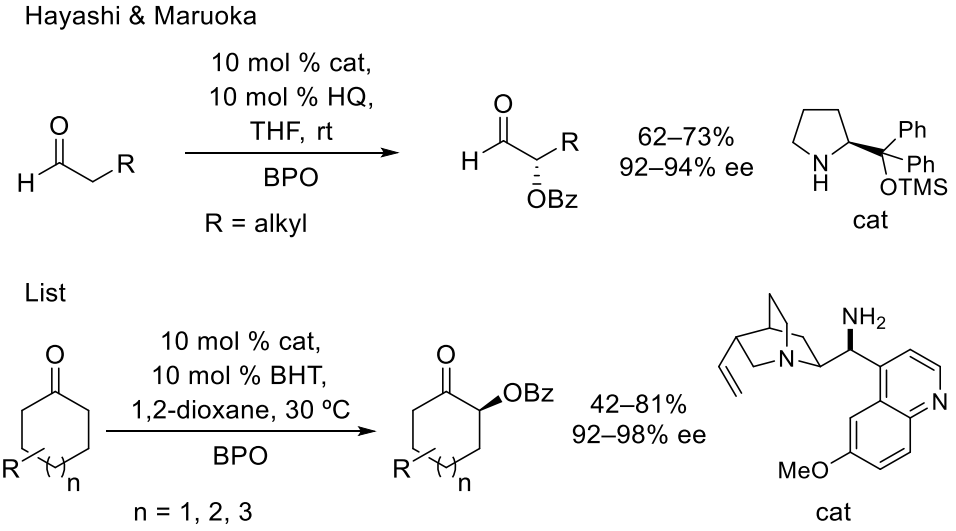
Scheme 85

Remarkably, the true product of the abovementioned reactions is the corresponding hydroperoxide, which is subsequently converted into the desired alcohol.

1.2. Indirect hydroxylations

1.2.1. Benzoyloxylation with benzoyl peroxide

An indirect approach to Cα-hydroxy compounds relies on the introduction of an α-acyloxy group, which can be easily removed to yield the desired alcohol. One of the most interesting oxidants to do so is benzoyl peroxide (BPO), a widely employed radical initiator for radical transformations. In this context, Hayashi and Maruoka independently reported the α-benzoyloxylation of aldehydes catalysed by the same prolinol derivative (Scheme 86).[117,118] In turn, List described an enantioselective phase transfer catalysed α-benzoyloxylation for cyclic ketones (Scheme 86).[119]

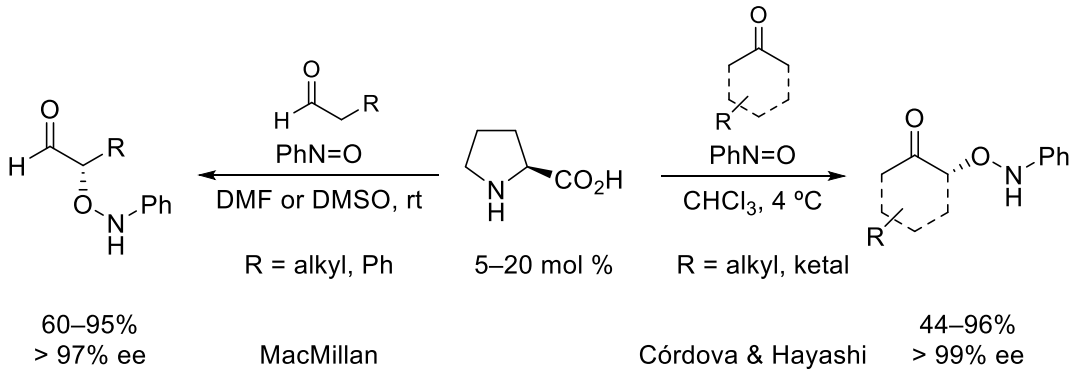


Scheme 86

Contrary to what might be expected, such an α- benzoyloxylation did not proceed through a radical pathway as BPO is known to be relatively stable at room temperature and the reactions take place in the presence of radical scavengers like hydroquinone (HQ) or butylated hydroxy toluene (BHT).

1.2.2. Aminoxylation with Nitrosobenzene

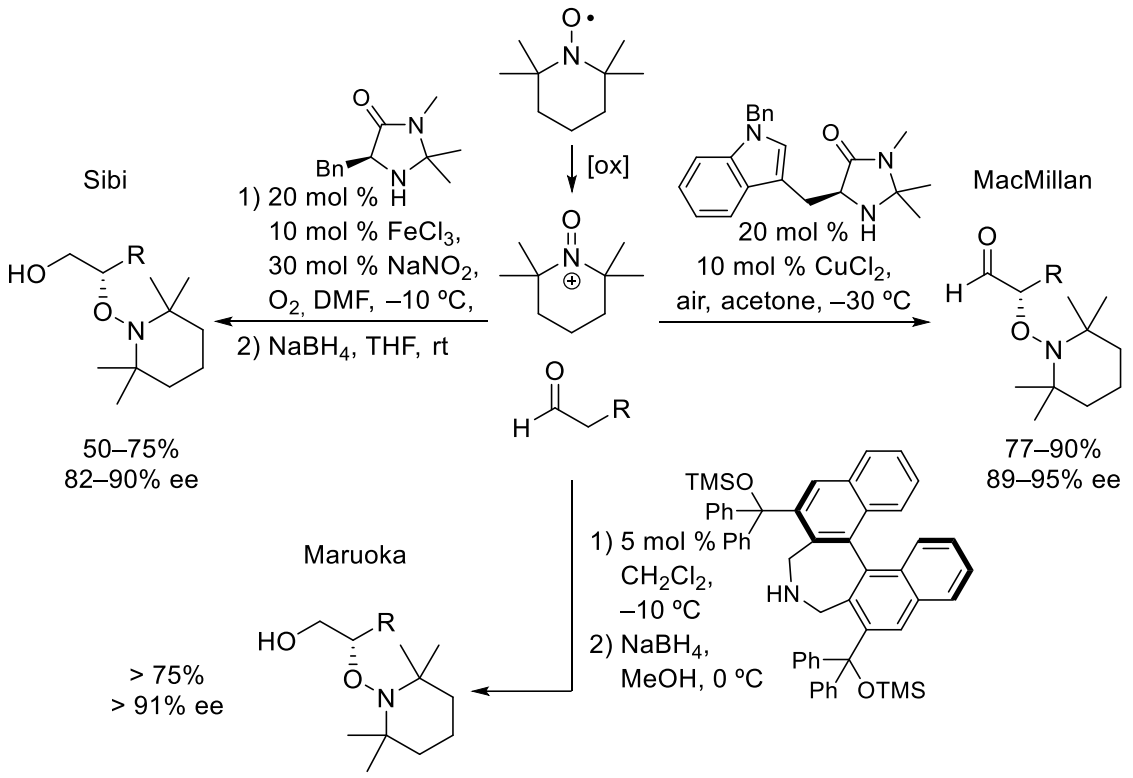
Even though the α-benzoyloxylation seemed promising at first glance, BPO is a relatively stable compound, but undergoes homolysis forming free radicals when heated, and it must be manipulated under strict safety rules. Thus, the more user-friendly nitrosobenzene attracted interest and many groups reported similar procedures to carry out the aminoxylation under organocatalytic conditions. Indeed, MacMillan,[120] Córdova,[121,122] and Hayashi[123,124] described the proline catalysed addition of aldehydes and cyclic ketones to nitrosobenzene with excellent enantioselectivities and moderate yields (Scheme 87). Furthermore, the easy release of the masked alcohol by hydrogenolysis or by copper(I) sulphate reduction made this transformation a powerful tool for synthetic chemists.



Scheme 87

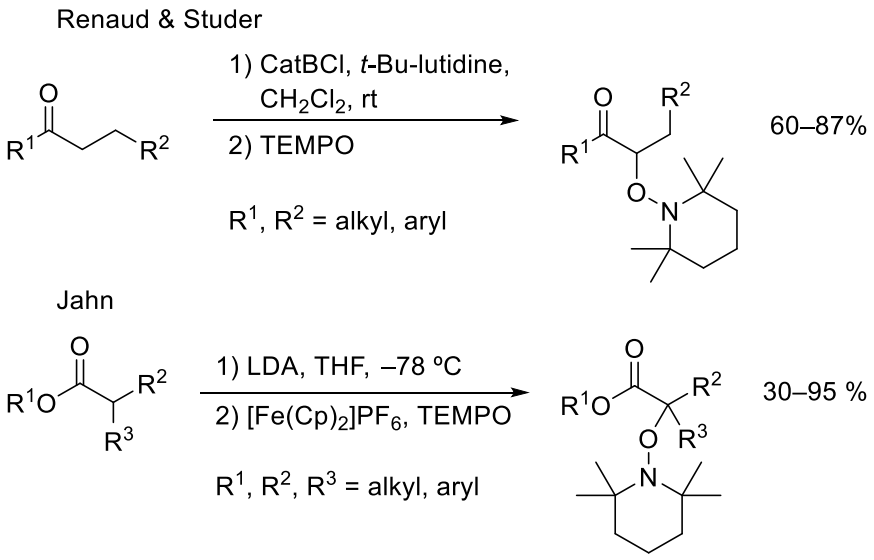
1.2.3. Aminoxylations with TEMPO

Commercially available (2,2,6,6-tetramethylpiperidine-1-yl)oxyl radical (TEMPO) is another source for the stereoselective oxidation of the Cα position. Despite being a radical, TEMPO has been used as precursor of electrophilic reagents for the stereoselective construction of C–O bonds. For instance, Sibi,[125] MacMillan[126,127] and Maruoka[128] reported the enantioselective aminoxylation of enamines catalytically prepared from aldehydes with electrophilic species formed upon oxidation of TEMPO (Scheme 88).



Scheme 88

In contrast, the use of TEMPO in radical-like reactions is scarce and restricted to non-stereoselective transformations. Indeed, Renaud and Studer reported the reaction between carbon radicals derived from catecholborane enolates of ketones with TEMPO to obtain the corresponding aminoxylation adducts.[129,130] In this case, the reaction between the boron enolate and an equivalent of TEMPO generates the corresponding radical α-carbonyl, which is subsequently trapped by a second equivalent of TEMPO to give an α-aminoxy ketone (Scheme 89). In addition, Jahn described the oxidation of lithium enolates from esters with $[Fe(Cp)_2]PF_6$ in the presence of TEMPO with moderate to good yields through a radical intermediate. (Scheme 89).[131]

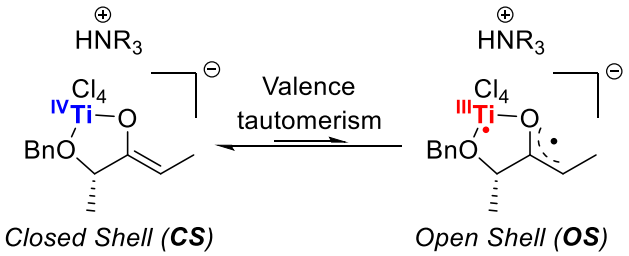


Scheme 89

2. Detailed study of the aminoxylations with TEMPO

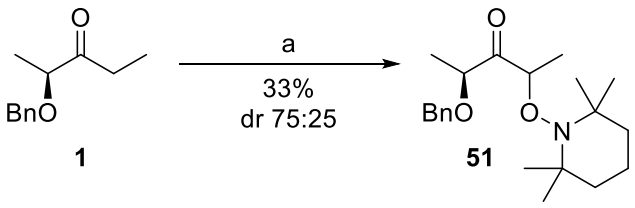
2.1. Introduction

As explained in the General Introduction, our group unveiled the unexpected biradical character of titanium enolates from α-hydroxy ketones some years ago.[35] Theoretical calculations and EPR studies proved that the titanium *ate-complex* of α-hydroxy ketones had to be considered using two electronic configurations related through a valence-tautomerism process. Indeed, one corresponds to a *closed shell* electronic state (***CS***, Scheme 90), whereas the other one has a marked *open shell* (***OS***, Scheme 90) delocalised biradical character.



Scheme 90

Thus, we envisaged that such a new paradigm might enable a novel radical-like reactivity for titanium(IV) enolates, complementary to the traditional nucleophilic character. Exploratory experiments to test such a hypothesis involved TEMPO. The initial results were promising but the expected aminoxylated adduct **51** was always isolated in low yields and poor diastereoselectivity (Scheme 91).

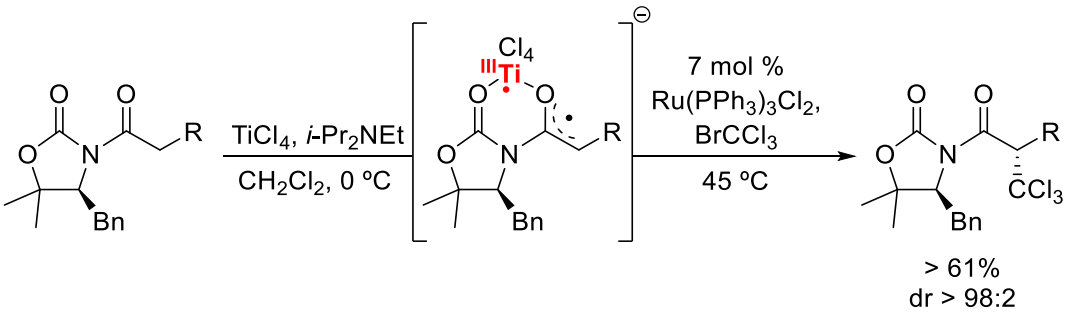


a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 2.1 eq TEMPO, –78 °C, 4 h.

Scheme 91

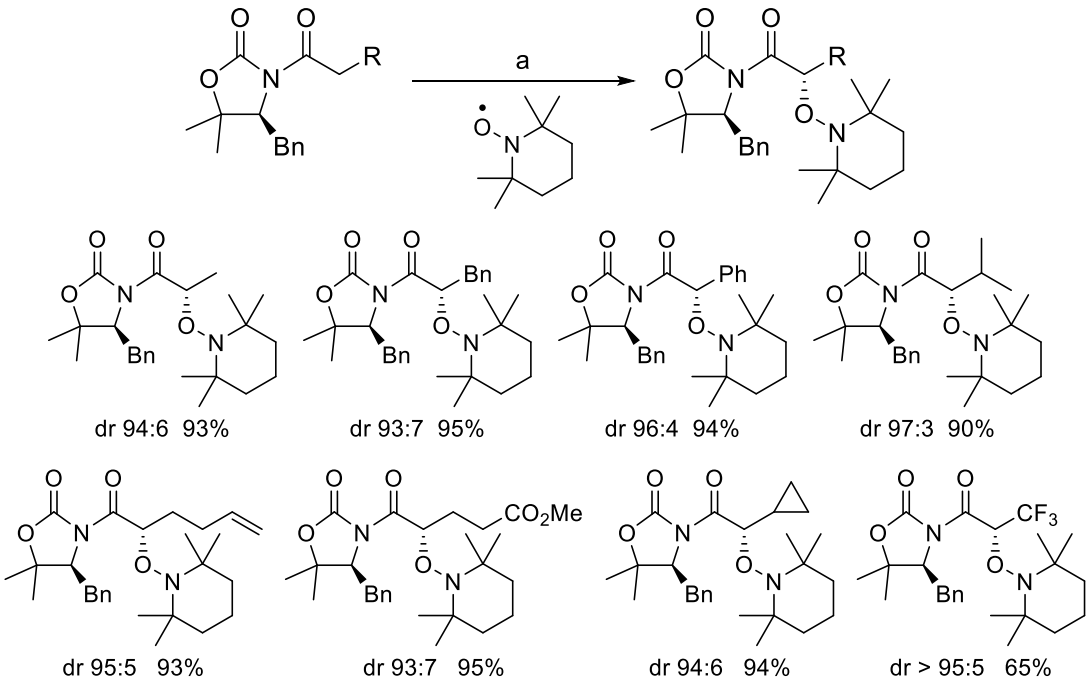
Such bittersweet results proved that the aminoxylation with TEMPO was possible, but the low yield and poor diastereoselectivity thwarted potential applications in synthesis. Attempts to improve the yield carrying out the reaction at 0 °C were unsuccessful due to the low stability of the titanium enolates from chiral α-benzyloxy ketones like **1** at temperatures higher than –20 °C.

At that moment, Zakarian reported that titanium(IV) enolates from *N*-acyl-4-benzyl-5,5-dimethyl oxazolidinones could indeed participate in highly stereoselective alkylation reactions with carbon radical intermediates generated in situ (Scheme 92).[37] The crucial reason for such a successful transformation laid in the robustness of the chelated enolate that provided the appropriate π-facial discrimination at temperatures from 0 °C to 45 °C. In summary, the SuperQuat chiral auxiliary could be the platform from which we could carry out stereoselective transformations based on the radical character of titanium(IV) enolates.



Scheme 92

According to these ideas, Miquel Pellicena established, at the end of his PhD, the feasibility of the stereoselective oxidation with TEMPO that gave excellent yields and diastereoselectivities of the α-aminoxylated adducts from a wide range of chiral oxazolidinones under straightforward experimental conditions (Scheme 93).[132]

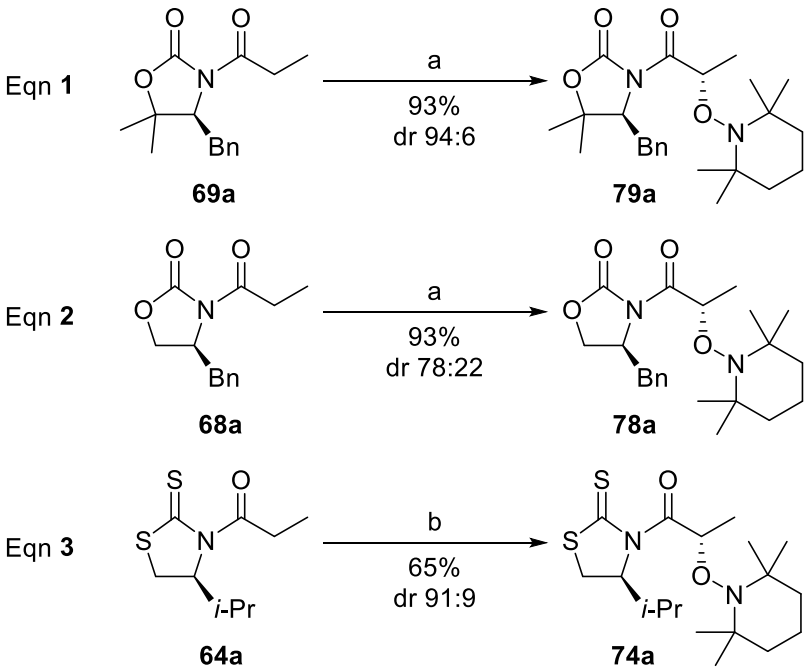


a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 2.1 eq TEMPO, 0 °C, 2 h.

Scheme 93

2.2. Influence of the chiral auxiliary

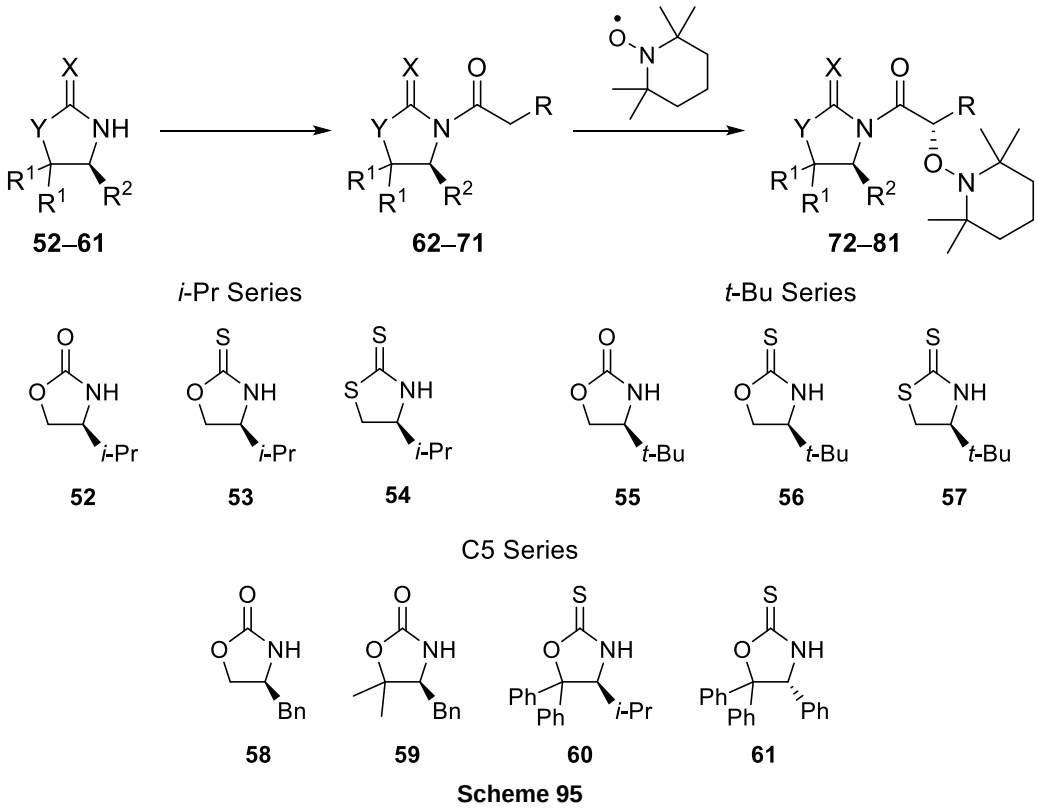
Initially, our group took advantage of Zakarian's findings and used the SuperQuat chiral auxiliary **69** as the platform for the stereoselective aminoxylations with TEMPO. Indeed, the resultant titanium(IV) enolate is very stable and it can even be heated without degradation. Furthermore, the geminal dimethyl groups lock the free rotation of the benzyl appendage and provides a better π-face selectivity than the related oxazolidinone **68a** (compare Eqn **1** and Eqn **2**, Scheme 94). Alternatively, thiazolidinethione **64a**, whose titanium enolate is delicate and might degrade at room temperature, produced the corresponding adduct **74a** in good yield and with comparable diastereoselectivity (compare Eqn **1** and Eqn **3**, Scheme 94)



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 2.1 eq TEMPO, 0 °C, 2 h; b) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –50 °C, 40 min; (ii) 2.1 eq TEMPO, –78 °C, 2 h.

Scheme 94

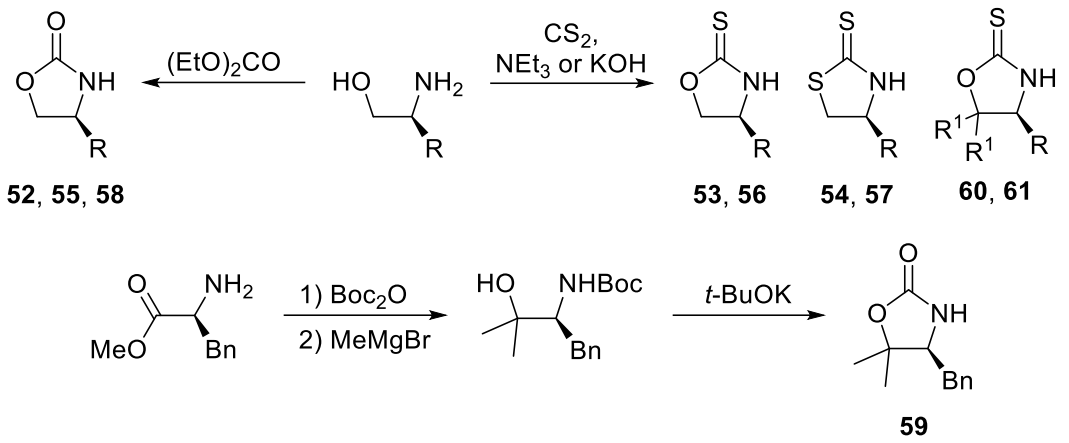
Even though the replacement of the oxygen-based chiral auxiliary by a sulphur-based moiety did not modify the stereochemical outcome of the addition, the thiazolidinethione chiral auxiliary represented an appealing alternative because of its easy removal under very mild conditions.[133,134] Hence, with the collaboration of Stuart Kennington[135] during his Erasmus exchange and Ernest Salomó during his Masters project,[136] we performed a comprehensive analysis of the effect of the chiral auxiliary on the stereochemical outcome of the aminoxylation of the corresponding titanium(IV) enolates with TEMPO (Scheme 95).



Scheme 95

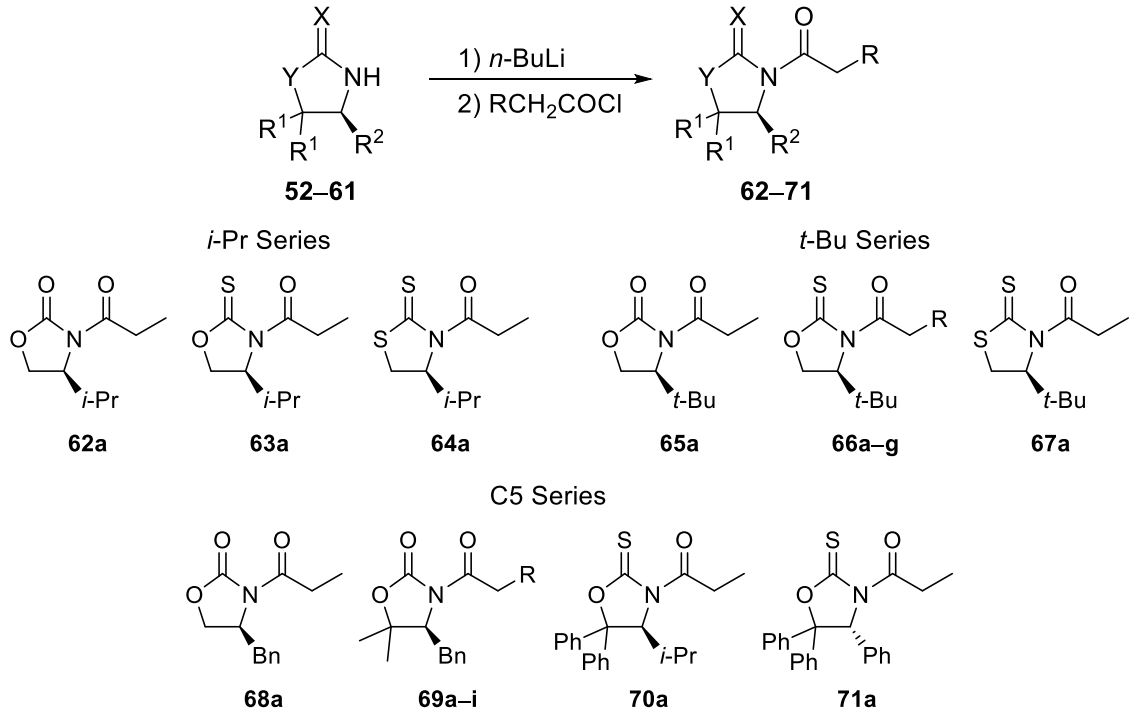
2.3. Preparation of the *N*-acylated chiral auxilliaries

The abovementioned chiral auxiliaries were prepared and acylated following standard procedures described in the literature (Scheme 96). Indeed, oxazolidinone auxiliaries **52**, **55** and **58** were prepared by cyclization of the corresponding aminoalcohols with ethyl carbonate following procedures adapted from that described by Evans and Tietze;[137–139] oxazolidinethiones **53** and **56**, and thiazolidinethiones **54** and **57** were prepared by treatment with CS_2 following the procedure described by our group.[140] 5,5-Diphenyl oxazolidinethione auxiliaries **60** and **61** were prepared by cyclization with CS_2 according to the procedure described by Phillips,[141] while oxazolidinone **59** was prepared from the Boc protected aminoalcohol with catalytic *t*-BuOK following the procedure described by Davies.[142]



Scheme 96

Finally, acylation of the heterocycles was conducted using a standard procedure.[140,143] Treatment of the chiral auxiliary with *n*-BuLi and the corresponding acyl chloride furnished the acylated scaffolds with excellent yields (Scheme 97).



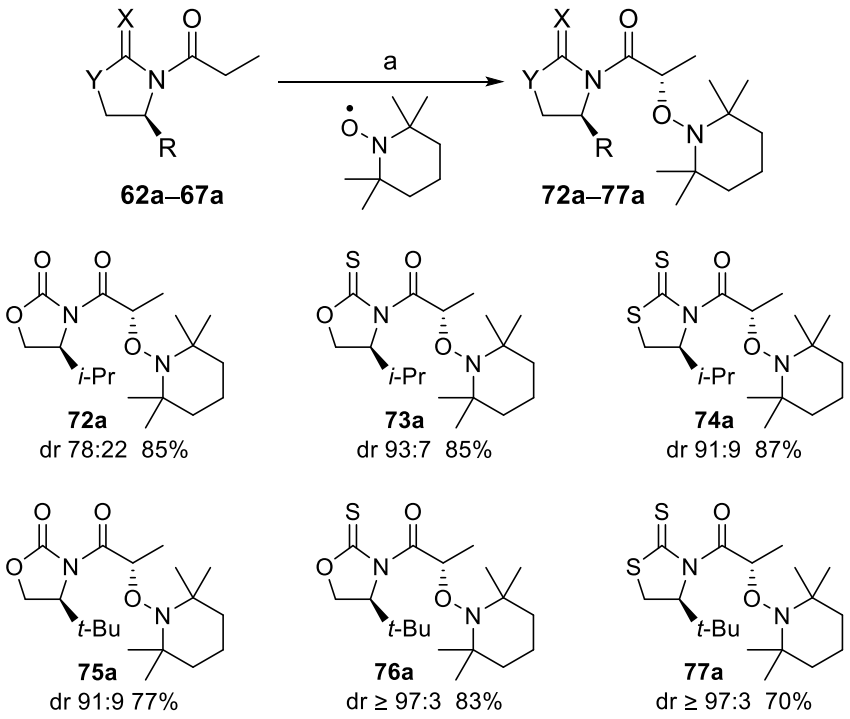
Conditions: (i) 1.1 eq *n*-BuLi, THF, –78 °C, 15 min; (ii) 1.3 eq acyl chloride, –78 to rt, 1 h.

Scheme 97

2.4. Chiral auxiliary screening

Taking advantage of our own study on the aminoxylation of titanium enolates from *N*-acyl oxazolidinones with TEMPO, we initially investigated the influence of the chiral auxiliaries **62a–67a** with various combination of *exo* and *endo* oxygen and sulphur heteroatoms in the heterocycle and bulky groups at C4. By choosing a wide range of chiral substrates we envisaged to fully understand the effect of the heteroatoms and the

groups at C4 and therefore to find the most effective scaffold for this type of reaction. The reactions were carried out following the optimised protocol for the aminoxylation of oxazolidinones that we previously described.[132] The results are summarised in Scheme 98.

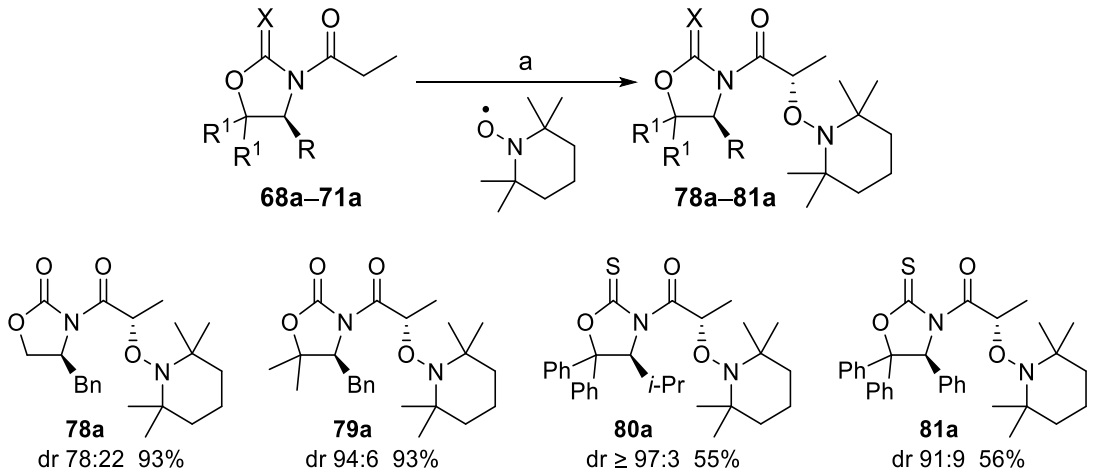


a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 2.1 eq TEMPO, 0 °C, 1 h.

Scheme 98

The results of this screening showed a clear trend. Indeed, substitution of the exocyclic oxygen by sulphur both in the isopropyl and *tert*-butyl series produced a significant improvement of the diastereoselectivity (compare **72a** with **73a**–**74a** and **75a** with **76a**–**77a**, Scheme 98). Moreover, the bulky *tert*-butyl group turned out to be crucial to obtain a single diastereomer (see **76a** and **77a**, Scheme 98). Thus, *tert*-butyl *N*-propanoyl oxazolidinethione **66a** and thiazolidinethione **67a**, corresponding to products **76a** and **77a** respectively, were the most appropriate platforms from which to carry out a completely stereocontrolled aminoxylation in high yields.

Having identified the crucial role of the exocyclic heteroatom and the C4 alkyl group, we next evaluated the consequences of placing geminal groups at C5. As we had already described the aminoxylation using chiral auxiliaries **69a**, in which the oxazolidinones possesses a geminal dimethyl at C5, and **68a**, which lacks any group at C5, we next evaluated the outcome of the reactions from oxazolidinethiones **70a** and **71a**. The results are summarised in Scheme 99.



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 2.1 eq TEMPO, 0 °C, 1 h.

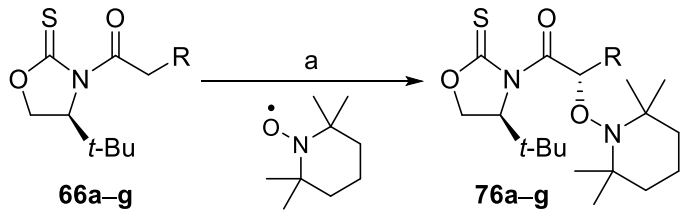
Scheme 99

As mentioned in the introduction of this section, *N*-propanoyl C4 benzyl oxazolidinones **68a** and **69a** clearly showed that the diastereoselectivity was largely increased by attaching two geminal methyl groups at C5 (compare **78a** and **79a**, Scheme 99). Furthermore, the introduction of two phenyl groups at C5 was also advantageous for the isopropyl oxazolidinethione **70a** since a single diastereomer was obtained although in a moderate yield (compare **73a** in Scheme 98 with **80a** in Scheme 99). Finally, oxazolidinethione **71a** proved that a C4 substituent larger than a phenyl group is required to obtain a single diastereomer (compare **80a** with **81a**, Scheme 99).

All together, these results indicate that only three of the ten different chiral auxiliaries evaluated, oxazolidinethiones **66a** and **70a**, and thiazolidinethione **67a**, offer complete control of the newly created stereocentre. Particularly, the *tert*-butyl oxazolidinethione **66a** emerged as the most appropriate choice. Certainly, it provided a slightly lower yield than the SuperQuat auxiliary **69a**, but gave a complete stereocontrol and it was easier to synthesise from readily available *tert*-leucine.

2.5. General procedure for the aminoxylation with TEMPO

Since the screening process led us to a new chiral auxiliary, we next re-examined the scope of the aminoxylation with TEMPO using this new scaffold. To do this we varied the acyl group of the heterocycle trying to test the impact of sterically hindered groups as well as others containing common functional groups. The reactions were carried out following the same protocol as in the former screening and the results are summarised in Table 15.



66a–g **76a–g**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 2.1 eq TEMPO, 0 °C, 1 h.

Entry	Substrate	R	Product	dr[a]	Yield (%)[b]
1	**66a**	Me	**76a**	≥ 97:3	83
2	**66b**	Bn	**76b**	≥ 97:3	81
3	**66c**	Ph	**76c**	50:50	90
4	**66d**	*i*-Pr	**76d**	≥ 97:3	83
5	**66e**	C_3H_5	**76e**	≥ 97:3	79
6	**66f**	$(CH_2)_2CO_2Me$	**76f**	≥ 97:3	93
7	**66g**	$(CH_2)_2CH=CH_2$	**76g**	≥ 97:3	90

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.

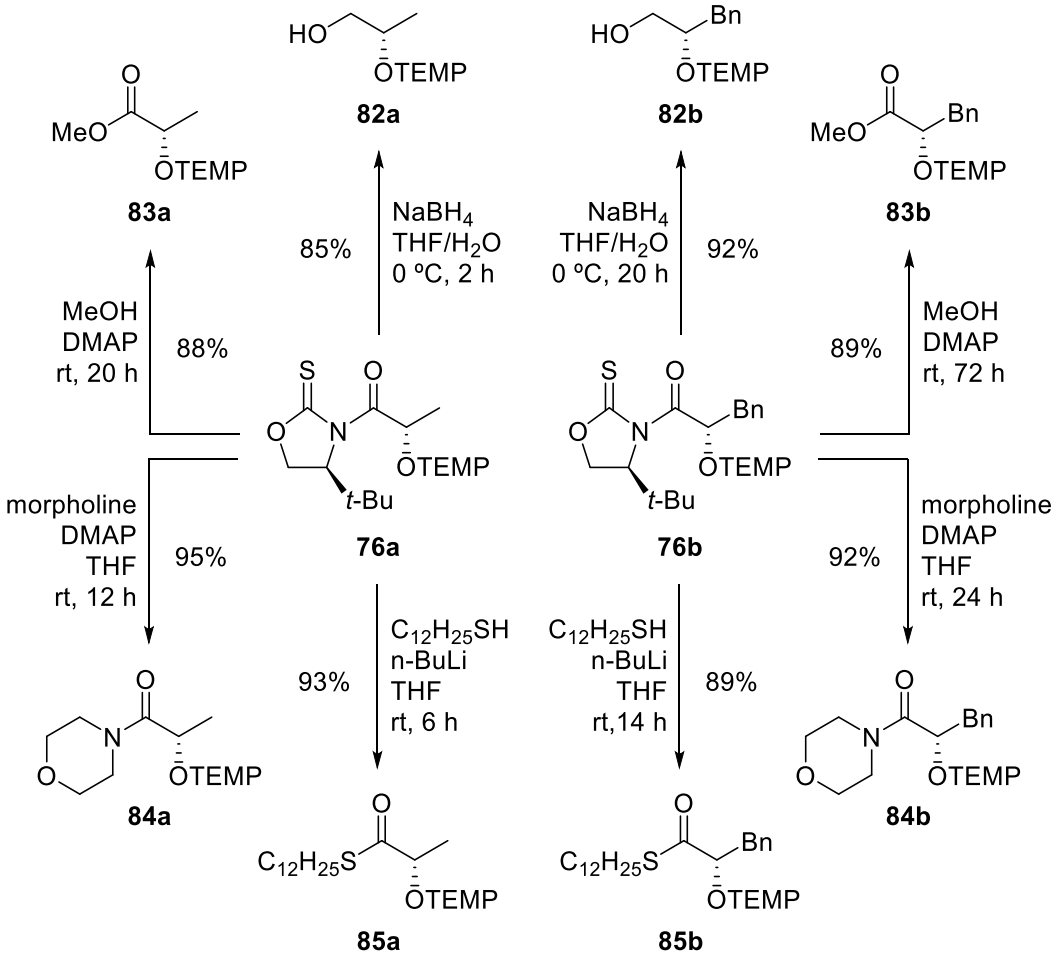
Table 15

The results from Table 15 established that the simple treatment of titanium enolates from a wide array of *N*-acyl *tert*-butyl oxazolidinethiones with TEMPO afforded a single diastereomer for almost all the substrates. Actually, the steric bulk of the acyl groups had little influence on the yield (compare entries 1–5, Table 15). Importantly, phenyl derivative **66c** provided an equimolar mixture of two diastereomers (entry 3, Table 15), probably because of the higher acidity of the Cα position. Apart from this result, other common functional groups such as alkenes and esters did not interfere with the reaction and the corresponding aminoxylated adducts were obtained as a single diastereomer in high yields (entries 6 and 7, Table 15).

2.6. Removal of the chiral auxiliary

We finally investigated the removal of the chiral auxiliary from adducts **76a** and **76b** (Scheme 100). First, we employed $NaBH_4$ to obtain the corresponding alcohols **82a** and **82b**. In the case of **76a** the reaction took only two hours while the more hindered adduct **76b** required longer time and temperature but also gave an excellent yield of the alcohol. In turn, methanol was used to displace the heterocycle and leave an ester. Both adducts performed in a similar manner and gave excellent yields of the enantiopure esters **83a** and **83b** with the latter taking longer to complete the reaction. When morpholine was used to displace the auxiliary, we obtained enantiopure amides **84a** and **84b**, again with excellent yields. Finally, displacement of the chiral scaffold with a thiol to form thioesters **85a** and **85b** also proceeded smoothly and both derivatives were isolated

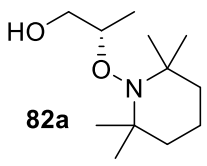
in excellent yields. Remarkably, all these reactions were carried out under mild conditions and the resulting functionalised compounds **82a**–**b**, **83a**–**b**, **84a**–**b** and **85a**–**b** were easily isolated in high yields; furthermore, the recovery of the auxiliary was excellent in all cases, with the minimum amount being 81% and an average of 91% over eight different reactions.



Scheme 100

2.7. Absolute configuration of adducts 76

Initially, the absolute configuration of these α-aminoxylated adducts was established by removal of the chiral auxiliary from **76a**, prepared in the previous section, and the correlation of the resultant alcohol **82a** with a product from the literature (Scheme 101).[128] It was later confirmed through X-ray analysis of **76b** (Figure 9).



82a

82a $[\alpha]_D$ = –35.6 (*c* 1.0, $CHCl_3$)
Maruoka[128] ***ent*-82a** $[\alpha]_D$ = +31.9 (*c* 1.3, $CHCl_3$, 90% *ee*)

Scheme 101

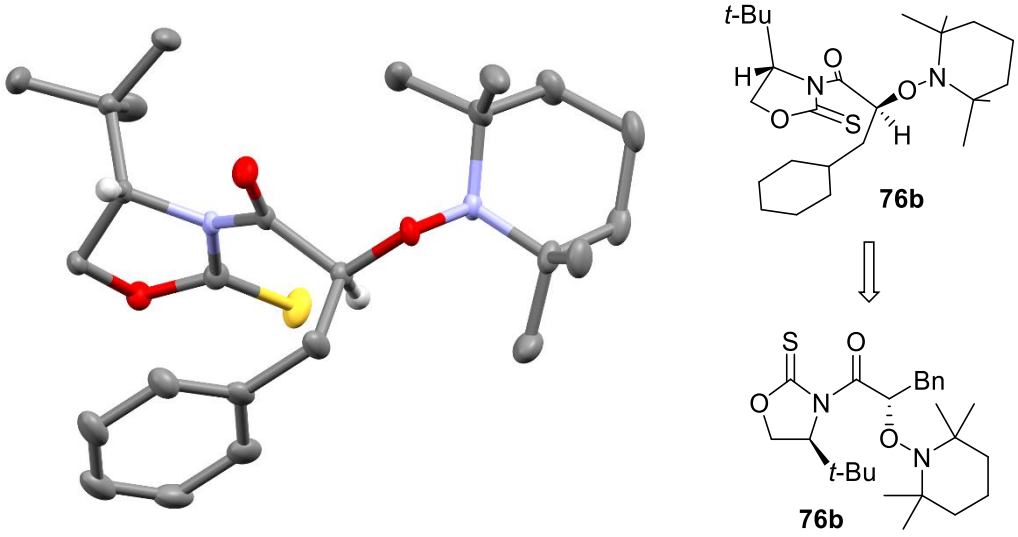
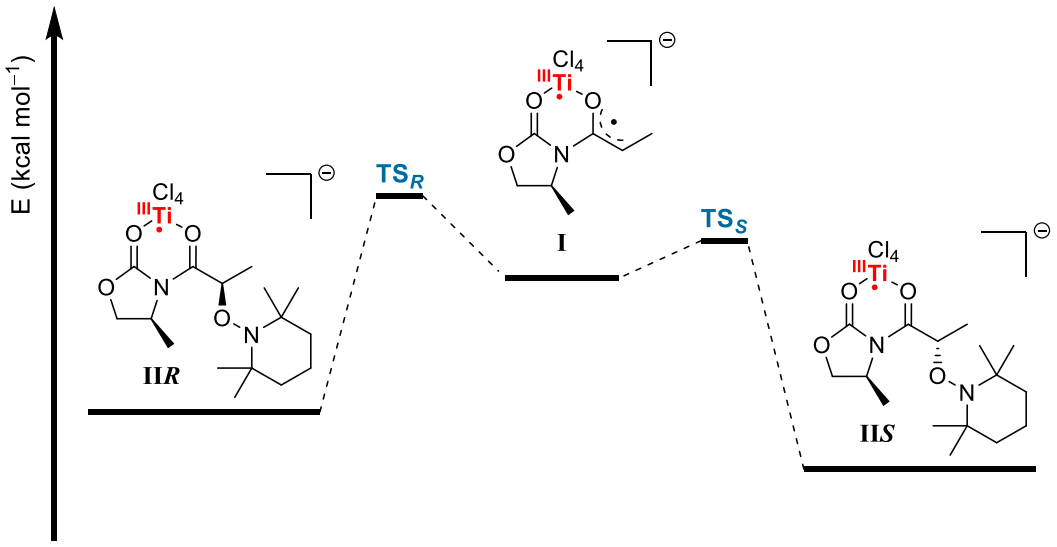


Figure 9

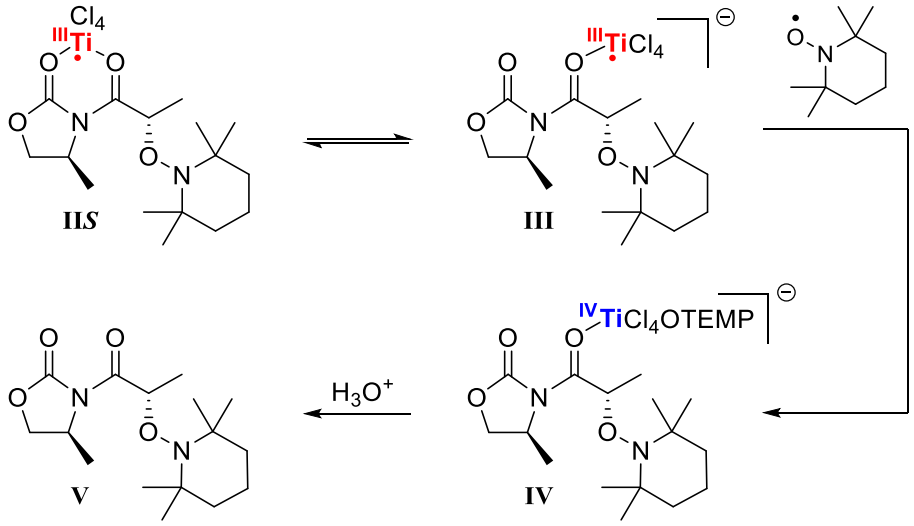
2.8. Theoretical calculations

Theoretical calculations carried out by Prof. Josep M. Bofill and Dr. Iberio de P. R. Moreira on the aminoxylation of the titanium(IV) enolates from 4-methyl-*N*-propanoyl oxazolidinone confirmed its biradical character.[36] They also established that the less sterically hindered π-face of the biradical configuration of the enolate, which could be viewed as a formal titanium(III) radical complex **I**, permitted an easy interaction with the TEMPO molecule. Then, the C–O bond could be formed through a low barrier transformation that produced the titanium(III) chelate **II*S*** (Scheme 102); whereas if the TEMPO molecule approached the enolate from the more sterically hindered π-face to form the titanium(III) chelate **II*R***, the barrier would be around 1−2 kcal mol^{-1} larger.



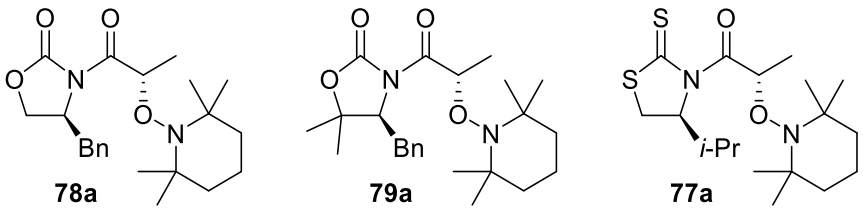
Scheme 102

Finally, the oxidation of the titanium(III) involved a multi-equilibrium process (Scheme 103) in which the hexacoordinated chelate **II*S*** possessing two weak dative bonds was transformed into a pentacoordinated titanium(III) complex **III**. This intermediate was oxidised by a second TEMPO molecule, thereby producing the titanium(IV) complex **IV**, which finally delivered the adduct **V** after the acid workup. Noticeably, the proposed mechanism requires much less energy than the direct oxidation of **II**, which makes it necessary to consider the formation of the nonchelated complex **III** and the subsequent ligand exchange (Scheme 103). Such a mechanism was in agreement with the configuration of the major diastereomer established by X-ray analysis and the experimental requirement of two equivalents of TEMPO to achieve full conversion.



Scheme 103

The energies of the TEMPO α-aminoxylation of the titanium enolates derived from *N*-propanoyl oxazolidinones **52a** and **57a**, and thiazolidinethione **59a** were examined and the diastereomeric ratios were estimated using the Boltzmann distribution. The predicted diastereomeric ratios nicely matched the experimental trends (Figure 10), which supported the theoretical analysis. Particularly, these calculations indicated that the excellent diastereoselectivity attained with the titanium enolate from chiral 4-benzyl-5,5-dimethyl-*N*-propanoyl-1,3-oxazolidin-2-one **69a** (product **79a**), better than that of the parent oxazolidinone **68a** (product **78a**), was due to the rigidity of the complex induced by steric repulsion of the geminal methyl groups with the benzyl group that provides a larger exposure of the π-face opposite to the benzyl group. In turn, the distortion produced by the long C-S bonds in the enolate from thiazolidinethione derived **67a** (product **77a**) also facilitates the approach of the radical to the opposite face to the *i*-Pr group and is thus the reason for the high stereocontrol achieved in this case.



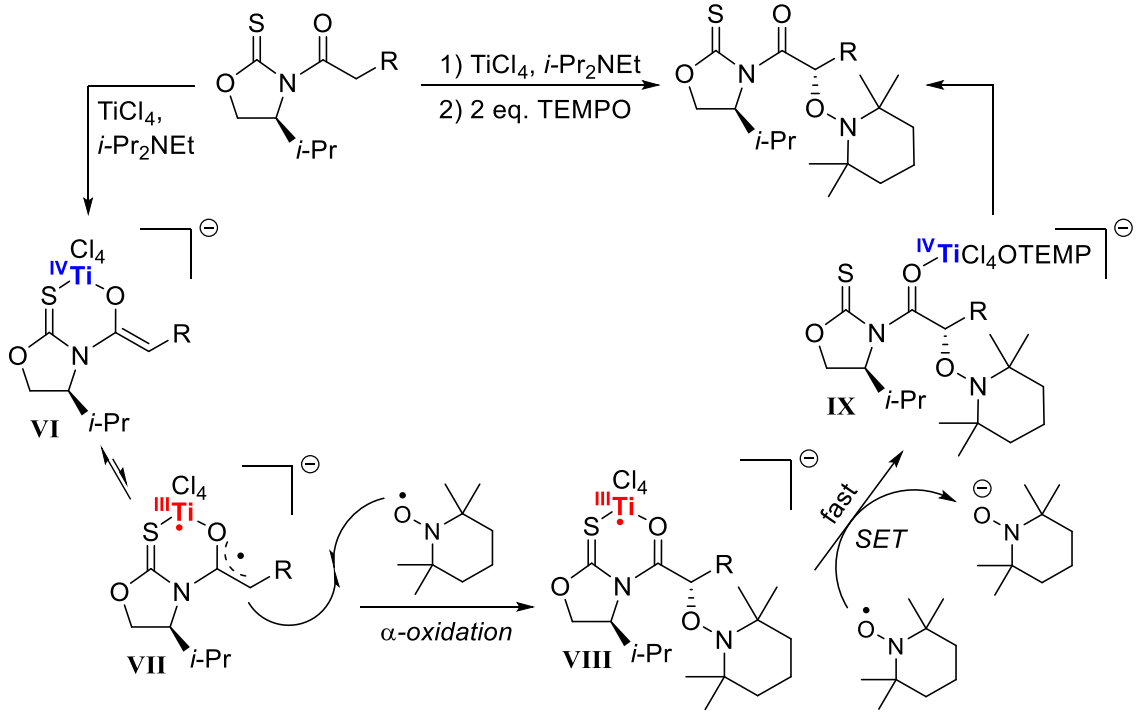
Exp dr 78:22
Calcd dr 86:14

Exp dr 94:6
Calcd dr 97:3

Exp dr 91:9
Calcd dr 98:2

Figure 10

In summary, both the experimental results and the theoretical calculations suggest that the aminoxylation of the titanium(IV) enolate from *N*-acyl *tert*-butyl oxazolidinethiones could be explained if the crucial step of the reaction is the aminoxylation of the biradical enolate **VII** by a TEMPO radical to the least hindered π-face (Scheme 104), forming a titanium(III) complex **VIII** with a strong reductant character, followed by a fast SET from another TEMPO radical to the remaining titanium(III) to form the final titanium(IV) complex **IX**.

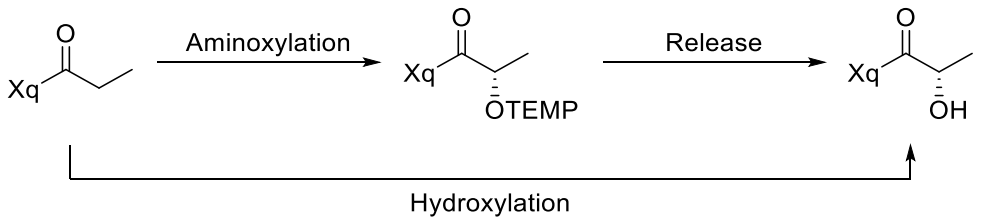


Scheme 104

3. Hydroxylations with oxygen

3.1. Introduction

Aminoxylation by means of the formerly discussed methodologies requires subsequent release of the latent α-hydroxyl group. Obviously, the direct hydroxylation of the titanium enolate would be the simplest strategy to obtain such type of α-hydroxy carbonyl structures (Scheme 105).



Scheme 105

Despite being little used for this purpose, molecular oxygen is undeniably the most suitable candidate as it is an abundant reagent that does not produce harmful by-products. Thus, oxygen represents an appealing agent to carry out such reactions. The oxygen molecule exists naturally as a triplet state, whose electron configuration contains two unpaired electrons occupying two π* molecular orbitals, making triplet oxygen an unusual example of a stable and commonly encountered biradical (Figure 11).

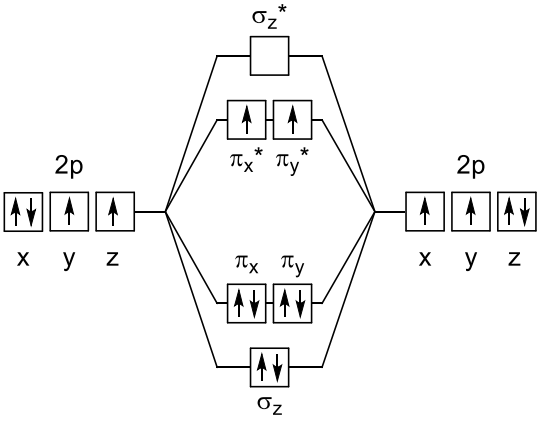
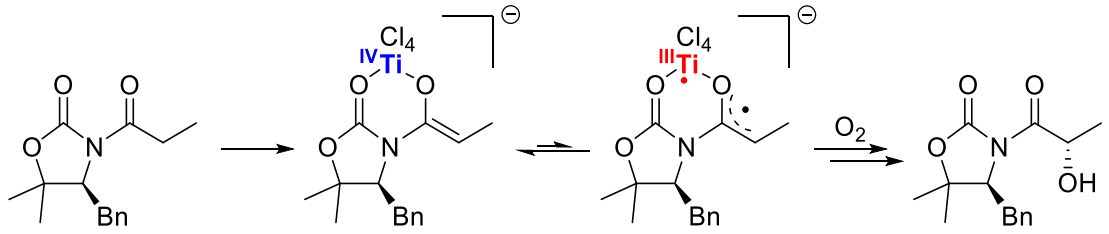


Figure 11

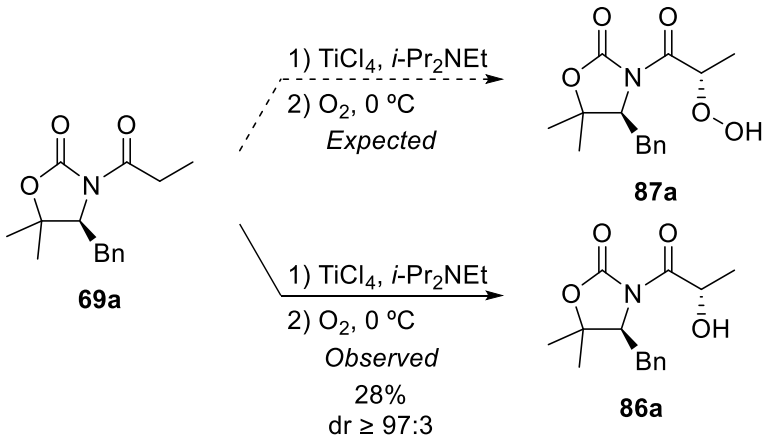
Considering this property and taking advantage of the biradical character of the titanium enolate and our experience with the radical aminoxylation using TEMPO, we envisaged that the treatment of titanium(IV) enolates from oxazolidinone **69a** with oxygen might lead to the desired α-hydroxy derivative **86a** (Scheme 106).



Scheme 106

3.2. Preliminary studies

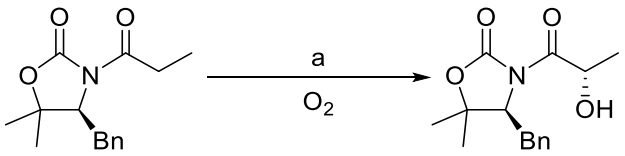
Preliminary experiments showed that bubbling dry oxygen through a solution of titanium(IV) enolate triggered an oxidative process. The reaction was allowed to evolve at room temperature, while the distinctive deep purple colour of the titanium enolate changed progressively to a yellow-orange colour. To our surprise, instead of the expected hydroperoxide **87a**, the hydroxylated product **86a** was directly obtained as a single diastereomer with a yield of 28% (Scheme 107).



Conditions: (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) O_2 bubbling for 15 min at 0 °C, then rt until colour changes to yellow-orange

Scheme 107

On the other hand, the dibutylboron, lithium, and sodium enolates from *N*-propanoyl oxazolidinone **69a** were unable to undergo any similar reaction at 0 °C, for the boron enolate, or at –20 °C, for the alkaline enolates. Only small amounts of the deacylated scaffold were found with unreacted starting material. A small screening of different ligands on the titanium atom (Table 16) showed that one *i*-PrO did not affect the selectivity nor the final yield significantly, while an increase of alkoxide or bromine ligands inhibited the reactivity of the biradical species and gave only traces of the hydroxylated product. Finally, the zirconium(IV) enolate of **69a** did also produce the α-hydroxylated adduct **86a** as a single diastereomer as well, but with a yield of 18%.



69a **86a**

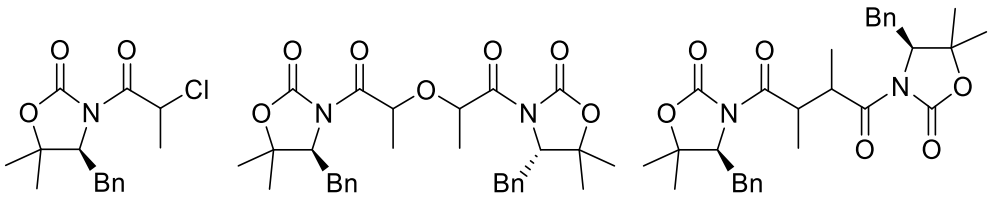
a) (i) 1.1 eq ML_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) O_2 bubbling for 15 min at 0 °C, then rt until colour changes to yellow-orange.

Entry	ML_4	dr[a]	Yield (%)[b]
1	$TiCl_4$	≥ 97:3	28
2	$TiCl_3$(*i*-PrO)	≥ 97:3	33
3	$TiCl_2$(*i*-PrO)$_2$	≥ 97:3	(4)
4	TiCl(*i*-PrO)$_3$	≥ 97:3	(3)
5	$TiBr_4$	≥ 97:3	(5)
6	$ZrCl_4$	-	-
7[c]	$ZrCl_4$	≥ 97:3	18

[a] Determined by ^1H NMR and HPLC analysis of the crude mixture.
[b] Isolated yield after column chromatography. NMR conversion into brackets.
[c] Performed with 3.5 eq of NEt_3.

Table 16

Remarkably, careful analysis of the crude reaction mixtures indicated the generation of low amounts of at least three by-products **88a**, **89a** and **90a** (Figure 12). Generally, the formation of these by-products was not a big deal, but more like a background noise.



88a **89a** **90a**

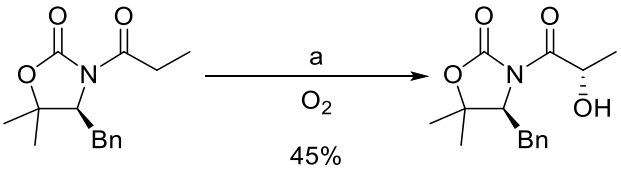
Figure 12

3.3. Optimisation of the hydroxylation with oxygen

As the abovementioned preliminary studies showed that both $TiCl_4$ and $TiCl_3$(*i*-PrO) enolates from *N*-propanoyl oxazolidinone **69a** were successfully oxidised by oxygen with a complete stereocontrol, we carried out a thorough analysis to improve the yield.

Initially, we had to cope with an experimental drawback. Since the gas we bubbled through the enolate solution had to be dried of any moisture, we originally decided to bubble it through concentrated sulphuric acid. This seemed to be the best

solution to dry the oxygen, but then, the flow of oxygen became a little unstable and the amount of evaporated dichloromethane was random. Therefore, we tested a different way to add the oxygen stream to the titanium enolate. Finally, a simple 5 minutes purge and stirring of the solution under an oxygen atmosphere was much more reliable than the former bubbling. Indeed, this new procedure led to an increase of the yield of the α-hydroxy adduct **86a** up to 45% after 2 h (Scheme 108).

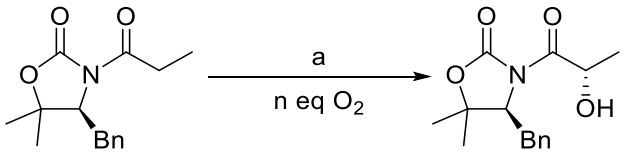


69a **86a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) O_2 atm for 5 min at 0 °C, then rt until colour changes to yellow-orange.

Scheme 108

However, this experimental procedure did not allow us to know the exact quantity of oxygen used during the reaction. We then examined the influence of the amount of oxygen on the yield of the reaction by adding different volumes of dried gas to the titanium(IV) enolate with a syringe (Table 17).



69a **86a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) n eq O_2 at 0 °C, then rt until colour changes to yellow-orange.

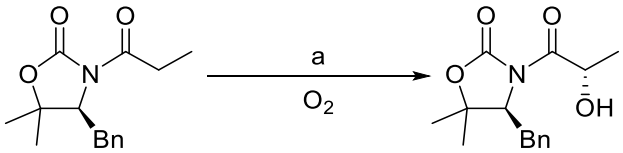
Entry	O_2 (eq)[a]	dr[b]	Yield (%)[c]
1	2.5	≥ 97:3	45
2	1.3	≥ 97:3	45
3	0.6	≥ 97:3	40

[a] Estimated amount of O_2 based on the equivalence 1 mol ≈ 22.4 L
[b] Determined by ^1H NMR and HPLC analysis of the crude mixture.
[c] Isolated yield after column chromatography.

Table 17

Surprisingly, both excess and 1.3 equivalents of oxygen produced the same yields of the hydroxylated product **86a** (entries 1 and 2, Table 17), whereas a substoichiometric amount of oxygen gave alcohol **86a** with a slightly lower yield (entry 3, Table 17). It was thus clear that an excess of oxygen was not required.

Next, we carried out an exploration of reaction conditions to choose the most appropriate Lewis acids for the enolization. The results are summarised in Table 18.



69a **86a**

a) (i) 1.1 eq TiL_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) O_2 atm for 5 min at T (0 °C when T = rt), then T until colour changes to yellow-orange.

Entry	TiL_4	T (°C)	Concentration (M)	dr[a]	Yield (%)[b]
1	$TiCl_4$	–50	0.25	–	> 5
2	$TiCl_4$	–20 → rt	0.25	≥ 97:3	44
3	$TiCl_4$	0	0.25	≥ 97:3	38
4	$TiCl_4$	rt	0.25	≥ 97:3	44
5	$TiCl_4$	rt	0.05	≥ 97:3	45
6	$TiCl_4$	rt	0.025	≥ 97:3	44
7	2 × $TiCl_4$	rt	0.25	≥ 97:3	41
8	$TiCl_3$(*i*-PrO)	0	0.25	≥ 97:3	41
9	$TiCl_3$(*i*-PrO)	rt	0.25	≥ 97:3	29
10	$TiCl_3$(*i*-PrO)	0	0.025	≥ 97:3	37
11	2 × $TiCl_3$(*i*-PrO)	0	0.25	≥ 97:3	(38)

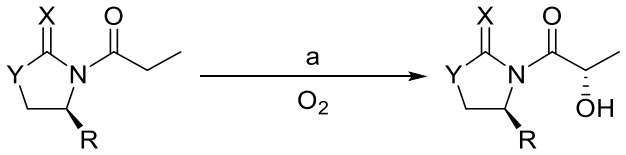
[a] Determined by ^1H NMR and HPLC analysis of the crude mixture.
[b] Isolated yield after column chromatography. NMR conversion into brackets.

Table 18

The oxidation seemed to be inhibited at temperatures below –20 °C (entries 1 and 2, Table 18) but was switched on if the temperature raised. For $TiCl_4$ enolates, running the reaction at 0 °C (entry 3, Table 18) or in diluted conditions (entries 5 and 6, Table 18) did not significantly affect the final yield of adduct **86a** (entry 4, Table 18). However, for $TiCl_3$(*i*-PrO), reactions carried out at 0 °C (entry 8, Table 18) performed better than at room temperature (entry 9, Table 18), while diluted conditions (entry 10, Table 18) did not affect significantly comparing the best results at 0 °C. Finally, titanium enolates activated with a second equivalent of Lewis acid afforded yields similar to those observed from their unactivated counterparts (compare entry 4 with 7 and entry 8 with 11, Table 18), but also triggered the formation of by-products which made the purification of the hydroxylated adducts much more painful.

The use of molecular sieves or the addition of reducing agents like $P(OEt)_3$ did not improve the yield but jeopardised it. In turn and taking advantage of our own study on the aminoxylation with TEMPO, we investigated the influence of different chiral *N*-

propanoyl scaffolds **68a**, **63a** and **64a** with various combination of oxygen and sulphur heteroatoms in the *exo* position of the heterocycle and without geminal groups at C5 (Table 19).



68a, **63a**, **64a** **91a–93a**

a) (i) 1.1 eq TiL_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii)) O_2 atm for 5 min at T, then T overnight.

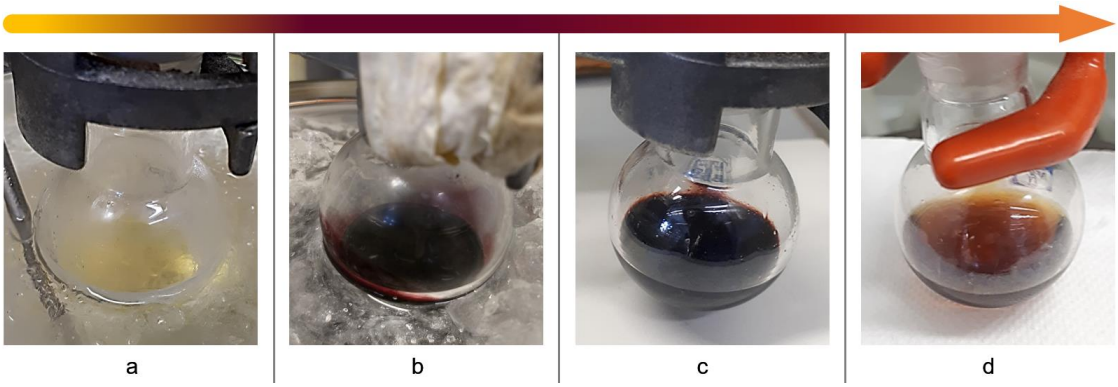
Entry	Substrate	X	Y	R	TiL_4	T (°C)	Product	dr[a]	Yield (%)[b]
1	**68a**	O	O	Bn	$TiCl_4$	rt	**91a**	≥ 97:3	42[c]
2	**68a**	O	O	Bn	$TiCl_3$(*i*-PrO)	rt	**91a**	≥ 97:3	27[c]
3	**63a**	S	O	*i*-Pr	$TiCl_4$	0	**92a**	-	-
4	**63a**	S	O	*i*-Pr	$TiCl_3$(*i*-PrO)	–20	**92a**	-	-
5	**64a**	S	S	*i*-Pr	$TiCl_3$(*i*-PrO)	–50 → rt	**93a**	-	-

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Impure isolated yield.

Table 19

The results summarised on Table 19 indicated that the direct α-hydroxylation of titanium enolates from sulphur containing chiral auxiliaries **63a** and **64a** did not occur, and only deacylation product and starting material were found in the crude mixtures (entries 3–5, Table 19). In turn, Evans chiral auxiliary **68a** performed like the SuperQuat substrate in terms of stereoselectivity and overall conversion (entries 1 and 2, Table 19), although the pure hydroxylated adduct **91a** could not be properly purified due to several impurities.

Finally, until this point we followed the reaction through changes in the colour, the reaction evolved and distinctive purple colour of the titanium enolate changed progressively to a yellow-orange colour, and at that time we quenched the reaction (Figure 13).



a: Titanium(IV) coordination complex; b: Titanium(IV) enolate; c: Addition of oxygen; d: Quenched reaction

Figure 13

However, we did not know the kinetics of the hydroxylation. Thus, we followed the conversion of a high scale hydroxylation of $TiCl_4$ enolate of **69a** by taking a small aliquot at different times. The graph in Figure 14 indicates that the reaction evolves until the first 90 minutes, a time in which the reaction loses completely the purple colour to an orange-yellow one. Interestingly, although the reaction is not quenched, the enolate does not react further after that time and no signs of degradation appear after 4 h. Then, from now on we will stir the reactions for a time comprised between 2 to 5 hours, time enough to allow each *N*-acyl chain to achieve maximum conversion.

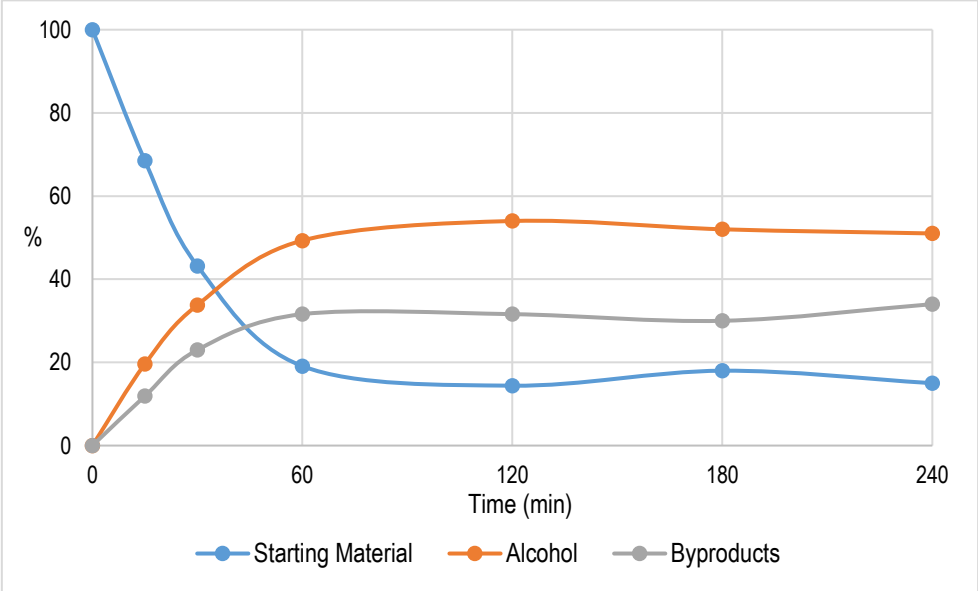
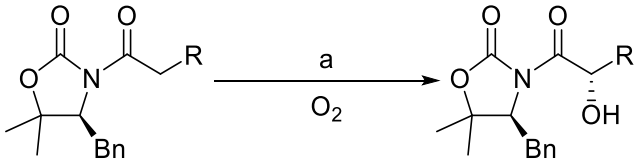


Figure 14

3.4. General procedure for the hydroxylation with oxygen

Once a general protocol for the α-hydroxylation was already established, we next applied the optimised reaction conditions to a number of *N*-acyl oxazolidinones **69a–i** containing a wide array of acyl groups with sterically bulky groups as well as other common functional groups. The results are summarised in Table 20.



69a–i **86a–i**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) O_2 atm for 5 min at 0 °C, then rt for 2–5 h.

Entry	Substrate	R	Product	dr[a]	Yield (%)[b]
1	**69a**	Me	**86a**	≥ 97:3	45
2	**69b**	Et	**86b**	≥ 97:3	43
3	**69c**	Bu	**86c**	≥ 97:3	30
4	**69d**	Bn	**86d**	≥ 97:3	34
5	**69e**	*i*-Pr	**86e**	≥ 97:3	31
6	**69f**	C_3H_5	**86f**	≥ 97:3	32
7	**69g**	$(CH_2)_2CH{=}CH_2$	**86g**	≥ 97:3	32
8	**69h**	$CH_2C{\equiv}CH$	**86h**	≥ 97:3	32
9	**69i**	$(CH_2)_2CO_2Me$	**86i**	≥ 97:3	33

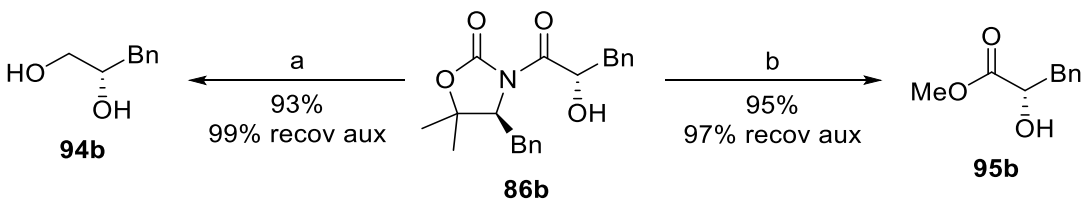
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.

Table 20

These reactions provided a single diastereomer of the hydroxylated adducts **86a**–**i** in moderate yields. The oxidation is somewhat sensitive to the steric hindrance of the *N*-acyl groups (compare entries 1–6, Table 20). Otherwise, the benzylic position of **86d**, the double and triple bonds in **86g** and **86h**, respectively, as well as the ester group in **86i** were not affected, which proves the chemoselectivity achieved in this oxidation of the Cα position (compare entries 4 and 7–9, Table 20).

3.5. Removal of the chiral auxiliary

Finally, the smooth removal of the chiral auxiliary from adduct **86b**, following reported procedures, generated excellent yields of up to 95% of the 1,2-diol **94b** by $NaBH_4$ reduction,[144] and the α-hydroxy ester **95b** by methanolysis (Scheme 109).[110,144]



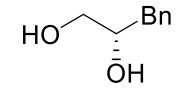
94b **86b** **95b**

a) $NaBH_4$, THF/H_2O, 0 °C, 1 h; b) MeMgBr, $MeOH/CH_2Cl_2$, 0 °C, 5 min.

Scheme 109

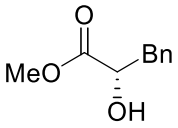
3.6. Absolute configuration of adducts 86

Although many of the α-hydroxylation adducts were solids, their low crystallographic properties did not allow us to obtain good enough crystals for an X-ray analysis. However, the derivatives **94b** and **95b** prepared in the previous section enabled us to establish the *S* configuration of the stereocentre by comparison with compounds whose physical and spectral data was already described in the literature (Scheme 110).[110,122]



94b

94b $[\alpha]_D$ = –18.3 (*c* 1.3, $CHCl_3$)
Córdova[122] **94b** $[\alpha]_D$ = –18.6 (*c* 1.3, $CHCl_3$)



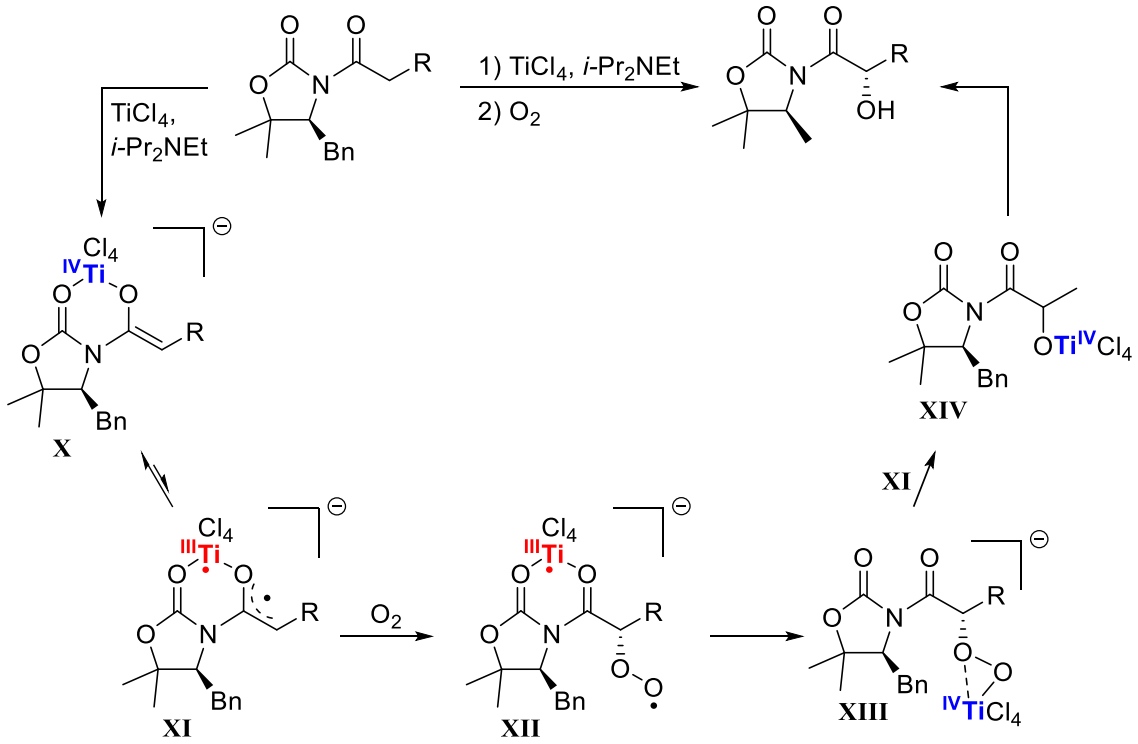
95b

95b $[\alpha]_D$ = –12.1 (*c* 1.1, CH_2Cl_2)
Evans[110] **95b** $[\alpha]_D$ = –13.7 (*c* 1.1, CH_2Cl_2)

Scheme 110

3.7. Mechanistic hypothesis

Although the mechanism of such α-hydroxylation is still unclear, the oxidation of titanium(IV) enolates might be rationalised by considering the biradical character of both species. Indeed, we hypothesised that a radical-like reaction of triplet oxygen with the biradical titanium enolate **XI** might trigger the formation of an initial peroxide **XII** (Scheme 111). The observed high π-face selectivity might be due to the chelated character of the enolate as shown previously. Taking into account a previous report by Adam,[145] the internal autoxidation of the titanium(III) centre of the resulting species might then generate a peroxytitanate intermediate like **XIII**, which might be responsible for the further oxidation of a titanium(IV) enolate **XI** that is not yet oxidised.



Scheme 111

Besides, the by-products mentioned in the preliminary studies could be also explained if a radical-like reaction is involved. The peroxytitanate **XIII** might have other reduction pathways that could lead to a number of different by-products, for example, oxidation of one on the ligands to radical chlorine would explain the α-chlorination observed **88a**. The other by-products **89a** and **90a** might also arise from alternative quenching pathways of the peroxytitanate **XIII**.

Remarkably, the formation of the peroxytitanate **XIII** might explain the results obtained with different amounts of oxygen in the optimisation (Table 17, page 97). With little above half equivalent of oxygen almost the same yield is obtained compared with the result when an excess of oxygen is added (40% vs 45%). Such similar results hinted that both atoms of the oxygen molecule were incorporated into the oxidised adduct, likely via further peroxytitanate oxidation.

4. Final considerations

In summary, aminoxylation of biradical titanium(IV) enolates derived from a new developed chiral oxazolidinethione provided the aminoxilated adducts as single diastereomers in all cases with excellent yields. Furthermore, the direct hydroxylation of

biradical titanium(IV) enolates derived from chiral oxazolidinones with O_2 proved to be feasible, and the corresponding diastereomerically pure alcohols were obtained with moderate yields. Finally, the chiral auxiliaries were easily removed, converting the products into other synthetical useful intermediates.

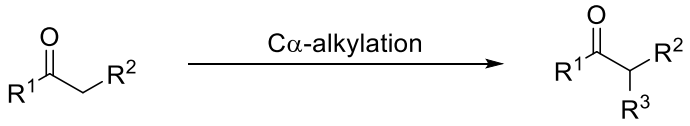
CHAPTER 4

Alkylations

CHAPTER 4. TABLE OF CONTENTS

1. Introduction

The stereocontrolled Cα-alkylation of a carbonylic or carboxylic compound is one of the most important C–C bond forming reactions in organic synthesis (Scheme 112).[2–5] Traditionally, chiral auxiliaries have been chosen as the most suitable platform for carrying out these transformations, but they can often only be applied to a narrow range of substrates. Remarkably, organocatalysis has emerged as a real alternative to tackle some of the limitations, and new concepts and insightful methods have been recently reported. Nevertheless, and despite such achievements, there is a lingering interest for developing new and increasingly more efficient stereoselective Cα-alkylations.

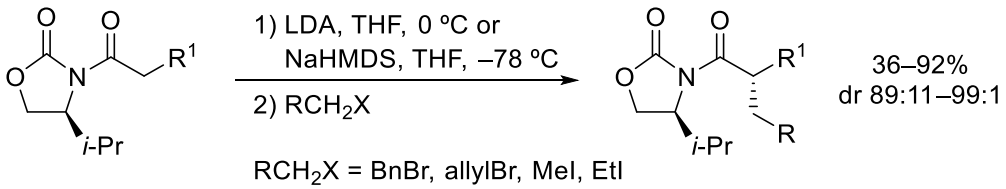


Scheme 112

1.1. Classical Cα-alkylation of metallic enolates

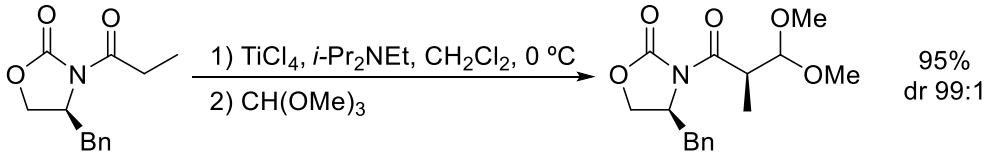
Metallic enolates are among the most valuable nucleophiles in organic synthesis. Indeed, the development of chiral auxiliaries and selective enolization methods to provide chiral metallic enolates capable of undergoing stereoselective alkylations has been the subject of intense investigation. Within the entire range of chiral auxiliaries, the three most popular classes are oxazolidinone-like, camphorsultams and pseudoephedrines.

Oxazolidinones as chiral auxiliaries were first reported by Evans in 1981 to perform asymmetric aldol additions.[146,147] Soon after, they were used for the stereoselective alkylation of lithium and sodium *Z*-enolates with allyl or benzyl halides and a few privileged alkyl iodides (Scheme 113).[148]



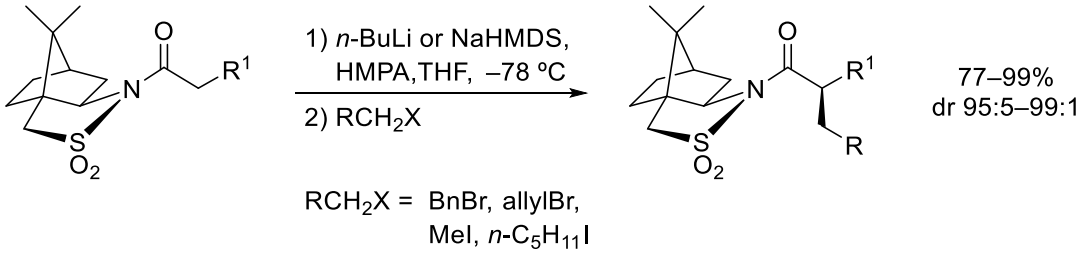
Scheme 113

This method was later complemented by titanium(IV) Z-enolates (Scheme 114),[149] which are more prone to react with electrophiles with a predisposition toward S_N1 reactivity, making orthoesters and acetals exceptionally good substrates.



Scheme 114

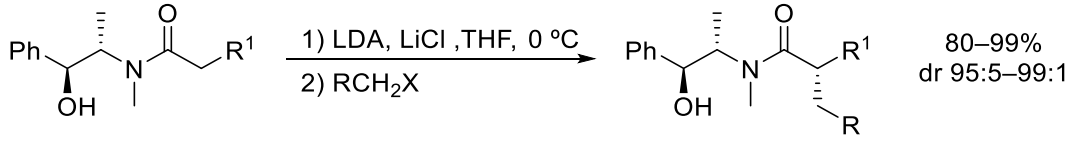
In turn, Oppolzer reported the alkylation of lithium and sodium enolates from a camphor-derived sultam with reactive electrophiles such as allyl or benzyl halides and some iodides with high diastereoselectivity and very good yields (Scheme 115).[150] Unfortunately, these enolates require the presence of HMPA to enhance their reactivity and they are hardly used.



RCH_2X = BnBr, allylBr, MeI, n-$C_5H_{11}I$

Scheme 115

Myers later found that commercially available pseudoephedrine was an effective chiral auxiliary for the stereoselective alkylation of amides (Scheme 116).[151] Indeed, the lithium enolates undergo highly diastereoselective alkylation reactions with a wide range of alkyl halides, from benzylic to primary iodides, including less reactive substrates such as β-branched alkyl iodides. Since pseudoephedrine can be transformed into illegal drug substances, a newer and safer pseudoephenamine substitute, in which the chiral methyl was changed for a phenyl moiety, was described with similar reactivity.[152]



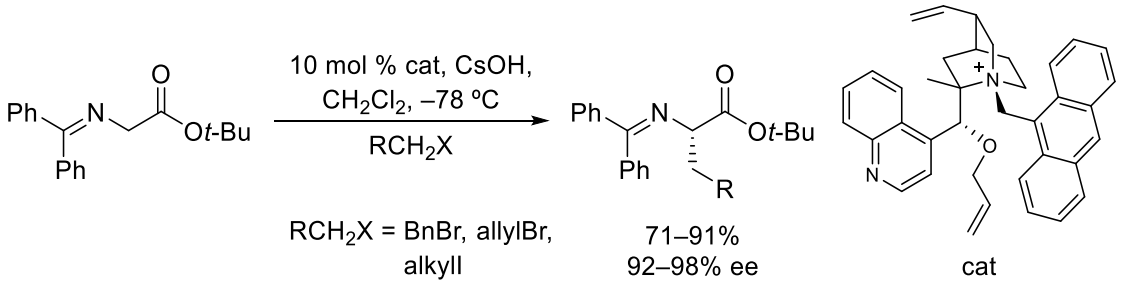
RCH_2X = BnBr, allylI, alkylI

Scheme 116

1.2. Organocatalytic alkylations

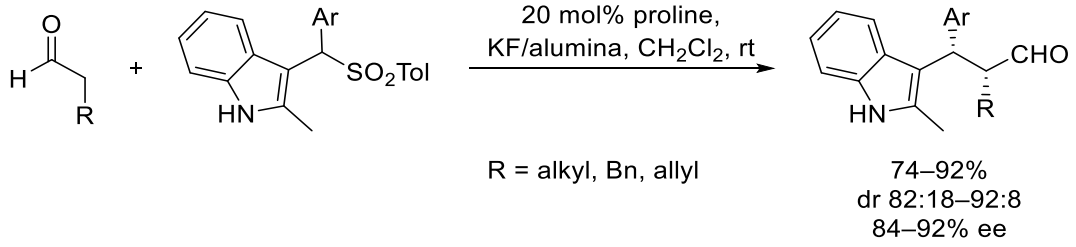
One of the major challenges in organocatalysis is to readily alkylate carboxylic derivatives as well as aldehydes and ketones. Pioneering studies by O'Donnel on the enantioselective synthesis of α-amino acids set the stage for phase-transfer catalysts to carry out a completely enantioselective Cα-alkylations.[153] In this context, Corey et al, reported that a cinchona derived alkaloid catalysed the alkylation of *tert*-butyl glycinate-

benzophenone imine with benzyl and allyl bromides and some alkyl iodides with good yields and excellent enantiocontrol (Scheme 117).[154]



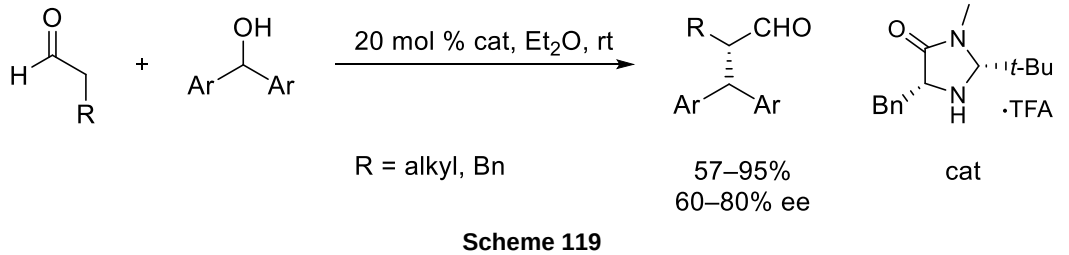
Scheme 117

After the “gold rush” of organocatalysis in which several types of reactions were successfully developed, some remained unsolved. One of them was the Cα-alkylation of aldehydes. Although some intramolecular cyclizations were reported, intermolecular counterparts still remain elusive.[155] Interestingly, S_N1-based intermolecular organocatalytic approaches based on the use of stable carbocations could avoid the major problems encountered with S_N2 reactions. For example, Melchiorre reported the α-alkylation of aldehydes with carbocations catalysed by proline.[156] The enamines trapped the carbocations, formed by treatment of the sulfonylindoles with potassium fluoride, with good yields and enantioselectivities but with good diastereoselectivities (Scheme 118).



Scheme 118

Following a similar approach, Cozzi described the Cα-alkylation of aldehydes with diaryl methanol derivatives catalysed by MacMillan’s catalyst.[157] The addition of a strong acid like TFA was crucial for carbocation formation. Then the carbocation was trapped as in the previous case (Scheme 119).

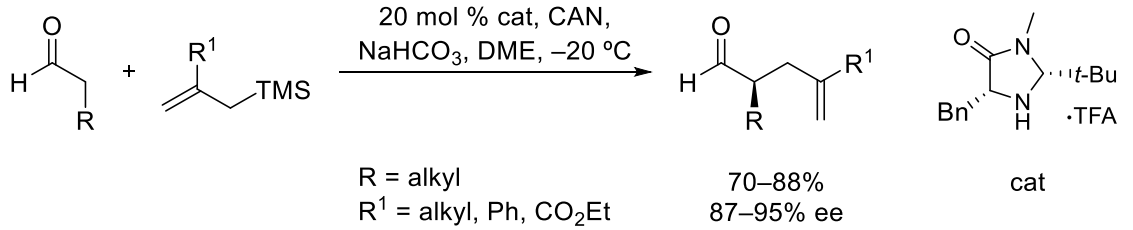


Scheme 119

1.3. SET activated alkylations

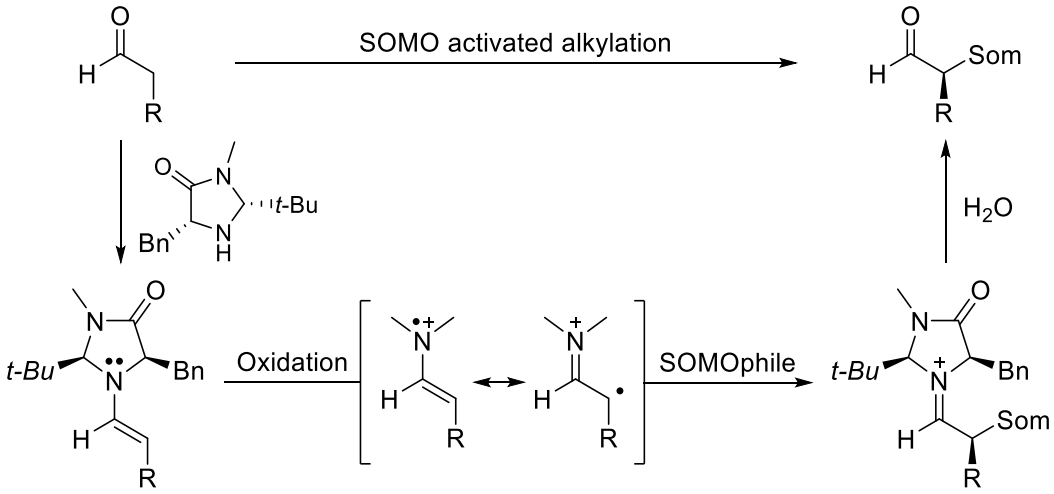
1.3.1. SOMO activation

In a 2007 seminal publication, MacMillan expanded the well-established chemistry of chiral amine catalysis with the concept of singly occupied molecular orbital (SOMO) activation for the alkylation with allyl silanes (Scheme 120).[158]



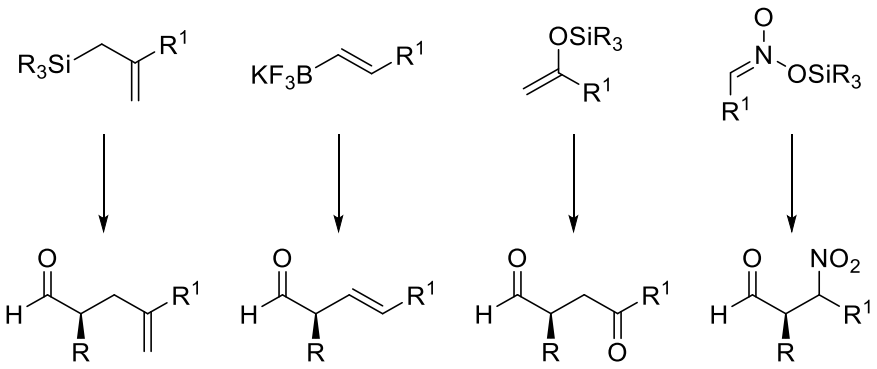
Scheme 120

The SOMO activation mode refers to the formation of a transient radical species from the enamine, which is subsequently trapped by a SOMO-nucleophile or SOMOphile (Scheme 121).



Scheme 121

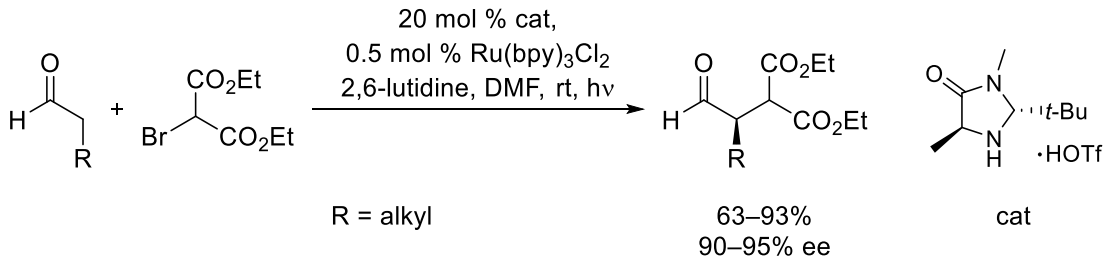
In contrast to nearly all organocatalytic bond constructions, which are restricted to two-electron pathways, this one-electron mode of activation enabled the development of alternative transformations. Indeed, several SOMO-nucleophiles such as allyl silanes[158] and vinyl trifluoroborates[159] have been reported to afford allyl and vinyl derivatives, whereas enolsilanes,[160] provide 1,4-dicarbonyl structures, and silyl nitronates,[161] give access to α-nitroalkylation products (Scheme 122).



Scheme 122

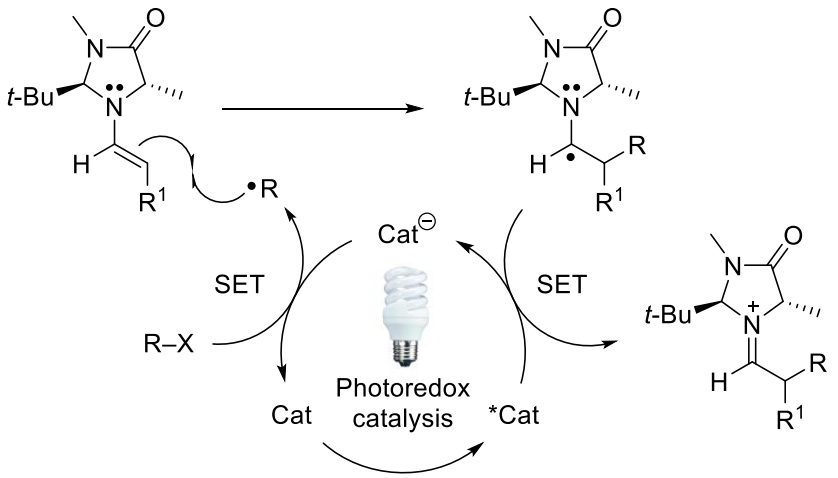
1.3.2. Photoredox catalysis

Aiming to avoid the use of stoichiometric oxidants, MacMillan unveiled in 2007 the first synergistic photoredox catalytic–organocatalytic transformation.[162] They merged two interconnected catalytic cycles to simultaneously generate an electron-rich enamine from the condensation of an aldehyde and an amine catalyst and an electron-deficient alkyl radical formed via reduction of an alkyl bromide with a ruthenium polypyridyl photoredox catalyst (Scheme 123). Furthermore, the interaction of a SOMOphilic enamine with an electron-deficient radical inverted the previously described SOMO activation concept and enabled new catalytic and asymmetric bond forming reactions.[163–165]



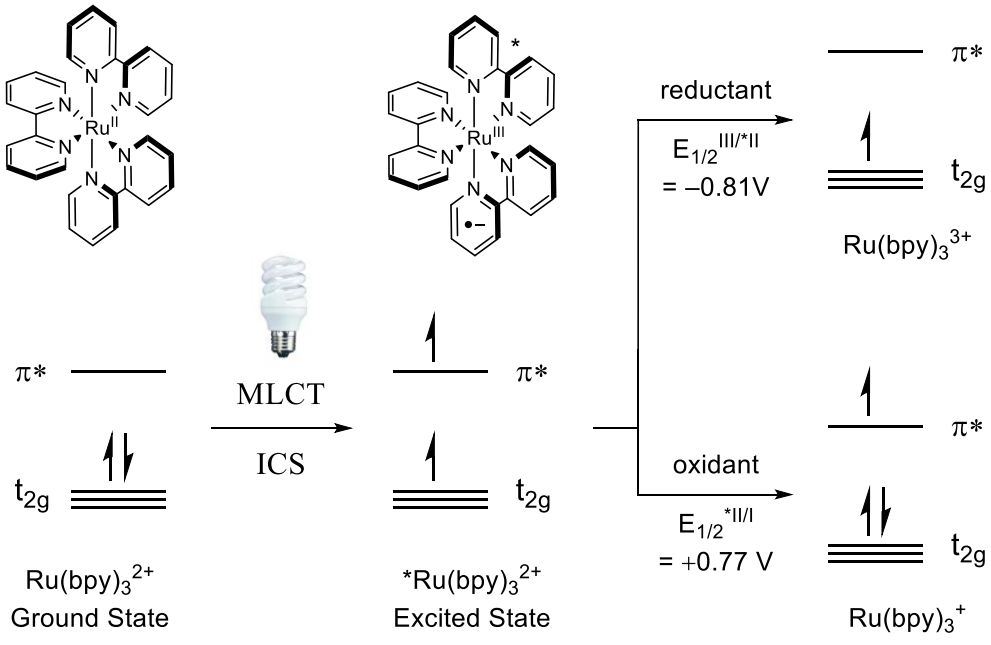
Scheme 123

To fully understand this kind of activation, it is necessary to pay attention to the role played by the photocatalyst. In a general sense, these approaches rely on the ability of the metal complexes to transform visible light into chemical energy by engaging in a single-electron transfer with organic substrates, thereby generating reactive intermediates that can be next trapped with other substrates (Scheme 124).[162–165]



Scheme 124

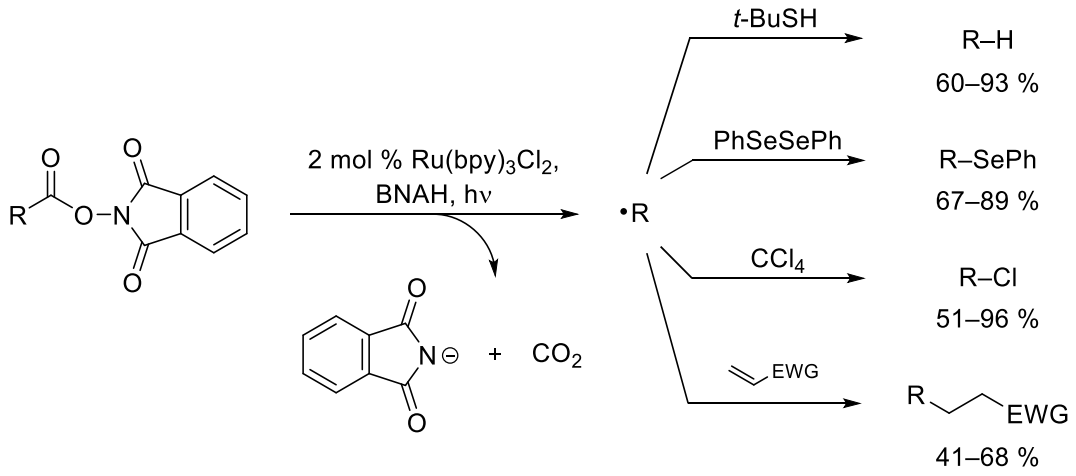
In detail, upon absorption of a photon in the visible region, an electron in one of the $Ru(bpy)_3^{2+}$ photocatalyst's metal-centred t_{2g} orbitals is excited to a ligand-centred π* orbital in a *Metal-Ligand-Charge-Transfer* (MLCT) process. The initially occupied singlet state undergoes rapid *intersystem crossing* (ISC) to give the lowest energy triplet state (Scheme 125).[163–165] This results in a reactive species in which the metal has been oxidised and the ligand framework has undergone a single-electron reduction. Furthermore, the photoactivated complex has long lifetime since decay to the singlet ground state is spin-forbidden. Importantly, the photoexcited species has the remarkable property of being both more oxidising and more reducing than the ground-state species, thus taking part in single-electron transfer with organic substrates and forming reactive radicals (Scheme 125).[163–165]



Scheme 125

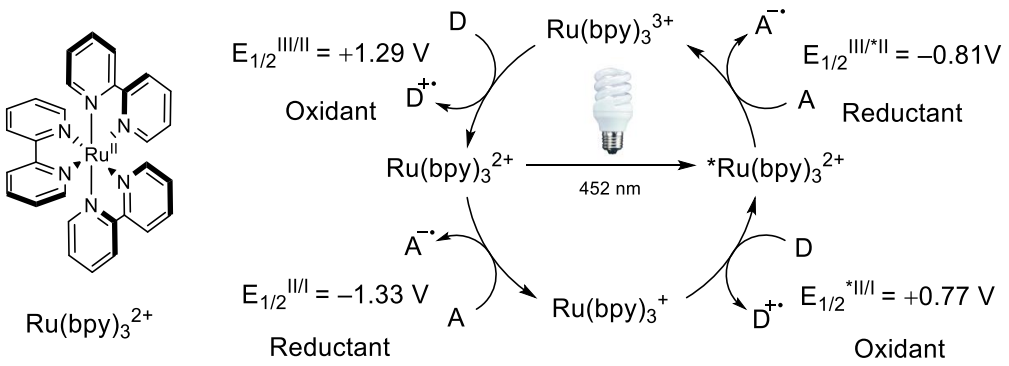
1.3.2.1. Photoredox activation of N-acyloxyphthalimides

MacMillan was not the first to take advantage of the radical forming properties of photocatalysts. Indeed, pioneering studies by Okada showed that alkyl *N*-acyloxyphthalimides could be used as a convenient source for alkyl radicals (Scheme 126). Following the single-electron reduction with $Ru(bpy)_3^{2+}$ photocatalyst, the redox-active ester decomposes to form phthalimide, carbon dioxide, and a carbon-centred radical. Alkyl radicals generated with this process may then undergo a range of subsequent reactions, including reduction,[166,167] phenylselenenylation[168], chlorination,[169] and conjugate addition.[170]



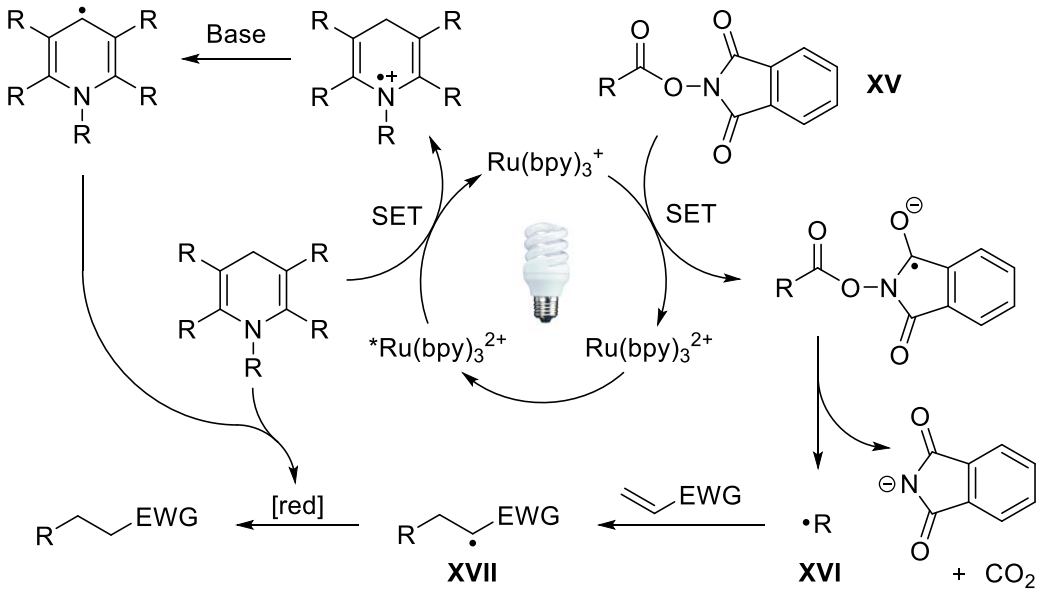
Scheme 126

N-Acyloxyphthalimides are bench stable compounds with standard reduction potentials around $E_{1/2}^{0/-1}$= –1.26/–1.39 V (SCE).[166,171,172] This means that the excited $*Ru(bpy)_3^{2+}$ photocatalyst ($E_{1/2}^{III/*II}$ = –0.81 V (SCE)) does not carry out the single electron reduction of the active esters. Instead, reduction of excited $*Ru(bpy)_3^{2+}$ with a dihydropyridine, such as *N*-benzyldihydronicotinamide or the Hantzsch ester, leads to a more powerful reductant species, $Ru(bpy)_3^{+}$ ($E_{1/2}^{II/I}$ = –1.33 V (SCE)) that is now able to reduce most *N*-acyloxyphthalimides (Scheme 127).



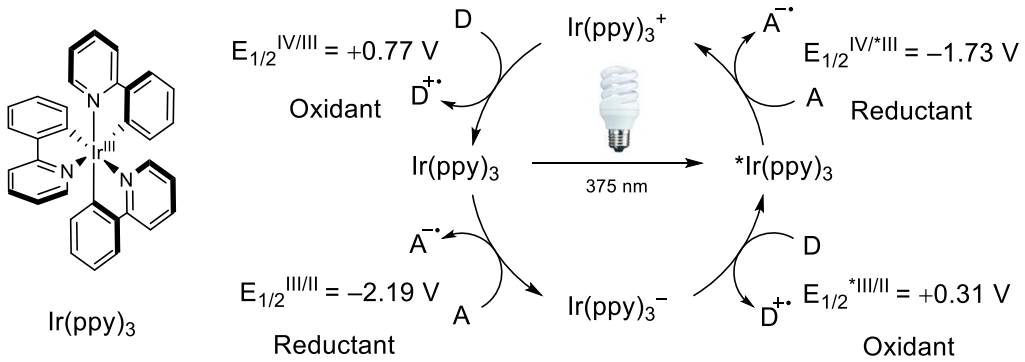
Scheme 127

Then, $Ru(bpy)_3^+$ may undergo SET to the *N*-acyloxyphthalimide and the one-electron-reduced active ester **XV** may decompose into carbon dioxide, phthalimide, and radical **XVI** which is reduced or trapped by a SOMOphile to afford radical **XVII** (Scheme 128). Finally, another molecule or the radical form of the Hantzsch ester quenches radical **XVII** to end the cycle.



Scheme 128

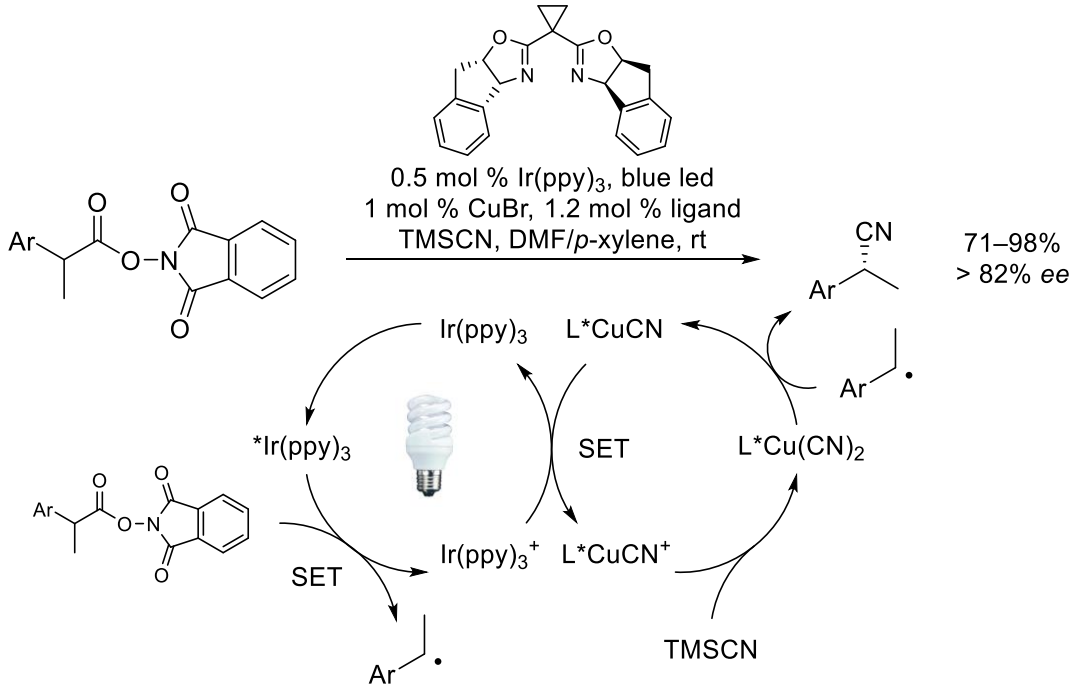
Iridium based $Ir(ppy)_3$ is another photocatalyst currently used in this class of transformations (Scheme 129).[163–165] Despite the similarities with the $Ru(bpy)_3^{2+}$ complex, there is a remarkable difference in their redox potentials. Indeed, excited $*Ir(ppy)_3$ is a stronger reducing agent ($E_{1/2}^{IV/*III}$ = –1.73 V for $Ir(ppy)_3$ vs $E_{1/2}^{III/*II}$ = –0.81 V for $Ru(bpy)_3(PF_6)_2$ (SCE)), whereas $*Ru(bpy)_3^{2+}$ is a better oxidising agent ($E_{1/2}^{*II/I}$ = +0.77 V for $Ru(bpy)_3(PF_6)_2$ vs $E_{1/2}^{*III/II}$ = +0.31 V for $Ir(ppy)_3$ (SCE)).[163–165]



Scheme 129

Due to the high reduction potential of excited $*Ir(ppy)_3$, it can directly participate in the single-electron reduction of active esters. For instance, Liu reported the

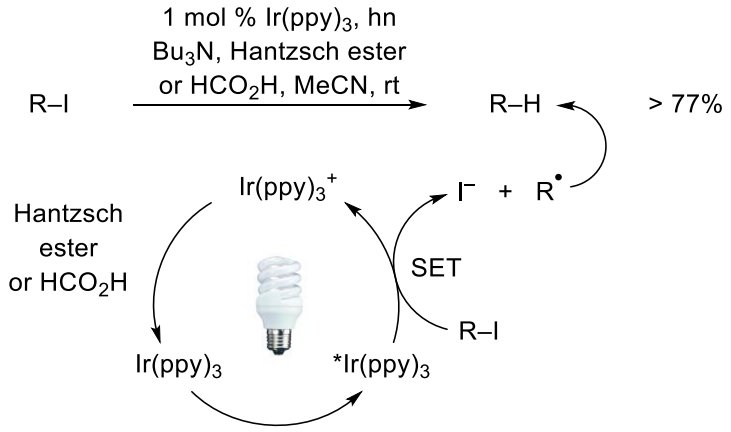
enantioselective cyanation of benzylic *N*-hydroxyphthalimides employing cooperative $Ir(ppy)_3$ photoredox catalysis and copper catalysis (Scheme 130).[172]



Scheme 130

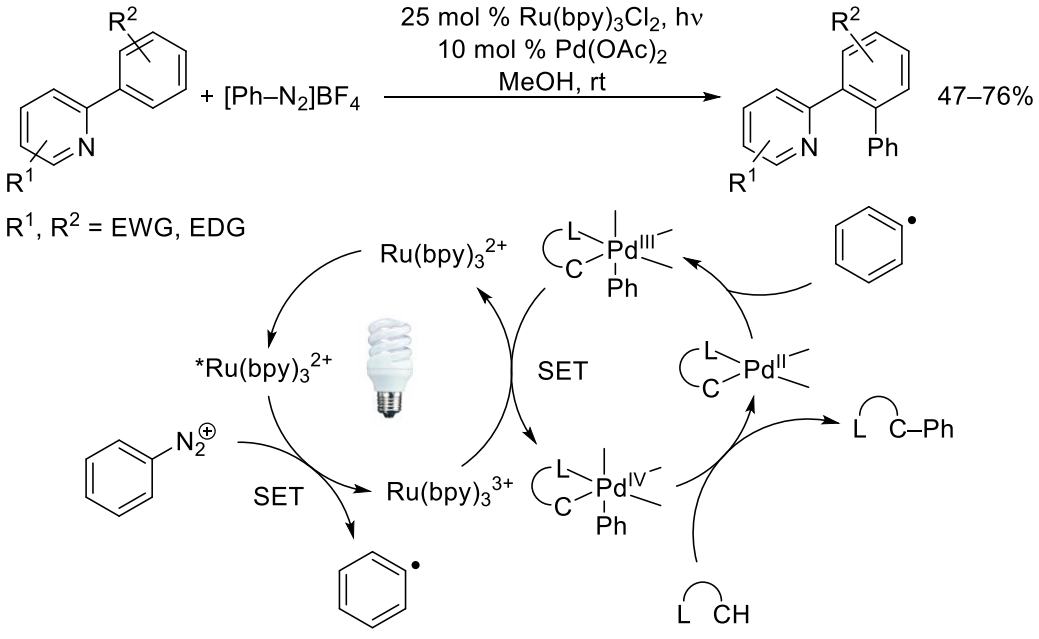
1.3.2.2. Photoredox activation of alkyl and aryl iodides, and arenediazonium salts

One of the most common methods for the reduction of carbon–halogen bonds is radical reductive dehalogenation. In this context, Stephenson, reported the photoredox reduction of unactivated alkyl ($E_{1/2}^{0/-1}$= –1.61/–2.10 V (SCE) for *s*-BuI), alkenyl and aryl iodides ($E_{1/2}^{0/-1}$= –1.59/–2.24 V (SCE) for PhI) (Scheme 131).[173] The carbon-centred radicals, formed upon SET from excited $Ir(ppy)_3$ to iodides, undergo reduction or cyclization under mild conditions. The catalytic cycle follows a pathway similar to the one explained for the active esters. First, excited photocatalyst undergoes SET to the iodide causing the formation of a radical. Then the radical and the oxidised iridium complex are reduced closing the redox cycle.



Scheme 131

Single-electron reduction of aryl diazonium salts is apparently facile ($E_{1/2}^{0/-1}$= −0.1 V (SCE) for phenyldiazonium tetrafluoroborate) and can occur together with the loss of nitrogen.[174] Exposure of aryldiazonium salts to excited *$Ru(bpy)_3^{2+}$ is enough to trigger a single-electron reduction capable of providing aryl radicals. For instance, Sanford developed a $Ru(bpy)_3Cl_2$/palladium-catalysed arylation at rt with aryldiazonium salts (Scheme 132).[175]



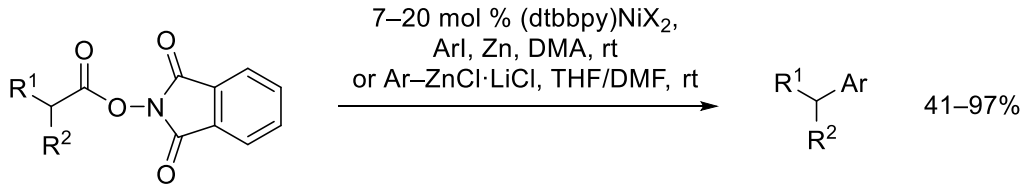
Scheme 132

1.3.3. Metal catalysed alkylations

1.3.3.1. Nickel(II) catalysed activation of N-acyloxyphthalimides

Besides the examples described in section 1.3.2.1, the reductive decarboxylation of *N*-acyloxyphthalimides esters has also been realised. Indeed, the single electron reduction-decarboxylation of these active esters was recently reported

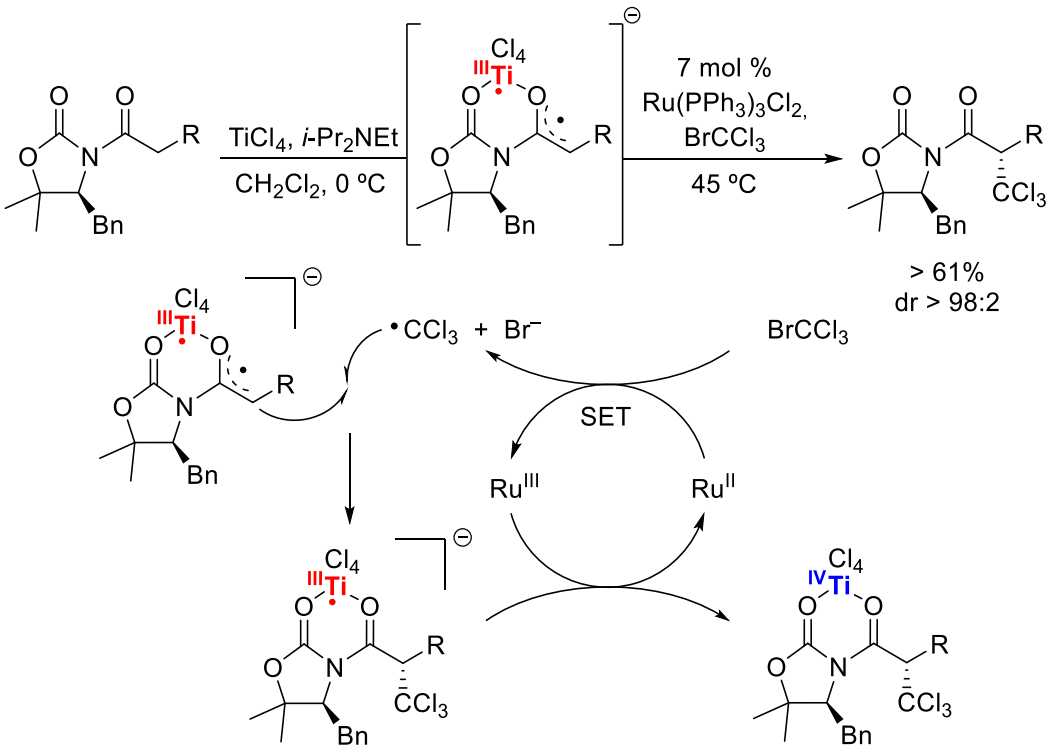
using conventional metal catalysis in combination with organozinc nucleophiles by the Weix and Baran groups to carry out cross-coupling reactions (Scheme 133).[176–178]



Scheme 133

1.3.3.2. Ruthenium(II) catalysed haloalkylation of titanium enolates

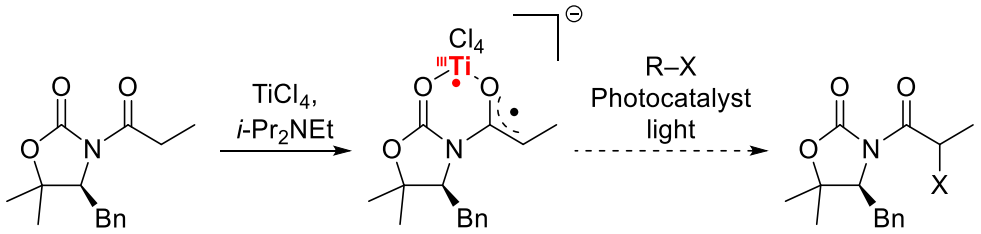
In 2010, Zakarian reported the direct ruthenium-catalysed radical chloroalkylation of *N*-acyl oxazolidinones based on the biradical character of titanium enolates unveiled by our group.[37] As represented in Scheme 134, the •CCl_3 radical is initially formed upon SET from a Ru(II) complex to $BrCCl_3$. Then, addition of the electrophilic radical to the titanium enolate is followed by reduction of Ru(III) species with the Ti(III) intermediate, thus regenerating the catalyst.



Scheme 134

2. Reactions with photoredox formed radicals

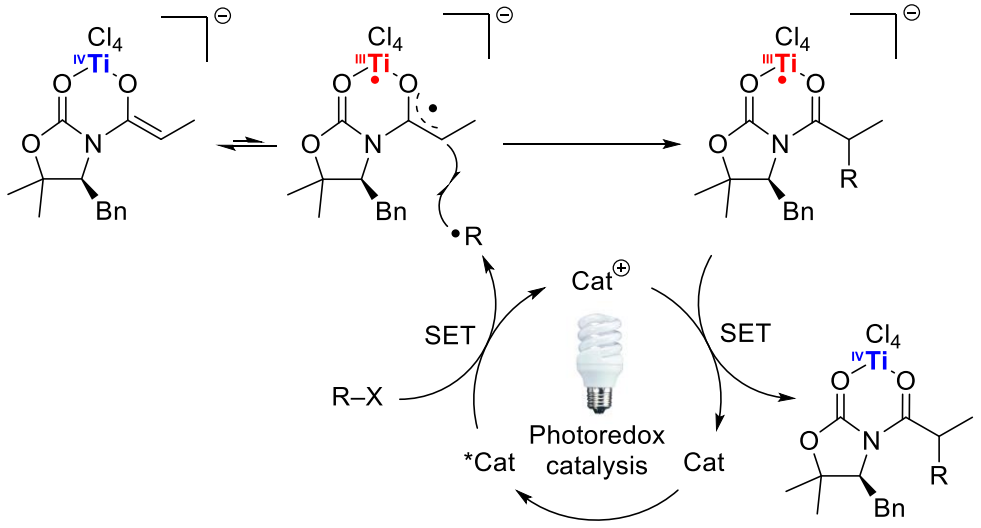
The example of trichloromethylation described in the previous section demonstrated the feasibility of merging catalytic SET radical forming processes with the natural biradical character of titanium enolates. Such precedents encouraged us to merge photocatalytic formed radicals with the biradical behaviour of titanium enolates from *N*-propanoyl oxazolidinone **69a** in a synergistic paradigm that might lead to a new reactivity (Scheme 135).



69a

Scheme 135

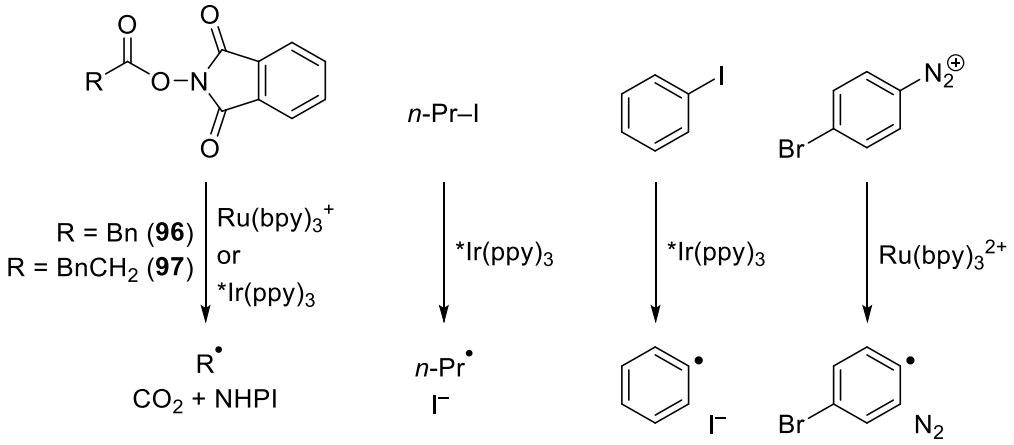
We were aware from the very beginning that we needed: (a) a viable radical precursor, together (b) with an appropriate photocatalyst to trigger the formation of carbon-centred radical, (c) capable of reacting with the titanium(IV) enolate for the stereocontrolled formation of a carbon-carbon bond in such a way that (d) the resultant titanium(III) atom converts the photocatalyst back to the original oxidation state (Scheme 136)



Scheme 136

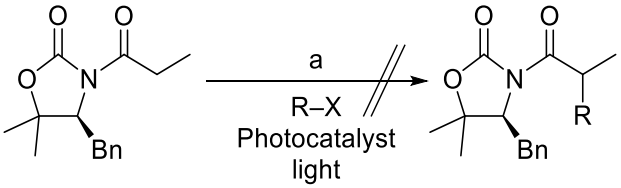
Initially, we chose a few radical precursors like *N*-acyloxyphthalimides **96** and **97**, iodobenzene and iodopropane, and *p*-bromobenzenediazonium trifluoroborate to explore the abovementioned process (Scheme 137). The activation of these compounds

has already been described in the introduction of this chapter and they thus seemed to be promising candidates to carry out radical-mediated carbon-carbon bond forming reactions.



Scheme 137

Unfortunately, and despite extensive tests using either $Ir(ppy)_3$ or $Ru(bpy)_3(PF_6)_2$ (Scheme 138), including the combination with the Hanztsch ester to form the stronger reductant $Ir(ppy)_3^-$ and $Ru(bpy)_3^+$, no traces of any kind of product was found using the radical precursors shown in Scheme 137.



69a

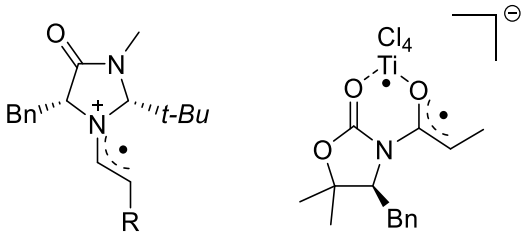
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 1.5 eq radical precursor, 1 mol % photocatalyst, 1.5 eq Hanztsch ester (if needed), rt, 16 h, light.

Scheme 138

To assess the causes of such disappointing results, we verified that the radical precursors, the photocatalysts, and the light sources used in our experiments underwent the reactions described in the literature. Despite these tests being successful, we did not find any experimental conditions that allowed us to obtain any transformation using titanium enolates. Apparently, photoredox catalysis is a very deep ocean of opportunities and it seems that it is easy to get lost in the current. We are still looking for a suitable island to lay the foundations for bright and novel transformations exploiting the biradical character of titanium enolates. A thorough analysis of the electronic behaviour of the titanium(IV) enolates is currently underway in our group.

3. Reactions with SOMOphiles

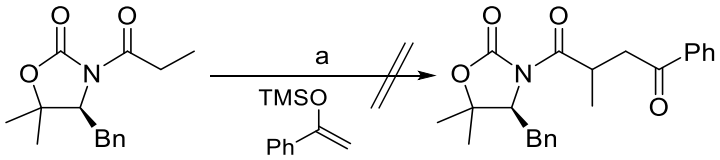
Considering the certain resemblance between the biradical titanium(IV) enolates and the radical cation formed upon oxidation of chiral enamines (Scheme 139), we speculated that our enolate might be able to react with SOMOphiles in the same way that SOMO-activated enamines do.



SOMO-activated enamine | Titanium biradical enolate

Scheme 139

To assess such a hypothesis, we performed some exploratory tests with the titanium(IV) enolate of *N*-propanoyl oxazolidinone **69a** and 1-phenyl-1-trimethylsilyloxyethylene, an enolsilane that would provide 1,4-dicarbonyl structures (Scheme 140). Unfortunately, no traces of the desired product were found and the oxazolidinone was always recovered unreacted.



69a

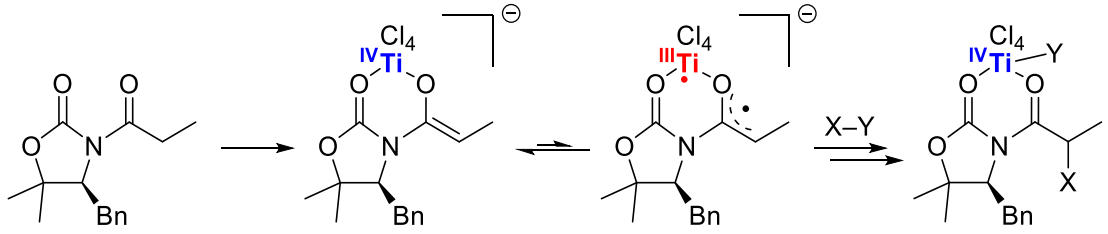
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 1.1 eq silyl enol ether, rt, 16 h.

Scheme 140

4. Reactions with compounds with weak bonds

In the previous chapter, we described the direct hydroxylation of *N*-acyl oxazolidinones with oxygen. In the preliminary studies we demonstrated that only titanium enolates participated in such transformations, whereas the dibutylboron, the lithium and the sodium enolates remained unreactive. This indicated that the biradical titanium enolate may be gifted with a special kind of activating power, similar to the Lewis acid activation discussed in Chapter 1. Thus, we wondered if titanium enolates might be able to trigger the homolytic cleavage of compounds bearing weak bonds. Therefore,

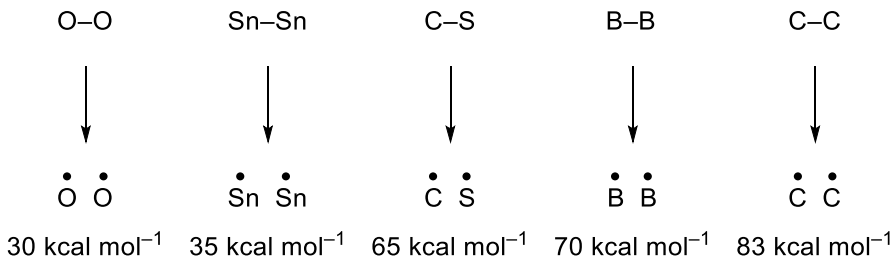
any compound capable of undergoing a homolytic cleavage forming two radicals might react with the titanium(IV) enolate as we described for the TEMPO aminoxylations, one radical for the scaffold and another to oxidise Ti(III) to Ti(IV) (Scheme 141).



69a

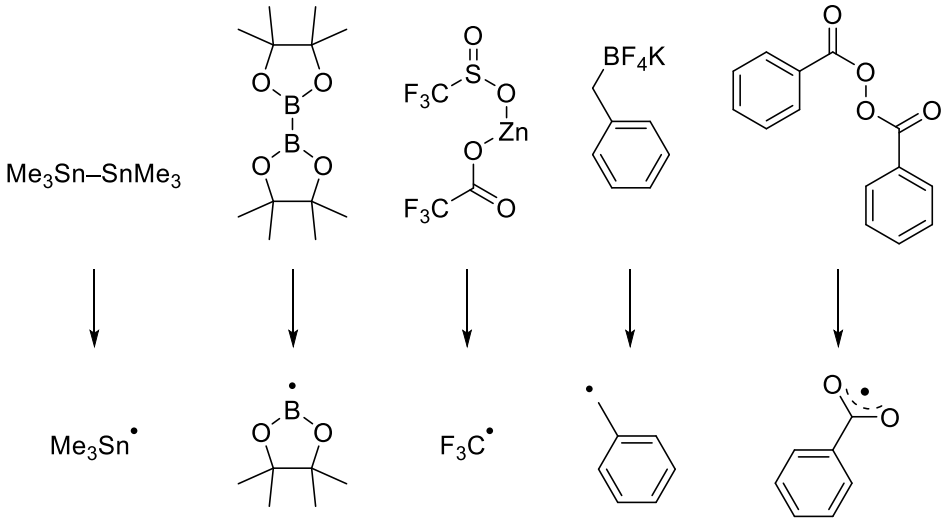
Scheme 141

Compounds containing weak covalent bonds are good candidates for such reactions. These involve peroxides, distannanes, diboranes and other substrates possessing carbon-sulphur or certain carbon-carbon bonds (Scheme 142).[179–181]



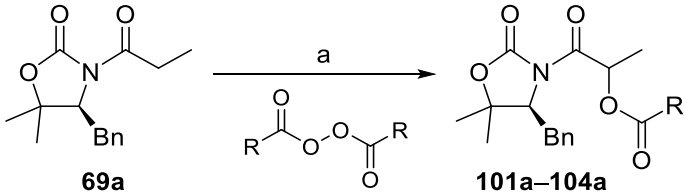
Scheme 142

According to these ideas, we examined the reaction of the titanium(IV) enolates from *N*-propanoyl oxazolidinone **69a** with compounds bearing a weak bond such as Sn_2Me_6, bis(pinacolato)diboron (B_2pin_2), zinc trifluoromethanesulfinate, potassium benzyltrifluoroborate salt and benzoyl peroxide (BPO) (Scheme 143). These reagents were already known to undergo homolytic cleavage under certain conditions, thus making them perfect candidates for our purpose.[165,181–183]



Scheme 143

Unfortunately, and despite great effort, all the compounds shown in Scheme 143 proved unreactive with the exception of benzoyl peroxide (BPO). Indeed, treatment of the titanium enolate from *N*-propanoyl oxazolidinone **69a** with 1.1 equivalents of BPO afforded the benzoyloxylated adduct in an estimated 65% NMR conversion and 80:20 diastereoselectivity. Attempts to increase the overall performance of the benzoyloxylation with BPO and related peroxides **98**–**100** are summarised in Table 21.



69a **101a–104a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) n eq diacyl peroxide, rt, 16 h.

Entry	Peroxide	R	Peroxide (eq)	Product	dr[a]	Conversion (%)[a]	Yield (%)[b]
1	**BPO**	Ph	1.1	**101a**	80:20	65	nd
2	**BPO**	Ph	1.5	**101a**	80:20	75	55
3	**BPO**	Ph	3.1	**101a**	80:20	76	nd
4[c]	**BPO**	Ph	1.5	**101a**	80:20	37	nd
5	**98**	*p*-CF_3Ph	1.5	**102a**	74:26	62	50
6	**99**	*p*-OMePh	1.5	**103a**	86:14	17	nd
7	**100**	CH=CHPh	1.5	**104a**	84:16	31	22

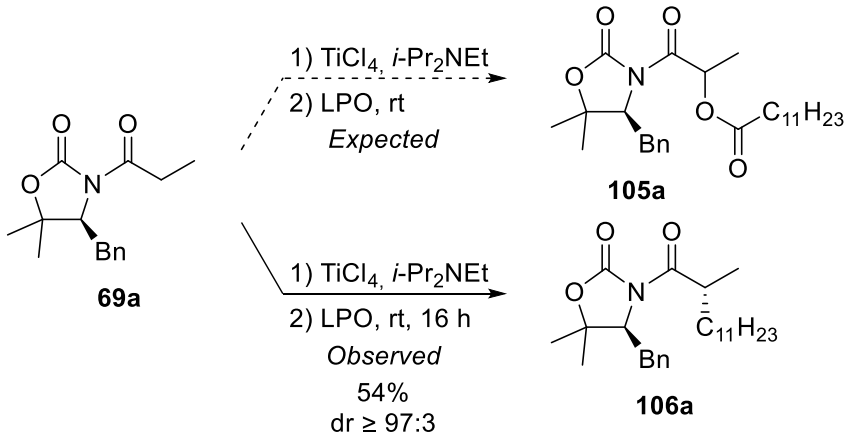
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Performed with 1.1 eq of $TiCl_3$(*i*-PrO).

Table 21

An excess of BPO had no real effect on the conversion (compare entries 1–3, Table 21). In turn, enolization with a weaker Lewis acid like $TiCl_3$(*i*-PrO) resulted in a

lower conversion (compare entries 2 and 4, Table 21). Interestingly, the electron-deficient **98** eroded the diastereoselectivity, down to 74:26, but afforded similar yield (compare entries 2 and 5, Table 21); whereas the electron-rich **99** increased the face selectivity, up to 86:24, but with a very low conversion (compare entries 2 and 6, Table 21). Finally, the peroxide prepared from cinnamic acid **100** proved to be diastereoselective too, but the yield resulted significantly lower than the achieved with BPO (compare entries 2 and 7, Table 21).

In a last attempt to improve such a transformation, commercially available lauroyl peroxide (LPO) was tested. Surprisingly, this alkyl diacyl peroxide displayed a completely different reactivity. First, analysis of the crude mixture revealed the formation of a single isomer (dr ≥ 97:3) with a 54% yield. Second, characterisation of this product showed that the adduct came from the decarboxylation of LPO instead of the expected radical addition of an acyloxy group. Therefore, the titanium enolate not only activated the peroxide by cleavage at rt, but also triggered a decarboxylative reaction leading to a carbon-centred radical that was stereoselectively trapped by the enolate (Scheme 144).



Conditions: 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 3.1 eq LPO, rt, 16 h.

Scheme 144

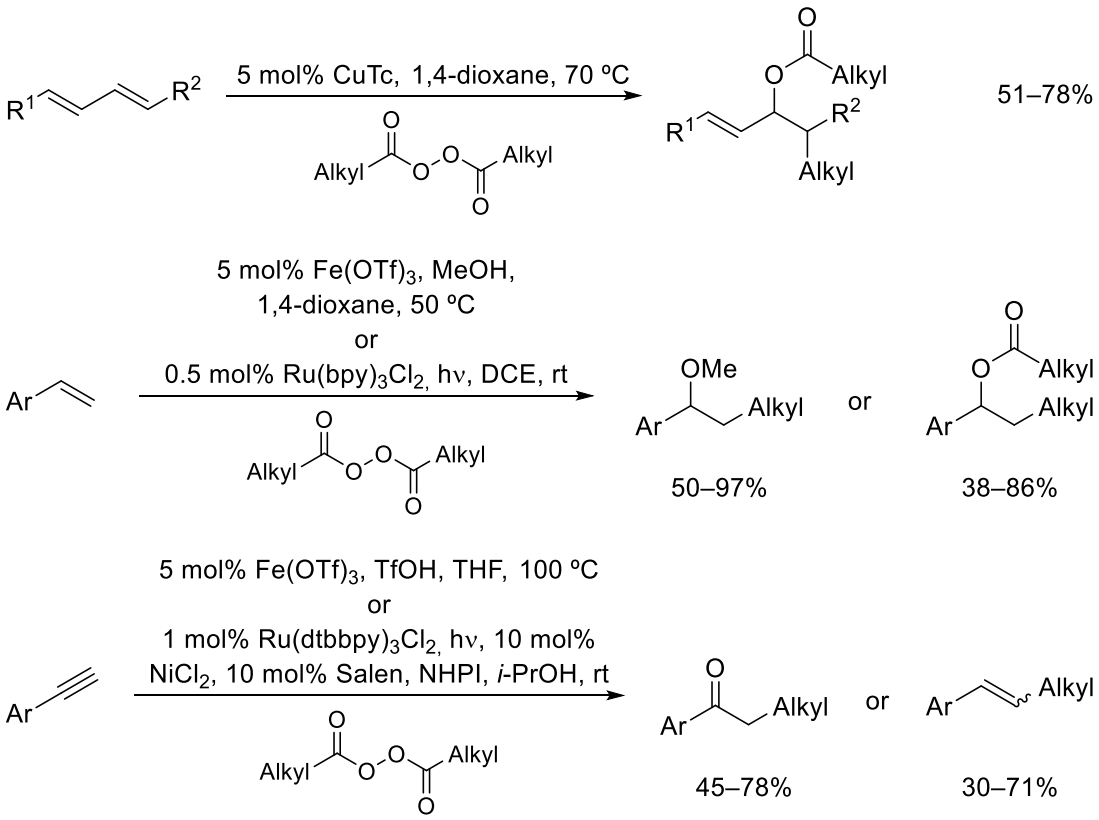
Following such a novel reactivity, we assessed the decarboxylative alkylation with diacyl peroxides that will be developed and discussed in the next section.

5. Decarboxylative alkylation with diacyl peroxides

5.1. Peroxides in decarboxylative processes

Aryl peroxides, like benzoyl peroxide, are mostly known as radical initiators in organic synthesis, but they have also been used occasionally as aryl radical donors by decarboxylation. Unfortunately, temperatures around 100 °C are needed to lose CO_2 thus generating aryl radicals.[184–187] Therefore, standard conditions at room temperature are unable to trigger such decarboxylation in BPO,[188] and that is the reason why it produced the benzoyloxylation of the titanium(IV) enolate described in the former section.

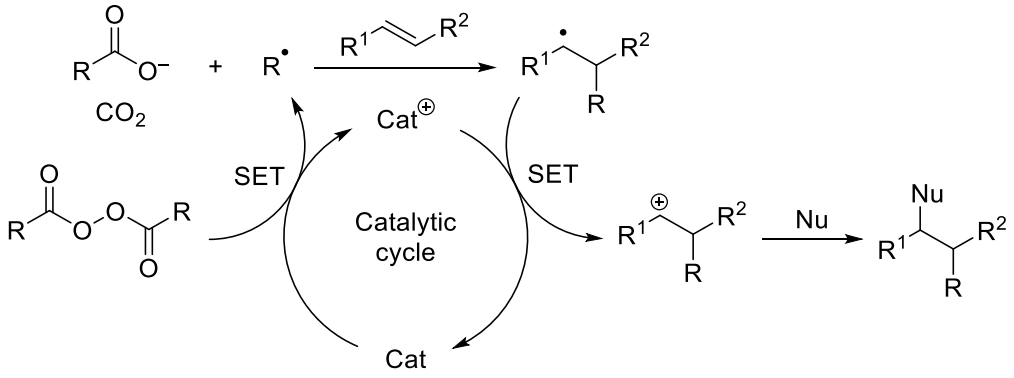
Contrarily, there are some examples in which alkyl diacyl peroxides play a leading role.[189] In 2016, during the course of this Thesis, Bao's group reported new applications of alkyl diacyl peroxides. For example, great effort was put into the trapping by alkenes or alkynes of radicals from decarboxylation of alkyl diacyl peroxides (Scheme 145).[190–194]



Scheme 145

In general, such decarboxylative processes were catalysed by metal complexes at temperatures from 50 °C to 100 °C or by photoredox catalysis. Then, trapping of the

resultant alkyl radicals by π-bonds formed the new C–C bond and, radical quench of the resulting intermediate produced a carbocation that finally reacted with a nucleophile (Scheme 146).

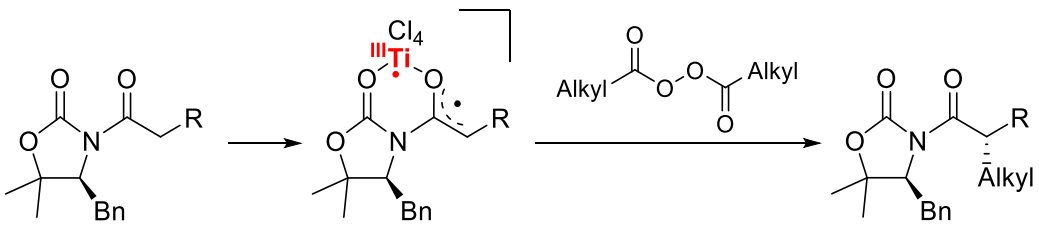


Scheme 146

5.2. A new alkylation reaction

As mentioned in the previous section, treatment of titanium enolates with diacyl peroxides afforded unexpected results. Indeed, peroxides from aromatic or α,β-unsaturated carboxylic acids reacted with the enolate to produce the α-acyloxy derivative with moderate diastereoselectivity and yield, whereas a diacyl peroxide from an aliphatic carboxylic acid took part in a decarboxylative alkylation leading to a single diastereomer in a good yield (Scheme 144, page 125).

This result indicated that the titanium enolate itself promoted the decarboxylation of the peroxide without the aid of any other reducing agent at room temperature. Presumably, such a transformation was closely associated with the biradical character of the titanium enolate, which obviously offered appealing opportunities for new stereoselective carbon-carbon bond forming reactions. Therefore, we decided to analyse carefully such transformations (Scheme 147).



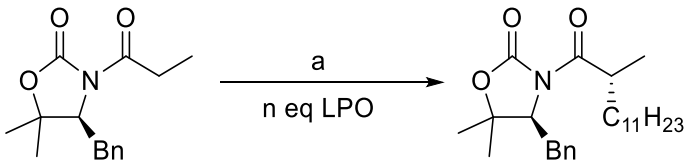
69

Scheme 147

5.3. Optimisation of the alkylation with peroxides

Preliminary experiments provided a simple way to alkylate titanium enolates using lauroyl peroxide (LPO). In turn, parallel reactions showed that neither the dibutylboron nor the lithium nor sodium enolates from *N*-propanoyl oxazolidinone **69a** were able to react with LPO (at 0 °C for the boron enolate, or at –20 °C, for the alkaline enolates), and only starting materials contaminated with traces of chiral auxiliary were recovered from the reaction mixtures.

Thus, we carried out a comprehensive optimisation in which the influence of equivalents, ligands on the Lewis acid, temperature, concentration and other chiral auxiliaries was evaluated. Initially, we focused our attention on finding the optimal quantity of peroxide to obtain the highest yield. The results are summarised in Table 22.



69a **106a**

a) (i) 1.1 eq TiC_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) n eq LPO, rt, 2 h.

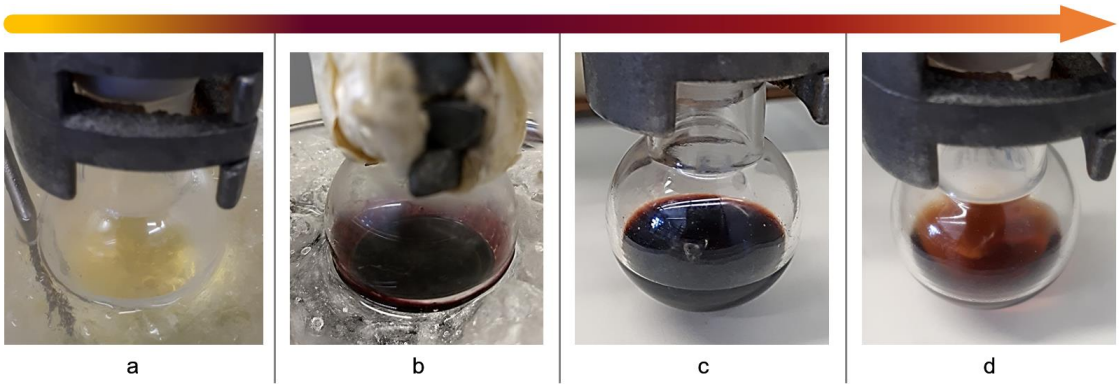
Entry	LPO (eq)	dr[a]	Yield (%)[b]
1	0.66	≥ 97:3	(35)
2	1.1	≥ 97:3	54
3	1.5	≥ 97:3	60
4	2.1	≥ 97:3	66
5	3.1	≥ 97:3	76
6	6.1	≥ 97:3	73

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography. NMR conversion into brackets.

Table 22

Results in Table 22 showed the benefits of working with an excess of LPO. Indeed, the yield increased from 54% to 76% depending on the equivalents of LPO (compare entries 2–5, Table 22), but larger quantities of LPO were useless (entry 6, Table 22). Furthermore, we noticed a similar colour evolution to that observed with the oxidation with oxygen (Figure 15). The distinctive deep purple enolate from **69a** became deep maroon a few minutes after the addition of the peroxide, and this colour changed progressively to a yellow-orange, which indicated the end of the reaction. It is worth mentioning that increasing amounts of peroxide provided higher kinetic rates, up to a

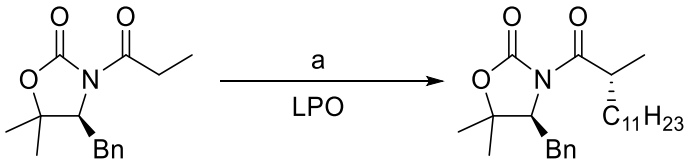
point in which the reaction was completed in less than two hours with 3.1 equivalents of LPO.



a: Titanium(IV) coordination complex; b: Titanium(IV) enolate; c: Addition of peroxide; d: Quenched reaction

Figure 15

With the optimal amount of peroxide determined, we carried out some experiments in which the enolate was prepared with different titanium Lewis acids as shown in Table 23. $TiBr_4$ and $TiCl_3$(*i*-PrO) proved to be significantly worse Lewis acids than $TiCl_4$ and yielded low conversions. Furthermore, the enolate formed with two equivalents of $TiCl_4$ gave similar conversions than the abovementioned $TiCl_3$(*i*-PrO), concluding that $TiCl_4$ was the best Lewis acid to carry out this transformation.



69a **106a**

a) (i) 1.1 eq TiL_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 3.1 eq LPO, rt, 2 h.

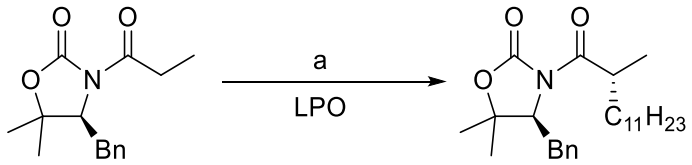
Entry	TiL_4	dr[a]	Conversion (%)[a]
1	$TiCl_4$	≥ 97:3	76[b]
2	2 × $TiCl_4$	≥ 97:3	32
3	$TiCl_3$(*i*-PrO)	≥ 97:3	31
4	$TiBr_4$	≥ 97:3	< 10

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.

Table 23

Next, we assessed the influence of the temperature and concentration. The results are shown in Table 24. As expected, the alkylation of the titanium enolate of **69a** became slower at 0 °C and at –20 °C, taking up to 16 h to fade. Moreover, low

conversions were achieved in both cases. Furthermore, the ten-fold diluted alkylation was slightly slower than the concentrated one and only produced 43% conversion.



69a **106a**

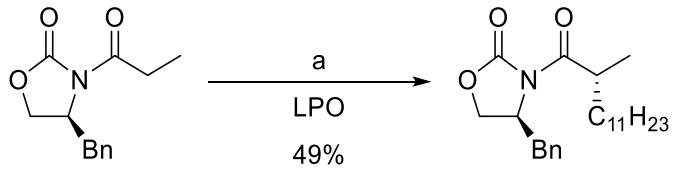
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 3.1 eq LPO, T, 2 h to 16 h.

Entry	T (°C)	Concentration (M)	dr[a]	Conversion (%)[a]
1	0	0.25	≥ 97:3	66
2	–20	0.25	≥ 97:3	15
3	rt	0.025	≥ 97:3	43

[a] Determined by ^1H NMR analysis of the crude mixture.

Table 24

Finally, we ran this reaction using Evans benzyl oxazolidinone **68a** (Scheme 148). The alkylation of **68a** turned out to be very stereoselective too. Unfortunately, the yield of the pure alkylated adduct **107a** was lower than the obtained with **69a**. This result exposed the importance of using a robust scaffold like the SuperQuat oxazolidinone and this is the reason why we decided to keep working with the 5,5-dimethyl oxazolidinone **69a**.



68a **107a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 3.1 eq LPO, rt, 2 h.

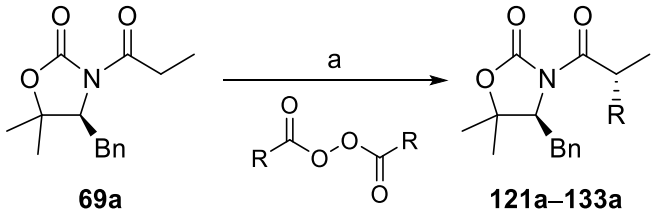
Scheme 148

5.4. General procedure for the alkylation with diacyl peroxides

5.4.1. Alkylation of **69a** with other diacyl peroxides

With a general procedure in our hands, we next examined other alkyl diacyl peroxides aiming to expand the scope of the process. Initially, diacyl peroxides were prepared by treatment of the carboxylic acids with H_2O_2, then DCC coupling catalysed by DMAP, filtration and careful evaporation. Such a procedure delivered the desired peroxides containing a little amount of solvent, which were used without further purification. It proved useful, but the results were not reproducible. Fortunately, Bao had

reported that diacyl peroxides could be easily purified by column chromatography. We found that highly pure peroxides could be obtained from primary carboxylic acids, while peroxides from secondary acids proved to be unstable and had to be filtered through a very short plug of basic alumina. Thus, secondary peroxides were not isolated as pure products, but the alkylation reactions were successful and reproducible. Finally, preparation of peroxides from very bulky acids like pivalic acid or acids prone to oxidation like phenylacetic or 3-butenoic proved hopeless. According to these limitations, the results achieved from freshly prepared diacyl peroxides (**108**–**120**) are summarised in Table 25.



69a **121a–133a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 3.1 eq peroxide, rt, 2 h.

Entry	Peroxide	R	Product	dr[a]	Yield (%)[b]
1	**108**	Pr	**121a**	≥ 97:3	87
2	**109**	CH_2Bn	**122a**	≥ 97:3	85
3	**LPO**	$C_{11}H_{23}$	**106a**	≥ 97:3	76
4	**110**	*i*-Bu	**123a**	≥ 97:3	71
5	**111**	$(CH_2)_2CH{=}CH_2$	**124a**	≥ 97:3	87
6	**112**	$(CH_2)_3CH{=}CH_2$	**125a**	≥ 97:3	81
7	**113**	$(CH_2)_3CH{\equiv}CH$	**126a**	≥ 97:3	72
8	**114**	$(CH_2)_3CO_2Bn$	**127a**	≥ 97:3	45
9	**115**	$(CH_2)_4CO_2Me$	**128a**	≥ 97:3	54
10	**116**	$(CH_2)_4CH_2Br$	**129a**	≥ 97:3	84
11	**117**	C_5H_9	**130a**	≥ 97:3	64
12	**118**	C_6H_{11}	**131a**	≥ 97:3	60
13	**119**	*i*-Pr	**132a**	≥ 97:3	78
14	**120**	CH(Me)Bn	**133a**	65:35[c]	70

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Diastereomeric ratio of the second chiral centre formed.

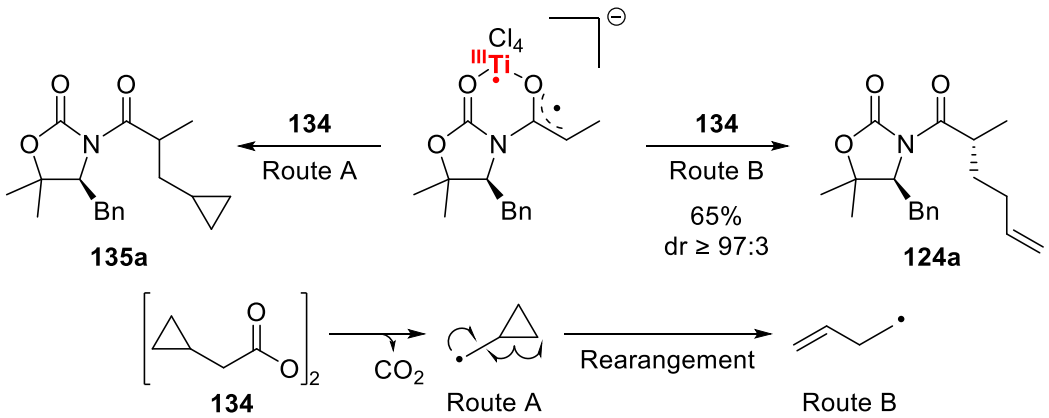
Table 25

The results in Table 25 proved the feasibility of this reaction, since only one diastereomer was obtained irrespective of the R group. Indeed, alkylation with simple carboxylic acids afforded the corresponding adducts with yields from 71% to 87%, observing a certain erosion with increasing bulky acids (entries 1–4, Table 25). Peroxides displaying terminal alkenes and even a terminal alkyne were tolerated, and the

corresponding products were isolated with yields from 72% to 87% (entries 5–7, Table 25). Significantly, the presence of benzyl and methyl esters in the peroxide proved to be detrimental, since their alkylated adducts were isolated in moderate yields (entries 8 and 9, Table 25). Likely, these lower yields might be due to a kind of harmful coordination of the ester group with the titanium that reduces the activity of the whole system. Interestingly, a terminal bromine was introduced with an 84% yield, adding a point of derivatisation towards other compounds via S_N2 (entry 10, Table 25).

Importantly, alkylation with acids leading to secondary radicals was also carried out successfully. Introduction of a cyclopentane and a cyclohexane appendage in a direct way was achieved with yields around 64% (entries 11 and 12, Table 25), whereas the alkylation with isobutyric acid afforded the isopropyl derivative in a 78% yield, similar to the alkylation with primary peroxides (compare entry 1–4 and 13, Table 25). In turn, alkylation with a racemic mixture of 2-methyl-3-phenylpropanoic acid afforded two diastereomers in a 65:35 ratio with a good combined 70% yield (entry 14, Table 25). Although the selectivity of the last example is poor, the stereocontrolled installation of up to two new stereocentres in a unique alkylation has never been reported, which confers a remarkable importance to that result.

Finally, we ran a radical clock experiment by incorporating a cyclopropyl next to the position where the putative radical would be formed in the peroxide (Scheme 149).[195] Indeed, two alkylated products could be expected from peroxide **134**: one involved the simple incorporation of a cyclopropyl ring at Cα (Route A, Scheme 149); whereas the other was based on the preceding rearrangement of the cyclopropylmethyl primary radical and the subsequent alkylation with the resulting 3-butenyl residue (Route B, Scheme 149).



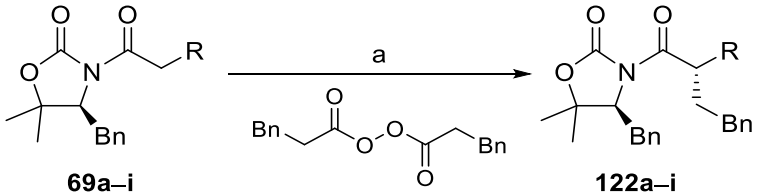
Conditions: (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 3.1 eq peroxide, rt, 2 h.

Scheme 149

As represented in Scheme 149, adduct **124a** was isolated with a yield of 65% (dr ≥ 97:3) without observing traces of the cyclopropyl adduct through route A. Apart from the synthetic interest of this reaction, this experiment provides a strong evidence for a radical mechanism of the alkylation of titanium(IV) enolates from *N*-propanoyl oxazolidinone **69a** with diacyl peroxides.

5.4.2. Alkylation of *N*-acyl oxazolidinones **69a**–**i**

Parallel to the preparation of a battery of different diacyl peroxides, Marina Perez, during her Masters project,[196] applied the optimised reaction conditions to a wide array of *N*-acyl oxazolidinones **69a**–**i**. The results of the alkylation of these substrates with dihydrocinnamoyl peroxide (**109**) are summarised in Table 26.



69a–i **122a–i**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 3.1 eq peroxide, rt, 2 h.

Entry	Substrate	R	Product	dr[a]	Yield (%)[b]
1	**69a**	Me	**122a**	≥ 97:3	85
2	**69b**	Et	**122b**	≥ 97:3	70
3	**69d**	Bn	**122d**	≥ 97:3	52
4[c]	**69e**	*i*-Pr	**122e**	≥ 97:3	39
5	**69g**	$(CH_2)_2CH{=}CH_2$	**122g**	≥ 97:3	64
6	**69h**	$(CH_2)_2C{\equiv}CH$	**122h**	≥ 97:3	55
7	**69i**	$(CH_2)_2CO_2Me$	**122i**	≥ 97:3	62

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Performed for 4 h.

Table 26

Remarkably, a single diastereomer was observed for all the substrates, which proves the wide scope of the process. Furthermore, they also show the dramatic impact of the bulk of the *N*-acyl group on the yield. Indeed, adducts **122a**–**e** were isolated with decreasing yields, related to the steric bulk of the side chain, starting from 85% for R = Me to 39% for R = *i*-Pr (compare entries 1–4, Table 26). Apart from these results, the reaction tolerated terminal alkenes, alkynes and ester groups in the side chain and their corresponding adducts were obtained with good yields (entries 5–7, Table 26).

5.5. Absolute configuration of alkylated adducts

The configuration of the alkylation products was established by X-ray diffraction analysis of crystalline pure adduct **122e** (Figure 16) allowing us to determine the *S* configuration of the stereocentre.

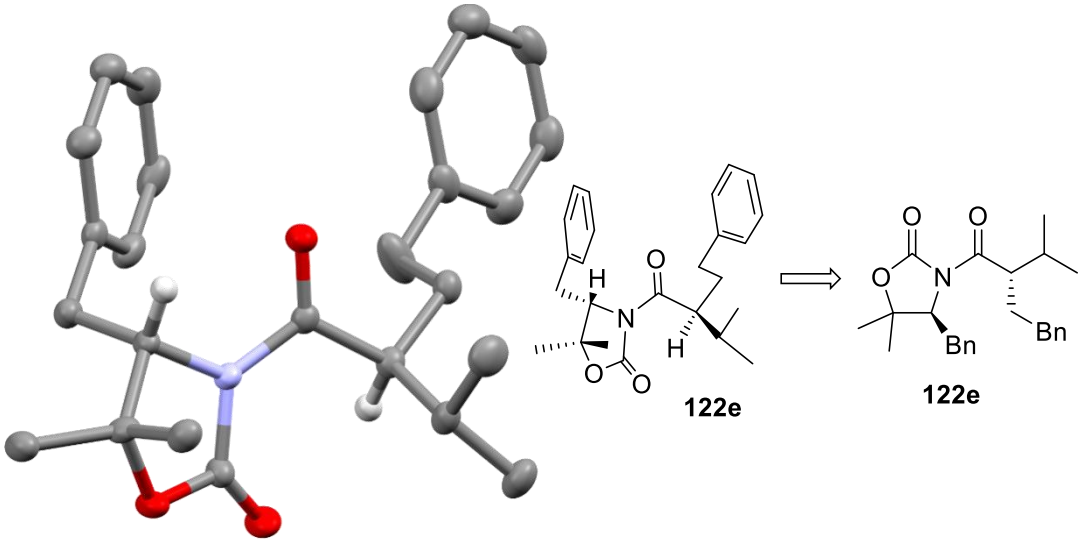
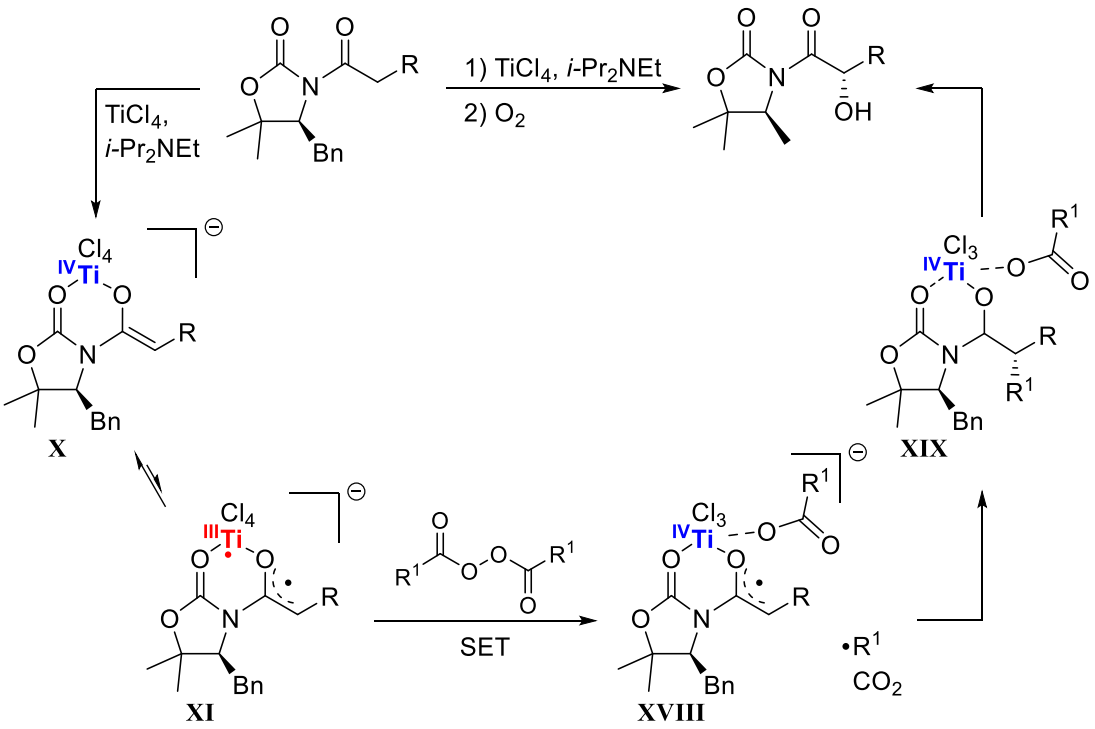


Figure 16

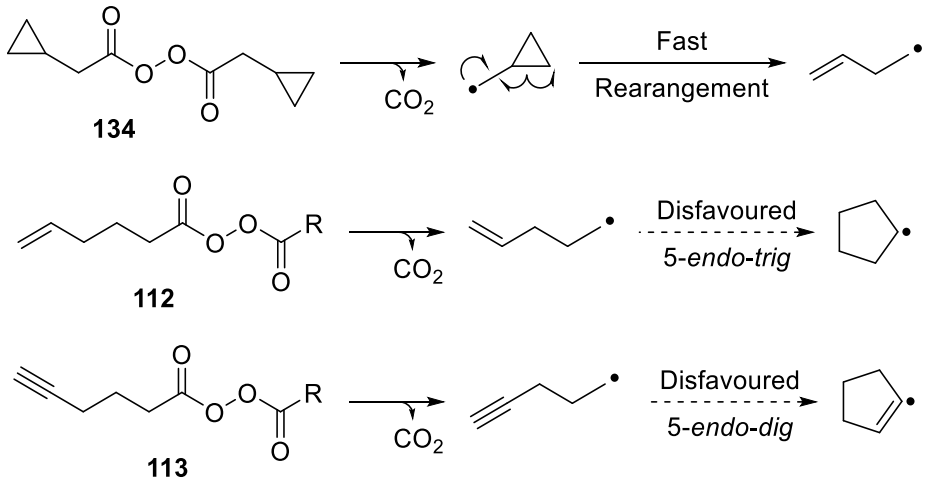
5.6. Mechanistic hypothesis

The mechanistic description of the decarboxylative alkylation of titanium enolates with diacyl peroxides is a challenging task. Supported by experimental clues, we speculated that the biradical enolate **XI** might interact with the diacyl peroxide in such a manner that the titanium(III) transfers an electron to the peroxide, triggering the reductive decarboxylation (Scheme 150). The resultant radical R• would then react with the C-radical centre of the enolate **XVIII**, which leads to the formation of the carbon-carbon bond and closes the “redox” cycle. Nevertheless, we were unable to confidently say anything further about the character of such a proposed mechanism.



Scheme 150

The positive radical clock test described in Scheme 149 (see section 5.4.1) lent support to a such proposal in which a pure radical formed from the peroxide is involved in the crucial alkylation step. Nevertheless, we were also aware of some potential flaws. Indeed, we did not observe any cyclization of the putative radical intermediates arising from 5-hexenoic and 5-hexynoic acids (Scheme 151), although disallowed 5-*endo-trig* and 5-*endo*-dig ring closing rearrangements according to Baldwin rules could be the reason for such behaviour.

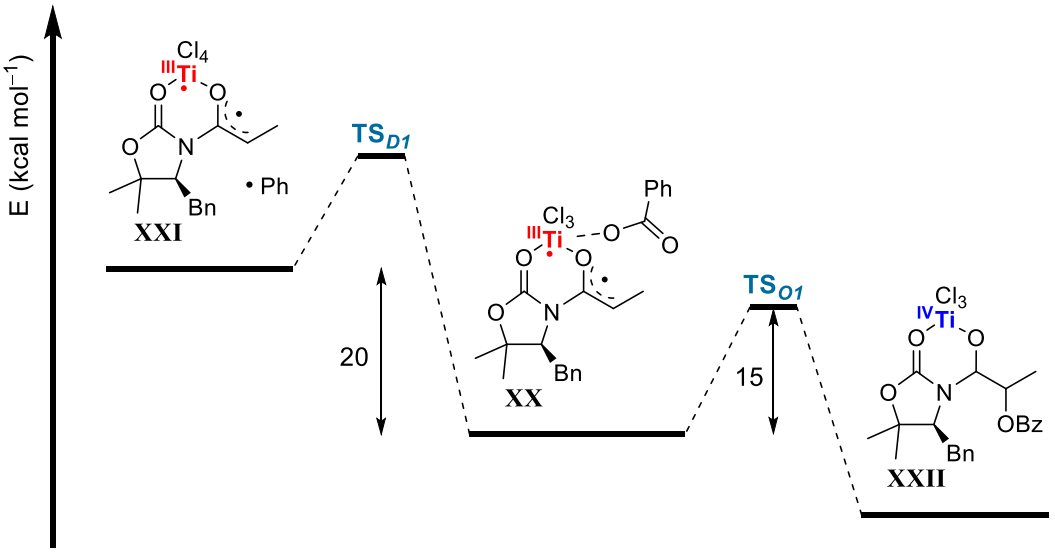


Scheme 151

In order to shed light on these details and the overall mechanism of the process, we have recently established a collaboration with Prof. Enrique Gómez Bengoa from the

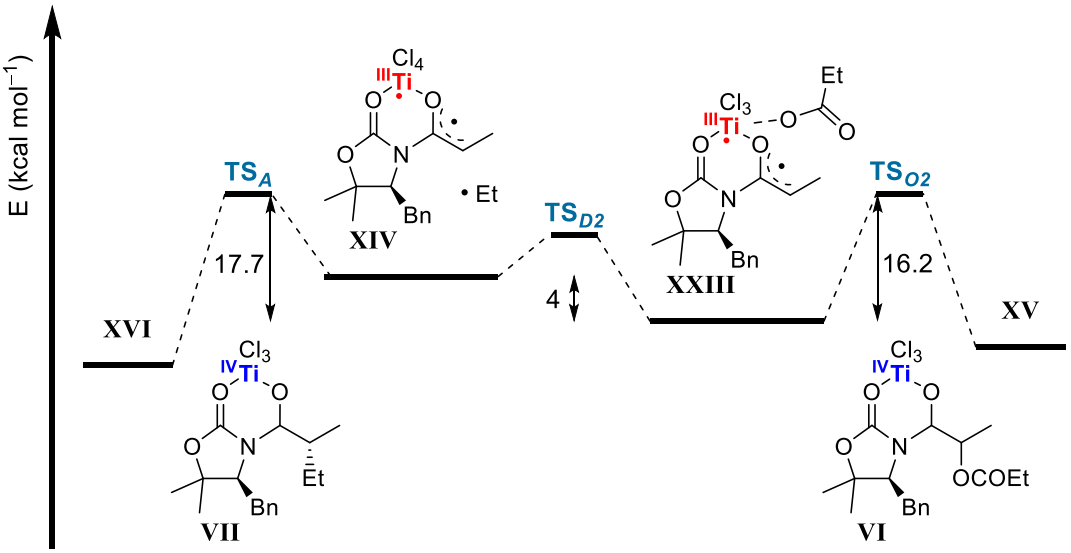
University of the Basque Country. For the moment, we can only discuss very preliminary results carried out by Lia Sotorríos.

First, they evaluated the energy of the ate-enolate containing a benzoate ligand **XX** and compared with that of the enolate with the phenyl radical formed upon decarboxylation **XXI**, and with that of the product of benzoyloxylation **XXII** (Scheme 152). The energy needed for the decarboxylation was estimated with the relative stability of the products. Hence, **XXI** was around 20 kcal mol^{-1} higher than **XX**, whereas the **TS$_{O1}$** to oxygenated adduct **XXII** was 15 kcal mol^{-1} above **XX**. This means that the benzoyloxylation is the most favoured pathway and that the competing decarboxylation leading to **XXI** requires a much more significant activation energy. These calculations matched the results obtained in the previous section, where we only saw formation of the benzoyloxylation product.



Scheme 152

In the case of the alkyl peroxides, the decarboxylation is much easier since the energy gap between the starting ate-enolate **XXIII** and the resulting enolate and ethyl radical **XIV** is small (ca 4 kcal mol^{-1}, Scheme 153), whereas the transition state **TS$_{O2}$** towards the acyloxy product **XV** is close to the calculated for the benzoate ligand (16.2 kcal mol^{-1}, Scheme 153). Altogether, these calculations suggest that the decarboxylation of aliphatic acids is more favoured than the parallel transformation for their aromatic counterparts. In summary, considering that the decarboxylation is an irreversible process, the lower estimated TS energy of **XXIII** to **XIV** versus **XV** might be the driving force of this transformation.



Scheme 153

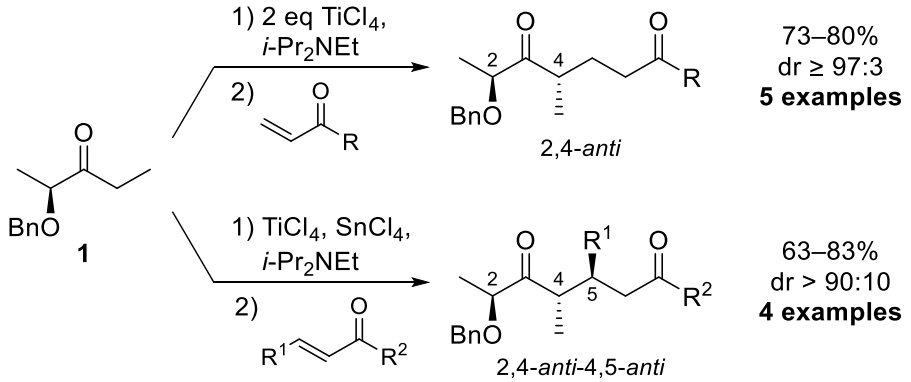
6. Final considerations

In summary, photoredox catalysed alkylation of titanium(IV) enolates has been attempted unsuccessfully. However, a highly stereoselective decarboxylative alkylation of biradical titanium(IV) enolates with aliphatic diacyl peroxides has been developed. Alkylation with diacyl peroxides derived from primary and secondary aliphatic acids allowed us to obtain the corresponding adducts as single diastereomers with excellent yields.

SUMMARY

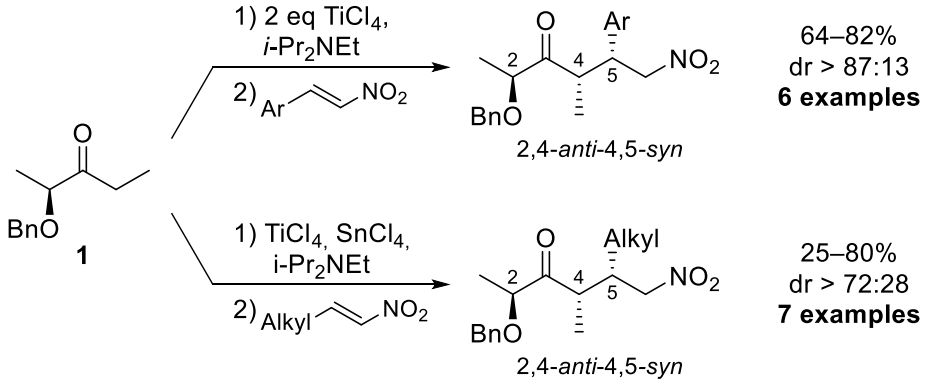
First of all, in the present Thesis we intended to continue a previous study of the nucleophilic character of titanium(IV) enolates. Particularly, we focused our attention on the analysis of substrate-controlled Michael additions to enones and other acceptors.

Thus, the Michael addition of (*S*)-2-benzyloxy-3-pentanone to enones was thoroughly evaluated in Chapter 1. In the case of vinyl ketones, the best reaction conditions involved the use of two $TiCl_4$ equivalents and afforded the 2,4-*anti* adducts as single diastereomers in excellent yields (Scheme 154). In addition, the developed methodology was also evaluated with β-substituted enones, whose optimised conditions using $TiCl_4$ and $SnCl_4$ afforded the 2,4-*anti*-4,5-*anti* adducts with diastereoselectivities above 90:10 in all cases with good yields (Scheme 154).



Scheme 154

Furthermore, the Michael addition of (*S*)-2-benzyloxy-3-pentanone to α,β-unsaturated nitroalkenes was also analysed in Chapter 1. The use of two equivalents of $TiCl_4$ and aromatic nitroalkenes led to the 2,4-*anti*-4,5-*syn* adducts with excellent yields and diastereoselectivities (Scheme 155). In turn, aliphatic nitroalkenes needed optimised conditions using $TiCl_4$ and $SnCl_4$ to afford the 2,4-*anti*-4,5-*syn* adducts in good diastereoselectivities and yields (Scheme 155). Finally, the nitro group was converted into other useful functional groups.



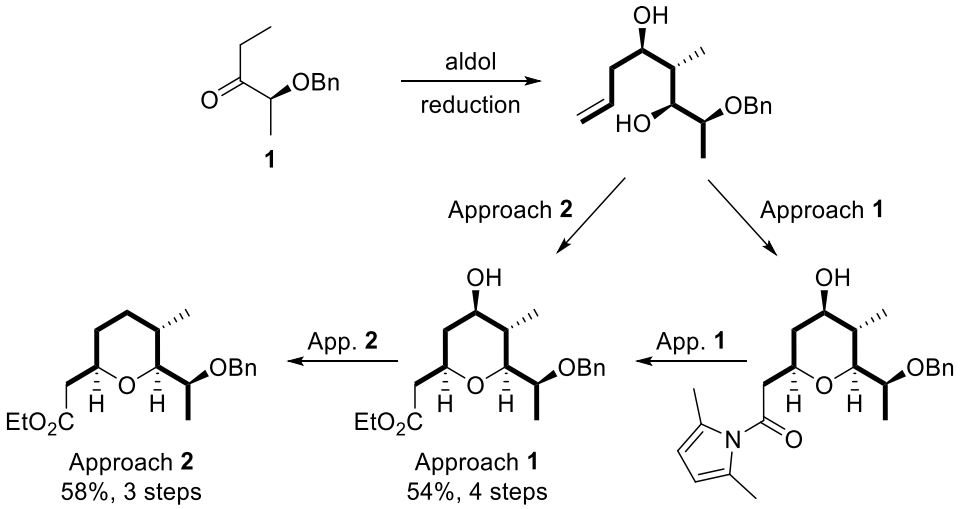
Scheme 155

The results described in Chapter 1 have been published in the following articles:

"*Stereoselective substrate-controlled Michael additions of chiral ketones to enones*", Gómez-Palomino, A., Pelicena, M., Reina, D., Fàbregas, M., Romea, P., Urpí, F., Font-Bardia, M. *Org. Lett.*, **2014**, *16,* 6220–6223. DOI: 10.1021/ol503133j

"*Substrate-controlled Michael additions of titanium enolates from chiral α-benzyloxy ketones to conjugated nitroalkenes*", Gómez-Palomino, A., Barrio, A., García-Lorente, P., Romea, P., Urpí, F., Font-Bardia, M. *Eur. J. Org. Chem.* **2017**, 5776–5784. DOI: 10.1002/ejoc.201701055

Another objective of the first part of this thesis was to re-evaluate the synthesis of the tetrahydropyran ring from the C1-C9 fragment of herboxidiene/GEX1A. Thus, in Chapter 2 we analysed the initial retrosynthesis of the C1-C9 fragment and studied the oxa-Michael cyclization. Finally, we designed two parallel sequences to improve the first synthetic approach (Scheme 156). The stereoselective synthesis of the tetrahydropyran ring was successfully accomplished following two different approaches. In approach **1**, the number of steps was increased, but the sequence pursued a fully stereoselective pathway taking advantage of the great selectivity offered by a dimethylpyrrole amide under acidic conditions attaining a 54% yield (46% for the original approach). In approach **2**, the original sequence of reactions was followed, but the suppression of unnecessary purification operations and a final isomerisation step increased notably the yield up to 58% (39% for the original approach).

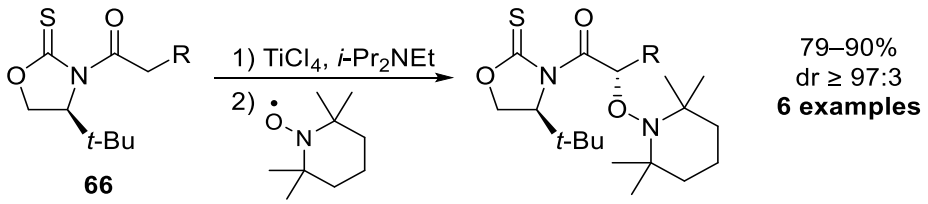


Scheme 156

The results described in Chapter 2 have been published in the following article:

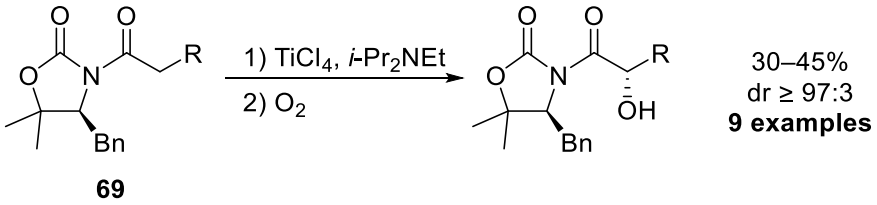
"*Total synthesis of (+)-herboxidiene/GEX 1A*", Gómez-Palomino, A., Pellicena, M., Krämer, K., Romea, P., Urpí, F., Aullón, G., Padrón, J., M. *Org. Biomol. Chem.,* **2017**, *15,* 1842–1862. DOI: 10.1039/c7ob00072c

Keeping in mind the biradical character of certain titanium enolates, the second objective of this Thesis was to further examine the uncommon radical reactivity of titanium enolates derived from chiral *N*-acyl oxazolidinones when exposed to radical reagents. In Chapter 3, the aminoxylation of chiral *N*-acyl oxazolidinones was improved using a chiral *tert*-butyl oxazolidinethione derived from *tert*-leucine (Scheme 157). This chiral auxiliary provided the aminoxylated products as single diastereomers in all cases with excellent yields. Finally, the resulting adducts were transformed into synthetical useful intermediates.



Scheme 157

In Chapter 3 we also reported a highly stereoselective oxidation of titanium enolates from chiral *N*-acyl oxazolidinones with molecular oxygen (Scheme 158). The direct hydroxylation of biradical titanium(IV) enolates derived from chiral oxazolidinones with O_2 proved to be feasible. Thus, we described a novel approach for the synthesis of enantiomerically pure α-hydroxy carboxylic derivatives.



Scheme 158

The results described in Chapter 3 have been published in the following articles:

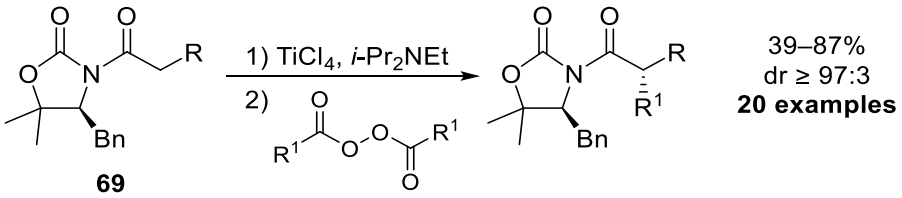
"*Stereoselective aminoxylation of biradical titanium enolates with TEMPO*", Gómez-Palomino, A., Pellicena, M., Romo, J. M., Solà, R., Romea, P., Urpí, F., Font-Bardia, M. *Chem. Eur. J.*, **2014**, *20*, 10153–10159. DOI: 10.1002/chem.201402127

"*Experimental and computational evidence of the biradical structure and reactivity of titanium(IV) enolates*", Heras, C., Gómez-Palomino, A., Romea, P., Urpí, F., Bofill, J. M., P. R. Moreira, I. *J. Org. Chem.*, **2017**, *82*, 8909–8916. DOI: 10.1021/acs.joc.7b01174

"*Stereoselective oxidation of titanium(IV) enolates with oxygen*", Gómez-Palomino, A., Romea, P., Urpí, F., Font-Bardia, M. *Synthesis* **2018**, *50*, 2721–2726. DOI: 10.1055/s-0037-1609966

"*General and stereoselective aminoxylation of biradical titanium(IV) enolates with TEMPO: a detailed study on the effect of the chiral auxiliary*", Kennington, S. C. D., Gómez-Palomino, A., Salomó, E., Romea, P., Urpí, F., Font-Bardia, M. Org. Biomol. Chem., **2018**, *16*, 4807–4815. 10.1039/C8OB01074A

We describe in Chapter 4 a comprehensive search of compounds capable of participating in radical reactions, which involved a brief exploration of photoredox catalysis. Finally, such research led to the discovery of a new and highly stereoselective alkylation with aliphatic diacyl peroxides. Decarboxylation of the diacyl peroxides from aliphatic acids promoted by the titanium enolates produced primary and secondary radicals and triggered the formation of the alkylated adducts as single diastereomers with excellent yields (Scheme 159).



Scheme 159

EXPERIMENTAL SECTION

Thin layer chromatography (TLC) was performed on analytical silica gel plates with 0.25 mm of thickness (F_{254} Merck). The eluents used are indicated in brackets in each case. UV light (254 nm) and solutions of phosphomolybdic acid, *p*-anisaldehyde, or $KMnO_4$ were used as TLC stains. R_f values are approximate. Column chromatography was performed at low pressure (flash) on silica gel (Merck 0.040–0.063 mm particle size). The eluents and the conditions of elution are indicated in brackets in each case.

Specific rotation ($[\alpha]^{20}_D$) were determined at rt with a Perkin-Elmer 241 MC polarimeter using the wavelength of the sodium D line (589 nm). Concentration (g/dL) and solvent used are indicated in brackets. IR spectra were performed in a Fourier transform spectrophotometer 6700 FT-IR Termo Scientific. In the spectrum description only the most significant frequencies are given in cm^{-1}. Melting points (M_p) were determined in a Gallenkamp aparatus.

NMR spectra were performed in a Varian Inova 300 (^1H at 300 MHz and ^{13}C at 75.4 MHz) in a Varian Mercury 400 (^1H at 400 MHz and ^{13}C at 100.6 MHz) and in a Bruker 400 Avance III (^1H at 400 MHz and ^{13}C at 100.6 MHz). Chemical shifts are given in δ unities (ppm) with respect to internal reference of tetramethylsilane in $CDCl_3$ (^1H NMR), or to the deuterated solvent (CD_3OD for ^1H NMR, $CDCl_3$ and CD_3OD for ^{13}C NMR), or to external reference of CF_3CO_2H for ^{19}F NMR and coupling constants (*J*) are given in Hz. Signal multiplicity in ^1H spectra are indicated with the following abbreviations: s = singlet, d = doublet, t = triplet, q = quadruplet, p = quintet, sext = sextet, h = septet, dd = double doublet, dq = double quadruplet, ddd = double doublet of doublets, td = triple doublet and m = multiplet.

High-resolution mass spectra HRMS (+ESI) were performed in a ThermoFinnigan GC/MS TRACE DSQ at the Molecular Characterisation Mass Spectrometry Service.

Anhidrous solvents and reagents used in the reactions were purified following standard procedures.[197] Solvents used for extractions, separations, TLC and chromatographic columns were only distilled.

Preparation of starting materials for Chapters 1 and 2

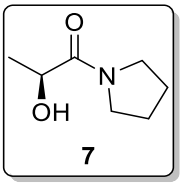
STARTING MATERIALS FOR CHAPTERS 1 AND 2
TABLE OF CONTENTS

1. Preparation of benzyloxy ketones[56,57]

1.1. (*S*)-2-Benzyloxy-3-pentanone (1)

1.1.1. (*S*)-2-Hydroxy-*N*,*N*-tetramethylenepropanamide (**7**)

Pyrrolidine (4.6 mL, 55 mmol) was added slowly to ethyl (*S*)-lactate (5.7 mL, 50 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C for 10 min and 6 d at rt. Pyrrolidine excess was eliminated in vacuum using a HCl trap to obtain an orange oil. The identity of the product was confirmed by ^{1}H-NMR analysis and it was used in the next reaction step without further purification.

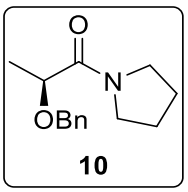


7

(*S*)-2-Hydroxy-*N*,*N*-tetramethylenepropanamide (7). Orange Oil. $\mathbf{R_f}$ (Hexanes/EtOAc 50:50) = 0.3; **IR** (film) ν 3994, 2974, 2876, 1623, 1127, 1029 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.30 (1H, q, *J* = 6.8 Hz, C<u>H</u>OH), 3.62–3.30 (4H, m, N(C<u>H</u>$_2$CH$_2$)$_2$), 2.06–1.82 (4H, m, N(CH$_2$C<u>H</u>$_2$)$_2$), 1.34 (3H, d, *J* = 6.8 Hz, C<u>H</u>$_3$); **^{13}C NMR** (75.4 MHz, $CDCl_3$) δ 172.4, 66.6, 46.5, 44.8, 27.8, 26.4, 18.7.

1.1.2. (*S*)-2-Benzyloxy-*N*,*N*-tetramethylenepropanamide (**10**)

A solution of **7** (4.31 g, 30 mmol), benzyl chloride (5.7 mL, 48 mmol) and [Oct$_3$NMe]Cl (0.69 mL, 1.5 mmol) in toluene (16 mL) was added via cannula to a solution of pulverised NaOH (3.60 g, 90 mmol) at 0 °C and under N_2 atmosphere. The mixture was stirred at 0 °C during 10 min and 15 h at rt. The reaction mixture was diluted with Et_2O (200 mL) and water (75 mL). The organic layer was washed with 2 M HCl (75 mL), sat. $NaHCO_3$ (75 mL), and brine (75 mL). The aqueous layer was extracted with Et_2O (3 × 60 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography (hexanes/EtOAc 50:50 to 25:75) to afford 5.21 g (75% yield) of (*S*)-2-benzyloxy-*N*,*N*-tetramethylenepropanamide (**10**).

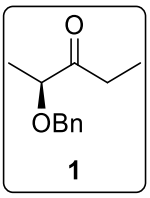


10

(*S*)-2-Benzyloxy-*N*,*N*-tetramethylenpropanamide (10). White solid. **Mp** = 40–42 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 50:50) = 0.1; $\mathbf{[\alpha]^{20}_D}$ = –62.9 (*c* 2.0, $CHCl_3$) [lit.[56,57] $\mathbf{[\alpha]^{20}_D}$ = –63.3 (*c* 2.0, $CHCl_3$)]; **IR** (KBr) ν 3031, 2977, 2077, 1654, 1455, 1430, 1107 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.25 (5H, m, Ar<u>H</u>), 4.61 (1H, d, *J* = 11.8 Hz, PhC<u>H</u>$_x$H$_y$), 4.44 (1H, d, *J* = 11.8 Hz, PhCH$_x$<u>H</u>$_y$), 4.20 (1H, q, *J* = 6.8 Hz, C<u>H</u>OBn), 3.55–3.38 (4H, m, N(C<u>H</u>$_2$CH$_2$)$_2$), 1.94–1.78 (4H, m, N(CH$_2$C<u>H</u>$_2$)$_2$), 1.42 (3H, d, *J* = 6.8 Hz, C<u>H</u>$_3$); **^{13}C NMR** (75.4 MHz, $CDCl_3$) δ 170.7, 137.7, 128.4, 127.9, 127.6, 74.6, 70.8, 46.2, 45.9, 26.2, 23.6, 17.3.

1.1.3. (*S*)-2-Benzyloxy-3-pentanone (**1**)

A solution of EtMgCl 2 M in THF (5.0 mL, 10 mmol) was added dropwise to a solution of **10** (2.33 g, 10 mmol) in THF (100 mL) at 0 °C under N_2 atmosphere. The reaction was quenched with 10 mL of sat. NH_4Cl after 15 min. The mixture was diluted with CH_2Cl_2 (220 mL) and sat. NH_4Cl (45 mL). The organic layer was extracted and washed with brine (3 × 45 mL). Aqueous phases were extracted with CH_2Cl_2 (3 × 45 mL). The organic extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The residue was purified by column chromatography (hexanes/EtOAc 85:15) to afford 1.56 g (81% yield) of (*S*)-2-benziloxy-3-pentanone (**1**).



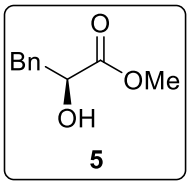
1

(*S*)-2-Benzyloxy-3-pentanone (1). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.5; $\mathbf{[\alpha]^{20}_D}$ = –35.7 (*c* 1.1, $CHCl_3$) [lit.[56,57] $\mathbf{[\alpha]^{20}_D}$ = –32.0 (*c* 1.0, $CHCl_3$)]; **IR** (film) ν 3089, 3065, 3032, 2979, 2938, 1878, 1717 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.24 (5H, m, Ar<u>H</u>), 4.56 (1H, d, *J* = 11.7 Hz, PhC<u>H</u>$_x$H$_y$), 4.50 (1H, d, *J* = 11.7 Hz, PhCH$_x$<u>H</u>$_y$), 3.95 (1H, q, *J* = 6.9 Hz, C<u>H</u>OBn), 2.68–2.52 (2H, m, C<u>H</u>$_2$CH$_3$), 1.35 (3H, d, *J* = 6.9 Hz, BnOCHC<u>H</u>$_3$), 1.05 (3H, t, *J* = 7.1 Hz, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (75.4 MHz, $CDCl_3$) δ 213.5 (C), 137.6 (C), 128.4 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 80.5 (CH), 71.8 (CH_2), 30.5 (CH_2), 17.5 (CH_3), 7.3 (CH_3).

1.2. (*S*)-2-Benzyloxy-1-phenyl-3-pentanone (2)

1.2.1. Methyl (*S*)-2-hydroxy-3-phenylpropanoate (**5**)

A mixture containing (*S*)-2-hydroxy-3-phenylpropanoic acid (4.0 g, 24 mmol), trimethyl orthoformate (2.7 mL, 24 mmol) and a catalytic quantity of *p*-toluenesulfonic acid in methanol (100 mL) was set to reflux for 24 h. The reaction mixture was concentrated to remove MeOH and then diluted with CH_2Cl_2 (150 mL). The organic layer was washed with sat. $NaHCO_3$ (50 mL). The aqueous layers were extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic extracts were washed with H_2O (50 mL), dried ($MgSO_4$), filtered, and concentrated to give 4.64 g (98% yield) of methyl (*S*)-2-hydroxy-3-phenylpropanoate (**5**), which was used in the next step without further purification.

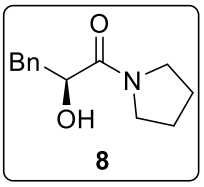


5

Methyl (*S*)-2-hydroxy-3-phenylpropanoate (5). White solid. $\mathbf{R_f}$ (CH_2Cl_2) = 0.5; **Mp** = 48–49 °C; $\mathbf{[\alpha]^{20}_D}$ = –7.1 (*c* 2.0, $CHCl_3$); **IR** (KBr) ν 3500, 1750 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (5H, m, Ar<u>H</u>), 4.50–4.40 (1H, m, C<u>H</u>OH), 3.77 (3H, s, COOC<u>H</u>$_3$), 3.13 (1H, dd, *J* = 13.9, 4.4 Hz, PhC<u>H</u>$_x$H$_y$), 2.96 (1H, dd, *J* = 13.9, 6.8 Hz, PhCH$_x$<u>H</u>$_y$), 2.72 (1H, d, *J* = 6.2 Hz, CHO<u>H</u>); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.4, 136.3, 129.3, 128.3, 126.7, 71.2, 52.3, 40.4.

1.2.2. (*S*)-2-Hydroxy-3-phenyl-*N*,*N*-tetramethylenepropanamide (**8**)

The experimental procedure described in section 1.1.1 was followed starting from **5** (4.64 g, 25.8 mmol). The resulting crude was purified by recrystallization in EtOAc/hexanes to obtain 3.82 g (68% yield) of (*S*)-2-hydroxy-3-phenyl-*N*,*N*-tetramethylenepropanamide (**8**).

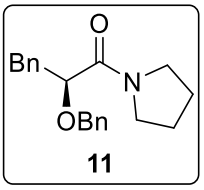


8

(*S*)-2-Hydroxy-3-phenyl-*N*,*N*-tetramethylenepropanamide (8). White needles. $\mathbf{R_f}$ (CH_2Cl_2/CH_3OH 98:2) = 0.4; **Mp** = 98–99 °C; $\mathbf{[\alpha]^{20}_D}$ = +4.6 (*c* 2.0, $CHCl_3$); **IR** (KBr) ν 3250, 1630 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (5H, m, ArH), 4.39 (1H, t, CHOH), 3.64 (1H, d, *J* = 8.4, CHOH), 3.60–3.50 (1H, m, $N(CH_2CH_2)_2$), 3.50–3.30 (2H, m, $N(CH_2CH_2)_2$), 3.00–2.85 (3H, m, $PhCH_2$, $N(CH_2CH_2)_2$), 1.90–1.70 (4H, m, $N(CH_2CH_2)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.9, 136.8, 129.2, 128.2, 126.5, 70.5, 45.9, 45.7, 41.7, 25.7, 23.6.

1.2.3. (*S*)-2-Benzyloxy-3-phenyl-*N*,*N*-tetramethylenepropanamide (**11**)

The experimental procedure described in section 1.1.2 was followed starting from **8** (3.82 g, 17 mmol) for 26 h. The resulting crude was purified by column chromatography (hexanes/EtOAc 1:1) to afford 4.66 g (87% yield) of (*S*)-2-benzyloxy-3-phenyl-*N*,*N*-tetramethylenepropanamide (**11**).

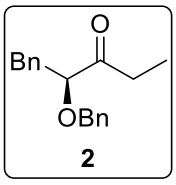


11

(*S*)-2-Benzyloxy-3-phenyl-*N*,*N*-tetramethylenepropanamide (11). White solid. $\mathbf{R_f}$ (Hexanes/AcOEt 50:50) = 0.3; **Mp** = 121–122 °C; $\mathbf{[\alpha]^{20}_D}$ = –41.7 (*c* 2.0, $CHCl_3$); **IR** (KBr) ν 1640 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (10H, m, ArH), 4.64 (1H, d, *J* = 12.1 Hz, $PhCH_xH_yO$), 4.39 (1H, d, *J* = 12.1 Hz, $PhCH_xH_yO$), 4.23 (1H, t, CHOBn), 3.55–3.35 (2H, m, $N(CH_2CH_2)_2$), 3.20-3.00 (3H, m, $PhCH_2$, $N(CH_2CH_2)_2$), 2.95–2.80 (1H, m, $N(CH_2CH_2)_2$), 1.80–1.60 (4H, m, $N(CH_2CH_2)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.7, 137.5, 137.1, 129.5, 128.2, 128.2, 127.7, 127.6, 126.5, 79, 71.2, 46.1, 45.9, 38.9, 26.1, 23.6.

1.2.4. (*S*)-2-Benzyloxy-1-phenyl-3-pentanone (**2**)

The experimental procedure described in section 1.1.3 was followed starting from **11** (1.60 g, 5 mmol) for 30 min. The resulting crude was purified by column chromatography (hexanes/EtOAc 4:1) to afford 1.28 g (96% yield) of (*S*)-2-benzyloxy-1-phenyl-3-pentanone (**2**).



2

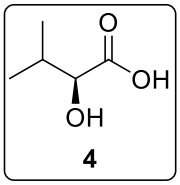
(*S*)-2-Benzyloxy-1-phenyl-3-pentanone (2). Colorless oil. $\mathbf{R_f}$ (CH_2Cl_2/hexanes 50:50) = 0.5; **IR** (film) ν 1710 cm^{-1}; $\mathbf{[\alpha]^{20}_D}$ = –76.3 (*c* 2.0, $CHCl_3$) [lit.[56,57] $\mathbf{[\alpha]^{20}_D}$ = –74.5 (*c* 2.0, $CHCl_3$)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (10H, m, ArH), 4.50 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.36 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.04 (1H, dd, *J* = 7.7, 4.7 Hz, CHOBn), 3.01 (1H, dd, *J* = 13.9, 4.7 Hz , $PhCH_xH_y$), 2.92 (1H, dd, *J* = 13.9, 7.7 Hz , $PhCH_xH_y$), 2.56–2.30 (2H, m, CH_2CH_3), 0.99 (3H, t, *J* = 7.2 Hz , CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 212.8 (C), 137.3 (C), 137.1 (C), 129.4 (2 × CH), 128.3 (2 × CH), 128.2

(2 × CH), 127.7 (2 × CH), 127.6 (CH), 126.5 (CH), 85.5 (CH), 72.5 (CH_2), 38.6 (CH_2), 31.7 (CH_2), 7.0 (CH_3).

1.3. (*S*)-4-Benzyloxy-5-methyl-3-hexanone (3)

1.3.1. (*S*)-2-Hydroxy-3-methylbutanoic acid (4)

A 3.5 M solution of sodium nitrite in water (60 mL, 200 mmol) was added to a solution of L-valine (11.71 g, 100 mmol) in 0.5 M H_2SO_4 (120 mL) over 1 h at 0 °C. The mixture was stirred for 1 h at 0 °C, and then for 12 h at rt. The reaction mixture was sat. with NaCl, followed by the addition of 2 M HCl until pH 1. The mixture was then extracted with Et_2O (4 × 120 mL). The organic layer was washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to give a solid, which was then recrystallised in hexanes/EtOAc to obtain 10.48 g (89% yield) of (*S*)-2-hydroxy-3-methylbutanoic acid (**4**).

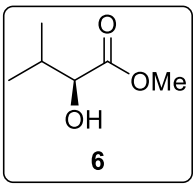


4

(*S*)-2-Hydroxy-3-methylbutanoic acid (4). White solid. **Mp** = 66–67 °C; **IR** (KBr) ν 3420, 3250, 2500, 1735 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.15 (1H, d, *J* = 3.4 Hz, C<u>H</u>OH), 2.30–2.10 (1H, m, C<u>H</u>(CH_3)$_2$), 1.06 (3H, d, *J* = 7.0 Hz, CH(C<u>H</u>$_3$)$_2$), 0.93 (3H, d, *J* = 7.0 Hz, CH(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 179.2, 74.8, 31.9, 18.7, 15.9.

1.3.2. Methyl (*S*)-2-hydroxy-3-methylbutanoate (6)

The experimental procedure described in section 1.2.1 was followed starting from **4** (5.0 g, 42.3 mmol) for 48 h to afford 3.03 g (55% yield) of methyl (*S*)-2-hydroxy-3-methylbutanoate (**6**), which was used in the next step without further purification.

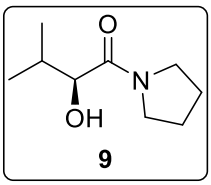


6

Methyl (*S*)-2-hydroxy-3-methylbutanoate (6). Yellow oil. **R_f** (CH_2Cl_2/MeOH 99:1) = 0.6; **$[\alpha]^{20}_D$** = +19.0 (*c* 1.0, $CHCl_3$); **IR** (KBr) ν 3500, 3000, 2900, 1760 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.06 (1H, d, *J* = 3.6 Hz, C<u>H</u>OH), 3.79 (3H, s, COOC<u>H</u>$_3$), 2.08 (1H, dh, *J* = 6.9, 3.6 Hz, C<u>H</u>(CH_3)$_2$), 1.02 (3H, d, *J* = 6.9 Hz, CH(C<u>H</u>$_3$)$_2$), 0.87 (3H, d, *J* = 6.9 Hz, CH(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.3, 75.0, 52.3, 32.1, 18.7, 15.9.

1.3.3. (*S*)-2-Hydroxy-3-methyl-*N*,*N*-tetramethylenebutanamide (9)

The experimental procedure described in section 1.1.1 was followed starting from **6** (1.60 g, 5 mmol) at 40 °C. The resulting crude was purified by column chromatography (CH_2Cl_2/MeOH 95:5) to afford 2.05 g (53% yield) of (*S*)-2-hydroxy-3-methyl-*N*,*N*-tetramethylenebutanamide (**9**).

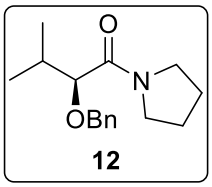


9

(*S*)-2-Hydroxy-3-methyl-*N*,*N*-tetramethylenebutanamide (9). White solid. **R$_f$** (CH_2Cl_2/MeOH 95:5) = 0.4; **[α]$^{20}_D$** = –9.9 (*c* 2.0, $CHCl_3$); **IR** (KBr) ν 3430, 3000, 2900, 1640 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.07 (1H, d, *J* = 3.0 Hz, C<u>H</u>OH), 3.65–3.30 (5H, m, CHO<u>H</u>, N(C<u>H</u>$_2$CH$_2$)$_2$), 2.05–1.80 (5H, m, C<u>H</u>(CH$_3$)$_2$, N(CH$_2$C<u>H</u>$_2$)$_2$), 1.06 (3H, d, *J* = 6.9 Hz, CH(C<u>H</u>$_3$)$_2$), 0.84 (3H, d, *J* = 6.9 Hz, CH(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.4, 73.6, 46.0, 45.9, 30.8, 25.9, 23.7, 19.6, 15.1.

1.3.4. (*S*)-2-Benzyloxy-3-methyl-*N*,*N*-tetramethylenebutanamide (**12**)

The experimental procedure described in section 1.1.2 was followed starting from **9** (2.00 g, 11.7 mmol) for 22 h. The resulting crude was purified by column chromatography (hexanes/EtOAc 1:1) to afford 2.28 g (75% yield) of (*S*)-2-benzyloxy-3-methyl-*N*,*N*-tetramethylenebutanamide (**12**).

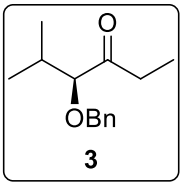


12

(*S*)-2-Benzyloxy-3-methyl-*N*,*N*-tetramethylenebutanamide (12). Yellow oil. **R$_f$** (Hexanes/EtOAc 50:50) = 0.4; **[α]$^{20}_D$** = –62.3 (*c* 2.2, $CHCl_3$); **IR** (KBr) ν 2950, 2850, 1630, 1420 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (5H, m, Ar<u>H</u>), 4.64 (1H, d, *J* = 12.0 Hz, PhC<u>H</u>$_x$H$_y$O), 4.39 (1H, d, *J* = 12.0 Hz, PhCH$_x$<u>H</u>$_y$O), 3.70 (1H, d, *J* = 8.4 Hz, C<u>H</u>OCH$_2$Ph), 3.60–3.25 (4H, m, N(C<u>H</u>$_2$CH$_2$)$_2$), 2.20–1.95 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.90–1.70 (4H, m, N(CH$_2$C<u>H</u>$_2$)$_2$), 1.06 (3H, d, *J* = 6.6 Hz, CH(C<u>H</u>$_3$)$_2$), 0.91 (3H, d, *J* = 6.6 Hz, CH(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.2, 137.8, 128.2, 127.7, 127.5, 84.5, 71.4, 46.0, 45.9, 30.6, 26.2, 23.5, 18.8, 18.6.

1.3.5. (*S*)-4-Benzyloxy-5-methyl-3-hexanone (**3**)

The experimental procedure described in section 1.1.3 was followed starting from **12** (1.00 g, 3.8 mmol) for 2 h. The resulting crude was purified by column chromatography (hexanes/EtOAc 90:10) to afford 0.71 g (84% yield) of (*S*)-4-benzyloxy-5-methyl-3-hexanone (**3**).



3

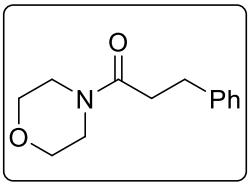
(*S*)-4-Benzyloxy-5-methyl-3-hexanone (3). Yellow oil. **R$_f$** (CH_2Cl_2) = 0.7; **IR** (KBr) ν 3050, 3000, 2850, 1710, 1450 cm^{-1}; **[α]$^{20}_D$** = –93.9 (*c* 2.0, $CHCl_3$) [lit.[56,57] **[α]$^{20}_D$** = –94.5 (*c* 2.0, $CHCl_3$)]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (5H, m, Ar<u>H</u>), 4.56 (1H, d, *J* = 11.7 Hz, PhC<u>H</u>$_x$H$_y$O), 4.38 (1H, d, *J* = 11.7 Hz, PhCH$_x$<u>H</u>$_y$O) 3.48 (1H, d, *J* = 6.6 Hz, C<u>H</u>OCH$_2$Ph), 2.55 (1H, dq, *J* = 18.5, 7.5 Hz, C<u>H</u>$_x$H$_y$CH$_3$), 2.49 (1H, dq, *J* = 18.5, 7.5 Hz, CH$_x$<u>H</u>$_y$CH$_3$), 2.07–1.94 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.04 (3H, t, *J* = 7.5 Hz, CH$_2$C<u>H</u>$_3$), 0.97 (3H, d, *J* = 6.6 Hz, CH(C<u>H</u>$_3$)$_2$), 0.89 (3H, d, *J* = 6.9 Hz, CH(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.8 (C), 137.7 (C), 128.3 (CH), 127.7 (CH), 127.6 (CH), 90.3 (CH), 72.9 (CH_2), 31.3 (CH_2), 31.1 (CH), 18.7 (CH_3), 18.1 (CH_3), 7.2 (CH_3).

2. Preparation of enones

2.1. 5-Phenyl-1-penten-3-one (Ec)

2.1.1. *N*-(3-Phenylpropanoyl)morpholine[41]

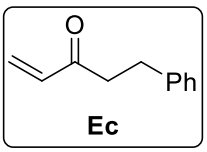
Pivaloyl chloride (2 mL, 15 mmol) was added to a solution of hidrocynnamic acid (2.30 g, 15 mmol) and *i*-Pr_2NEt (4 mL, 22.5 mmol) in THF (50 mL) at 0 °C under a N_2 atmosphere. The mixture was stirred for 1 h at 0 °C, then, morpholine (2.5 mL, 30 mmol) and DMAP (183 mg, 1.5 mmol) were added. The reaction was stirred overnight at rt. It was diluted with Et_2O (200 mL) and washed with 2 M HCl (50 mL), sat. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The resultant yellow oil was purified by column chromatography (hexanes/EtOAc 20:80) to afford 2.75 g (84% yield) of *N*-(3-phenylpropanoyl)morpholine.



***N*-(3-Phenylpropanoyl)morpholine**. Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 20:80) = 0.4; **IR** (ATR) ν 1640 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.19 (5H, m, ArH), 3.62 (4H, m, CH_2N, CH_2O), 3.52–3.50 (2H, m, CH_2O), 3.37–3.34 (2H, m, CH_2N), 3.00–2.96 (2H, m, $PhCH_2$), 2.64–2.60 (2H, m, CH_2CO); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 170.8, 141.0, 128.5, 128.4, 126.2, 66.8, 66.4, 45.9, 41.9, 34.8, 31.4.

2.1.2. 5-Phenyl-1-penten-3-one (**Ec**)[198]

A solution of vinylmagnesium bromide 1 M in THF (12 mL, 12 mmol) was added dropwise to a solution of *N*-(3-phenylpropanoyl)morpholine (658 mg, 3 mmol) in THF (30 mL) under N_2 atmosphere at 0 °C for 1 h. The reaction mixture was added via cannula to 9 mL of AcOH at 0 °C. The mixture was diluted with CH_2Cl_2 (200 mL) and washed with sat. $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to obtain a yellow oil. This was purified by column chromatography (hexanes/EtOAc 90:10) to give 409 mg (85% yield) of 5-phenyl-1-penten-3-one (**Ec**).

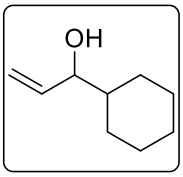


5-Phenyl-1-penten-3-one (Ec). Pale yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.5; **IR** (ATR) ν 1860, 1610 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.18 (5H, m, ArH), 6.36 (1H, dd, *J*= 17.7, 10.5 Hz, CH=CH_2), 6.21 (1H, dd, *J* = 17.7, 1.1 Hz, CH=CH_xH_y), 5.83 (1H, dd, *J* = 10.5, 1.1 Hz, CH=CH_xH), 2.99–2.90 (4H, m, $Ph(CH_2)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 199.7, 141.0, 136.4, 128.5, 128.3, 128.3, 126.1, 41.2, 29.7.

2.2. 1-Cyclohexyl-2-propen-1-one (Ed)[199]

2.2.1. 1-Cyclohexyl-2-propen-1-ol

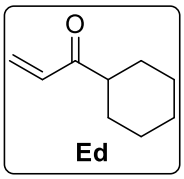
Cyclohexanecarbaldehyde (1.2 mL, 10 mmol) was added dropwise to a solution of vinylmagnesium bromide 1 M in THF (12 mL, 12 mmol) at 0 °C under N_2 atmosphere. The reaction was stirred for 2 h at 0 °C. It was quenched with NH_4Cl (20 mL) with vigorous stirring at rt. The mixture was diluted with Et_2O (25 mL) and washed with brine (15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 954 mg (70% yield) of 1-cyclohexyl-2-propen-1-ol.



1-Cyclohexyl-2-propen-1-ol. Pale yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.91 (1H, ddd, *J* = 17.1, 10.4, 6.6 Hz, C<u>H</u>=CH_2), 5.23–5.12 (2H, m, C<u>H</u>$_2$=CH), 3.87–3.83 (1H, m, C<u>H</u>OH), 1.88–1.82 (1H, m, C<u>H</u>COH), 1.79–0.94 (10H, m, (C<u>H</u>$_2$)$_5$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 139.8, 115.4, 77.7, 43.4, 28.7, 28.3, 26.5, 26.1, 26.0.

2.2.2. 1-Cyclohexyl-2-propen-1-one (**Ed**)

DMSO (1.2 mL, 16 mmol) was added dropwise to a solution of oxalyl chloride (670 µL, 1.2 mmol) in CH_2Cl_2 (8.5 mL) under N_2 atmosphere at –78 °C. Then, 1-cyclohexyl-2-propen-1-ol (954 mg, 6.8 mmol) was added to the solution. The mixture was stirred 30 min and Et_3N (3.5 mL, 25 mmol) was added dropwise, the reaction mixture was stirred for 30 min at –78 °C. The solution was allowed to warm slowly to rt. It was diluted with H_2O (15 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with 1% HCl (15 mL), 5% Na_2CO_3 (15 mL), and brine (15 mL), dried ($MgSO_4$), filtrated and carefully concentrated (volatile product) to obtain a light-yellow oil. Due to the production of Me_2S, hydrogen peroxide trap was used during the removal of volatiles. The residue was purified by column chromatography (hexanes/EtOAc 95:5) obtaining 837 mg (90% yield) of 1-cyclohexyl-2-propen-1-one (**Ed**).

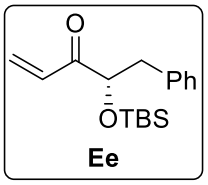


1-Cyclohexyl-2-propen-1-one (Ed). Pale yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.6; **IR** (ATR) ν 2927, 2853, 1694, 1672, 1610, 1449, 1401, 1145, 1000 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.43 (1H, dd, *J* = 17.5, 10.5 Hz, C<u>H</u>=CH_2), 6.25 (1H, dd, *J* = 17.5, 1.5 Hz, CH=CH$_x$<u>H</u>$_y$), 5.75 (1H, dd, *J* = 10.5, 1.5 Hz, CH=C<u>H</u>$_x$H$_y$), 2.65–2.58 (1H, m, C<u>H</u>CO), 1.85–1.21 (10H, m, (C<u>H</u>$_2$)$_5$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 203.4, 134.9, 127.7, 48.1, 28.5, 25.8, 25.6.

2.3. (S)-4-(*tert*-Butyldimethylsilyloxy)-5-phenyl-1-penten-3-one (Ee)

The experimental procedure described in section 2.1.2 was followed starting from *N*-[(*S*)-2-*tert*-butyldimethylsilyloxy-3-phenylpropanoyl]-morpholine (569 mg, 1.62 mmol). The

resulting crude was purified by column chromatography (hexanes/EtOAc 80:20) to afford 353 mg (75% yield) of (*S*)-4-(*tert*-butyldimethylsilyloxy)-5-phenyl-1-penten-3-one (**Ee**)**.**

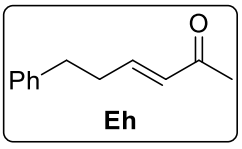


Ee

(*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-phenyl-1-penten-3-one (Ee). Pale yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 70:30) = 0.8; **IR** (ATR) ν 1706, 1099, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30–7.20 (5H, m, Ar<u>H</u>), 6.83 (1H, dd, *J* = 17.5, 10.6 Hz, C<u>H</u>=CH_2), 6.40 (1H, dd, *J* = 17.5, 1.9 Hz, CH=CH_x<u>H_y</u>), 5.76 (1H, dd, *J* = 10.6, 1.9 Hz, CH=CH_x<u>H_y</u>), 4.30 (1H, dd, *J* = 9.0, 3.9 Hz, C<u>H</u>OTBS), 2.93 (1H, dd, *J* = 13.4, 3.9 Hz, PhC<u>$H_x$$H_y$</u>), 2.80 (1H, dd, *J* = 13.4, 9.0 Hz, PhCH_x<u>H_y</u>), 0.81 (9H, s, ($C\underline{H}_3$)$_3$CSi), –0.17 (3H, s, $C\underline{H}_3$Si), –0.29 (3H, s, $C\underline{H}_3$Si); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 201.2, 137.1, 131.0, 129.9, 129.5, 128.2, 126.6, 79.6, 41.4, 25.7, 18.1, 5.6, 5.3.

2.4. (*E*)-6-Phenyl-3-hexen-2-one (Eh)[200]

1-(Triphenylphosphoranylidene)-2-propanone (1.90 g, 6 mmol) was added in one portion to a solution of hydrocinnamaldehyde (0.53 mL, 4 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at rt overnight and concentrated in vacuo. The residue was purified by column chromatography (hexanes/EtOAc 80:20) to afford 638 mg (92% yield) of (*E)*-6-phenyl-3-hexen-2-one (**Eh**).



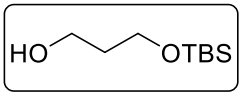
Eh

(*E)*-6-Phenyl-3-hexen-2-one (Eh). Pale yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.5; **IR** (ATR) ν 3026, 2925, 2857,1670, 1624, 1252 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.29 (2H, m, Ar<u>H</u>), 7.24–7.18 (3H, m, Ar<u>H</u>), 6.82 (1H, dt, *J* = 16.0, 6.8 Hz, COCH=C<u>H</u>), 6.10 (dt, *J* = 16.0, 1.5 Hz, 1H, COC<u>H</u>), 2.79 (2H, t, *J* = 6.8, C<u>H_2</u>Ph) , 2.58–2.52 (2H, m, CHC<u>H_2</u>), 2.23 (3H, s, C<u>H_3</u>); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 198.6, 147.1, 140.6, 131.7, 128.5, 128.3, 126.2, 34.4, 34.1,26.9.

2.5. (*E*)-6-(*tert*-Butyldimethylsilyloxy)-3-hexen-2-one (Ei)

2.5.1. <u>3-(*tert*-Butildimethylsilyloxy)-1-propanol</u>[201]

1.3-Propanediol was added dropwise (3.0 mL, 40 mmol) to a solution of NaH 60% (1.60 g, 40 mmol) in THF (80 mL) under N_2 atmosphere at rt. The mixture was stirred for 1 h, then, *tert*-butyldimethylsilyl chloride (6.20 g, 40 mmol) was added in one portion. The resulting slurry was stirred overnight and quenched with Na_2CO_3 10% (50mL), and concentrated in vacuo. The residue was extracted with CH_2Cl_2 (50 mL) and washed with Na_2CO_3 10% (50 mL) and Brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 3.90 g (52% yield) of 3-(*tert*-butildimetilsililoxy)-1-propanol.

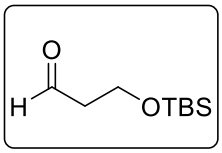


3-(*tert*-Butildimetilsililoxy)-1-propanol. Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.87–3.77

(4H, m, C<u>H</u>$_2$CH$_2$C<u>H</u>$_2$), 2.56 (1H, s, O<u>H</u>), 1.78 (2H, p, *J* = 5.2 Hz, CH$_2$C<u>H</u>$_2$CH$_2$), 0.91 (9H, s, OSiC(C<u>H</u>$_3$)$_3$), 0.08 (6H, s, OSi(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 62.2, 61.3, 38.8, 28.6, 18.6, –5.1, –5.2.

2.5.2. 3-*tert*-Butyldimethylsilyloxypropanal[202]

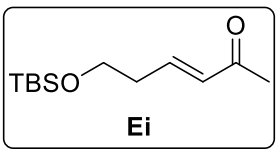
Pyridine-SO_3 complex (2.40 g, 15 mmol) was added in one portion to a solution of 3-(*tert*-butildimetilsililoxy)-1-propanol (1.20 g, 6.3 mmol), DMSO (4.3 mL, 60 mmol) and Et_3N (4.2 mL, 30 mmol) in CH_2Cl_2 (25 mL) under N_2 atmosphere at 0 °C. The resultant mixture was stirred for 2 h at 0 °C and concentrated in vacuo. The residue was extracted with Et_2O (20 mL) and washed with citric acid 0.5 M (2 × 20mL), H_2O (2 × 20 mL) and Brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was filtered through a plug of silica gel (hexanes/EtOAc 90:10) to afford 1.20 g (quantitative yield) of 3-*tert*-butyldimethylsilyloxypropanal**.**



3-tert-Butyldimethylsilyloxypropanal. Pale yellow oil. **R_f** (Hexanes/EtOAc 80:20) = 0.5; **IR** (ATR) ν 2954, 2930, 2856, 1726, 1471, 1254, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80 (1H, t, *J* = 2.1 Hz, C<u>H</u>O), 3.99 (2H, t, *J* = 6.0 Hz, C<u>H</u>$_2$OSi), 2.60 (2H, td, *J* = 6.0, 2.1 Hz, HCOC<u>H</u>$_2$), 0.88 (9H, s, OSiC(C<u>H</u>$_3$)$_3$), 0.07 (6H, s, OSi(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 202.2 , 57.6, 46.7, 26.0, 18.4, –5.3, –5.3.

2.5.3. (*E*)-6-(*tert*-Butyldimethylsilyloxy)-3-hexen-2-one **(Ei)**

The experimental procedure described in section 2.4 was followed starting from 3-*tert*-butyldimethylsilyloxypropanal (1.13 g, 6 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 90:10) to afford 1.16 g (85% yield) of (*E*)-6-(*tert*-butyldimethylsilyloxy)-3-hexen-2-one (**Ei**).



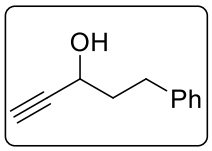
Ei

(*E*)-6-(*tert*-Butyldimethylsilyloxy)-3-hexen-2-one (Ei). Colourless oil. **R_f** (Hexanes/EtOAc 90:10) = 0.3; **IR** (ATR) ν 2954, 2928, 2856, 1700, 1677, 2521 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ6.82 (1H, dt, *J* = 16.1, 7.0 Hz, CH=C<u>H</u>CH$_2$), 6.12 (1H, dt, *J* = 16.1, 1.4 Hz, COC<u>H</u>), 3.75 (2H, t, *J* = 6.4 Hz, C<u>H</u>$_2$OSi), 2.44 (2H, dq, *J* = 6.4, 1.4 Hz, HCOC<u>H</u>$_2$), 2.25 (3H, s, CH_3CO), 0.88 (9H, s, OSiC(C<u>H</u>$_3$)$_3$), 0.06 (6H, s, OSi(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 198.1, 145.0, 132.6, 61.3, 35.7, 26.4, 25.7, 18.1, –5.5.

2.6. 5-Phenyl-1-pentyn-3-one[203]

2.6.1. 5-Phenyl-1-pentyn-3-ol

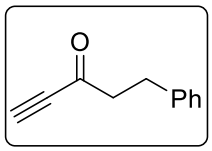
Hydrocinnamaldehyde (4.0 mL, 30.4 mmol) was added dropwise to a 0.5 M solution of ethynylmagnesium bromide in THF (72 mL, 35.6 mmol) at 0 °C under N_2 atmosphere. The reaction was quenched with NH_4Cl (10 mL) after 2 h. The reaction mixture was then extracted with CH_2Cl_2 (3 × 45 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to obtain yellow oil. The reaction crude was purified by column chromatography (hexanes/EtOAc 85:15) to afford 3.42 g (70% yield) of 5-phenyl-1-pentyn-3-ol.



5-Phenyl-1-pentyn-3-ol. Yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.6; **IR** (ATR) ν 3285, 3026, 2862, 1602, 1453, 1289, 1009 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.16 (5H, m, ArH), 4.36 (1H, td, *J* = 6.6, 2.1 Hz, CHOH), 2.80 (2H, t, *J* = 6.6 Hz, PhCH_2), 2.50 (1H, d, *J* = 2.1 Hz, CCH), 2.11–1.97 (2H, m, CH_2CHOH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 141.1, 128.5, 126.0, 84.6, 73.3, 61.6, 39.1, 31.2.

2.6.2. 5-Phenyl-1-pentyn-3-one

MnO_2 (6.572 g, 75.6 mmol) was added to a solution of 5-phenyl-1-pentyn-3-ol (667 mg, 4.2 mmol) in CH_2Cl_2 (20 mL) and the resultant mixture was stirred overnight at rt. The residue was then filtered through a plug of silica gel (CH_2Cl_2) to remove the remaining MnO_2 to afford 354 mg (54% yield) of 5-phenyl-1-pentyn-3-one.

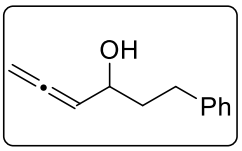


5-Phenyl-1-pentyn-3-one. Yellowish oil. $\mathbf{R_f}$ (CH_2Cl_2) = 0.6; **IR** (ATR) ν 3083, 3022, 2918, 2086, 1674, 1493, 1448, 1398, 1215, 1102 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.17 (5H, m, ArH), 3.23 (1H, s, CCH), 3.02–2.96 (2H, m, PhCH_2), 2.95–2.89 (2H, m, PhCH_2CH_2); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 186.2, 139.9, 128.6, 128.3, 126.4, 81.3, 78.8, 46.9, 29.6.

2.7. 1-Phenyl-4,5-hexadien-3-one

2.7.1. 1-Phenyl-4,5-hexadien-3-ol[204]

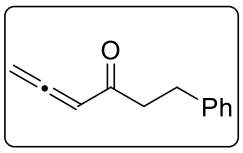
A mixture containing 5-phenyl-1-pentyn-3-ol (2.75 g, 17.2 mmol), formaldehyde (887 mg, 28.4 mmol), diisopropilamine (3.4 mL, 24.1 mmol) and CuI (1.69 g, 8.9 mmol) in 1,4-dioxane (35 mL) was set to reflux for 24 h. The reaction crude was first concentrated and then purified by column chromatography (hexanes/EtOAc 85:15) obtaining 717 mg (24% yield) of 1-phenyl-4,5-hexadien-3-ol.



1-Phenyl-4,5-hexadien-3-ol. Orange oil. R_f (Hexanes/EtOAc 80:20) = 0.6; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.16 (5H, m, ArH), 5.32–5.25 (1H, m, CHCCH$_2$), 4.88 (2H, dd, *J* = 6.6, 2.4 Hz, CHCCH$_2$), 4.25–4.14 (1H, m, CHOH), 2.83–2.65 (2H, m, PhCH$_2$), 1.95–1.84 (2H, m, PhCH$_2$CH$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 207.0, 141.8, 128.5, 128.4, 125.8, 94.7, 77.7, 68.9, 39.0, 31.7.

2.7.2. 1-Phenyl-4,5-hexadien-3-one[199]

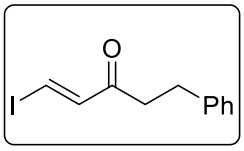
The experimental procedure described in section 2.2.2 was followed starting from 1-phenyl-4,5-hexadien-3-ol (564 mg, 3.2 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 80:20) to afford 202 mg (36% yield) of 1-phenyl-4,5-hexadien-3-one.



1-Phenyl-4,5-hexadien-3-one. Dark orange oil. R_f (Hexanes/EtOAc 80:20) = 0.4; **IR** (ATR) ν 3060, 3022, 2980, 2920, 1955, 1923, 1673, 1600, 1496, 1445, 1157 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.17 (5H, m, ArH), 5.79 (1H, t, *J* = 6.5 Hz, CHCCH$_2$), 5.20 (2H, d, *J* = 6.5 Hz, CCH$_2$), 2.94–2.90 (4H, m, PhCH$_2$CH$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 216.7, 199.6, 141.1, 128.4, 128.4, 126.1, 96.7, 79.5, 40.8, 30.4.

2.8. (*E*)-1-Iodo-5-phenyl-1-penten-3-one

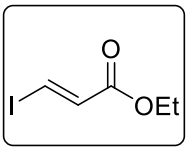
LiI (335 mg, 2.5 mmol) was added in one portion to a solution of 5-phenyl-1-pentyn-3-one (335 mg, 2.1 mmol) in acetic acid (2.0 mL) under N_2 atmosphere at rt. The reaction was stirred overnight at rt. H_2O (10 mL) was added and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with $NaHCO_3$(10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexanes/EtOAc 95:5) to afford 367 mg (61% yield) of (*E*)-1-iodo-5-phenyl-1-penten-3-one.



(*E*)-1-iodo-5-phenyl-1-penten-3-one. Orange oil. R_f (Hexanes/EtOAc 90:10) = 0.6; **IR** (ATR) ν 3056, 3025, 2923, 2883, 2847, 1674, 1564, 1495 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (1H, d, *J* = 15.0 Hz, CHI), 7.33–7.14 (6H, m, ArH, CH=CHI), 2.96–2.82 (4H, CH$_2$CH$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 202.3, 140.3, 137,8, 128.5, 128.2, 126.6, 95.4, 44.6, 33.1.

2.9. Ethyl (*E*)-3-iodoacrylate

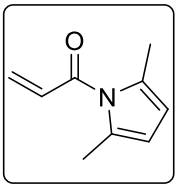
The experimental procedure described in section 2.8 was followed starting from ethyl propilate (700 mg, 7 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 90:10) to afford 681 mg (43% yield) of ethyl (*E)*-3-iodoacrylate.



Ethyl (*E*)-3-iodoacrylate. Orange oil. **R_f** (Hexanes/EtOAc 90:10) = 0.6; **IR** (ATR) ν 3039, 2955, 1728, 1638 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (1H, d, *J* = 14.9 Hz, ICH), 6.88 (1H, d, *J* = 14.9 Hz, CHCO), 4.20 (2H, q, *J* = 7.1 Hz, CH_2), 1.29 (3H, t, *J* = 7.1 Hz, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.6, 135.5, 96.3, 61.4, 15.8.

2.10. *N*-Acryloyl-2,5-dimethylpyrrole[205]

Acrylamide (5.0 g, 70 mmol), 2,5-hexanedione (1.8 mL, 15.3 mmol), *p*-toluenesulfonic acid (0.44 g, 2.3 mmol) and trimethyl orthoformate (3.4 mL, 30.6 mmol) were dissolved in toluene (200 mL) and heated to reflux for 24 h. The reaction mixture was diluted and washed with water (3 × 50 mL) and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography (hexanes/EtOAc 90:10) to afford 654 mg (29% yield) of *N*-acryloyl-2,5-dimethylpyrrole.

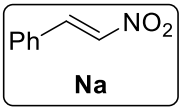


***N*-Acryloyl-2,5-dimethylpyrrole**. Yellow oil. **R_f** (Hexanes/EtOAc 90:10) = 0.7; **IR** (ATR) ν 2927, 1693, 1619, 1401, 1363, 1258, 976, 773 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.69 (1H, dd, *J* = 17.0 Hz, *J* = 10.3, CHCO), 6.48 (1H, dd, *J* = 17.0, 1.4 Hz, H_xH_yC=CH), 5.95 (1H, dd, *J* = 10.3 Hz, *J* = 1.4 Hz, H_xH_yC=CH), 5.85 (2H, s, $N(CH_3CCH)_2$), 2.34 (6H, s, $N(CH_3CCH)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 167.1, 132.2, 131.3, 130.1, 111.2, 15.7.

3. Preparation of nitroalkenes

3.1. (*E*)-β-Nitrostyrene (Na)[206]

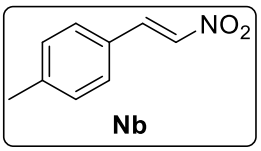
A solution of NaOH (3.15 g, 79 mmol) in H_2O (10 mL) was added dropwise to a solution of benzaldehyde (7.6 mL, 75 mmol) and nitromethane (4.58 g, 75 mmol) in methanol (10 mL) at 0 °C. After stirring for 30 min, 50 mL of ice water was poured into the solution. This solution was then poured into 8 M HCl (20 mL) to obtain a yellow solid, which was filtered, and washed with water. It was then purified by recrystallization in hot ethanol to afford 7.80 g (70% yield) of (*E*)-β-nitrostyrene (**Na**).



(*E*)-β-Nitrostyrene (Na). Yellow solid. **Mp** = 56–58 °C. **R_f** (Hexanes/EtOAc 90:10) = 0.4; **IR** (ATR) ν 3107, 3041, 2961, 1629, 1575, 1511, 1492, 1334, 1261 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (1H, d, *J* = 13.7 Hz, PhCH=CHNO$_2$), 7.59 (1H, d, *J* = 13.7 Hz, PhCH=CHNO$_2$), 7.57–7.43 (5H, m, ArH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 139.1, 137.1, 132.1, 130.1, 129.4, 129.1.

3.2. (*E*)-4-Methyl-β-nitrostyrene (Nb)

The experimental procedure described in section 3.1 was followed starting from 4-methylbenzaldehyde (2.4 mL, 20 mmol). The resulting crude was filtered through a plug of silica gel (CH_2Cl_2) to afford 3.10 g (96% yield) of *(E)*-4-methyl-β-nitrostyrene (**Nb**).

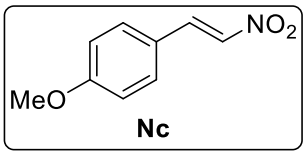


Nb

(*E*)-4-Methyl-β-nitrostyrene (Nb). Yellow solid. **Mp** = 102–104 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.5; **IR** (ATR) ν 3112, 3039, 2960, 1560, 1503, 1498, 1336 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (1H, d, *J* = 13.7 Hz, PhCH=C<u>H</u>NO_2), 7.57 (1H, d, *J* = 13.7 Hz, PhC<u>H</u>=CHNO_2), 7.45 (2H, d, *J* = 8.2 Hz,Ar<u>H</u>$_A$H$_B$), 7.26 (2H, d, *J* = 8.2 Hz, ArH$_A$<u>H</u>$_B$), 2.41 (3H, s, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 143.1, 139.2, 136.3, 130.1, 129.2, 127.3, 21.7.

3.3. (*E*)-4-Methoxy-β-nitrostyrene (Nc)

The experimental procedure described in section 3.1 was followed starting from 4-methoxybenzaldehyde (10.20 g, 75 mmol). The resulting crude was purified by recrystallization in hot ethanol to afford 4.20 g (31% yield) of *(E)*-4-methoxy-β-nitrostyrene (**Nc**).

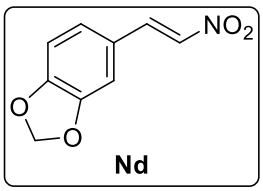


Nc

(*E*)-4-Methoxy-β-nitrostyrene (Nc). Yellow solid. **Mp** = 88–89 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.4; **IR** (ATR) ν 3101, 2959, 2933, 2905, 2839, 1597, 1490, 1597, 1490, 1419, 1303 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 13.6 Hz, ArC<u>H</u>=HNO_2), 7.52 (1H, d, *J* = 13.6 Hz, ArCH=C<u>H</u>NO_2), 7.51 (2H, d, *J* = 9.0 Hz, Ar<u>H</u>$_A$H$_B$), 6.98 (2H, d, *J* = 9.0 Hz, ArH$_A$<u>H</u>$_B$), 3.87 (3H, s, C<u>H</u>$_3$O); **^{13}C NMR** (100.6 MHz, CDCl3) δ 162.9, 139.0, 135.0, 131.2, 122.5, 115.0, 55.5.

3.4. (*E*)-3,4-Methylenedioxy-β-nitrostyrene (Nd)

The experimental procedure described in section 3.1 was followed starting from piperonal (3.00 g, 20 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 80:20) to afford 2.40 g (62% yield) of (*E*)-3,4-methylenedioxy-β-nitrostyrene (**Nd**).

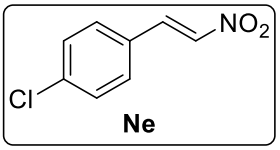


Nd

(*E*)-3,4-Methylenedioxy-β-nitrostyrene (Nd). Yellow solid. **Mp** = 112–114 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.5; **IR** (ATR) ν 3050, 2954, 1921, 2850, 1455, 1334 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 13.6 Hz, PhCH=C<u>H</u>NO_2), 7.47 (1H, d, *J* = 13.5 Hz, PhC<u>H</u>=CHNO_2), 7.08 (1H, dd, *J* = 8.0, 1.8 Hz, Ar<u>H</u>$_A$H$_B$H$_C$), 7.00 (1H, d, *J* = 1.8 Hz, ArH$_A$<u>H</u>$_B$H$_C$), 6.87 (1H, d, *J* = 8.0 Hz, ArH$_A$H$_B$<u>H</u>$_C$), 6.06 (2H, s, CH_2); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 151.4, 148.8, 139.1, 135.4, 126.6, 124.2, 109.1, 107.0, 102.1.

3.5. (*E*)-4-Chloro-β-nitrostyrene (Ne)

The experimental procedure described in section 3.1 was followed starting from 4-chlorobenzaldehyde (2.80 g, 20 mmol). The resulting crude was purified by recrystallization in hot ethanol to afford 1.80 g (49% yield) of *(E)*-4-chloro-β-nitrostyrene (**Ne**).

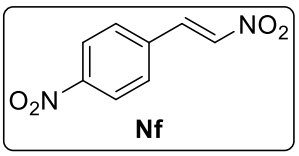


Ne

(*E*)-4-Chloro-β-nitrostyrene (Ne). Yellow solid. **Mp** = 114–116 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.6; **IR** (ATR) ν 3101, 3040, 2965, 2911, 2825, 1632, 1486, 1327 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (1H, d, *J* = 13.7 Hz, ArC<u>H</u>=CHNO$_2$), 7.56 (1H, d, *J* = 13.7 Hz, ArCH=C<u>H</u>NO$_2$), 7.51–7.42 (2H, m, Ar<u>H</u>), 6.98–6.94 (2H, m, Ar<u>H</u>); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 138.3, 137.7, 137.4, 130.3, 129.7, 128.3.

3.6. (*E*)-4-Nitro-β-nitrostyrene (Nf)

The experimental procedure described in section 3.1 was followed starting from 4-nitrobenzaldehyde (3.00 g, 20 mmol). The resulting crude was filtered through a plug of silica gel (CH_2Cl_2) to afford 2.00 g (52% yield) of *(E)*-4-nitro-β-nitrostyrene (**Nf**).



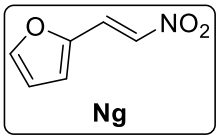
Nf

(*E*)-4-Nitro-β-nitrostyrene (Nf). Orange solid. **Mp** = 123–125 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.5; **IR** (ATR) ν 3108, 3050, 2940, 1520, 1498, 1350 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (2H, d,*J* = 8.9 Hz, Ar<u>H</u>$_A$H$_B$), 8.04 (1H, d, *J* = 13.8 Hz, PhC<u>H</u>=CHNO$_2$), 7.73 (2H, d, *J* = 8.8 Hz, ArH$_A$<u>H</u>$_B$), 7.64 (1H, d, *J* = 13.8 Hz, PhCH=C<u>H</u>NO$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.1, 138.6, 137.2, 137.1, 129.0, 123.8.

3.7. (*E*)-2-(2-Nitrovinyl)furan (Ng)[206]

KF (218 mg, 3.8mmol) was added to a solution of furfural (2.1 mL, 25 mmol) and $MeNO_2$ (2.7 mL, 50 mmol) in *i*-PrOH (15 mL) at 0 °C. The reaction was stirred for 24 h at rt. The suspension was filtered, and the mixture was concentrated in vacuo. The residue was diluted with Et_2O (20 mL) and washed with H_2O (10 mL), dried ($MgSO_4$), filtered, and concentrated to afford the intermediate nitroaldol.

Et_3N (8.7 mL, 63 mmol) was added dropwise to a solution of the crude nitroaldol and MsCl (2.9 mL, 37 mmol) in CH_2Cl_2 (75 mL) under N_2 atmosphere at 0 °C. The reaction was stirred overnight at rt. H_2O (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with sat. $NaHCO_3$(10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The solid residue was purified by column chromatography (hexanes/EtOAc 80:20) to afford 1.60 g (53% yield) of *(E)*-2-(2-nitrovinyl)furan (**Ng**).

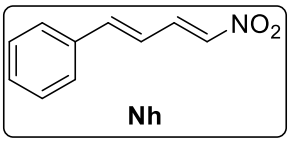


Ng

(*E*)-2-(2-nitrovinyl)furan (Ng). Brown solid. **Mp** = 75–76 °C; **R_f** (Hexanes/EtOAc 80:20) = 0.5; **IR** (ATR) ν 3115, 3030, 2970, 1629, 1520, 1345, 1165 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (1H, d, *J* = 13.2 Hz, PhCH=C<u>H</u>NO_2), 7.59 (1H, m, Ar<u>H</u>$_A$H$_B$H$_C$), 7.53 (1H, d, *J* = 13.2 Hz, PhC<u>H</u>=CHNO_2), 6.89 (1H, d, *J* = 3.5 Hz, ArH$_A$<u>H</u>$_B$H$_C$), 6.58 (1H, dd, *J* = 3.5, 1.8 Hz, ArH$_A$H$_B$<u>H</u>$_C$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 146.8, 146.6, 134.9, 125.4, 120.0, 113.3.

3.8. (1*E*,3*E*)-1-Nitro-4-phenyl-1,3-butadiene (Nh)

A solution of benzaldehyde cinnamaldehyde (2.6 mL, 20 mmol) in $MeNO_2$ (7 mL) was added to a suspension of ammonium acetate (3.8 g, 50 mmol) in $MeNO_2$ (7 mL). The mixture was heated for 5 h at 60 °C. The solvent was removed in vacuo and the residue was extracted with Et_2O (3 × 20 mL), washed with H_2O (20 mL), dried ($MgSO_4$) and concentrated. The resulting nitroaldol crude underwent elimination following experimental procedure described in section 3.7. The resulting crude was purified by column chromatography (hexanes/EtOAc 80:20. hexanes/$CH_2Cl_2$60:40) obtaining 175mg (5% yield) of (1*E*,3*E*)-1-nitro-4-phenyl-1,3-butadiene (**Nh**).

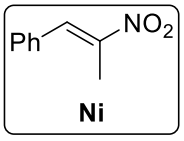


Nh

(1*E*,3*E*)-1-Nitro-4-phenyl-1,3-butadiene (Nh). Brownish oil. **R_f** (Hexanes/EtOAc 80:20) = 0.50; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81–7.75 (1H, m, C<u>H</u>=CHNO_2), 7.53–7.5 (2H, m, Ar<u>H</u>), 7.43–7.38 (3H, m, Ar<u>H</u>), 7.24 (1H, d, *J* = 12.9 Hz, CH=C<u>H</u>NO_2), 7.16 (1H, d, *J* = 15.5 Hz, PhC<u>H</u>CH), 6.87 (1H, dd, *J* = 15.5, 11.6, PhCHC<u>H</u>); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ138.4, 135.6, 135.2, 134.2, 128.6, 128.5, 127.9, 125.2.

3.9. (*E*)-β-Methyl-β-nitrostyrene (Ni)[207]

A solution of benzaldehyde (2.5 mL, 25 mmol) in $EtNO_2$ (12.5 mL, 174 mmol) was added to a suspension of ammonium acetate (4.8 g, 62.5 mmol) in $EtNO_2$ (12.5 mL, 174 mmol). The mixture was heated for 5 h at 60 °C. The solvent was removed in vacuo and the residue was extracted with Et_2O (3 × 20 mL), washed with H_2O (20 mL), dried ($MgSO_4$) and concentrated. The residue was then purified by column chromatography (hexanes/EtOAc 90:10) to afford 1.10 g (6.7 mmol, 27% yield) of (*E*)-β-methyl-β-nitrostyrene (**Ni**).

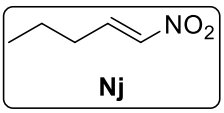


Ni

(*E*)-β-Methyl-β-nitrostyrene (Ni). Pale yellow solid. **Mp** = 63–64 °C; **R_f** (Hexanes/EtOAc 90:10) = 0.5; **IR** (ATR) ν3083, 3052, 2968, 2923, 2847, 2803, 1646, 1512, 1312 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (1H, br s, PhC<u>H</u>), 7.49–7.39 (5H, m, Ar<u>H</u>), 2.46 (3H, d, *J* = 1.1 Hz, C(C<u>H</u>$_3$)NO_2); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 147.7, 133.5, 132.4, 129.9, 129.8, 128.9, 14.0.

3.10. (*E*)-1-Nitro-1-pentene (Nj)

The experimental procedure described in section 3.7 was followed starting from butyraldehyde (2.3 mL, 25 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 80:20) to afford 862 mg (36% yield) of (*E*)-1-nitro-1-pentene (**Nj**).

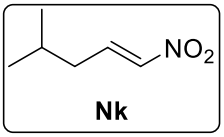


Nj

(*E*)-1-Nitro-1-pentene (Nj). Yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (1H, dt, *J* = 13.5, 7.4 Hz, C<u>H</u>=CHNO_2), 6.99 (1H, dt, *J* = 13.5, 1.5 Hz, CH=C<u>H</u>NO_2), 2.26 (2H, qd, *J* = 7.4, 1.5 Hz, C<u>H</u>$_2$CH), 1.61–1.52 (2H, m, C<u>H</u>$_2$$CH_3$), 0.99 (6H, d, *J* = 7.4 Hz, C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 142.5, 139.6, 30.3, 21.0, 13.5.

3.11. (*E*)-4-Methyl-1-nitro-1-pentene (Nk)

The experimental procedure described in section 3.7 was followed starting from isovaleraldehyde (2.7 mL, 25 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 80:20) to afford 865 mg (40% yield) of (*E*)-4-methyl-1-nitro-1-pentene (**Nk**).

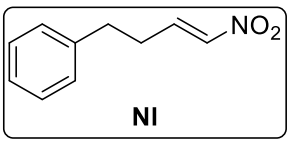


Nk

(*E*)-4-Methyl-1-nitro-1-pentene (Nk). Yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (1H, dt, *J* = 13.3, 8.0 Hz, C<u>H</u>=CHNO_2), 6.98 (1H, dt, *J* = 13.3, 1.4 Hz, CH=C<u>H</u>NO_2), 2.15 (2H, ddd, *J* = 8.0, 6.8, 1.4 HZ, C<u>H</u>$_2$), 1.91–1.78 (1H, m, C<u>H</u>CH_2), 0.97 (6H, d, *J* = 6.7 Hz, C(CH_3)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 141.5, 140.1, 37.2, 27.8, 22.2.

3.12. (*E*)-1-Nitro-4-phenyl-1-butene (Nl)

The experimental procedure described in section 3.7 was followed starting from hidrocinnamaldehyde (3.3 mL, 25 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 85:15) to afford 3.405 g (76% yield) of (*E*)-1-nitro-4-phenyl-1-butene (**Nl**).

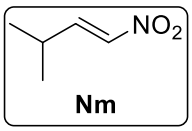


Nl

(*E*)-1-Nitro-4-phenyl-1-butene (Nl). Yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.7; **IR** (ATR) ν 3101, 3057, 3025, 2919, 2856, 1642, 1517, 1348 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.15 (6H, m, Ar<u>H</u>, C<u>H</u>=CHNO_2), 6.96 (1H, dt, *J* = 13.4, 1.5 Hz, CH=C<u>H</u>NO_2), 2.84 (2H, t, *J* = 7.3 Hz, PhC<u>H</u>$_2$), 2.60 (2H, dtd, *J* = 7.4, 7.3, 1.6 Hz, PhCHC<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 141.4, 140.0, 139.6, 128.7, 128.3, 126.6, 33.9, 30.1.

3.13. (*E*)-3-Methyl-1-nitro-1-butene (Nm)

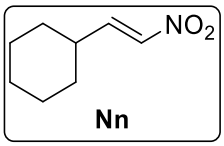
The experimental procedure described in section 3.7 was followed starting from isobutyraldehyde (2.3 mL, 25 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 90:10) to afford 1.88 g (65% yield) of (*E*)-3-methyl-1-nitro-1-butene (**Nm**).



(*E*)-3-Methyl-1-nitro-1-butene (Nm). Yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.6; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (1H, dd, *J* = 13.5, 7.0 Hz, C<u>H</u>=CHNO$_2$), 6.94 (1H, dt, *J* = 13.5, 1.4 Hz, CH=C<u>H</u>NO$_2$), 2.65–2.53 (1H, m, C<u>H</u>CH$_3$), 1.15 (6H, d, *J* = 6.8 Hz, C(C<u>H</u>$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 148.4, 138.1, 28.3, 20.9.

3.14. (*E*)-1-Nitro-2-cyclohexylethylene (Nn)

The experimental procedure described in section 3.7 was followed starting from cyclohexanecarbaldehyde (1.70 g, 15 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 95:5) obtaining 464 mg (20% yield) of (*E*)-1-nitro-2-cyclohexylethylene (**Nn**).

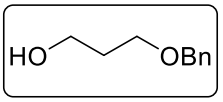


(*E*)-1-Nitro-2-cyclohexylethylene (Nn). Yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 95:5) = 0.5; **IR** (ATR) ν 3110, 2923, 2852, 1642, 1512, 1343 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (1H, dd, *J* = 13.5, 7.2 Hz, C<u>H</u>=CHNO$_2$), 6.93 (1H, dd, *J* = 13.5, 1.4 Hz, CH=C<u>H</u>NO$_2$), 2.32–2.20 (1H, m, (CH$_2$)$_5$C<u>H</u>), 1.86–1.67 (5H, m, (C<u>H</u>$_2$)$_5$), 1.41–1.13 (5H, m, (C<u>H</u>$_2$)$_5$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 147.3, 138.3, 37.5, 31.4, 25.6, 25.4.

3.15. (*E*)-4-Benzyloxy-1-nitro-1-butene (No)

3.15.1. <u>3-Benzyloxypropanol</u>[201,202]

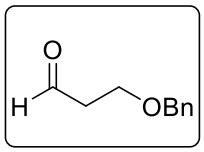
1.3-Propanediol was added dropwise (2.2 mL, 30 mmol) to a solution of NaH 60% (1.30 g, 33 mmol) in DMF (30 mL) under N_2 atmosphere at rt. The mixture was stirred for 1 h, then benzyl bromide (3.9 mL, 33 mmol) was added. The resulting mixture was stirred overnight, quenched with H_2O (10 mL), and concentrated in vacuo. The residue was extracted with Et_2O (3 × 30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexanes/EtOAc 60:40) to afford 2.40 g (49% yield) of 3-benzyloxypropanol.



3-Benzyloxypropanol. Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 60:40) = 0.2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.26 (5H, m, Ar<u>H</u>), 4.53 (2H, s, PhC<u>H</u>$_2$), 3.79 (2H, t, *J* = 5.8 Hz, C<u>H</u>$_2$O), 3.67 (2H, t, *J* = 5.8 Hz, C<u>H</u>$_2$O), 1.87 (2H, p, *J* = 5.8 Hz, CH$_2$C<u>H</u>$_2$CH$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 137.3, 128.4, 126.4, 71.0, 68.8, 61.2, 31.6.

3.15.2. 3-Benzyloxypropanal

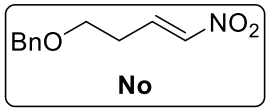
The experimental procedure described in 2.5.2 was followed starting from 3-benzyloxypropanol (1.50 g, 9 mmol). The resulting crude was filtered through a plug of silica gel (hexanes/EtOAc 80:20) to afford 1.20 g (99%) of 3-benzyloxypropanal.



3-Benzyloxy-propanal. Pale yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.3; **IR** (ATR) ν 3089, 3066, 3033, 2865, 2734, 1725, 1454, 1097 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.8 Hz, C<u>H</u>O), 7.35–7.31 (5H, m, Ar<u>H</u>), 4.53 (2H, s, PhC<u>H</u>$_2$), 3.81 (2H, t, *J* = 6.0 Hz, BnOC<u>H</u>$_2$), 2.70 (2H, td, *J* = 6.0, 1.8 Hz, HCOC<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 201.0, 137.8, 128.4, 127.7, 127.6, 73.2, 63.8, 43.9.

3.15.3. (*E*)-4-Benzyloxy-1-nitro-1-butene (**No**)

The experimental procedure described in section 3.7 was followed starting from 3-benzyloxypropanal (0.7 g, 4.3 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 80:20) to afford 594 mg (67% yield) of (*E*)-4-benzyloxy-1-nitro-1-butene (**No**).



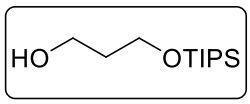
No

(*E*)-4-Benzyloxy-1-nitro-1-butene (No). Yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.5; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.37–7.25 (6H, m, Ar<u>H</u> and C<u>H</u>=CHNO$_2$), 7.03 (1H, dt, *J* = 13.5, 1.6 Hz, C<u>H</u>=NO$_2$), 4.52 (2H, s, PhC<u>H</u>$_2$O), 3.61 (2H, t, *J* = 6.0 Hz, BnOC<u>H</u>$_2$), 2.53 (2H, dtd, *J* = 7.5, 6.0, 1.6 Hz, C<u>H</u>$_2$CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 140.7, 139.6, 137.7, 128.5, 127.9, 127.7, 73.2, 67.3, 28.9.

3.16. (*E*)-1-Nitro-4-triisopropylsilyloxy-1-butene (Np)

3.16.1. 3-Triisopropylsilyloxy-1-propanol[201,202]

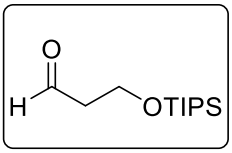
1.3-Propanediol was added dropwise (1.5 mL, 20 mmol) to a solution of NaH 60% (1.20 g, 30 mmol) in THF (24 mL) under N_2 atmosphere at 0 °C. The mixture was stirred for 1 h at rt, then TIPSOTf (2.7 mL, 10 mmol) was added dropwise and the reaction stirred for 18 h and quenched by slow addition of water (20 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL). The combined oirganic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography (hexanes/EtOAc 80:20) to afford 464 mg (20% yield) of 3-triisopropylsilyloxy-1-propanol.



3-Triisopropylsilyloxy-1-propanol. Yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.2; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.94 (2H, t, *J* = 5.5 Hz, C<u>H</u>$_2$OSi), 3.82 (2H, t, *J* = 5.3 Hz, C<u>H</u>$_2$OH), 2.74 (1H, bs, CH$_2$O<u>H</u>), 1.84–1.76 (2H, m, C<u>H</u>$_2$CH$_2$OSi), 1.10–1.04 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); **^{13}C NMR** (100.6 Hz, $CDCl_3$) δ 63.8, 62.9, 34.3, 18.1, 11.9.

3.16.2. 3-Triisopropylsilyloxypropanal

The experimental procedure described in section 2.5.2 was followed starting from 3-triisopropylsilyloxypropanol (250 mg, 1.1 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 4:1) to afford 242 mg (97% yield) of 3-triisopropylsilyloxypropanal.

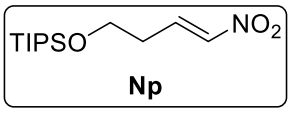


3-Triisopropylsilyloxypropanal. Colorless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.84 (1H, t, *J* = 2.2 Hz, C<u>H</u>O), 4.08 (2H, t, *J* = 6.1 Hz, C<u>H</u>$_2$OSi), 2.62 (2H, td, *J* = 6.1, 2.2 Hz, C<u>H</u>$_2$CH$_2$OSi), 1.10–1.00 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 202.2, 57.9, 46.7, 17.9, 11.9.

3.16.3. (*E*)-1-Nitro-4-triisopropylsilyloxy-1-butene (**Np**)

A solution of 3-triisopropylsilyloxypropanal (550 mg, 2.4 mmol), $MeNO_2$ (190 µL, 3.6 mmol) and Et_3N (66 µL, 0.47 mmol) was stirred for 24 h under a N_2 atmosphere at rt. The mixture was acidified with 2 M HCl (1 mL) and then diluted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (2 × 20 mL), brine (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated to afford the intermediate nitroaldol.

Et_3N (0.7 mL, 5.0 mmol) was added dropwise to a solution of the crude nitroaldol and MsCl (210 µL, 3.2 mmol) in CH_2Cl_2 (8 mL) under N_2 atmosphere at 0 °C. The reaction was stirred overnight at rt. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL). The organic layer was washed with sat. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography (hexanes/EtOAc 90:10) to afford 291 mg (55% yield) of (*E*)-1-nitro-4-triisopropylsilyloxy-1-butene (**Np**).



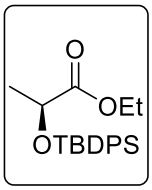
(*E*)-1-Nitro-4-triisopropylsilyloxy-1-butene (Np). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.7; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (1H, dt, *J* = 13.5, 7.4 Hz, C<u>H</u>=CHNO$_2$), 7.07 (1H, dt, *J* = 13.5, 1.5 Hz, C<u>H</u>NO$_2$), 3.87 (2H, t, *J* = 6.0 Hz, C<u>H</u>$_2$OSi), 2.49 (2H, dtd, *J* = 7.4, 6.0 Hz, *J* = 1.5 Hz, C<u>H</u>$_2$CH$_2$OSi), 1.10–1.02 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 140.6, 139.8, 61.0, 32.0, 17.9, 11.9.

3.17. (*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-1-nitro-1-butene (Nq)

3.17.1. Ethyl (*S*)-2-*tert*-butyldiphenylsilyloxypropanoate[34]

TBDPSCl (5.2 mL, 18.6 mmol) was added dropwise to a solution of ethyl (*S*)-lactate (2.0 mL, 16.9 mmol) and imidazole (2.6 g, 37.2 mmol) in CH_2Cl_2 (30 mL) under a N_2 atmosphere at 0 °C. The resulting mixture was stirred at 0 °C for 15 min and at rt for 24 h. It was diluted with sat. $NaHCO_3$ (15 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2

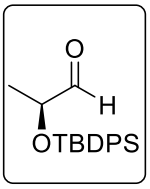
(3 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography (95:5 hexane/EtOAc) to afford 5.40 g (90% yield) of ethyl (*S*)-2-*tert*-butyldiphenylsilyloxypropanoate.



Ethyl (*S*)-2-*tert*-butyldiphenylsilyloxypropanoate. Colourless oil. $\mathbf{R_f}$ (hexane/EtOAc 95:5) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = –32.2 *(c* 1.1, $CHCl_3$); **IR** (film) ν 2930, 2856, 1752, 1470, 1426, 1133, 1110 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76–7.59 (4H, m, ArH), 7.47–7.31 (6H, m, ArH), 4.26 (1H, q, *J* = 6.9 Hz, CH_3CHOSi), 4.02 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 1.37 (3H, d, *J* = 6.9 Hz, CH_3CHOSi), 1.15 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.09 (9H, s, $(CH_3)_3C$); **^{13}C NMR** (75.4 MHz, $CDCl_3$) δ 173.7, 135.9, 135.7, 133.6, 133.3, 129.7, 129.6, 127.6, 127.5, 69.0, 60.5, 26.8, 21.2, 19.2, 14.0.

3.17.2. (*S*)-2-*tert*-Butyldiphenylsilyloxypropanal[34]

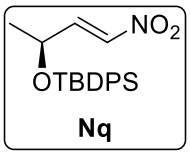
A 1 M solution of DIBALH in toluene (11 mL, 11 mmol) was added dropwise to a solution of ethyl (*S*)-2-*tert*-butyldiphenylsilyloxypropanoate (1.78 g, 5 mmol) in hexane (42 mL) under a N_2 atmosphere at –90 °C. The resulting mixture was stirred at –90 °C for 1 h, quenched by a slow addition of MeOH (3.2 mL), then treated with 1 M sodium potassium tartrate (16 mL) and vigorously stirred at rt for 1.5 h. The mixture was partitioned with EtOAc (40 mL) and H_2O (15 mL), and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography (hexane/EtOAc 95:5) to afford 1.56 g (99% yield) of (*S*)-2-*tert*-butyldiphenylsilyloxypropanal.



(*S*)-2-*tert*-Butyldiphenylsilyloxypropanal. Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 95:5) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = +10.7 *(c* 1.6, EtOH); **IR** (film) ν 2870, 1740, 1600, 1115 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.65 (1H, d, *J* = 1.2 Hz, CHO), 7.80–7.60 (4H, m, ArH), 7.50–7.30 (6H, m, ArH), 4.09 (1H, qd, *J* = 6.9, 1.2 Hz, CHOSi), 1.22 (3H, d, *J* = 6.9 Hz, CH_3CH), 1.11 (9H, s, $(CH_3)_3C$); **^{13}C NMR** (75.4 MHz, $CDCl_3$) δ 203.7, 135.7, 135.7, 133.2, 132.9, 130.0, 129.9, 127.8, 127.7, 74.4, 26.8, 19.2, 18.4.

3.17.3. (*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-1-nitro-1-butene (**Nq**)

The experimental procedure described in section 3.16.3 was followed starting from (*S*)-2-*tert*-butyldiphenylsilyloxypropanal (1.56 g, 5 mmol). The resulting crude was purified by column chromatography (hexanes/EtOAc 95:5) to afford 1.275 g (70% yield) of (*S*,*E*)-3-(*tert*-butyldimethylsilyloxy)-1-nitro-1-butene (**Nq**).



(*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-1-nitro-1-butene (Nq). Colourless oil. $\mathbf{R_f}$ (hexane/EtOAc 95:5) = 0.5; $\mathbf{[\alpha]^{20}_D}$ = +10.7 *(c* 1.6, EtOH); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68–7.61 (4H, m, ArH), 7.48–7.35 (6H, m, ArH), 7.16 (1H, dd, *J* = 13.1, 3.9 Hz, $CH{=}CHNO_2$), 7.09 (1H, dd, *J* = 13.1, 1.4 Hz, $CHNO_2$), 4.57 (1H,

qdd, *J* = 6.6, 3.9, 1.4 Hz, C<u>H</u>OSi), 1.21 (3H, d, *J* = 6.6 Hz, C<u>H</u>$_3$CH), 1.09 (9H, s, (C<u>H</u>$_3$)$_3$C); **^{13}C NMR** (75.4 MHz, $CDCl_3$) δ 145.3, 139.0, 135.9, 135.8, 133.3, 132.8, 130.3, 130.2, 128.0, 127.9, 66.6, 27.0, 23.2, 19.3.

CHAPTER 1

Michael additions of α-benzyloxy ethyl ketones

EXPERIMENTAL SECTION FOR CHAPTER 1
TABLE OF CONTENTS

1. Michael additions to vinyl ketones

1.1. Preliminary studies

1.1.1. Enolization with *n*-Bu_2BOTf[208]

A 1 M solution of *n*-Bu_2BOTf in CH_2Cl_2 (1.2 mL, 1.2 mmol) and *i*-Pr_2NEt (244 µL, 1.4 mmol) were added to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) under N_2 atmosphere at –78 °C. The resulting yellowish solution was stirred at 0 °C for 2.5 h and cooled to –78 °C. Then, methyl vinyl ketone (98 µL, 1.2 mmol) was added. The resulting mixture was stirred at –78 °C for 1 h and at 0 °C for further 16 h.

The reaction was quenched by the addition of pH 7 phosphate buffer solution (5 mL) at rt with vigorous stirring and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The solvent was removed, and the product was dissolved in MeOH (3 mL) and 30% H_2O_2 (1mL) at 0 °C and stirred for 2 h. H_2O (10 mL) was added and the methanol was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^1H NMR, which showed that it was essentially starting materials.

1.1.2. Enolization with LDA[208]

A 1.6 M solution of *n*-BuLi in hexanes (344 µL, 0.55 mmol) was added dropwise to a solution of *i*-Pr_2NH (78 µL, 0.55 mmol) in THF (1 mL) under N_2 atmosphere at –78 °C. After 10 min, a solution of ketone **1** (96 mg, 0.5 mmol) in THF (0.5 mL) was added via cannula (2 × 0.5 mL) and the resulting mixture was stirred at –78 °C for 2.5 h. TMEDA (135 µL, 0.9 mmol) was added followed 2 min later by methyl vinyl ketone (49 µL, 0.6 mmol) and stirred at –78 °C for 2 h.

The reaction was quenched by the addition of sat. $NaHCO_3$ (2 mL) at rt with vigorous stirring. The mixture was partitioned in Et_2O (50 mL) and water (30 mL), and the organic layer was washed with 1 M HCl (10 mL), sat. $NaHCO_3$ (10 mL), and brine (10 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^1H NMR, which showed that it was essentially starting materials.

1.1.3. Enolization with $TiCl_4$

Neat $TiCl_4$ (120 µL, 1.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, methyl vinyl ketone (98 µL, 1.2 mmol) was added, and the resultant mixture was stirred at –78 °C for 2 h.

The reaction was quenched by the addition of sat. NH_4Cl (5 mL) at rt with vigorous stirring. The mixture was partitioned in Et_2O (50 mL) and water (30 mL), and the organic layer was washed with sat. $NaHCO_3$ (30 mL), and brine (30 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 27 and spectroscopic data is shown in section 1.3.

1.1.4. Enolization with 2 equivalents of $TiCl_4$

Neat $TiCl_4$ (232 µL, 2.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, methyl vinyl ketone (98 µL, 1.2 mmol) was added, and the resultant mixture was stirred at –78 °C for 2 h and 5 h.

The reaction was quenched and treated as in section 1.1.3. The residue was analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 27 and spectroscopic data is shown in section 1.3.

1.1.5. Enolization with $TiCl_4$ and $BF_3{\cdot}OEt_2$

Neat $TiCl_4$ (120 µL, 1.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, $BF_3{\cdot}OEt_2$ (1,4 mL, 1.1 mmol) was added, followed 5 min later by methyl vinyl ketone (98 µL, 1.2 mmol), and the resultant mixture was stirred at –78 °C for 2 h.

The reaction was quenched and treated as in section 1.1.3. The residue was analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 27 and spectroscopic data is shown in section 1.3.

1.1.6. Enolization with $TiCl_4$ and $MgBr_2{\cdot}OEt_2$

Neat $TiCl_4$ (120 µL, 1.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, $MgBr_2{\cdot}OEt_2$ (284 mg, 1.1 mmol) was added, followed 5 min later by methyl vinyl ketone (98 µL, 1.2 mmol), and the resultant mixture was stirred at –78 °C for 2 h.

The reaction was quenched and treated as in section 1.1.3. The residue was analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 27 and spectroscopic data is shown in section 1.3.

1.1.7. Enolization with $TiCl_4$ and Et_2AlCl

Neat $TiCl_4$ (120 µL, 1.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, a 1 M solution of Et_2AlCl in CH_2Cl_2 (1.1 mL, 1.1 mmol) was added, followed 5 min later by methyl vinyl ketone (98 µL, 1.2 mmol), and the resultant mixture was stirred at –78 °C for 2 h.

The reaction was quenched and treated as in section 1.1.3. The residue was analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 27 and spectroscopic data is shown in section 1.3.

1.1.8. Enolization with $TiCl_4$ and $Ti(i\text{-}PrO)_4$

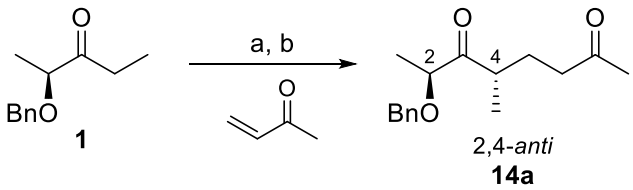
Neat $TiCl_4$ (120 µL, 1.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, neat $Ti(i\text{-}PrO)_4$ (319 µL, 1.1 mmol) was added, followed 5 min later by methyl vinyl ketone (98 µL, 1.2 mmol), and the resultant mixture was stirred at –78 °C for 2 h.

The reaction was quenched and treated as in section 1.1.3. The residue was analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 27 and spectroscopic data is shown in section 1.3.

1.1.9. Enolization with $TiCl_4$ and $SnCl_4$

Neat $TiCl_4$ (120 µL, 1.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, a 1 M solution of $SnCl_4$ in CH_2Cl_2 (1.1 mL, 1.1 mmol) was added, followed 5 min later by methyl vinyl ketone (98 µL, 1.2 mmol), and the resultant mixture was stirred at –78 °C for 2 h.

The reaction was quenched and treated as in section 1.1.3. The residue was analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 27 and spectroscopic data is shown in section 1.3.



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq LA, –78 °C, 10 min; b) 1.2 eq CH_2=$CHCOCH_3$, –78 °C, 2 h.

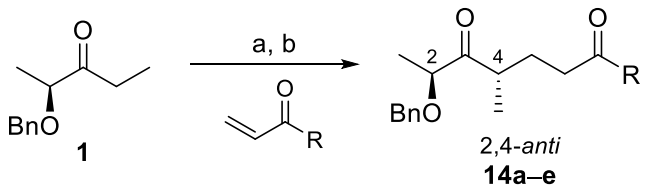
Entry	LA	dr[a]	Yield 14a (%)[b]
1	-	≥ 97:3	23
2	$BF_3{\cdot}OEt_2$	-	-
3	$MgBr_2{\cdot}OEt_2$	≥ 97:3	29
4	Et_2AlCl	≥ 97:3	26
5	$Ti(i\text{-}PrO)_4$	≥ 97:3	13
6	$TiCl_4$	≥ 97:3	62
7	$SnCl_4$	≥ 97:3	60
8[c]	$TiCl_4$	≥ 97:3	80

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Reaction performed for 5 hours.

Table 27

1.2. Michael addition to vinyl ketones. General procedure

The experimental procedure described in section 1.1.4 was followed starting from ketone **1** (192 mg, 1.0 mmol) and the corresponding enone (1.2 mmol) for a selected time. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 28 and spectroscopic data is shown in section 1.3.



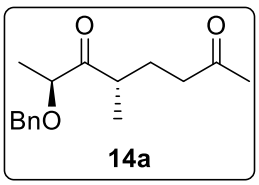
a) 2.1 eq $TiCl_4$, 1.1 *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq CH_2=CHCOR, –78 °C, t.

Entry	Enone	R	Time (h)	dr[a]	Yield[b] (%)
1	Ea	Me	2	≥97:3	64
2	Ea	Me	5	≥97:3	80
3	Eb	Et	2	≥97:3	62
4	Eb	Et	5	≥97:3	79
5	Ec	$(CH_2)_2Ph$	2	≥97:3	62
6	Ec	$(CH_2)_2Ph$	5	≥97:3	75
7	Ed	C_6H_{11}	2	≥97:3	65
8	Ed	C_6H_{11}	5	≥97:3	73
9	Ee	(*S*)-CH(OTBS)Bn	2	≥97:3	78

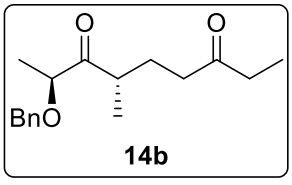
[a] Determined by 1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.

Table 28

1.3. Spectroscopic data of Michael adducts derived from ketone 1 and vinyl ketones

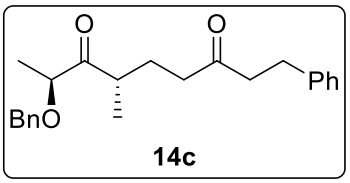


(5*S*,7*S*)-7-Benzyloxy-5-methyl-2,6-octanedione (**14a**) was prepared according to the general procedure described in section 1.2 from ketone **1** (192 mg, 1.0 mmol) and methyl vinyl ketone (97µL, 1.2 mmol) at –78 °C for 5 h. Purification of the crude product by column chromatography (hexanes/EtOAc 85:15) afforded **14a** (210 mg, 0.80 mmol, 80% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = –12.2 *(c* 1.6, $CHCl_3$); **IR** (ATR) ν 2974, 2933, 2874, 1713, 1455, 1367, 1165, 1110, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.26 (5H, m, Ar<u>H</u>), 4.57 (1H, d, *J* = 11.7 Hz, PhC<u>H</u>$_x$H$_y$), 4.53 (1H, d, *J* = 11.7 Hz, PhCH$_x$<u>H</u>$_y$), 4.04 (1H,q, *J* = 6.8 Hz, C<u>H</u>OBn), 3.05–2.95 (1H, m, COC<u>H</u>CH$_3$), 2.44–2.30 (2H, m, C<u>H</u>$_2$CO), 2.09 (3H, s, C<u>H</u>$_3$CO), 1.95–1.85 (1H, m, CH$_3$CHC<u>H</u>$_x$H$_y$), 1.67–1.57 (1H, m, CH$_3$CHCH$_x$<u>H</u>$_y$), 1.35 (3H,d, *J* = 6.8 Hz, C<u>H</u>$_3$CHOBn), 1.07 (3H,d, *J* = 6.9 Hz, COCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.8 (C), 208.0 (C), 137.6 (C), 128.4 (2 × CH), 127.8 (C), 127.7 (2 × CH), 79.3 (CH), 71.7 (CH_2), 40.8 (CH_2), 40.0 (CH), 29.8 (CH_3), 26.6 (CH_2), 16.6 (CH_3), 16.4 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{16}H_{26}NO_3$ $[M+NH_4]^+$: 280.1907, found: 280.1899.



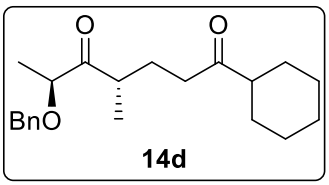
(2*S*,4*S*)-2-Benzyloxy-4-methyl-3,7-nonanedione (**14b**) was prepared according to the general procedure described in section 1.2 from ketone **1** (192 mg, 1.0 mmol) and ethyl vinyl ketone (119 µL, 1.2 mmol) at –78 °C for 5 h. Purification of the crude product by column

chromatography (hexanes/EtOAc 85:15) afforded **14b** (219 mg, 0.79 mmol, 79% yield) as a colourless oil. Scaled up to 3 mmol and 77% yield. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = –10.2 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 2974, 2935, 1709, 1453, 1412, 1370, 1108 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.26 (5H, m, ArH), 4.57 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 4.53 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 4.05 (1H,q, *J* = 6.8 Hz, CHOBn), 3.04–2.95 (1H, m, $COCHCH_3$), 2.42–2.28 (4H, m, CH_2COCH_2), 1.95–1.87 (1H, m, $CH_3CHCH_xH_y$), 1.67–1.60 (1H, m, $CH_3CHCH_xH_y$), 1.35 (3H,d, *J* = 6.8 Hz, CH_3CHOBn), 1.07 (3H,d, *J* = 6.9 Hz, $COCHCH_3$), 1.02 (3H, t, *J* = 7.3 Hz, CH_3CH_2CO); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.8 (C), 210.7 (C), 137.6 (C), 128.4 (2 × CH), 127.8 (CH), 127.7 (2 × CH), 79.3 (CH), 71.6 (CH_2), 40.1 (CH_2), 39.4 (CH), 35.8 (CH_2), 26.7 (CH_2), 16.6 (CH_3), 16.4 (CH_3), 7.7 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{17}H_{28}NO_3$ $[M+NH_4]^+$: 294.2064, found: 294.2058.



14c

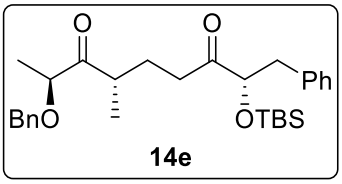
(2*S*,4*S*)-2-Benzyloxy-4-methyl-9-phenyl-3,7-nonanedione (**14c**) was prepared according to the general procedure described in section 1.2 from ketone **1** (190 mg, 1.0 mmol) and 5-phenyl-1-penten-3-one (192 mg, 1.2 mmol) at –78 °C for 5 h. Purification of the crude product by column chromatography (hexanes/EtOAc 85:15) afforded **14c** (264 mg, 0.75 mmol, 75% yield) as a pale-yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = –11.3 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2931, 1709, 1602, 1495, 1452, 1408, 1098 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.14 (5H, m, ArH), 4.55 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.51 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.02 (1H,q, *J* = 6.8 Hz, CHOBn), 2.99–2.92 (1H, m, $COCHCH_3$), 2.88–2.85 (2H, t, *J* = 7.6 Hz, $PhCH_2CH_2$), 2.74–2.61 (2H, m, $PhCH_2CH_2$), 2.40–2.26 (2H, m, CH_2CO), 1.94–1.84 (1H, m, $CH_3CHCH_xH_y$), 1.65–1.57 (1H, m, $CH_3CHCH_xH_y$), 1.33 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 1.04 (3H,d, *J* = 6.9 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.8 (C), 209.2 (C), 140.9 (C), 137.6 (C), 128.4 (4 × CH), 128.2 (2 × CH), 127.8 (CH), 127.7 (2 × CH), 126.0 (CH), 79.3 (CH), 71.6 (CH_2), 44.1 (CH_2), 40.1 (CH), 29.7 (CH_2), 26.6 (CH_2), 16.6 (CH_3), 16.4 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{23}H_{28}O_3Na$ $[M+Na]^+$: 175.1931, found: 375.1930.



14d

(2*S*,4*S*)-2-Benzyloxy-7-cyclohexyl-4-methyl-3,7-heptanedione (**14d**) was prepared according to the general procedure described in section 1.2 from ketone **1** (191 mg, 1.0 mmol) and 1-cyclohexyl-2-propen-1-one (166 mg, 1.2 mmol) at –78 °C for 5 h. Purification of the crude product by column chromatography (hexanes/EtOAc 85:15) afforded **14d** (241 mg, 0.73 mmol, 73% yield) as a yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.4; $\mathbf{[\alpha]^{20}_D}$ = –9.7*(c* 1.0, $CHCl_3$); **IR** (ATR) ν 2928, 2853, 1705, 1449, 1370, 1101, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.26 (5H, m, ArH), 4.57 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 4.52 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 4.05 (1H,q, *J* = 6.8 Hz, CHOBn), 3.02–2.94 (1H, m, $COCHCH_3$), 2.46–2.34 (2H, m, CH_2CO), 2.32–2.25 (1H, m, $CH(CH_2)_5$), 1.94–1.85 (1H, m, $CH_3CHCH_xH_y$), 1.83–1.71 (5H, m, $(CH_2)_5$), 1.69–1.56 (1H, m, $CH_3CHCH_xH_y$), 1.35 (3H,d, *J* = 6.8 Hz, CH_3CHOBn), 1.31–1.16 (5H, m, $(CH_2)_5$), 1.06 (3H,d, *J* = 6.9 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.8

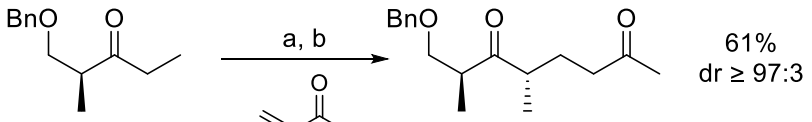
(C), 213.3 (C), 137.7 (C), 128.4 (2 × CH), 127.8 (CH_2), 127.7 (2 × CH), 79.3 (CH), 71.6 (CH_2), 50.7 (CH), 40.2 (CH), 37.6 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 26.6 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 25.6 (CH_2), 16.7 (CH_3), 16.3 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{34}NO_3$ $[M+NH_4]^+$: 348.2533, found: 348.2522.



14e

(2*S*,4*S*,8*S*)-2-Benzyloxy-8-(*tert*-butyldimethylsilyloxy)-4-methyl-9-phenyl-3,7-nonanedione (**14e**) was prepared according to the general procedure described in section 1.2 from ketone **1** (190 mg, 1.0 mmol) and (*S*)-4-(*tert*-butyldimethylsilyloxy)-5-phenyl-1-penten-3-one (349 mg, 1.2 mmol) at –78 °C for 2 h. Purification of the crude product by column chromatography (hexanes/EtOAc 95:5) afforded **14e** (378 mg, 0.78 mmol, 78% yield) as a yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 95:5) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = –47.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2928, 2855, 1712, 1453, 1252, 1094, 1004 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.15 (10H, m, ArH), 4.56 (1H, d, *J* = 11.6 Hz, PhCH_xH_yO), 4.49 (1H, d, *J* = 11.6 Hz, PhCH_xH_yO), 4.17 (1H, dd, *J* = 8.1, 4.0 Hz, CHOTBS), 4.03 (1H, q, *J* = 6.8 Hz, CHOBn), 2.98–2.86 (2H, m, COCHCH_3& PhCH_xH_y), 2.80–2.74 (1H, m, PhCH_xH_y), 2.57–2.49 (1H, m, CH_xH_yCO), 2.37–2.28 (1H, m, CH_xH_yCO), 1.92–1.83 (1H, m, CH_3CHCH_xH_y), 1.52–1.47 (1H, m, CH_3CHCH_xH_y), 1.33 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 1.02 (3H, d, *J* = 6.9 Hz, COCHCH_3), 0.84 (9H, s, (CH_3)$_3$CSi), –0.11 (3H, s, CH_3Si), –0.30 (3H, s, CH_3Si); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.8 (C), 212.9 (C), 137.7 (C), 137.0 (C), 129.9 (2 × CH), 128. (2 × CH)4, 128.2 (2 × CH), 127.8 (CH), 127.7 (2 × CH), 126.6 (CH), 79.9 (CH), 79.4 (CH), 71.6 (CH_2), 41.4 (CH), 40.1 (CH_2), 35.0 (CH_2), 25.9 (CH), 25.7 (3 × CH_3), 18.0 (C), 16.9 (CH_3), 16.3 (CH_3), –5.3 (CH_3), –5.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{29}H_{46}NO_4$ $[M+NH_4]^+$: 500.3191, found: 500.3188.

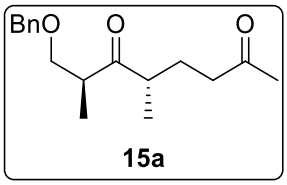
1.4. Michael addition of 13 to methyl vinyl ketone



13 **15a**

a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (b) 1.2 eq CH_2=CHCOCH_3, –78 °C, 4 h.

The experimental procedure described in section 1.2 was followed starting from ketone **13** (206 mg, 1.0 mmol) and methyl vinyl ketone (98 µL, 1.2 mmol) at –78 °C for 4 h. The residue was analysed by ^{1}H NMR and purified by column chromatography (hexanes/EtOAc 70:30) to afford 168 mg (0.61 mmol, 61% yield) of (5*S*,7*S*)-8-benzyloxy-5,7-dimethyl-2,6-octanedione (**15a**) as a colourless oil.



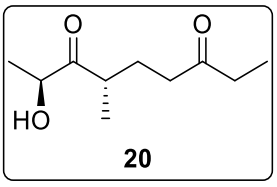
15a

(5*S*,7*S*)-8-Benzyloxy-5,7-dimethyl-2,6-octanedione (**15a**). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 70:30) 0.60; $\mathbf{[\alpha]^{20}_D}$ = +0.1 (*c* 1.0, $CHCl_3$); **IR** (ATR): 1709, 1453, 1357, 1166, 1097, 989, 734, 699 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.25 (5H, m, ArH), 4.46 (2H, s, $PhCH_2O$), 3.64 (1H, t, *J* = 8.8 Hz, $BnOCH_xH_y$), 3.45 (1H, dd, *J* = 8.8, 5.1 Hz, $BnOCH_xH_y$), 3.12–3.02 (1H, m, $BnOCH_2CHCH_3$), 2.79–2.69 (1H, m, $COCHCH_3CH_2CH_2$), 2.44–2.24 (2H, m, CH_2COCH_3), 1.97 (3H, s, $COCH_3$), 1.98–1.85 (1H, m, $CH_xH_yCH_2COCH_3$), 1.67–1.56 (1H, m, $CH_xH_yCH_2COCH_3$), 1.08 (3H, d, *J* = 7.0 Hz, $COCHCH_3CH_2CH_2$), 1.04 (3H, d, *J* = 7.0 Hz, $BnOCH_2CHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 216.4 (C), 208.5 (C), 138.0 (C), 128.3 (2 × CH), 127.6 (CH), 127.5 (2 × CH), 73.2 (CH_2), 73.0 (CH_2), 45.1 (CH), 45.0 (CH), 40.7 (CH_2), 29.7 (CH_3), 26.0 (CH_2), 16.3 (CH_3), 13.7 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{17}H_{24}NaO_3$ $[M+Na]^+$: 300.1698, found : 300.1705.

1.5. Configuration of Michael adduct 14b

1.5.1. Removal of the benzyl protecting group of **14b**[99]

A mixture of **14b** (200 mg, 0.73 mmol) and Pd/C 10% (202 mg, 0.19 mmol) in absolute ethanol (25 mL) was purged with H_2 and stirred for 3 h at rt. H_2 was replaced with N_2 and the mixture was filtered over Celite® and eluted with CH_2Cl_2. Solvents were removed in vacuo to obtain a yellow oil to afford 137 mg (cuantitative yield) of (2*S*,4*S*)-2-hydroxy-4-methyl-3,7-nonanedione (**20**), which was used in the next step without further purification.

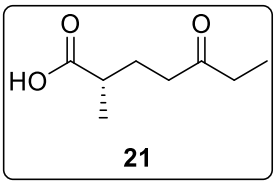


20

(2*S*,4*S*)-2-Hydroxy-4-methyl-3,7-nonanedione (20). Yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 70:30) = 0.30; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.33 (1H, dq, *J* = 7.1, 5.0 Hz, $COCHCH_3$), 3.50 (1H, d, *J* = 5.0 Hz, CHOH), 2.88–2.80 (1H, m, $COCHCH_3$), 2.46–2.32 (4H, m, CH_2COCH_2), 1.97–1.88 (1H, m, $CH_3CHCH_xH_y$), 1.73–1.64 (1H, m, $CH_3CHCH_xH_y$), 1.39 (3H, d, *J* = 7.1 Hz, CH_3CHOH), 1.10 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 1.05 (3H, t, *J* = 7.3 Hz, $COCH_2CH_3$).

1.5.2. Oxidative cleavage of **20**

A solution of **20** (137 mg, 0.74 mmol) in 2:1 MeOH/H_2O (7.5 mL) at rt was treated with an excess of $NaIO_4$ (1.24 g, 5.8 mmol). The reaction was followed by TLC until total conversion. The reaction mixture was diluted with Et_2O (7 mL), cooled to 0 °C and acidified with 0.5 M HCl to pH = 1. The solution was partitioned with Et_2O (7 mL) and H_2O (7 mL). The aqueous layer was extracted with Et_2O (4 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 110 mg (94% yield) of (*S*)-2-methyl-5-oxoheptanoic acid (**21**), which was used in the next step without further purification.

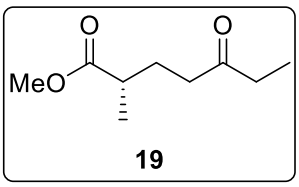


21

(*S*)-2-Methyl-5-oxoheptanoic acid (21). Yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 70:30) = 0.20; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.52–2.47 (3H, m, HOOCC<u>H</u>& $CH_2C\underline{H}_2CO$), 2.44 (2H, q, *J* = 7.4 Hz, $COC\underline{H}_2CH_3$), 1.96–1.86 (1H, m, $CH_3CHC\underline{H}_xH_y$), 1.84–1.75 (1H, m, $CH_3CHCH_x\underline{H}_y$), 1.21 (3H, d, *J* = 7.0 Hz, $COCHC\underline{H}_3$), 1.06 (3H, t, *J* = 7.3 Hz, $COCH_2C\underline{H}_3$).

1.5.3. <u>Esterification of **21**</u>[41]

Pivaloyl chloride (1.9 mL, 15 mmol) and *i*-Pr_2NEt (185 µL, 1.05 mmol) were added to a solution of **21** (110 mg, 0.70 mmol) in THF (7 mL) under N_2 at 0 °C. The resultant mixture was stirred for 1 h and MeOH (0.9 mL, 20 mmol) and DMAP (85 mg, 0.7 mmol) were added in the minimum amount of THF. The reaction mixture was stirred overnight at rt. It was then diluted with Et_2O (20 mL) and washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by column chromatography (hexanes/EtOAc 20:80) afforded 86 mg (72% yield) of methyl (*S*)-2-methyl-5-oxoheptanoate (**19**).



19

Methyl (*S*)-2-methyl-5-oxoheptanoate (19). Light yellow oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.20; **$[\alpha]^{20}_D$** = +21.2 *(c* 1.05, $CHCl_3$) [lit.[41] **$[\alpha]^{20}_D$** = –25.0 *(c* 1.05, $CHCl_3$) for 2*R* enantiomer]; **IR** (ATR) ν 2974, 1731, 1712, 1459, 1201, 1163, 1110 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.67 (3H, s, $C\underline{H}_3O$), 2.53–2.38 (3H, m, COC<u>H</u>& $CH_2C\underline{H}_2CO$), 2.42 (2H, q, *J* = 7.3 Hz, $COC\underline{H}_2CH_3$), 1.95–1.82 (1H, m, $CH_3CHC\underline{H}_xH_y$), 1.82–1.70 (1H, m, $CH_3CHCH_x\underline{H}_y$), 1.17 (3H, d, *J* = 7.0 Hz, $COCHC\underline{H}_3$), 1.05 (3H, t, *J* = 7.4 Hz, $COCH_2C\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 210.7 (C), 176.6 (C), 51.5 (CH_3), 39.6 (CH_2), 38.6 (CH), 35.9 (CH_2), 27.4 (CH_2), 17.1 (CH_3), 7.7 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_9H_{17}O_3$ $[M+H]^+$: 173.1172, found: 173.1168.

2. Michael additions to β-substituted enones

2.1. Preliminary studies

2.1.1. <u>Optimisation studies of the Michael addition to β-substituted enones</u>

Neat $TiCl_4$ (232 µL, 2.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, (*E*)-4-phenyl-3-butenone (176 mg, 1.2 mmol) was added, and the resulting mixture was stirred for 10 min at –78 °C and fot **t** at **T**. The reaction was quenched following two methods.

Method **A**: the reaction was quenched with a suspension of silica (1.5 g) in CH_2Cl_2 (5 mL) at rt with vigorous stirring. The mixture was filtered over silica, eluted with EtOAc, and concentrated.

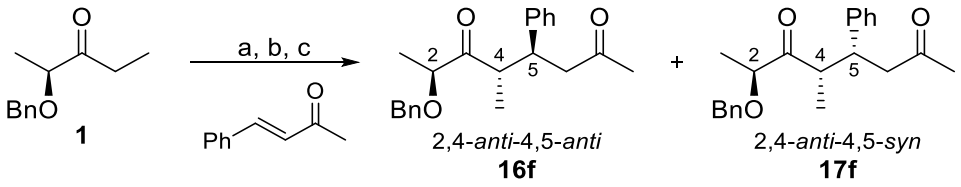
Method **B**: the reaction was quenched with sat. NH_4Cl (5 mL) at rt with vigorous stirring. The mixture was partitioned with Et_2O (50 mL) and H_2O (30 mL), and the organic layer was extracted and washed with sat. $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated.

The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 29 and spectroscopic data is shown in section 2.4.

2.1.2. Enolization with $TiCl_4$ and $SnCl_4$

Neat $TiCl_4$ (120 µL, 1.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, a 1 M solution of $SnCl_4$ in CH_2Cl_2 (1.1 mL, 1.1 mmol) was added, followed 5 min later by (*E*)-4-phenyl-3-butenone (176 mg, 1.2 mmol), and the resultant mixture was stirred at –20 °C for 3 h.

The reaction was quenched by the addition of sat. NH_4Cl (5 mL) at rt with vigorous stirring. The mixture was partitioned in Et_2O (50 mL) and water (30 mL), and the organic layer was washed with sat. $NaHCO_3$ (30 mL), and brine (30 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 29 and spectroscopic data is shown in section 2.4.



a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq (*E*)-PhCH=CHCOCH$_3$, T, t. c) quench

Entry	T (°C)	Time (h)	Quench	dr[a]	Yield[b] (%)
1	–78	2	A NH_4Cl	90:10	5
2	–40	2	A NH_4Cl	90:10	35
3	–40	2	B SiO_2	83:17	25
4	–40	3	B SiO_2	89:11	30
5	–20	3	A NH_4Cl	90:10	55
6	–20	3	B SiO_2	82:18	40
7	–20	15	A NH_4Cl	88:12	55
8[c]	–20	3	A NH_4Cl	90:10	83

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Reaction performed with 1.1 eq of $TiCl_4$ and 1.1 eq of $SnCl_4$.

Table 29

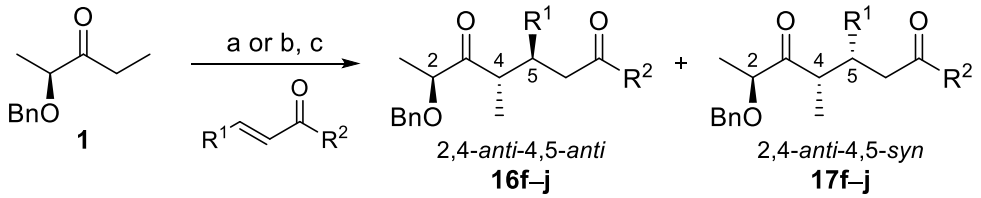
2.2. Michael addition to β-substituted enones. General procedure A

Neat $TiCl_4$ (232 µL, 2.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, the corresponding enone (1.2 mmol) was added and the resulting mixture was stirred at –20 °C for 3 h.

The reaction was quenched and treated as in section 2.1.2. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 30 and spectroscopic data is shown in section 2.4.

2.3. Michael addition to β-substituted enones. General procedure B

The experimental procedure described in section 2.1.2 was followed starting from ketone **1** (192 mg, 1.0 mmol) and the corresponding enone (1.2 mmol). The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 30 and spectroscopic data is shown in section 2.4.



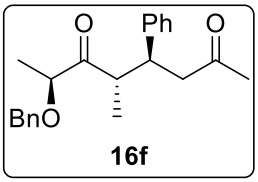
a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; c) 1.2 eq $R^1CH{=}CHCOR^2$, –20, 3 h.

Entry	Enone	R^1	R^2	LA	Product	dr (16:17)[a]	Yield 16 (%)[b]
1	**Ef**	Ph	Me	$TiCl_4$	**16f**	90:10	55
2	**Ef**	Ph	Me	$SnCl_4$	**16f**	90:10	83
3	**Eg**	Me	Et	$TiCl_4$	**16g**	90:10	(90)
4	**Eg**	Me	Et	$SnCl_4$	**16g**	94:6	(81)
5	**Eh**	$(CH_2)_2Ph$	Me	$TiCl_4$	**16h**	90:10	67
6	**Eh**	$(CH_2)_2Ph$	Me	$SnCl_4$	**16h**	94:6	63
7	**Ei**	$(CH_2)_2OTBS$	Me	$TiCl_4$	**16i**	90:10	68
8	**Ei**	$(CH_2)_2OTBS$	Me	$SnCl_4$	**16i**	-	complex mixture
9	**Ej**	$–(CH_2)_3–$		$TiCl_4$	**16j**	66:34	(19)
10	**Ej**	$–(CH_2)_3–$		$SnCl_4$	**16j**	75:25	(81)

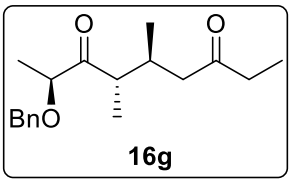
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography. Isolated overall yield into brackets.

Table 30

2.4. Spectroscopic data of Michael adducts derived from ketone 1 and β-substituted enones

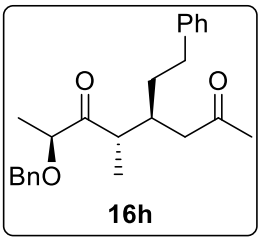


(5*S*,7*S*,4*S*)-7-benzyloxy-5-methyl-4-phenyl-2,6-octanedione (**16f**) was prepared according to the general procedure described in section 2.3 from ketone **1** (191 mg, 1.0 mmol) and (*E*)-4-phenyl-3-butenone (175 mg, 1.2 mmol) at –20 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 85:15) afforded **16f** (281 mg, 0.83 mmol, 83% yield) as a white solid. A sample of this material was recrystallised in hexane to give **16f** as white needles. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = +51.8 *(c* 1.3, $CHCl_3$); **IR** (ATR) ν 3061, 2979, 2933, 2881, 1716, 1699, 1455, 1363, 1246, 1167, 1110, 1091, 1016 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ7.32–7.17 (10H, m, ArH), 4.26 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 3.94 (1H, d, *J* = 11.7, $PhCH_xH_y$), 3.67 (1H, q, *J* = 7.0 Hz, CHOBn), 3.55 (1H, td, *J* = 8.8, 5.8 Hz, CHPh), 3.24–3.17 (1H, m, $COCHCH_3$), 2.87–2.76 (2H, m, CH_2CO), 1.99 (3H, s, CH_3CO), 1.12 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 1.08 (3H, d, *J* = 7.0 Hz, CH_3CHOBn); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.1 (C), 207.0 (C), 142.3 (C), 137.9 (C), 128.5 (CH), 128.3 (2 × CH), 127.6 (2 × CH), 126.9 (CH), 80.9 (CH), 71.4 (CH_2), 46.7 (CH), 45.9 (CH_2), 43.2 (CH), 30.4 (CH_3), 16.6 (CH_3), 14.5 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{22}H_{30}NO_3$ $[M+NH_4]^+$: 356.2220, found: 356.2211.



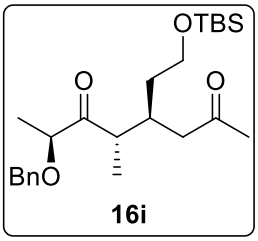
16g

(2*S*,4*S*,5*S*)-2-Benzyloxy-4,5-dimethyl-3,7-nonanedione (**16g**) was prepared according to the general procedure described in section 2.3 from ketone 1 (192 mg, 1.0 mmol) and (*E*)-4-hexen-3-ona (137 µL, 1.2 mmol) at –20 °C for 3 h. Purification of the crude product by chromatography (hexanes/EtOAc 90:10) afforded **16g** (231 mg, 0.81 mmol, 81% yield) as a 94:6 mixture of diastereomers. Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.4; $\mathbf{[\alpha]^{20}_D}$ = +15.7 *(c* 1.2, $CHCl_3$, 80% *ed*); **IR** (ATR) ν 2972, 2934, 2876, 1709, 1454, 1371, 1109, 1027, 1013 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.27 (5H, m, ArH), 4.57 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.49 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.04 (1H, q, *J* = 6.9 Hz, CHOBn), 2.91 (1H, qd, *J* = 6.9, 5.2 Hz, $COCHCH_3$), 2.51–2.26 (4H, m, CH_2CH_3, $CH_3CHCH_xH_y$), 2.17 (1H, dd, *J* = 17.3, 10.2 Hz, $CH_3CHCH_xH_y$), 1.36 (3H, d, *J* = 6.9 Hz, CH_3CHOBn), 1.03 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.00 (3H, d, *J* = 6.9 Hz, $COCHCH_3$), 0.92 (3H, d, *J* = 6.7 Hz, CH_3CHCH_2); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.7 (C), 210.6 (C), 137.8 (C), 128.4 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 79.7 (CH), 71.6 (CH_2), 45.4 (CH), 44.7 (CH_2), 36.5 (CH_2), 30.4 (CH), 18.8 (CH_3), 17.1 (CH_3), 12.1 (CH_3), 7.7 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{26}NaO_3$ $[M+Na]^+$: 313,1774, found: 313.1773.



16h

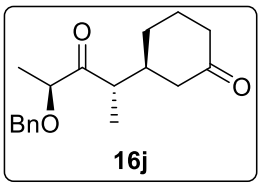
(4*S*,5*S*,7*S*)-7-Benzyloxy-5-methyl-4-phenethyl-2,6-octanedione (**16h**) was prepared according to the general procedure described in section 2.3 from ketone **1** (192 mg, 1.0 mmol) and (*E)*-6-phenyl-3-hexen-2-one (209 mg, 1.2 mmol) at –20 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **16h** (233 mg, 0.63 mmol, 63% yield) as a yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.4; $\mathbf{[\alpha]^{20}_D}$ = +35.1 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2978, 2935, 2861, 1708, 1679, 1451, 1363, 1114 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.27 (5H, m, ArH), 7.24–7.13 (5H, m, ArH), 4.51 (1H, d, *J* = 11.7 Hz, Ph), 4.44 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 3.99 (1H, q, *J* = 7.0 Hz, CHOBn), 3.17–3.11 (1H, m, $COCHCH_3$), 2.67–2.46 (4H, m, $PhCH_2$, $COCHCH$, $COCH_xH_y$), 2.26 (1H, dd, *J* = 18.5, 9.3 Hz, $COCH_xH_y$), 2.08 (3H, s, CH_3CO), 1.70–1.52 (2H, m, $PhCH_2CH_2$), 1.33 (3H,d, *J* = 6.9 Hz, $COCHCH_3$), 0.96 (3H,d, *J* = 6.9 Hz, CH_3CHOBn); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.5 (C), 207.4 (C), 141.5 (C), 137.6 (C), 128.3 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 125.8 (CH), 79.3 (CH), 71.5 (CH_2), 43.7 (CH), 42.1 (CH_2), 34.6 (CH_2), 33.7 (CH), 33.5 (CH_2), 30.3 (CH_3), 17.2 (CH_3), 10.2 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{26}NaO_3$ $[M+Na]^+$: 313,1774, found: 313.1773.



16i

(4*S*,5*S*,7*S*)-7-Benzyloxy-4-(2-(*tert*-butyldimethylsilyloxy)ethyl)-5-methyl-2,6-octanedione (**16i**) was prepared according to the general procedure described in section 5.2 from ketone **1** (192 mg, 1.0 mmol) and (*E*)-6-(*tert*-butyldimethylsilyloxy)-3-hexen-2-one (274 mg, 1.2 mmol) at –20 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **16i** (293 mg, 0.68

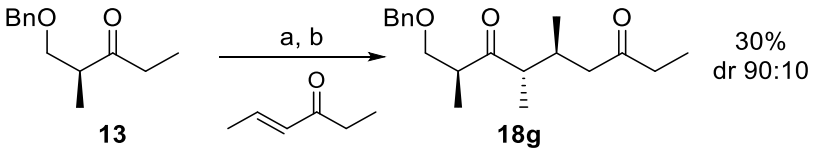
mmol, 68% yield) as a yellowish oil. **R_f** (Hexanes/EtOAc 80:20) = 0.5; **$[\alpha]^{20}_D$** = +29.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2952, 2928, 2882, 2856, 1713, 1252, 1089 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.27 (5H, m, ArH), 4.54 (1H, d, *J* = 11.8 Hz, Ph), 4.45 (1H, d, *J* = 11.8, $PhCH_xH_y$), 4.09 (1H, q, *J* = 6.9 Hz, CHOBn), 3.61 (2H, t, *J* = 6.5 Hz, $SiOCH_2$), 3.13 (1H, dq, *J* = 3.4, 6.8 Hz, $COCHCH_3$), 2.54–2.47 (2H, m, $CHCH_2$, CH_xH_yCO), 2.32–2.28 (1H, m, CH_xH_yCO), 2.09 (3H, s, $COCH_3$), 1.54–1.49 (2H, m, CH_2CH_2OSi), 1.36 (3H, d, *J* = 6.9 Hz, CH_3CHOBn), 0.97 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 0.87 (9H, s, $C(CH_3)_3$), 0.02 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.6 (C), 207.6 (C), 137.8 (C), 128.4 (2 × CH), 127.7 (2 × CH), 127.7 (CH), 79.3 (CH), 71.6 (CH_2), 61.4 (CH_2), 44.0 (CH_2), 42.6(CH), 35.7(CH_2), 31.6(CH), 30.3 (CH_3), 25.9 (3 × CH_3),18.2 (C), 17.3 (CH_3), 10.6 (CH_3), -5.4 (CH_3), -5.4 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{24}H_{44}NO_4Si$ $[M+NH_4]^+$: 438,3034, found: 438.3028.



16j

(*R*)-3-((2*S*,4*S*)-4-(Benzyloxy-3-oxo-2-pentanyl)cyclohexanone (**16j**) was prepared according to the general procedure described in section 2.3 from ketone **1** (192 mg, 1.0 mmol) and cyclohexenone (115 mg, 1.2 mmol) –20 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **16j** (205 mg, 0.71 mmol, 71% yield) as a 75:25 mixture of diastereomers. Colourless oil. **R_f** (Hexanes/EtOAc 80:20) = 0.2; **IR** (ATR) ν 2935, 2867, 1707, 1454, 1100 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.28 (5H, m, ArH), 4.61 (1H, d, *J* = 11.8 Hz, Ph), 4.56 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.00 (1H, q, *J* = 6.9 Hz, CHOBn), 3.00–2.92 (1H, dq, *J* = 6.8, 3.4 Hz, $COCHCH_3$), 2.45–2.30 (2H, m, CH_xH_y), 2.27–2.18 (1H, m, CH_xH_y), 2.16–2.09 (1H, m, COCHCH), 2.10–1.97 (2H, m, CH_xH_y, CH_xH_y), 1.77–1.70 (1H, m, CH_xH_y), 1.67–1.54 (1H, m, CH_xH_y), 1.42–1.32 (1H, m, CH_xH_y), 1.36 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 1.03 (3H, d, *J* = 6.9 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.3, 210.9, 137.6, 128.5, 127.9, 127.7, 79.8, 71.7, 45.8, 44.5, 41.3, 40.5, 29.9, 25.1, 16.6, 13.6; **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{24}NaO_3$ $[M+Na]^+$: 311.1618, found: 311.1615.

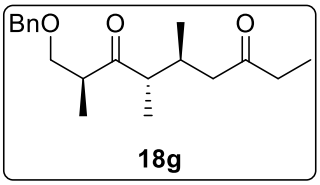
2.5. Michael addition of 13 to (*E*)-4-hexen-3-one



13 **18g**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; (b) 1.2 eq (*E*)-MeCH=CHCOEt, –40 °C, 3.5 h.

The experimental procedure described in section 2.3 was followed starting from ketone **13** (206 mg, 1.0 mmol) and (*E*)-4-hexen-3-one (137 µL, 1.2 mmol) at –40 °C for 3.5 h. The residue was analysed by ^{1}H NMR and purified by column chromatography (hexanes/EtOAc 90:10) to afford 90 mg (0.30 mmol, 30% yield) of (2*S*,4*S*,5*S*)-1-benzyloxy-2,4,5-trimethyl-3,7-nonanedione (**18g**) as a 90:10 mixture of two diastereomers.



18g

(2*S*,4*S*,5*S*)-1-Benzyloxy-2,4,5-trimethyl-3,7-nonanedione (18g). Colourless oil. **R_f** (Hexanes/EtOAc 80:20) = 0.15; **$[\alpha]^{20}_D$** = –25.9 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2950, 1706, 1576, 1558, 1540, 1533, 1507, 1456, 1374, 1099, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.24 (5H, m, ArH), 4.47 (1H, d, *J* = 12.0 Hz, $PhCH_xH_yO$), 4.42 (1H, d, *J* = 12.0 Hz, $PhCH_xH_yO$), 3.67 (1H, dd, *J* = 9.0, 8.3 Hz, $BnOCH_xH_y$), 3.38 (1H, dd, *J* = 9.0, 5.3 Hz, $BnOCH_xH_y$), 3.10–3.00 (1H, m, $BnOCH_2CH$), 2.68 (1H, qd, *J* = 7.0, 5.0 Hz, $COCHCH_3$), 2.53–2.40 (2H, m, CH_2COEt), 2,36–2.21 (2H, m, $CH_2COCH_2CH_3$), 2.20–2.10 (1H, m, $CHCH_2COEt$), 1.04 (3H, d, *J* = 7.1 Hz, $CHCH_3$), 1.01 (3H, d, *J* = 7.0 Hz, $CHCH_3$), 0.97 (3H, t, *J* = 7.3 Hz, $COCH_2CH_3$), 0.93 (3H, d, *J* = 7.0 Hz, $CHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 216.0 (C), 210.9 (C), 138.1 (C), 128.3 (2 × CH), 127.6 (2 × CH), 127.5 (CH), 73.3 (CH_2), 72.2 (CH_2), 49.9 (CH), 45.5 (CH_2), 45.0 (CH), 36.1 (CH), 30.1 (CH_3), 18.4 (CH_3), 14.0 (CH_3), 12.0 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{19}H_{28}NaO_3$ $[M+Na]^+$: 327.1931, found : 327.1925.

3. Michael addition to aromatic nitroalkenes

3.1. Preliminary studies

3.1.1. Enolization with $TiCl_4$

Neat $TiCl_4$ (120 µL, 1.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, *(E)*-β-nitrostyrene (179 mg, 1.2 mmol) was added and the resultant mixture was stirred at –78 °C for 1.5 h.

The reaction was quenched by the addition of sat. NH_4Cl (5 mL) at rt with vigorous stirring. The mixture was partitioned in CH_2Cl_2 (10 mL) and water (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Analysis of the residue by ^{1}H NMR indicated that is was composed of starting materials.

3.1.2. Enolization with 2 equivalents of $TiCl_4$

Neat $TiCl_4$ (232 µL, 2.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, *(E)*-β-nitrostyrene (179 mg, 1.2 mmol) was added and the resultant mixture was stirred at –78 °C for 1.5 h.

The reaction was quenched and treated as in section 3.1.1. The residue was analysed by ^{1}H NMR and purified by column chromatography to afford 140 mg (0.41 mmol, 41% yield) of

2*S,4S,5R*)-2-benzyloxy-4-methyl-6-nitro-5-phenyl-3-hexanone. Spectroscopic data is shown in section 3.3.

3.1.3. Optimisation studies of the Michael the addition to aromatic nitroalkenes

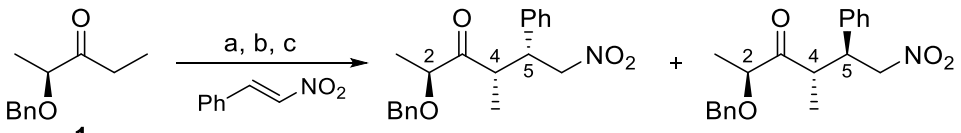
Neat $TiCl_4$ (232 µL, 2.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, *(E)*-β-nitrostyrene (179 mg, 1.2 mmol) was added and the resultant mixture was stirred at –78 °C for $\mathbf{t_{reaction}}$. The reaction was quenched following three methods.

Method **A**: the reaction was quenched with sat. NH_4Cl (5 mL) at rt with vigorous stirring

Method **B**: the reaction was quenched with 1 M HCl (5 mL) at rt and stirred for $\mathbf{t_{quench}}$ at rt.

Method **C**: the reaction was quenched with NH_4F 25% (3 mL) at rt and stirred for $\mathbf{t_{quench}}$ at rt.

The mixture was partitioned in CH_2Cl_2 (10 mL) and water (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 31 and spectroscopic data is shown in section 3.3.



a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq (*E*)-PhCH=$CHNO_2$, –78 °C, $t_{reaction}$; c) quench, t_{quench}.

Entry	$\mathbf{Time_{reaction}}$ (h)	$\mathbf{Time_{quench}}$	Quench	dr (22a:23a)[a]	Yield 22a (%)[b]
1	1.5	10 min	NH_4Cl	87:13	41
2	1.5	15 min	HCl	87:13	52
3	1.5	1.5 h	HCl	87:13	55
4	1.5	12 h	HCl	87:13	47
5	1.5	1.5 h	NH_4F	87:13	79
6	1	1 h	NH_4F	87:13	77
7	1	0.5	NH_4F	87:13	80

[a] Determined by ^{1}H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.

Table 31

3.1.4. Enolization with $TiCl_4$ and $BF_3{\cdot}OEt_2$

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, $BF_3{\cdot}OEt_2$ (68 µL, 0.55 mmol) was added, followed 5 min later by *(E)*-β-nitrostyrene (90 mg, 0.6 mmol), and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched by the addition of a 25% solution of NH_4F (3 mL) at rt with vigorous stirring for 30 min. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Analysis of the residue by ^1H NMR indicated that is was composed of starting materials.

3.1.5. Enolization with $TiCl_4$ and $MgBr_2{\cdot}OEt_2$

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, $MgBr_2{\cdot}OEt_2$ (142 mg, 0.55 mmol) was added, followed 5 min later by *(E)*-β-nitrostyrene (90 mg, 0.6 mmol), and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.1.4. Analysis of the residue by ^1H NMR indicated that is was composed of starting materials.

3.1.6. Enolization with $TiCl_4$ and Et_2AlCl

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, a 1 M solution of Et_2AlCl in CH_2Cl_2 (0.55 mL, 0.55 mmol) was added, followed 5 min later by *(E)*-β-nitrostyrene (90 mg, 0.6 mmol), and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.1.4. Analysis of the residue by ^1H NMR showed a 60% of a 75:25 diastereomeric mixture of Michael adducts (**22a**:**23a**). Spectroscopic data is shown in section 3.3.

3.1.7. Enolization with $TiCl_4$ and $Ti(O\textit{i}\text{-}Pr)_4$

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension

was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, neat Ti(*i*-PrO)$_4$ (165 µL, 0.55 mmol) was added, followed 5 min later by *(E)*-β-nitrostyrene (90 mg, 0.6 mmol), and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.1.4. Analysis of the residue by ^{1}H NMR indicated that is was composed of starting materials.

3.1.8. Enolization with $TiCl_4$ and $SnCl_4$

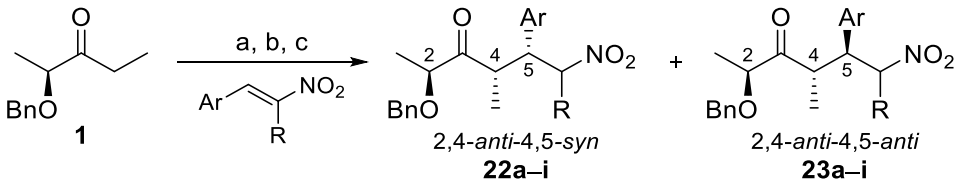
Neat $TiCl_4$ (364 µL, 3.3 mmol) was added dropwise to a solution of ketone **1** (577 mg, 3.0 mmol) in CH_2Cl_2 (12 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (0.6 mL, 3.3 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, a 1 M solution of $SnCl_4$ in CH_2Cl_2 (3.1 mL, 3.1 mmol) was added, followed 5 min later by *(E)*-β-nitrostyrene (90 mg, 0.6 mmol), and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.1.4. The residue was analysed by ^{1}H NMR and purified by column chromatography (hexanes/EtOAc 90:10) to afford **23a** (379 mg, 1.1 mmol, 37% yield) as a white solid. Spectroscopic data is shown in section 3.3.

3.2. Michael addition to aromatic nitroalkenes. General procedure

Neat $TiCl_4$ (116 µL, 1.05 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, the corresponding nitroalkene (0.6 mmol) was added and the resultant mixture was stirred at –78°C for 1 h.

The reaction was quenched by the addition of a 25% solution of NH_4F (3 mL) at rt with vigorous stirring for 30 min. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 32 and spectroscopic data is shown in section 3.3.



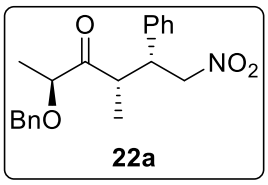
a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.2 eq (*E*)-ArCH=$CRNO_2$, –78 °C, 1 h; c) NH_4F, rt, 30 min.

Entry	Nitroalkene	Ar, R	Product	dr (22:23)[a]	Yield 22 (%)[b]
1	**Na**	Ph, H	**22a**	87:13	80
2	**Nb**	4-Me-Ph, H	**22b**	88:12	80
3	**Nc**	4-MeO-Ph, H	**22c**	93:7	80
4	**Nd**	4-Cl-Ph, H	**22d**	90:10	82
5	**Ne**	4-NO_2-Ph, H	**22e**	87:13	70
6	**Nf**	3,4-(–OCH_2O–)-Ph, H	**22f**	-	< 5%
7	**Ng**	Furyl, H	**22g**	93:7	60
8	**Nh**	PhCH=CH, H	**22h**	-	complex mixture
9[c]	**Nh**	PhCH=CH, H	**22h**	-	complex mixture
10	**Ni**	Ph, Me	**22i**	(1:1):(1:1)	(81)
11[c]	**Ni**	Ph, Me	**22i**	(3:3):(1:1)	(23)

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Reaction performed with 1.1 eq of $TiCl_4$ and 1.1 eq of $SnCl_4$.

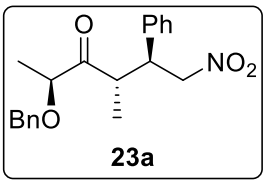
Table 32

3.3. Spectroscopic data of Michael adducts derived from ketone 1 and aromatic nitroalkenes



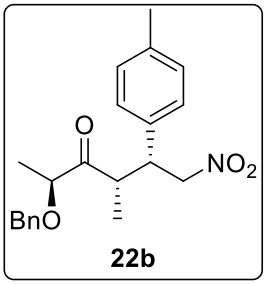
22a

(2*S*,4*S*,5*R*)-2-Benzyloxy-4-methyl-6-nitro-5-phenyl-3-hexanone (**22a**) was prepared according to the general procedure described in section 3.2 from ketone **1** (192 mg, 1.0 mmol) and *(E)*-β-nitrostyrene (179 mg, 1.2 mmol) at –78 °C for 1 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **22a** (276 mg, 0.8 mmol, 80% yield) as a purple oil. **R_f** (Hexanes/EtOAc 90:10) = 0.2; **$[\alpha]^{20}_D$** = +99.0 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3014, 3082, 3060, 3028, 2974, 2930, 2870, 1708, 1549, 1451, 1369 cm^{-1}; **^1H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.14 (10H, m, ArH), 4.64 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.62 (1H, dd, *J* = 12.6, 10.1 Hz, $CH_xH_yNO_2$), 4.54 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.52 (1H, dd, *J* = 12.6, 4.6 Hz, $CH_xH_yNO_2$), 4.01 (1H, q, *J* = 6.7 Hz, $BnOCHCH_3$), 3.72 (1H, td, *J* = 10.0, 4.5 Hz, $PhCHCHCH_3$), 3.41 (1H, dq, *J* = 9.8, 7.0 Hz, $PhCHCHCH_3$), 1.32 (3H, d, *J* = 6.7 Hz, $BnOCHCH_3$), 0.92 (3H, d, *J* = 6.7 Hz, $PhCHCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 231.5 (C), 137.6 (C), 137.3 (C), 128.9 (2 × CH), 128.6 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.8 (CH), 79.1 (CH), 78.2 (CH_2), 71.9 (CH_2), 46.2 (CH3), 43.8 (CH), 16.3 (CH_3), 15.8 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{23}NNaO_4$ $[M+Na]^+$: 364.1519, found: 364.1522.



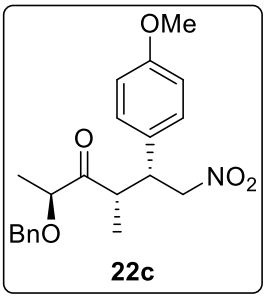
23a

(2*S*,4*S*,5*S*)-2-Benzyloxy-4-methyl-6-nitro-5-phenyl-3-hexanone (**23a**) was prepared according to the general procedure described in section 3.2 from ketone **1** (577 mg, 3.0 mmol), 1 M solution of $SnCl_4$ in CH_2Cl_2 (3.1 mL, 3.1mmol) and *(E)*-β-nitrostyrene (537 mg, 3.6 mmol) at –78 °C for 1 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **23a** (379 mg, 1.1 mmol, 37% yield) as a white solid. A sample of this material was recrystallised in hexane to give **23a** as white needles. **Mp** = 93–95 °C; **R_f** (Hexanes/EtOAc 90:10) = 0.2; **$[\alpha]^{20}_D$** = +14.9 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3025, 2976, 2918, 2874, 1708, 1548, 1454, 1370, 1107 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.17 (10H, m, ArH), 4.76 (1H, dd, *J* = 12.7, 5.1 Hz, $CH_xH_yNO_2$), 4.69 (1H, dd, *J* = 12.7, 9.8 Hz, $CH_xH_yNO_2$), 4.28 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 4.10 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 3.84 (1H, td, *J* = 9.8, 5.1 Hz, CHAr), 3.73 (1H, q, *J* = 6.9 Hz, CHOBn), 3.42 (1H, dq, *J* = 9.8, 6.9 Hz, $COCHCH_3$), 1.17 (3H, d, *J* = 6.9 Hz, CH_3CHOBn), 1.04 (3H, d, *J* = 6.9 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 212.9 (C), 138.3 (C), 137.7 (C), 129.0 (2 × CH), 128.6 (2 × CH), 128.3 (2 × CH), 128.1 (2 × CH), 128.0 (CH), 127.8 (CH), 80.6 (CH), 77.7 (CH_2), 71.5 (CH_2), 45.9 (CH), 44.5 (CH), 16.4 (CH_3), 14.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{23}NNaO_4$ $[M+Na]^+$: 364.1519, found: 364.1516.



22b

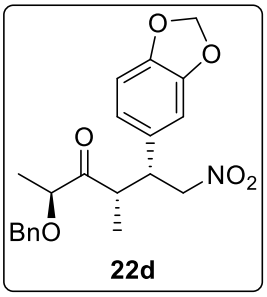
(2*S*,4*S*,5*R*)-2-Benzyloxy-4-methyl-5-(4-methylphenyl)-6-nitro-3-hexanone (**22b**) was prepared according to the general procedure described in section 3.2 from ketone **1** (96 mg, 0.5 mmol) and *(E)*-4-methyl-β-nitrostyrene (98 mg, 0.6 mmol) at –78 °C for 1 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **22b** (141 mg, 0.40 mmol, 80% yield) as a purple oil. **R_f** (Hexanes/EtOAc 90:10) = 0.2; **$[\alpha]^{20}_D$** = +12.1 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3025, 2976, 2918, 2874, 1708, 1548, 1454, 1370, 1107 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.31 (5H, m, ArH), 7.11–7.04 (4H, m, ArH), 4.63 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 4.58 (1H, dd, *J* = 12.5, 10.2 Hz, $CH_xH_yNO_2$),4.54 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 4.50 (1H, dd, *J* = 12.5, 4.6 Hz, $CH_xH_yNO_2$), 4.00 (1H, q, *J* = 6.8 Hz, CHOBn), 3.70–3.64 (1H, m, CHAr), 3.42–3.34 (1H, m, $COCHCH_3$), 2.31 (3H, s, CH_3Ar), 1.32 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 0.92 (3H, d, *J* = 7.0 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.7 (C), 137.7 (C), 137.5 (C), 134.6 (C), 129.7 (2 × CH), 128.7 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 128.0 (2 × CH), 79.3 (CH), 78.5 (CH_2), 72.0 (CH_2), 46.0 (CH), 43.9 (CH), 21.2 (CH_3), 16.5 (CH_3), 15.9 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{29}N_2O_4$ $[M+NH_4]^+$: 373.2122, found: 373.2130.



22c

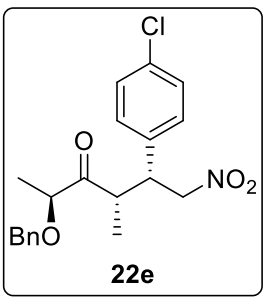
(2*S*,4*S*,5*R*)-2-Benzyloxy-5-(4-methoxyphenyl)-4-methyl-6-nitro-3-hexanone (**22c**) was prepared according to the general procedure described in section 3.2 from ketone **1** (192 mg, 1.0 mmol) and *(E)*-4-methoxy-β-nitrostyrene (215 mg, 1.2 mmol) at –78 °C for 1 h. Purification of the crude product by column chromatography (hexanes/EtOAc 85:15) afforded **22c** (215 mg, 0.8 mmol, 80% yield) as

a brownish oil. **R_f** (Hexanes/EtOAc 85:15) = 0.3; **$[\alpha]^{20}_D$** = +146.0 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3085, 3057, 3030, 2981, 2933, 2870, 2834, 1708, 1549, 1450, 1375 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.33 (5H, m, ArH), 7.10–7.05 (2H, m, ArH), 6.86–6.82 (2H, m, ArH), 4.64 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.56 (1H, dd, *J* = 12.3, 4.7 Hz, $CH_xH_yNO_2$), 4.54 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.49 (1H, dd, *J* = 12.3, 4.7 Hz, $CH_xH_yNO_2$), 4.01 (1H, q, *J* = 6.6 Hz, $BnOCHCH_3$), 3.78 (3H, s, CH_3O), 3.67 (1H, td, *J* = 9.9, 4.7 Hz, $PhCHCHCH_3$), 3.37 (1H, dq, *J* = 9.9, 7.0 Hz, $PhCHCHCH_3$), 1.32 (3H, d, *J* = 6.6 Hz, $BnOCHCH_3$), 0.92 (3H, d, *J* = 7.0 Hz, $PhCHCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.7 (C), 159.1 (C), 137.3 (C), 129.4 (C), 129.1 (2 × CH), 128.6 (2 × CH), 128.1 (2 × CH), 127.9 (2 × CH), 114.3 (2 × CH), 79.2 (CH), 78.4 (CH_2), 71.8 (CH_2), 55.2 (CH_3), 45.5 (CH), 43.9 (CH), 16.3 (CH_3), 15.8 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{25}NNaO_5$ $[M+Na]^+$: 394.1625, found: 394.1636.



22d

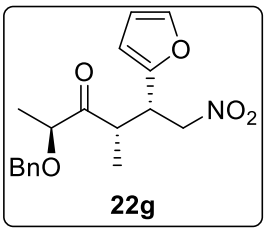
(2*S*,4*S*,5*R*)-2-Benzyloxy-4-methyl-5-(3,4-methylenedioxyphenyl)-6-nitro-3-hexanone (**22d**) was prepared according to the general procedure described in section 3.2 from ketone **1** (96 mg, 0.5 mmol) and *(E)*-3,4-methylenedioxy-β-nitrostyrene (116 mg, 0.69 mmol) at –78 °C for 1 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **22d** (157 mg, 0.41 mmol, 82% yield) as a yellow oil. **R_f** (Hexanes/EtOAc 90:10) = 0.2; **$[\alpha]^{20}_D$** = +16.5 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3025, 2985, 2927, 2900, 2869, 1712, 1543, 1499, 1485, 1441, 1370, 1241, 1031 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.31 (5H, m, CH_2ArH), 6.75–6.73 (1H, m, ArH), 6.63–6.60 (2H, m, ArH), 5.95 (2H, s, CH_2O_2), 4.66 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 4.54 (1H, d, *J* = 11.7 Hz, $PhCH_xH_y$), 4.51 (1H, dd, *J* = 12.5, 9.9 Hz, $CH_xH_yNO_2$), 4.46 (1H, dd, *J* = 12.5, 4.9 Hz, $CH_xH_yNO_2$), 4.02 (1H, q, *J* = 6.7 Hz, CHOBn), 3.63 (1H, td, *J* = 9.9, 4.9 Hz, CHAr), 3.33 (1H, dq, *J* = 9.9, 7.0 Hz, $COCHCH_3$), 1.33 (3H, d, *J* = 6.7 Hz, CH_3CHOBn), 0.92 (3H, d, *J* = 7.0 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.6 (C), 148.2 (C), 147.3 (C), 137.4 (C), 131.3 (C), 128.8 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 121.8 (CH), 108.7 (CH), 108.1 (CH), 101.3 (CH_2), 79.2 (CH), 78.6 (CH_2), 72.0 (CH_2), 46.1 (CH), 44.0 (CH), 16.4 (CH_3), 15.9 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{27}N_2O_6$ $[M+NH_4]^+$: 403.1864, found: 403.1873.



22e

(2*S*,4*S*,5*R*)-2-Benzyloxy-5-(4-chlorophenyl)-4-methyl-6-nitro-3-hexanone (**22e**) was prepared according to the general procedure described in section 3.2 from ketone **1** (196 mg, 1.0 mmol) and *(E)*-4-chloro-β-nitrostyrene (220 mg, 1.2 mmol) at –78 °C for 1 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **22e** (262 mg, 0.7 mmol, 70% yield) as a violet oil. **R_f** (Hexanes/EtOAc 85:15) = 0.3; **$[\alpha]^{20}_D$** = +42.0 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3083, 3063, 3030, 2977, 2928, 2874, 1708, 1549, 1490, 1370 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44–7.27 (7H, m, ArH), 7.12–7.08 (2H, m, ArH), 4.67 (1H, d, *J* = 11.6 Hz, $PhCH_xH_yO$), 4.56 (1H, dd, *J* = 12.7, 10.0 Hz, $CH_xH_yNO_2$), 4.54 (1H, d, *J* = 11.6 Hz, $PhCH_xH_yO$), 4.50 (1H, dd, *J* =

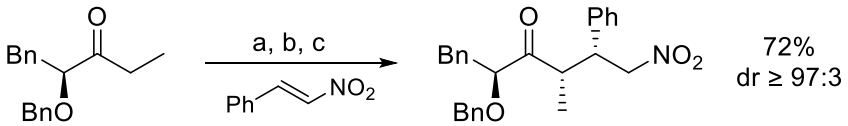
12.7, 4.7 Hz, $CH_xH_yNO_2$), 4.02 (1H, q, *J* = 6.7 Hz, BnOC<u>H</u>CH_3), 3.70 (1H, td, *J* = 10.0, 4.7 Hz, PhC<u>H</u>$CHCH_3$), 3.38 (1H, dq, *J* = 10.0, 7.0 Hz, PhCHC<u>H</u>CH_3), 1.32 (3H, d, *J* = 6.7 Hz, BnOCHC<u>H</u>$_3$), 0.90 (3H, d, *J* = 7.0 Hz, PhCHCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.2 (C), 137.2 (C), 136.1 (C), 133.7 (C), 129.4 (2 × CH), 129.1 (2 × CH), 128.6 (2 × CH), 128.2 (CH), 128. (2 × CH)0, 78.9 (CH), 78.1 (CH_2) ,71.9 (CH_2), 45.6 (CH_2), 43.1 (CH_2), 16.2 (CH_3), 15.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{22}ClNNaO_4$ $[M+Na]^+$: 398.113, found: 398.1133.



22g

(2*S*,4*S*,5*R*)-2-Benzyloxy-5-(2-furyl)-4-methyl-6-nitro-3-hexanone (**22g**) was prepared according to the general procedure described in section 3.2 from ketone **1** (96 mg, 0.5 mmol) and *(E)*-2-(2-nitrovinyl)furan (84 mg, 0.6 mmol) at –78 °C for 1. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **22g** (104 mg, 0.32 mmol, 63% yield) as a brown solid. A sample of this material was recrystallised in hexane to give **22g** as brown needles. **M_P** = 93–95 °C; **R_f** (Hexanes/EtOAc 90:10) = 0.2; **$[\alpha]^{20}_D$** = +19.1 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 2980, 2936, 2860, 1717, 1548, 1508, 1450, 1365, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.30 (6H, m, Ar<u>H</u> and furyl<u>H</u>), 6.28 (1H, dd, *J* = 3.2, 1.9 Hz, furyl<u>H</u>), 6.18–6.16 (1H, m, furyl<u>H</u>), 4.66 (1H, dd, *J* = 12.7, 9.9 Hz, $C\underline{H}_xH_yNO_2$), 4.62 (1H, d, *J* = 11.7 Hz, $PhC\underline{H}_xH_y$), 4.54 (1H, d, *J* = 11.8 Hz, $PhCH_x\underline{H}_y$), 4.49 (1H, dd, *J* = 12.7, 4.4 Hz, $CH_x\underline{H}_yNO_2$), 4.01 (1H, q, *J* = 6.8 Hz, C<u>H</u>OBn), 3.95–3.89 (1H, m, furylC<u>H</u>), 3.54–3.47 (1H, m, COC<u>H</u>CH_3), 1.33 (3H, d, *J* = 6.8 Hz, C<u>H</u>$_3$CHOBn), 1.01 (3H, d, *J* = 7.1 Hz, COCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.0 (C), 150.9 (C), 142.6 (CH), 137.5 (C), 128.7 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 110.5 (CH), 108.9 (CH), 79.3 (CH), 76.3 (CH_2), 71.9 (CH_2), 42.4 (CH), 40.0 (CH), 16.1 (CH_3), 15.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{25}N_2O_5$ $[M+NH_4]^+$: 349.1758, found: 349.1760.

3.4. Michael addition of 2 to *trans*-β-nitrostyrene

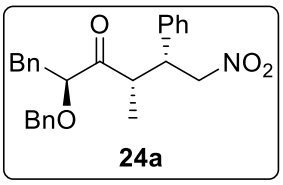


2 **24a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $TiCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$PhCH{=}CHNO_2$, –40 °C, 1 h; c) NH_4F, rt, 30 min.

Neat $TiCl_4$ (61µL, 0.55 mmol) was added dropwise to a solution of ketone **2** (134 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, neat $TiCl_4$ (61µL, 0.55 mmol) was added dropwise, followed 10 min later by the addition of *(E)*-β-nitrostyrene (90 mg, 0.6 mmol). The resultant mixture was stirred at –40 °C for 1 h.

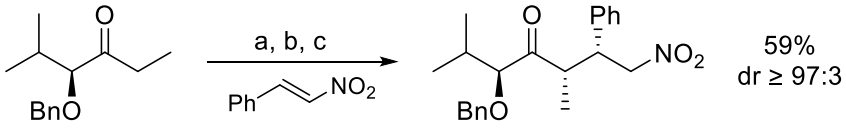
The reaction was quenched at –40 °C and treated as in section 3.2. The residue was analysed by ^{1}H NMR (dr ≥ 97:3) and purified by column chromatography (hexanes/EtOAc 90:10) to afford 151 mg (0.36 mmol, 72% yield) of (2*S,4S,5R*)-2-benzyloxy-4-methyl-6-nitro-1,5-diphenyl-3-hexanone (**24a**).



24a

(2*S*,4*S*,5*R*)-2-Benzyloxy-4-methyl-6-nitro-1,5-diphenyl-3-hexanone (24a). Purple oil. $\mathbf{R_f}$ (Hexanes/ EtOAc 90:10) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = –8.4 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3081, 3062, 3024, 2926, 2872, 1707, 1549, 1492, 1454, 1372, 1087, 732, 697 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.05 (15H, m, ArH), 4.56 (1H, d, *J* = 11.4 Hz, OCH_xH_yPh), 4.46 (1H, d, *J* = 11.4 Hz, OCH_xH_yPh), 4.17 (1H, dd, *J* = 6.8, 4.5 Hz, CHOBn), 4.14 (1H, d, *J* = 10.7 Hz, $CH_xH_yNO_2$), 4.07 (1H, dd, *J* = 10.7, 4.5 Hz, $CH_xH_yNO_2$), 3.64 (1H, td, *J* = 10.3, 4.5 Hz, $CHCH_2NO_2$), 3.22 (1H, dq, *J* = 10.3, 7.0 Hz, $CHCH_3$), 3.15 (1H, dd, *J* = 14.1, 4.5 Hz, $PhCH_xH_yCH$), 2.94 (1H, dd, *J* = 14.1, 6.8 Hz, $PhCH_xH_yCH$), 0.78 (3H, d, *J* = 7.0 Hz, $CHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 212.9 (C), 137.5 (C), 136.9 (C), 136.8 (C), 129.9 (2 × CH), 128.8 (2 × CH), 128.6 (2 × CH), 128.5 (2 × CH), 128.2 (CH), 128.2 (2 × CH), 128.0 (2 × CH), 127.8 (CH), 126.9 (CH), 83.9 (CH), 77.8 (CH_2), 73.1 (CH_2), 45.8 (CH), 44.3 (CH), 36.4 (CH_2), 15.9 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{26}H_{31}N_2O_4$ $[M+NH_4^+]^+$: 435.2278, found: 435.2279.

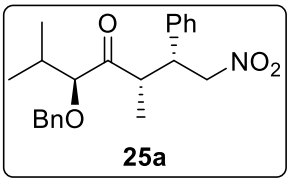
3.5. Michael addition of 3 to *trans*-β-nitrostyrene



3 **25a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $TiCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$PhCH{=}CHNO_2$, –40 °C, 1 h; c) NH_4F, rt, 30 min.

The experimental procedure described in section 3.4 was followed starting from ketone **3** (176 mg, 0.8 mmol) and *(E)*-β-nitrostyrene (143 mg, 0.96 mmol) at –40 °C for 1 h. The resulting crude was analysed by ^{1}H NMR (dr ≥ 97:3) and purified by column chromatography (hexanes/EtOAc 95:5 to 90:10) to afford 173 mg (0.47 mmol, 59% yield) of (2*S,4S,5R*)-5-benzyloxy-3,6-dimethyl-1-nitro-2-phenyl-4-heptanone (**25a**).

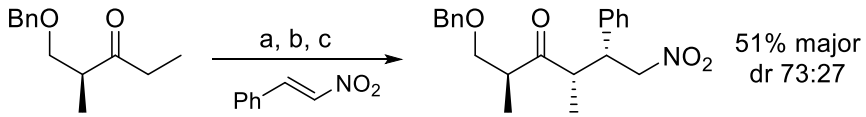


25a

(2*S*,4*S*,5*R*)-5-Benzyloxy-3,6-dimethyl-1-nitro-2-phenyl-4-heptanone (25a). Clear oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.4; $\mathbf{[\alpha]^{20}_D}$ = +11.5 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3024, 2961, 2936, 2869, 1707, 1564, 1451, 1378, 1064, 729, 697 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.10 (10H, m, ArH), 4.60 (1H, d, *J* = 11.5 Hz, CH_xH_yPh), 4.56 (1H, dd, *J* = 12.6, 10.3 Hz, $CH_xH_yNO_2$), 4.49 (1H, d, *J* = 11.5 Hz, CH_xH_yPh), 4.48 (1H, dd, *J* = 12.6, 4.5 Hz, $CH_xH_yNO_2$), 3.70 (1H, td, *J* = 9.4, 4.5 Hz, $CHCH_2NO_2$), 3.66 (1H, d, *J* = 4.8 Hz, CHOBn), 3.19 (1H, dq, *J* = 9.4, 6.8 Hz, $CHCH_3$), 2.21–2.10 (1H, m, $(CH_3)_2CH$), 0.98 (3H, d, *J* = 6.8 Hz, $COCHCH_3$), 0.95 (3H, d, *J* =

6.9 Hz, C<u>H</u>$_3$), 0.93 (3H, d, *J* = 6.9 Hz, C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.0 (C), 137.5 (C), 137.4 (C), 128.9 (2 × CH), 128.5 (2 × CH), 128.0 (CH), 128.0 (2 × CH), 127.9 (2 × CH), 127.9 (CH), 88.9 (CH), 77.7 (CH_2), 73.8 (CH_2), 46.5 (CH), 44.8 (CH), 29.9 (CH), 19.5 (CH_3), 17.1 (CH_3), 16.3 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{22}H_{31}N_2O_4$ $[M+NH_4^+]^+$: 387.2278, found: 387.2281.

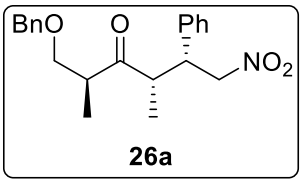
3.6. Michael addition of 13 to *trans*-β-nitrostyrene



13 **26a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $TiCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$PhCH{=}CHNO_2$, –40 °C, 1 h; c) NH_4F, rt, 30 min.

The experimental procedure described in section 3.2 was followed starting from ketone **13** (206 mg, 1.0 mmol) and *(E)*-β-nitrostyrene (90 mg, 0.6 mmol) at –40 °C for 1 h. The residue was analysed by ^{1}H NMR and purified by column chromatography (hexanes/EtOAc 90:10) to afford 90 mg (0.26 mmol, 51% yield) of (2*S,4S,5R*)-1-benzyloxy-2,4-dimethyl-6-nitro-5-phenyl-3-hexanone (**26a**).



26a

(2*S*,4*S*,5*R*)-1-Benzyloxy-2,4-dimethyl-6-nitro-5-phenyl-3-hexanone (26a). Red oil. **R_f** (Hexanes/EtOAc 90:10) = 0.3; **$[\alpha]^{20}_D$** = +24.5 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3061, 3029, 2967, 2932, 2878, 2856, 1708, 1548, 1450, 1370, 1085 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.23 (10H, m, Ar<u>H</u>), 4.58 (1H, dd, *J* = 12.8, 4.2 Hz, C<u>H</u>$_x$H$_y$$NO_2$), 4.47 (2H, s, PhC<u>H</u>$_2$O), 4.28 (1H, dd, *J* = 12.8, 10.6 Hz, CH_x<u>H</u>$_y$$NO_2$), 3.71 (1H, td, *J* = 10.6, 4.3 Hz, C<u>H</u>Ar), 3.61–3.56 (2H, m, BnOC<u>H</u>$_2$), 3.16–3.07 (1H, m, COC<u>H</u>CH_2O), 3.01 (1H, dq, *J* = 10.6, 7.2 Hz, COC<u>H</u>CHAr), 1.05 (3H, d, *J* = 6.9 Hz, C<u>H</u>$_3$$CHCH_2O$), 0.86 (3H, d, *J* = 7.2 Hz, $COCHC$<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 216.1 (C), 138.0 (C), 137.5 (C), 128.9 (2 × CH), 128.8 (2 × CH), 128.3 (CH), 128.2 (4 × CH), 127.8 (CH), 78.7 (CH_2), 74.1 (CH_2), 73.9 (CH_2), 49.9 (CH), 45.9 (CH), 45.5 (CH), 15.7 (CH_3), 13.4 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{25}NNaO_4$ $[M+Na]^+$: 378.1676, found: 378.1672.

4. Michael addition to aliphatic nitroalkenes

4.1. Preliminary studies

4.1.1. <u>Enolization with 2 equivalents $TiCl_4$</u>

Neat $TiCl_4$ (116 µL, 1.05 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing

dark red solution was stirred for 30 min at –78 °C. Then, (*E*)-1-nitro-4-phenyl-1-butene (107 mg, 0.6 mmol) was added and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.2. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 33 and spectroscopic data is shown in section 4.3.

4.1.2. Enolization with $TiCl_4$ and Et_2AlCl

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, a 1 M solution of Et_2AlCl in CH_2Cl_2 (0.55 mL, 0.55 mmol) was added, followed 5 min later by (*E*)-1-nitro-4-phenyl-1-butene (107 mg, 0.6 mmol), and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.2. The residue was analysed by ^{1}H NMR. Results are summarised in Table 33 and spectroscopic data is shown in section 4.3.

4.1.3. Enolization with $TiCl_4$ and $TiCl_3$(O*i*-Pr)

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, a freshly prepared $TiCl_3$(O*i*-Pr) solution in CH_2Cl_2 (1 mL, 0.55 mmol) was added, followed 5 min later by (*E*)-1-nitro-4-phenyl-1-butene (107 mg, 0.6 mmol), and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.2. The residue was analysed by ^{1}H NMR. Results are summarised Table 33 and spectroscopic data is shown in section 4.3.

4.1.4. Enolization with $TiCl_4$ and TiBr4

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, $TiBr_4$ (202 mg, 0.55 mmol) was added in one portion, followed 5 min later by (*E*)-1-nitro-4-phenyl-1-butene (107 mg, 0.6 mmol), and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.2. The residue was analysed by ^{1}H NMR indicated that is was composed of starting materials. Results are summarised in Table 33.

4.1.5. Enolization with 2 equivalents $TiBr_4$

A solution of ketone **1** (96 mg, 0.5 mmol) was added to a $TiBr_4$ (386 mg, 1.05 mmol) suspension in CH_2Cl_2 (2 mL) at –78 °C under N_2. The mixture was stirred at –40 °C for 1 h and cooled down to –78 °C. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 1 h at –78 °C. Then, (*E*)-1-nitro-4-phenyl-1-butene (107 mg, 0.6 mmol) was added and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.2. The residue was analysed by ^{1}H NMR indicated that is was composed of starting materials. Results are summarised in Table 33.

4.1.6. Enolization with $TiCl_4$ and $ZrCl_4$

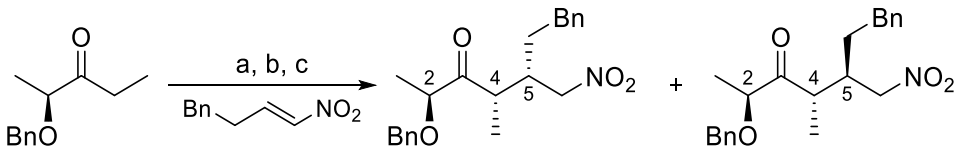
Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of chiral ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 and the resultant yellow suspension was stirred for 5 min. Anhydrous *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, $ZrCl_4$ (130 mg, 0.55 mmol) were added in one portion, followed 5 min later by (*E*)-1-nitro-4-phenyl-1-butene (107 mg, 0.6 mmol), and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.2. The residue was analysed by ^{1}H NMR. Results are summarised in Table 33 and spectroscopic data is shown in section 4.3.

4.1.7. Enolization with $TiCl_4$ and $SnCl_4$

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of chiral ketone **1** (96 mg, 3.0 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 and the resultant yellow suspension was stirred for 5 min. Anhydrous *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, 1 M $SnCl_4$ in CH_2Cl_2 (0.55 mL, 0.55 mmol) was added, followed 5 min later by (*E*)-1-nitro-4-phenyl-1-butene (107 mg, 0.6 mmol) and the resultant mixture was stirred at –78 °C for 1 h.

The reaction was quenched and treated as in section 3.2. The residue was analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 33 and spectroscopic data is shown in section 4.3.



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq LA, –78 °C, 10 min; b) 1.2 eq (*E*)-$BnCH_2CH{=}CHNO_2$, –78 °C, 1 h; c) NH_4F, rt, 30 min.

Entry	LA	dr (27l:28l)[a]	Yield 27l (%)[b]
1	Et_2AlCl	62:38	(49)[c]
2	$TiCl_3$(*i*-PrO)	65:35	(25)[c]
3	$TiCl_4$	60:40	(60)
4	$TiBr_4$	-	-
5[d]	$TiBr_4$	-	-
6	$ZrCl_4$	70:30	(38)[c]
7	$SnCl_4$	84:10:6[e]	46 (55)

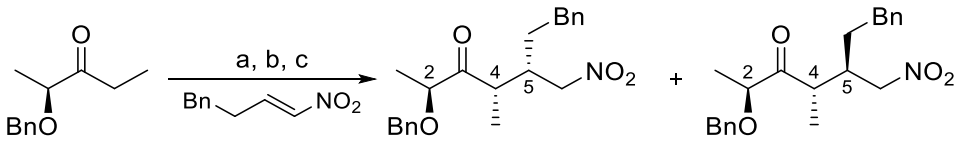
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography. Isolated overall yield into brackets.
[c] Overall conversion determined by ^1H NMR analysis of the crude mixture.
[d] Performed with 2.1 eq of $TiBr_4$.
[e] Other minor diastereomer.

Table 33

4.1.8. Optimisation studies of the Michael addition to aliphatic nitroalkenes

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of chiral ketone **1** (96 mg, 3.0 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 and the resultant yellow suspension was stirred for 5 min. Anhydrous *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, 1 M $SnCl_4$ in CH_2Cl_2 (0.55 mL, 0.55 mmol) was added, followed 5 min later by (*E*)-1-nitro-4-phenyl-1-butene (107 mg, 0.6 mmol) and the resultant mixture was stirred at **T** for **t**.

The reaction was quenched and treated as in section 3.2. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 34 and spectroscopic data is shown in section 4.3.



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$BnCH_2CH{=}CHNO_2$, T, t; c) NH_4F, rt, 30 min.

Entry	T (°C)	Time (h)	dr (27l:28l)[a]	Yield 27l (%)[b]
1	−78	1	84:10:6[c]	46 (55)
2	−78	3	84:10:6[c]	54 (66)
3	−78 → −40	1+1	83:12:5[c]	56 (66)
4[d]	−78 → −40	1+1	79:15:6[c]	51 (64)
5	−78 → −20	1+1	n.d	(33)[e]

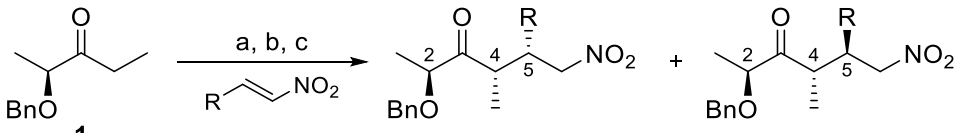
[a] Determined by ^1H NMR and HPLC analysis of the crude mixture.
[b] Isolated yield after column chromatography. Isolated overall yield into brackets.
[c] Other minor diastereomer.
[d] Performed with 1.8 eq of nitroalkene.
[e] Overall conversion determined by ^1H NMR analysis of the crude mixture.

Table 34

4.2. Michael addition to aliphatic nitroalkenes. General procedure

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of chiral ketone **1** (96 mg, 3.0 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 and the resultant yellow suspension was stirred for 5 min. Anhydrous *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, 1 M $SnCl_4$ in CH_2Cl_2 (0.55 mL, 0.55 mmol) was added, followed 5 min later by the corresponding nitroalkene (0.6 mmol), and the resultant mixture was stirred at –78 °C for 3 h.

The reaction was quenched and treated as in section 3.2. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results are summarised in Table 35 and spectroscopic data is shown in section 4.3.



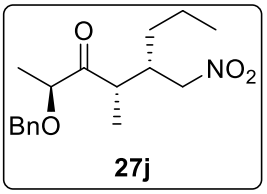
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-RCH=$CHNO_2$, –78 °C, 3 h; c) NH_4F, rt, 30 min.

Entry	Nitroalkene	R	Product	dr (27:28)[a]	Yield 27 (%)[b]
1	**Nj**	Pr	**27j**	89:6:5[c]	69 (77)
2	**Nk**	*i*-Bu	**27k**	88:12	80
3	**Nl**	$BnCH_2$	**27l**	84:10:6[c]	54 (66)
4	**Nm**	*i*-Pr	**27m**	72:21:6[c]	28 (38)
5	**Nn**	C_6H_{11}	**27n**	nd	(< 5)[a]
6	**No**	$BnO(CH_2)_2$	**27o**	94:4:2[c]	25 (27)
7[d]	**No**	$BnO(CH_2)_2$	**27o**	94:4:2[c]	(32)[a]
8[e]	**No**	$BnO(CH_2)_2$	**27o**	nd	(< 5)[a]
9	**Np**	$TIPSO(CH_2)_2$	**27p**	≥ 97:3	64
10	**Nq**	(*S*)-CH(OTBDPS)Me	**27q**	-	-

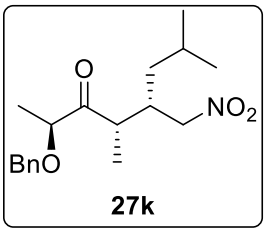
[a] Determined by ^1H NMR and HPLC analysis of the crude mixture.
[b] Isolated yield after column chromatography. Isolated overall yield into brackets.
[c] Other minor diastereomer.
[d] Reaction performed with 2 eq of electrophile.
[e] Reaction performed with 0.5 eq of electrophile.

Table 35

4.3. Spectroscopic data of Michael adducts derived from ketone 1 and aliphatic nitroalkenes

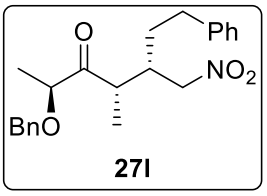


(2*S*,4*S*,5*S*)-2-Benzyloxy-4-methyl-5-(nitromethyl)-3-octanone (**27j**) was prepared according to the general procedure described in section 4.2 from ketone **1** (96 mg, 0.5 mmol) and (*E*)-1-nitro-1-pentene (74 mg, 0.6 mmol) at –78 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **27j** (105 mg, 0.4 mmol, 69% yield) as a yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = +22.9 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2963, 2932, 2869, 1708, 1552, 1450, 1370, 1111 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.29 (5H, m, ArH), 4.60 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.56 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.49 (1H, dd, *J* = 12.6, 4.3 Hz, $CH_xH_yNO_2$), 4.24 (1H, dd, *J* = 12.6, 8.2 Hz, $CH_xH_yNO_2$), 4.04 (1H, q, *J* = 6.8 Hz, CHOBn), 3.28–3.20 (1H, m, $COCHCH_3$), 2.61–2.54 (1H, m, $CHCH_2NO_2$), 1.39 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 1.38–1.31 (4H, m, $CH_2CH_2CH_3$), 1.01 (3H, d, *J* = 7.1 Hz, $COCHCH_3$), 0.87 (3H, m, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.1 (C), 137.5 (C), 128.7 (2 × CH), 128.1 (C), 128.0 (2 × CH), 79.7 (CH), 76.8 (CH_2), 71.9 (CH_2), 41.3 (CH), 38.3 (CH), 32.7 (CH_2), 20.1 (CH_2), 17.0 (CH_3), 13.9 (CH_3), 11.7 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{17}H_{29}N_2O_4$ $[M+NH_4]^+$: 325.2122, found: 325.2118.



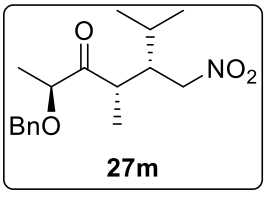
27k

(2*S*,4*S*,5*S*)-2-Benzyloxy-4,7-dimethyl-5-(nitromethyl)-3-octanone (**27k**) was prepared according to the general procedure described in section 4.2 from ketone **1** (96 mg, 0.5 mmol) and (*E*)-4-methyl-1-nitro-1-pentene (78 mg, 0.6 mmol) at –78 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **27k** (128 mg, 0.40 mmol, 80% yield) as a yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = +21.4 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3029, 2954, 2932, 2865, 1708, 1552, 1450, 1378, 1111 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.28 (5H, m, ArH), 4.59 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.56 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.47 (1H, dd, *J* = 12.6, 4.3 Hz, $CH_xH_yNO_2$), 4.21 (1H, dd, *J* = 12.6, 8.1 Hz, $CH_xH_yNO_2$), 4.03 (1H, q, *J* = 6.8 Hz, CHOBn), 3.26–3.19 (1H, m, $COCHCH_3$), 2.67–2.60 (1H, m, $CHCH_2NO_2$), 1.65–1.55 (1H, m, $CH(CH_3)_2$), 1.40 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 1.30–1.17 (2H, m, $CH_2CH(CH_3)_2$), 1.00 (3H, d, *J* = 7.0 Hz, $COCHCH_3$), 0.88 (3H, d, *J* = 6.6 Hz, $C(CH_3)_2$), 0.82 (3H, d, *J* = 6.6 Hz, $C(CH_3)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.2 (C), 137.5 (C), 128.7 (2 × CH), 128.2 (C), 128.1 (2 × CH), 79.7 (CH), 77.0 (CH_2), 71.9 (CH_2), 41.4 (CH), 39.7 (CH_2), 36.2 (CH), 25.2 (CH), 22.8 (CH_3), 22.2 (CH_3), 17.1 (CH_3), 11.4 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{31}N_2O_4$ $[M+NH_4]^+$: 339.2278, found: 339.2276.



27l

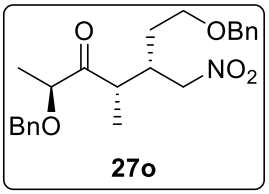
(2*S*,4*S*,5*S*)-2-Benzyloxy-4-methyl-5-(nitromethyl)-7-phenyl-3-heptanone (**27l**) was prepared according to the general procedure described in section 4.2 from ketone **1** (96 mg, 0.5 mmol) and (*E*)-1-nitro-4-phenyl-1-butene (107 mg, 0.6 mmol) at –78 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **27l** (99 mg, 0.27 mmol, 54% yield) as a yellowish oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = +164.0 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3083, 3057, 3025, 2976, 2927, 2860, 1708, 1544, 1450, 1375, 1112 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.09 (10H, m, ArH), 4.57 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.53 (1H, d, *J* = 11.7 Hz, $PhCH_xH_yO$), 4.52 (1H, dd, *J* = 12.7, 4.4 Hz, $CH_xH_yNO_2$), 4.29 (1H, dd, *J* = 12.7, 8.0 Hz, $CH_xH_yNO_2$), 3.99 (1H, q, J = 6.8 Hz, $BnOCHCH_3$), 3.28 (1H, qd, *J* = 7.1, 5.1 Hz, COCHCH), 2.65–2.55 (2H, m, $BnCH_2$), 2.63 (2H, t, *J* = 8.1 Hz, $PhCH_2CH_2$), 1.36 (3H, d, *J* = 6.8 Hz, $BnOCHCH_3$) 1.03 (3H, d, *J* = 7.1 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.7 (C), 140.7 (C), 137.4 (C), 128.5 (2 × CH), 128.5 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 127.8 (2 × CH), 126.2 (CH), 79.4 (CH), 76.4 (CH_2), 71.7 (CH_2), 41.3 (CH), 38.1 (CH), 33.1 (CH_2), 32.0 (CH_2), 16.7 (CH_3), 11.8 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{22}H_{27}NNaO_4$ $[M+Na]^+$: 392.1832, found: 392.1839.



27m

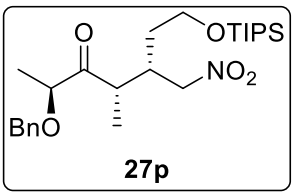
(2*S*,4*S*,5*S*)-2-Benzyloxy-4,6-dimethyl-5-(nitromethyl)-3-heptanone (**27m**) was prepared according to the general procedure described in section 4.2 from ketone **1** (96 mg, 0.5 mmol) and (*E*)-3-methyl-1-nitro-1-butene (72 mg, 0.6 mmol) at –78 °C and the resultant mixture was stirred at –78 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **27m** (44 mg, 0.14 mmol, 28% yield) as a

yellowish oil. **R_f** (Hexanes/EtOAc 90:10) = 0.3; **$[\alpha]^{20}_D$** = +15.9 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3025, 2963, 2932, 2883, 1708, 1543, 1454, 1374, 1107 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.29 (5H, m, ArH), 4.61 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.56 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.45 (1H, dd, *J* = 13.8, 4.4 Hz, $CH_xH_yNO_2$), 4.29 (1H, dd, *J* = 13.8, 7.1 Hz, $CH_xH_yNO_2$), 4.06 (1H, q, *J* = 6.8 Hz, CHOBn), 3.39–3.33 (1H, m, $COCHCH_3$), 2.61–2.55 (1H, m, $CHCH_2NO_2$), 1.74–1.66 (1H, m, $CH(CH_3)_2$), 1.41 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 0.97 (3H, d, *J* = 7.0 Hz, $COCHCH_3$), 0.96 (3H, d, *J* = 6.8 Hz, $C(CH_3)_2$), 0.87 (3H, d, *J* = 6.8 Hz, $C(CH_3)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.2 (C), 137.6 (C), 128.7 (2 × CH), 128.1 (C), 128.0 (2 × CH), 79.5 (CH), 75.1 (CH_2), 71.8 (CH_2), 43.5 (CH), 40.5 (CH), 30.1 (CH), 20.6 (CH_3), 19.2 (CH_3), 17.1 (CH_3), 12.1 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{17}H_{29}N_2O_4$ $[M+NH_4]^+$: 325.2122, found: 325.2125.



27o

(2*S*,4*S*,5*S*)-2,7-Dibenzyloxy-4-methyl-5-(nitromethyl)-3-hepanone (**27o**) was prepared according to the general procedure described in section 4.2 from ketone **1** (96 mg, 0.5 mmol) and (*E*)-4-benzyloxy-1-nitro-1-butene (125 mg, 0.6 mmol) at –78 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **27o** (51 mg, 0.13 mmol, 25% yield) as a colourless oil. **R_f** (Hexanes/EtOAc 80:20) = 0.2; **$[\alpha]^{20}_D$** = +10.2 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 3025, 2972, 2927, 2856, 1717, 1548, 1459, 1378, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.26 (5H, m, ArH), 4.55 (2H, s, $PhCH_2OCH$), 4.52 (1H, dd, *J* = 13.0, 4.6 Hz, $CH_xH_yNO_2$), 4.42 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.38 (1H, d, *J* = 11.8 Hz, $PhCH_xH_y$), 4.36 (1H, dd, *J* = 13.0, 7.7 Hz, $CH_xH_yNO_2$), 4.04 (1H, q, *J* = 6.8 Hz, CHOBn), 3.49 (2H, t, *J* = 6.0 Hz, CH_2OBn), 3.30–3.24 (1H, m, $COCHCH_3$), 2.77–2.69 (1H, m, $CHCH_2NO_2$), 1.71 (2H, ddd, *J* = 12.5, 6.1, 2.4 Hz, CH_2CH_2OBn), 1.34 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 1.03 (3H, d, *J* = 7.0 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.8 (C), 138.1 (C), 137.6 (C), 128.6 (2 × CH), 128.5 (2 × CH), 128.1 (C), 128.0 (2 × CH), 127.8 (C, 2 × CH), 79.4 (CH), 76.6 (CH_2), 73.1 (CH2), 71.8 (CH_2), 67.9 (CH_2), 41.8 (CH), 36.6 (CH), 30.3 (CH_2), 16.8 (CH_3), 12.2 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{23}H_{33}N_2O_5$ $[M+NH_4]^+$: 417.2384, found: 417.2393.

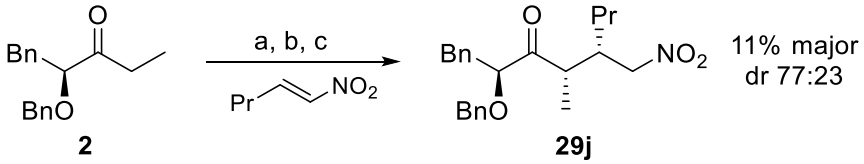


27p

(2*S*,4*S*,5*S*)-2-(Benzyloxy)-4-methyl-5-(nitromethyl)-7-triisopropylsilyloxy-3-heptanone (**27p**) was prepared according to the general procedure described in section 4.2 from ketone **1** (96 mg, 0.45 mmol) and (*E*)-4-triisopropylsilyloxy-1-nitro-1-butene (155 mg, 0.55 mmol) at –78 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 95:5) afforded **27p** (133 mg, 0.29 mmol, 64% yield) as a colourless oil. **R_f** (Hexanes/EtOAc 90:10) = 0.3; **$[\alpha]^{20}_D$** = +11.6 *(c* 1.0, $CHCl_3$); **IR** (ATR) ν 2942, 2860, 1710, 1546, 1457, 1372, 1096 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (5H, m, ArH), 4.56 (1H, dd, *J* = 12.9, 5.0 Hz, $CH_xH_yNO_2$), 4.56 (2H, s, $PhCH_2OCH$), 4.40 (1H, dd, *J* = 12.9, 7.3 Hz, $CH_xH_yNO_2$), 4.07 (1H, q, *J* = 6.8 Hz, CHOBn), 3.75 (2H, t, *J* = 5.9 Hz, CH_2OTIPS), 3.30 (1H, qd, *J* = 7.0, 5.2 Hz, $COCHCH_3$), 2.79–2.70 (1H, m, $CHCH_2NO_2$), 1.67–1.50 (2H, m, CH_2CH_2OTIPS), 1.37 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 1.05 (3H, d, *J* = 7.0 Hz, $COCHCH_3$), 1.10–

1.00 (21H, m, Si(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.6 (C), 137.5 (C), 128.5 (2 × CH), 127.9 (C, 2 × CH), 79.3 (CH), 76.6 (CH_2), 71.6 (CH_2), 61.1 (CH_2), 41.5 (CH), 36.3 (CH), 32.9 (CH_2), 17.9 (CH), 16.7 (CH_3), 12.3 (CH_3), 11.8 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{25}H_{43}NNaO_5Si$ $[M+Na]^+$: 488.2803, found: 488.2806.

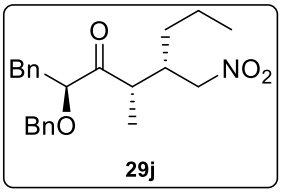
4.4. Michael addition of 2 to (*E*)-1-nitro-1-pentene



2 **29j**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$RCH=CHNO_2$, –78 °C, 3 h; c) NH_4F, rt, 30 min.

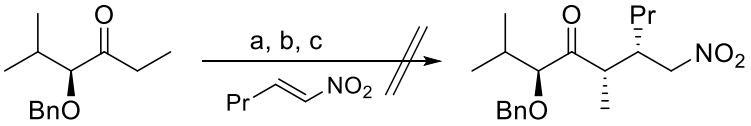
The experimental procedure described in section 4.2 was followed starting from ketone **2** (268 mg, 1.0 mmol) and (*E*)-1-nitro-1-pentene (138 mg, 1.2 mmol). The residue was analysed by ^{1}H NMR (dr 77:23) and purified by column chromatography (hexanes/EtOAc 90:10) to afford 41 mg (0.11 mmol, 11% yield) of (2*S*,4*S*,5*S*)-2-benzyloxy-4-methyl-5-nitromethyl-1-phenyl-3-octanone (**29j**).



29j

(2*S*,4*S*,5*S*)-2-Benzyloxy-4-methyl-5-nitromethyl-1-phenyl-3-octanone (29j). Yellow oil. **R_f** (Hexanes/EtOAc/ 90:10) = 0.3; **$[\alpha]^{20}_D$** = –2.9 (*c* 2.0, $CHCl_3$); **IR** (ATR) ν 3027, 2955, 2929, 2872, 1707, 1543, 1454, 1375, 1087, 735, 684 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.14 (10H, m, Ar<u>H</u>), 4.51–4.38 (3H, m, OC<u>H</u>$_2$Ph, C<u>H</u>$_x$H$_y$NO$_2$), 4.20–4.13 (2H, m, C<u>H</u>OBn, CH$_x$<u>H</u>$_y$NO$_2$), 3.13–2.93 (3H, m, PhC<u>H</u>$_2$CHOBn, COC<u>H</u>CH$_3$), 2.52–2.43 (1H, m, C<u>H</u>CH$_2$NO$_2$), 1.32–1.12 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$), 0.91 (3H, d, *J* = 7.0 Hz, C<u>H</u>$_3$CHCO), 0.82 (3H, t, *J* = 7.0 Hz CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 213.2 (C), 137.1 (C), 137.0 (C), 129.5 (2 × CH), 128.5 (2 × CH), 128.4 (C), 127.9 (2 × CH), 126.7 (C), 84.6 (CH), 76.5 (CH_2), 72.9 (CH_2), 41.8 (CH), 38.0 (CH_2), 37.7 (CH), 32.3 (CH_2), 19.8(CH_2), 13.7 (CH_3), 11.0 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{23}H_{33}N_2O_4$ $[M+NH_4^+]^+$: 401.2435, found: 401.2437.

4.5. Michael addition of 3 to (*E*)-1-nitro-1-pentene

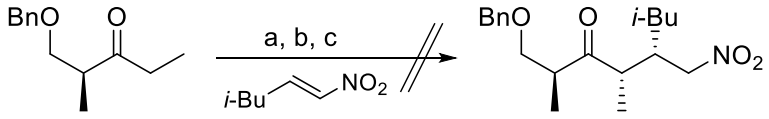


3 **30j**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$RCH=CHNO_2$, –78 °C, 3 h; c) NH_4F, rt, 30 min.

The experimental procedure described in section 4.2 was followed starting from ketone **3** (220 mg, 1.0 mmol) and *(E)*-1-nitro-1-pentene (138 mg, 1.2 mmol). The residue was analysed by ^{1}H NMR but no product was observed.

4.6. Michael addition of 13 to (*E*)-4-methyl-1-nitro-1-pentene



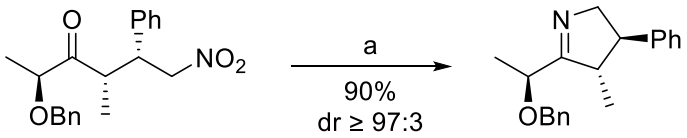
13 **31k**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) 1.1 eq $SnCl_4$, –78 °C, 10 min; b) 1.2 eq (*E*)-$RCH{=}CHNO_2$, –78 °C, 3 h; c) NH_4F, rt, 30 min.

The experimental procedure described in section 4.2 was followed starting from ketone **13** (103 mg, 0.5 mmol) and (*E*)-4-methyl-1-nitro-1-pentene (78 mg, 0.6 mmol) at –40 °C or –20 °C for 3-6 h. The resulting crudes were analysed by ^{1}H NMR. The expected Michael **31k** adduct was never observed in yields higher than 10%.

4.7. Nitroalkane transformation of 22a

4.7.1. Reduction to amine with Ni_2B[51,58]

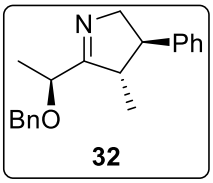


22a **32**

a) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, CH_2Cl_2, 0 °C, 30 min.

Solid $NaBH_4$ (6 mg, 0.15 mmol) was added in one portion to a solution of $NiCl_2{\cdot}6H_2O$ (12 mg, 5 µmol) in MeOH (2 mL) at rt to observe the formation of a black clumps and heavy frothing. The solution was sonicated for 30 min and resulting black dispersion was cooled to 0 °C. Nitroalkane **22a** (34 mg, 0.1 mmol) was added in MeOH (0.5 mL) followed by the addition of solid $NaBH_4$ (19 mg, 0.5 mmol) in one portion causing more frothing. The resultant mixture was stirred at 0 °C for 30 min.

The reaction was quenched by the addition of sat. NH_4Cl (5 mL) at rt with vigorous stirring. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^{1}H NMR and purified by column chromatography (CH_2Cl_2/MeOH 96:4) to afford 26 mg (90 µmol, 90% yield) of (3*R*,4*S*)-5-((*S*)-1-(benzyloxy)ethyl)-4-methyl-3-phenyl-3,4-dihydro-2H-pyrrole (**32**).

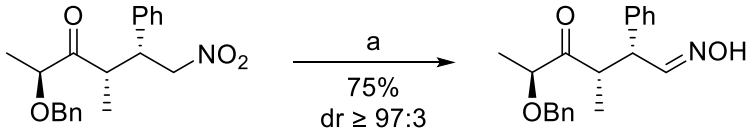


32

(3*R*,4*S*)-5-([(*S*)-1-(Venzyloxyethyl)]-4-methyl-3-phenyl-3,4-dihydro-2*H*-pyrrole (32). Colourless oil. $\mathbf{R_f}$ (CH_2Cl_2/MeOH 96:4) = 0.5; $\mathbf{[\alpha]^{20}_D}$ = +4.3 *(c* 1.1, $CHCl_3$); **IR** (ATR) ν 3083, 3061, 3034, 2976, 2923, 2865, 1574, 1499, 1454, 1365, 1205, 1067 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.19 (10H, m, Ar<u>H</u>), 5.15 (1H, q, *J* = 6.7 Hz, BnOC<u>H</u>), 4.63 (1H, d, *J* = 11.7 Hz, PhC<u>H</u>$_x$H$_y$O), 4.57 (1H, d, *J* = 11.7 Hz, PhC<u>H</u>$_x$H$_y$O), 4.43 (1H, ddd, *J* = 14.1, 8.7, 2.3 Hz, C<u>H</u>$_x$H$_y$N), 4.09 (1H, dd, *J* = 14.1, 7.0,

2.0 Hz, CH_xH_yN), 3.16–3.06 (2H, m, PhC<u>H</u>, CNC<u>H</u>), 1.42 (3H, d, *J* = 6.7 Hz, BnOCHC<u>H</u>$_3$), 1.07 (3H, d, *J* = 6.7 CNCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 149.9 (C), 141.1 (C), 138.2 (C), 129.2 (2 × CH), 128.5 (2 × CH), 127.8 (CH), 127.8 (2 × CH), 127.6 (CH), 127.0 (2 × CH), 72.0 (CH_2), 69.0 (CH_2), 68.6 (CH), 46.4 (CH_2), 46.4 (CH_2), 18.3 (CH_3), 17.3 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{24}NO$ $[M+H]^+$: 294.1852; found 294.1861.

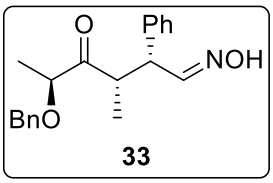
4.7.2. <u>Reduction to oxime with $SnCl_2$</u>[59]



22a **33**

a) 1:3:3 $SnCl_2$/PhSH/Et_3N, CH_2Cl_2, rt, 30 min.

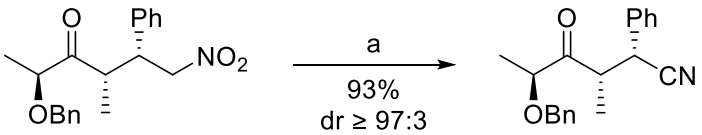
PhSH (140 µL, 1.35 mmol) and Et_3N (210 µL, 1.5 mmol) were added to a stirred suspension of anh. $SnCl_2$ (86 mg, 0.45 mmol) in CH_3CN (0.6 mL) at rt. Then, a solution of nitroalkane **22a** (103 mg, 0.3 mmol) in CH_3CN (1.2 mL) was added. After 30 min, the reaction mixture was concentrated under vacuum and the residue was purified by column chromatography (hexanes/EtOAc 80:20) to afford 73 mg (0.23 mmol, 75% yield) of ((2*R*,3*S*,5*S*,)-5-benzyloxy-3-methyl-4-oxo-2-phenylhexanal oxime (**33**).



33

(2*R*,3*S*,5*S*,)-5-Benzyloxy-3-methyl-4-oxo-2-phenylhexanal oxime (33). Yellow oil. **R_f** (Hexanes/EtOAc) = 0.2; **$[\alpha]^{20}_D$** = –104.2 *(c* 1.3, $CHCl_3$); **IR** (ATR) ν 3278 (br), 3084, 3062, 3024, 2974, 2932, 2875, 1495, 1451, 1368, 1096 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.18 (11H, m, Ar<u>H</u>, NC<u>H</u>), 4.72 (1H, d, *J* = 11.8 Hz, PhC<u>H</u>$_x$H$_y$O), 4.48 (1H, d, *J* = 11.8 Hz, PhC<u>H</u>$_x$H$_y$O), 3.79 (1H, q, *J* = 6.4 Hz, BnOC<u>H</u>), 3.27 (1H, dd, *J* = 11.7, 1.5 Hz, PhC<u>H</u>), 2.28 (1H, dq, *J* = 11.7, 6.6 Hz, COC<u>H</u>CH$_3$), 1.40 (3H, d, *J* = 6.4 Hz, BnOCHC<u>H</u>$_3$), 0.83 (3H, d, *J* = 6.6 Hz, CNCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 152.1 (CH), 139.2 (C), 138.0 (C), 129.1 (2 × CH), 129.0 (2 × CH), 128.5 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.6 (CH), 76.6 (CH), 71.4 (CH_2), 43.4 (CH), 34.7 (CH), 13.0 (CH_3), 12.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{24}NO_4$ $[M+H]^+$: 326.1751, found: 326.1750.

4.7.3. <u>Reduction to nitrile with $Sn(SPh)_4$</u>[60]

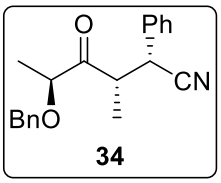


22a **34**

a) $Sn(SPh)_4$, PMe_3, DEAD, DMAP, CH_2Cl_2, rt, 30 min.

To a stirred suspension of $Sn(SPh)_4$ (11 mg, 0.02 mmol) [prepared from $SnCl_4$/4 PhSH/4 Et_3N in toluene 1 M by mixture and filtration], DMAP (13 mg, 0.11 mmol), 1 M solution of Me_3P in

THF (0.22 mL, 0.22 mmol) and 40% solution of DEAD in toluene (50 µL, 0.11 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C under N_2 atmosphere, nitroalkane **22a** (34 mg, 0.1 mmol) was added with CH_2Cl_2 (0.5 mL) and the resulting mixture was stirred at 0 °C. After 30 min, the reaction mixture was concentrated under vacuum and the residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 28 mg (0.09 mmol, 93% yield) of (2*R*,3*S*,5*S*)-5-benzyloxy-3-methyl-4-oxo-2-phenylhexanenitrile (**34**).



34

(2*R*,3*S*,5*S*)-5-Benzyloxy-3-methyl-4-oxo-2-phenylhexanenitrile (34). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = –104.2 *(c* 1.3, $CHCl_3$); **IR** (ATR) ν 3084, 3059, 3031, 2974, 2929, 2869cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.28 (10H, m, ArH,), 4.56 (1H, s, PhCH_2O), 4.10 (1H, q, *J* = 6.9 Hz, BnOCH), 3.94 (1H, d, *J* = 9.5 Hz, PhCH), 3.57 (1H, dq, *J* = 9.5, 7.0 Hz, COCHCH$_3$) 1.35 (3H, d, *J* = 6.9 Hz, BnOCHCH_3), 1.01 (3H, d, *J* = 7.0 CNCHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 212.0 (C), 137.5 (C), 133.5 (C), 129.2 (2 × CH), 128.7 (CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.1 (CH), 127.9 (2 × CH), 120.2 (C), 80.0 (CH), 71.7 (CH_2), 46.0 (CH), 39.4 (CH), 16.4 (CH_3), 15.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{22}N_2O_2$ $[M+NH_4]^+$: 325.1911; found 325.1913.

5. Double Michael additions

5.1. General Procedure[202]

Neat $TiCl_4$ (116 µL, 1.05 mmol) was added dropwise to a solution of ketone **1** (96 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, the first electrophile, either methyl vinyl ketone or *trans*-β-nitrostyrene (0.6 mmol) was added and the resultant mixture was stirred at –78 °C for 4 h. After this time, if needed, neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise and the solution was stirred for 5 min. Then, the second electrophile, either methyl vinyl ketone or *trans*-β-nitrostyrene (0.6 mmol) was added and the reaction was stirred at **T** for **t**.

The reaction was quenched by the addition of sat. NH_4Cl (3 mL), or with a 25% solution of NH_4F (3 mL) if there is a nitroalkene in the rection, at rt with vigorous stirring for 30 min. The mixture was partitioned with CH_2Cl_2 (2 mL) and H_2O (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting crudes were analysed by ^{1}H NMR but no double Michael adduct was ever observed in the reaction mixtures.

6. Michael additions to other α-β-unsaturated carbonyl compounds

6.1. Addition to DEAD

The experimental procedure described in section 2.2 was followed starting from ketone **1** (192 mg, 1.0 mmol) and 40% solution of DEAD in toluene (650 µL, 1.5 mmol) at –20 °C for 16 h. Analysis of the residue by ^{1}H NMR indicated that is was composed of starting materials.

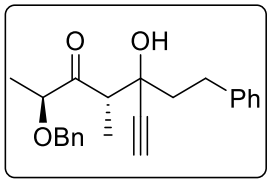
6.2. Addition to iodoalkenes

The experimental procedure described in section 2.2 was followed starting from ketone **1** (192 mg, 1.0 mmol) and (*E*)-1-iodo-5-phenyl-1-penten-3-one (343 mg, 1.2 mmol) at –20 °C for 16 h. Analysis of the residue by ^{1}H NMR indicated that is was composed of starting materials. Reaction carried out with ethyl (*E*)-3-iodoacrylate (271 mg, 1.2 mmol) performed in the same way.

6.3. Addition to alkynyl ketones

The experimental procedure described in section 2.2 was followed starting from ketone **1** (192 mg, 1.0 mmol) and 5-phenyl-1-pentyn-3-one (190 mg, 1.2 mmol) at –20 °C for 16 h. Analysis of the residue by ^{1}H NMR indicated that is was composed of starting materials. Reaction carried out with ethyl propiolate (122 µL, 1.2 mmol) performed in the same way.

The experimental procedure described in section 2.3 was followed starting from ketone **1** (192 mg, 1.0 mmol) and 5-phenyl-1-pentyn-3-one (190 mg, 1.2 mmol) at –20 °C for 16 h. The resulting crude was analysed by ^{1}H NMR and purified by column chromatography (hexanes/EtOAc 85:15) afforded the aldol adducts (60 mg, 0.17 mmol, 17% yield) as an 83:17 a mixture of diastereomers.

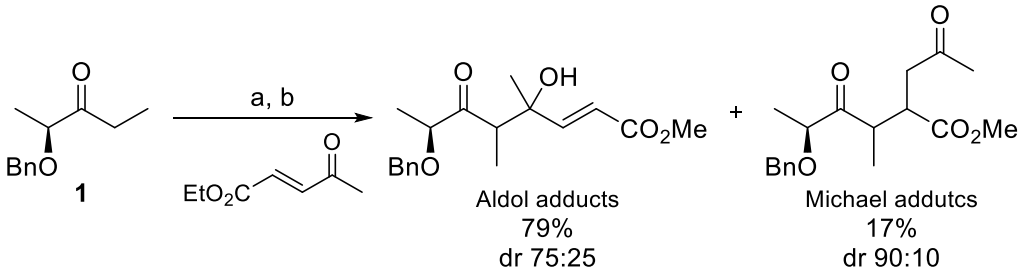


(2S,4S)-2-benzyloxy-5-hydroxy-4-methyl-5-phenethyl-6-heptyn-3-one. Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.20; **IR** (ATR) ν 2935, 2867, 1707, 1454, 1100 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.15 (10 H, m, ArH), 4.59–4.49 (2H, m, $PhCH_2O$), 4.02 (1H, q, *J* = 6.9 Hz, CHOBn), 3.23 (1H, q, *J* = 7.2 Hz, COCH), 2.99–2.83 (2H, m, CH_2CH_2Ph), 2.55 (1H, d, *J* = 2.0 Hz, C≡CH), 1.94– 1.87 (2H, m, CH_2CH_2Ph), 1.39 (3H, d, *J* = 6.9 Hz, CH_3CHOBn), 1.37 (3H, d, *J* = 7.2 Hz, $COCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 216.3, 141.9, 137.3, 128.5, 128.4, 128.4, 128.0, 127.8, 125.9, 83.8, 79.8, 73.9, 73.0, 71.7, 49.2, 43.1, 30.6, 17.2, 13.7; **HRMS** (+ESI): *m*/*z* calcd. for $C_{23}H_{30}NO_3$ $[M+NH_4]^+$: 368.2220, found: 368.2217.

6.4. Addition to allenyl ketones

The experimental procedure described in section 2.2 and 2.3 were followed starting from ketone **1** (192 mg, 1.0 mmol) and 1-phenyl-4,5-hexadien-3-one (207 mg, 1.2 mmol) at –20 °C for 16 h. Analysis of the crude mixtures by ^{1}H NMR indicated that they were composed of starting materials.

6.5. Addition to Methyl *trans*-4-oxo-2-pentenoate



a) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; b) 1.5 eq (*E*)-$MeO_2CCH{=}CHCOCH_3$, –20 °C, 3 h.

The experimental procedure described in section 2.2 was followed starting from ketone **1** (192 mg, 1.0 mmol) and methyl *trans*-4-oxo-2-pentenoate (192 mg, 1.5 mmol) at –20 °C for 3 h. The resulting crude were analysed by ^{1}H NMR and purified by column chromatography (hexanes/EtOAc 85:15) afforded 61 mg (0.19 mmol, 19% yield) of Michael adducts (dr 90:10) and 227 mg (0.71 mmol, 71% yield) of aldol adducts (dr 75:25). Reaction carried out at –78 °C afforded 35 mg (0.11 mmol, 11% yield) of Michael adducts (dr 90:10) and 192 mg (0.60 mmol, 60% yield) of aldol adducts (dr 75:25).

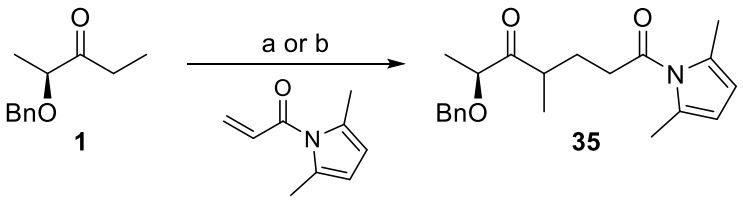
6.6. Addition to *N*-acryloyl-2,5-dimethylpyrrole

6.6.1. Enolization with 2 equivalents of $TiCl_4$

The experimental procedure described in section 2.2 was followed starting from ketone **1** (96 mg, 0.5 mmol) and *N*-acryloyl-2,5-dimethylpyrrole (90 mg, 0.6 mmol) at **T** for **t**. The resulting crude was analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 36 and spectroscopic data is shown in section 6.6.2.

6.6.2. Enolization with $TiCl_4$ and $SnCl_4$

The experimental procedure described in section 2.3 was followed starting from ketone **1** (96 mg, 0.5 mmol) and *N*-acryloyl-2,5-dimethylpyrrole (90 mg, 0.6 mmol) at **T** for **t**. The resulting crudes were analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 36.

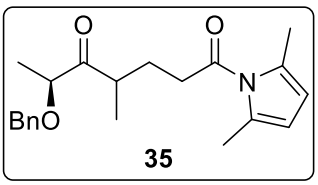


a) (i) 2.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (i) 1.2 eq *N*-acryloyl-2,5-dimethylpyrrole, T, time; b) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, –78 °C, 30 min; (ii) (i) 1.1 eq $SnCl_4$, –78 °C, 10 min; (iii) 1.2 eq *N*-acryloyl-2,5-dimethylpyrrole, T, time.

Entry	LA	T (°C)	t (h)	dr[a]	Yield[b] (%)
1	$TiCl_4$	–78	1	94:6	10
2	$TiCl_4$	–40	3	93:7	10
3	$TiCl_4$	–20	24	-	5
4	$SnCl_4$	–78	3	>97:3	11
5	$SnCl_4$	–40	3	>97:3	15

[a] Determined by ^1H NMR and HPLC analysis of the crude mixture.
[b] Isolated overall yield after column chromatography.

Table 36



(6*S*)-6-Benzyloxy-1-(2,5-dimethylpyrrolyl)-4-methyl-1,5-heptanedione (35) was prepared according to the procedure described in section 6.6.2 from ketone **1** (96 mg, 0.5 mmol) and *N*-acryloyl-2,5-dimethylpyrrole (90 mg, 0.6 mmol) at –40 °C for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 90:10) afforded **35** (26 mg, 0.07 mmol, 15% yield) as an orange oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = –8.4 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3024, 2967, 2926, 2866, 1707, 1675, 1448, 1359, 1261, 1239, 1090, 976, 732, 697 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.25 (5H, m, ArH), 5.80 (2H, s, $N(CH_3CCH)_2$), 4.54 (2H, s, CH_2Ph), 4.05 (1H, q, *J* = 6.8 Hz, CHOBn), 3.20–3.10 (1H, m, $COCHCH_3$), 2.80–2.65 (2H, m, CH_2CO), 2.36 (6H, s, $N(CH_3CCH)_2$), 2.15–2.04 (1H, m, $CH_xH_yCH_2CO$), 1.85–1.75 (1H, m, $CH_xH_yCH_2CO$), 1.34 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 1.12 (3H, d, *J* = 6.7 Hz, CH_3CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 214.7 (C), 174.0 (C), 137.5 (C), 130.3 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 111.5 (CH), 79.3 (CH), 71.7 (CH_2), 40.0 (CH), 36.1 (CH_2), 27.9 (CH_2), 16.7 (CH_3), 16.7 (CH_3), 16.5 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{31}N_2O_3$ $[M+NH_4^+]^+$: 359.2329, found: 359.2315.

CHAPTER 2

Synthesis of the tetrahydropyran ring of (+)-herboxidiene

EXPERIMENTAL SECTION FOR CHAPTER 2
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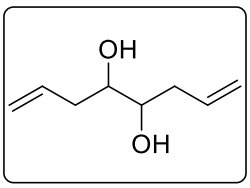
1. Synthesis of the tetrahydropyran ring of (+)-herboxidiene

1.1. Aldol reaction of 1

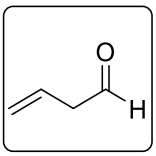
1.1.1. 3-Butenal[209]

40% aqueous glyoxal (4.6 mL, 40 mmol) and allyl bromide (8.7 mL, 0.1 mol) were added to a suspension of tin powder (11.87 g, 0.1 mol) in 1:1 THF/H_2O (20 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at rt for 1 h. A solution of 12% HCl (10 mL) was added and the mixture was stirred vigorously for 10 min. The resulting emulsion was partitioned with Et_2O (20 mL) and a solution of 12% HCl (10 mL), filtered through a cotton plug and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated. The resulting oil was purified by column chromatography (60:40 EtOAc/hexanes) to afford 4.27 g (30 mmol, 75% yield) of 1,7-octadiene-4,5-diol as a 2:1 mixture of diastereomers.



1,7-Octadiene-4,5-diol. Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 40:60) = 0.5; **IR** (film) ν 3419 (br), 3074, 2976, 2933, 2910, 1642, 1439, 1054 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 5.95–5.78 (2H, m, 2 × CH_2=C<u>H</u>), 5.24–5.11 (4H, m, 2 × C<u>H</u>$_2$=CH), 3.61–3.53 (2H, m, 2 × C<u>H</u>OH), 2.45–2.17 (4H, m, 2 × C<u>H</u>$_2$CHOH), 2.22–1.88 (2H, br s, 2 × O<u>H</u>); ^{13}**C NMR** (100.6 MHz, $CDCl_3$) δ 134.4, 117.9, 72.7, 38.1.

A suspension of diol 1,7-octadiene-4,5-diol (1.78 g, 12.5 mmol) and $NaIO_4$ (4.00 g, 18.7 mmol) in 1:1 CH_2Cl_2/H_2O (12 mL) was stirred vigorously at 0 °C for 5 min and then at rt for 2.5 h. The resulting emulsion was partitioned with CH_2Cl_2 (15 mL) and H_2O (25 mL). The organic layer was separated, washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$), and filtered. The resulting solution of 3-butenal in CH_2Cl_2 was concentrated by distillation of most of the CH_2Cl_2 at atmospheric pressure to afford 2.83 g of a solution containing 3-butenal (*ca*. 39% by weight, 63% yield) in CH_2Cl_2.



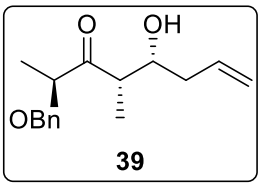
3-Butenal. ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 9.70 (1H, t, *J* = 1.9, C<u>H</u>O), 5.92 (1H, ddt, *J* = 17.2, 10.3, 6.9 Hz, C<u>H</u>=CH_2), 5.30–5.16 (2H, m, CH=C<u>H</u>$_2$), 3.25–3.15 (2H, m, COC<u>H</u>$_2$).

1.1.2. (2*S*,4*S*,5*R*)-2-Benzyloxy-5-hydroxy-4-methyl-7-octen-3-one (**39**)[27,28]

Neat $TiCl_4$ (485 µL, 4.4 mmol) was added dropwise to a solution of ketone **1** (769 mg, 4.0 mmol) in CH_2Cl_2 (8 mL) at –78 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (766 µL, 4.4 mmol) was added dropwise and the ensuing dark solution was stirred for 30 min at –78 °C. Then, neat $TiCl_4$ (441 µL, 4.0 mmol) was added

dropwise, followed 10 min later by the addition of 3-butenal in CH_2Cl_2 (*ca*. 39% by weight, 1.80 g, 10.0 mmol). The resultant mixture was stirred at –78 °C for 30 min.

The reaction was quenched by the addition of sat. NH_4Cl (5 mL) at rt with vigorous stirring. The mixture was partitioned in Et_2O (50 mL) and water (30 mL), and the organic layer was washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified by column chromatography (hexanes/EtOAc 80:20) to afford 902 mg (3.44 mmol, 86% yield) of (2*S*,4*S*,5*R*)-2-benzyloxy-5-hydroxy-4-methyl-7-octen-3-one (**39**) as a single diastereomer.

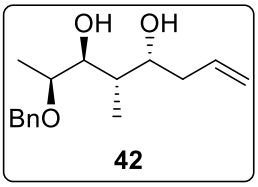


39

(2*S*,4*S*,5*R*)-2-Benzyloxy-5-hydroxy-4-methyl-7-octen-3-one (39). Colourless oil. **R_f** (Hexanes/EtOAc 80:20) = 0.4; **$[\alpha]^{20}_D$** = +31.3 (*c* 1.3, EtOH); **IR** (film) ν 3475 (br), 2981, 2934, 2876, 1713, 1455, 1374, 1114, 1072, 1030 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.29 (5H, m, ArH), 5.79 (1H, ddt, *J* = 17.4, 10.4, 7.1 Hz, CH=CH_2), 5.17–5.08 (2H, m, CH=CH_2), 4.57 (2H, s, PhCH_2), 4.07 (1H, q, *J* = 6.8 Hz, CHOBn), 3.91 (1H, ddd, *J* = 7.9, 5.6, 3.6 Hz, CHOH), 3.13 (1H, qd, *J* = 7.1, 3.6 Hz, COCHCH_3), 2.57 (1H, br s, OH), 2.30–2.12 (2H, m, CHOHCH_2), 1.37 (3H, d, *J* = 6.8 Hz, CH_3CHOBn), 1.12 (3H, d, *J* = 7.1 Hz, COCHCH3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 216.0 (C), 137.5 (C), 134.5 (CH), 128.5 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 117.9 (CH_2), 79.6 (CH), 71.7 (CH_2), 70.7 (CH), 44.7 (CH), 38.6 (CH_2), 16.5 (CH_3), 10.2 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1461, found: 285.1460.

1.2. *Anti* reduction of 39[81]

To a stirred suspension of $(Me_4N)HB(OAc)_3$ (3.367 g, 12.8 mmol) in CH_3CN (6.5 mL) was added dry AcOH (6.5 mL). The mixture was stirred at rt for 30 min and then cooled to –35 °C. A solution of aldol **39** (419 mg, 1.6 mmol) in CH_3CN (2.0 mL) was added via cannula (2 × 0.5 mL) and the resulting mixture was stirred at –35 °C for 5 h, kept at –20 °C overnight, and stirred at 0 °C for 30 min. A 1 M solution of sodium potassium tartrate (20 mL) was added followed by vigorous stirring at rt for 1 h. The mixture was partitioned with EtOAc (50 mL) and sat. $NaHCO_3$ (40 mL), and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (5 × 30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexanes/EtOAc 60:40) to afford 405 mg (1.5 mmol, 96% yield) of (2*S*,3*S*,4*S*,5*R*)-2-benzyloxy-4-methyl-7-octen-3,5-diol (**42**) (dr 94:6).



42

(2*S*,3*S*,4*S*,5*R*)-2-Benzyloxy-4-methyl-7-octen-3,5-diol (42). White solid. **Mp** = 45–47 °C; **R_f** (Hexanes/EtOAc 60:40) = 0.4; **$[\alpha]^{20}_D$** = +60.5 (*c* 1.5, $CHCl_3$, dr 94:6); **IR** (ATR) ν 3412 (br), 2975, 2929, 2878, 1455, 1376, 1114, 1088, 1066, 1026 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.27 (5H, m, ArH), 5.80 (1H, ddt, *J* = 17.1, 10.1, 7.1 Hz, CH=CH_2), 5.16–5.05 (2H, m, CH=CH_2), 4.70 (1H, d, *J* = 11.5 Hz, PhCH_xH_y), 4.44 (1H, d, *J* = 11.5 Hz, PhCH_xH_y), 3.95 (1H,ddd, *J* = 7.8, 6.3,

1.7 Hz, C<u>H</u>OHCH$_2$), 3.68 (1H, p, *J* = 6.4 Hz, C<u>H</u>OBn), 3.47 (1H, dd, *J* = 6.4, 4.4 Hz, CHOBnC<u>H</u>OH), 3.23 (1H, br s, O<u>H</u>), 3.00 (1H, br s, O<u>H</u>), 2.39–2.28 (1H, m, CHOHC<u>H$_x$H$_y$</u>), 2.23–2.09 (1H, m, CHOHCH$_x$<u>H$_y$</u>), 1.77 (1H, qdd, *J* = 7.1, 4.4, 1.7 Hz, CHOHC<u>H</u>CH$_3$), 1.20 (3H, d, *J* = 6.4 Hz, C<u>H$_3$</u>CHOBn), 1.01 (3H, d, *J* = 7.1 Hz, CHOHCHC<u>H$_3$</u>); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 138.0 (C), 135.4 (CH), 128.5 (CH), 127.8 (2 × CH), 117.1 (CH_2), 79.7 (CH), 75.9 (CH), 71.0 (CH, CH_2), 38.7 (CH_2), 36.8 (CH), 15.6 (CH_3), 11.0 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{16}H_{24}NaO_3$ $[M+Na]^+$: 287.1618, found: 287.1618.

1.3. *N*-Acryloyl-2,5-dimethylpyrrole approach

1.3.1. Cross metathesis of **42** with *N*-acryloyl-2,5-dimethylpyrrole[101,102]

A mixture of diol **42** (26 mg, 0.1 mmol), *N*-acryloyl-2,5-dimethylpyrrole (45 mg, 0.3 mmol), and Hoveyda–Grubbs II catalyst (3 mg, 5 μmol, 5 mo l%) in CH_2Cl_2 (5 mL) was stirred at rt for 24 h under N_2 atmosphere. Then, a second portion of the catalyst (38 mg, 60 μmol, 5 mol %) was added and the reaction mixture was stirred for further 24 h. It was filtered through Celite®, eluted with 95:5 hexanes/EtOAc and concentrated. The residue was analysed by ^{1}H NMR and purified by column chromatography (hexanes/EtOAc 95:5) to afford (2*E*,5*R*,6*S*,7*S*,8*S*)-*N*-(8-benzyloxy-5,7-dihydroxy-6-methyl-2-nonenoyl)-2,5-dimethylpyrrole (**47**). Results are summarised in Table 37.

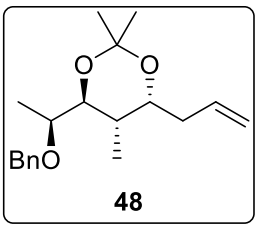
Entry	% HG-II	T (°C)	Time (h)	Yield 47 (%)[a]
1	5 + 5	rt	24+24	26 (50)
2	5 + 5	35	24+24	30 (16)
3	5 +5 +5	35	24+24+24	15 (25)

[a] Isolated overall yield after column chromatography. Recovered starting material into brackets.

Table 37

1.3.2. Formation of acetonide **48**

A solution of diol **42** (500 mg, 1.9 mmol) and CSA (44 mg, 0.19 mmol, 10 mol%) in 1:1 CH_2Cl_2/$Me_2C(OMe)_2$ (20 mL) was stirred at rt for 16 h under N_2 atmosphere. Volatiles were removed, and the resultant oil was purified by column chromatography (CH_2Cl_2/hexanes 50:50) to afford 520 mg (1.7 mmol, 90% yield) of (2*S*,3*S*,4*S*,5*R*)-2-benzyloxy-3,5-*O*-isopropylidene-4-methyl-7-octen-3,5-diol (**48**).



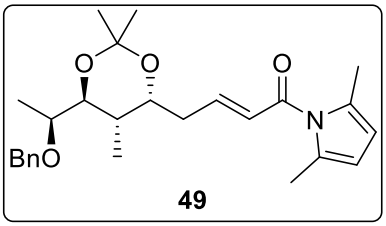
48

(2*S*,3*S*,4*S*,5*R*)-2-Benzyloxy-3,5-*O*-isopropylidene-4-methyl-7-octen-3,5-diol (48). Colourless oil. **R$_f$** (CH_2Cl_2/hexanes 50:50) = 0.3; **$[\alpha]^{20}_D$** = −23.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3063, 3028, 2980, 2930, 2876, 1454, 1372, 1217, 1173, 1106, 1065, 995 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.26 (5H, m, Ar<u>H</u>), 5.85–5.74 (1H, m, C<u>H</u>=CH$_2$), 5.14–5.08 (1H, m, CH=C<u>H$_x$H$_y$</u>), 5.06–5.02 (1H, m, CH=CH$_x$<u>H$_y$</u>), 4.68 (1H, d, *J* = 12.0 Hz, PhC<u>H$_x$H$_y$</u>), 4.52 (1H, d, *J* =

12.0 Hz, PhCH$_x$H$_y$), 3.87 (1H, ddd, *J* = 8.6, 5.7, 4.7 Hz, CHOCH$_2$), 3.59 (1H, qd, *J* = 6.4, 4.0 Hz, CHOBn), 3.32 (1H, dd, *J* = 7.6, 4.0 Hz, CHCHOCH), 2.27–2.17 (1H, m, CH$_2$=CHCH$_x$H$_y$), 2.15–2.07 (1H, m, CH$_2$=CHCH$_x$H$_y$), 2.07–1.98 (1H, m, OCHCHCHO), 1.35 (3H, s, C(CH$_3$)$_2$), 1.34 (3H, s, C(CH$_3$)$_2$), 1.22 (3H, d, *J* = 6.4 Hz, BnOCHCH$_3$), 0.82 (3H, d, *J* = 6.8 Hz, CHCH$_3$); **^{13}C NMR** (100.6 MHz, CDCl$_3$) δ 138.8 (C), 135.3 (CH), 128.2 (2 × CH), 127.7 (CH), 127.4 (2 × CH), 116.4 (CH$_2$), 100.6 (C), 77.2 (CH), 74.6 (CH), 71.3 (CH$_2$), 69.3 (CH), 35.1 (CH$_2$), 34.5 (CH), 25.3 (CH$_3$), 23.5 (CH$_3$), 15.3 (CH$_3$), 12.1 (CH$_3$); **HRMS** (+ESI): *m*/*z* calcd. for $C_{19}H_{28}NaO_3$ [M+Na]$^+$: 327.1931, found: 327.1928.

1.3.3. Cross metathesis of **48** with *N*-acryloyl-2,5-dimethylpyrrole[101,102]

A mixture of acetonide **48** (365 mg, 1.2 mmol), N-acryloyl-2,5-dimethylpyrrole (536 mg, 3.6 mmol), and Hoveyda–Grubbs II catalyst (38 mg, 60 µmol, 5 mol %) in CH_2Cl_2 (5 mL) was stirred at rt for 15 h under N_2 atmosphere. Then, a second portion of the catalyst (38 mg, 60 µmol, 5 mol %) was added and the reaction mixture was stirred for further 6 h. It was filtered through Celite®, eluted with 95:5 hexanes/EtOAc and concentrated. The residue was purified by column chromatography (hexanes/EtOAc 95:5) to afford 418 mg (0.96 mmol, 80% yield) of (2*E*,5*R*,6*S*,7*S*,8*S*)-*N*-(8-benzyloxy-5,7-dihydroxy-5,7-*O*-isopropylidene-6-methyl-2-nonenoyl)-2,5-dimethylpyrrole (**49**).



49

(2*E*,5*R*,6*S*,7*S*,8*S*)-*N*-(8-Benzyloxy-5,7-dihydroxy-5,7-*O*-isopropylidene-6-methyl-2-nonenoyl)-2,5-dimethylpyrrole (49). Pale brown oil. **R_f** (Hexanes/EtOAc 95:5) = 0.2; **$[\alpha]^{20}_D$** = −6.6 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2980, 2933, 2870, 1736, 1676, 1635, 1451, 1366, 1226, 1059 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.25 (5H, m, ArH), 6.97 (1H, dt, *J* = 15.4, 7.1 Hz, COCH=CHCH$_2$), 6.42 (1H, dt, *J* = 15.4, 1.4 Hz, COCH=CHCH$_2$), 5.83 (2H, s, CH=CN), 4.69 (1H, d, *J* = 12.1 Hz, PhCH$_x$H$_y$), 4.50 (1H, d, *J* = 12.1 Hz, PhCH$_x$H$_y$), 3.98 (1H, dt, *J* = 9.3, 4.7 Hz, CH$_2$CHO), 3.60 (1H, qd, *J* = 6.4, 3.9 Hz, CHOCH$_3$), 3.32 (1H, dd, *J* = 7.7, 3.9 Hz, OCHCHOCH$_3$), 2.50–2.36 (1H, m, CH=CHCH$_x$H$_y$), 2.33 (6H, s, ArCH$_3$), 2.34–2.27 (1H, m, CH=CHCH$_x$H$_y$), 2.12–2.04 (1H, m, OCHCHCHO), 1.34 (3H, s, C(CH$_3$)$_2$), 1.33 (3H, s, C(CH$_3$)$_2$), 1.23 (3H, d, *J* = 6.4 Hz, CHOCH$_3$), 0.83 (3H, d, *J* = 6.8 Hz, OCCHCH$_3$CHO); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 167.2 (C), 147.4 (CH), 138.7 (C), 129.9 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 110.6 (CH), 100.9 (C), 77.2 (CH), 74.2 (CH), 71.2 (CH$_2$), 68.4 (CH), 34.8 (CH), 34.1 (CH$_2$), 25.3 (CH$_3$), 23.4 (CH$_3$), 15.5 (CH$_3$), 15.3 (CH$_3$), 12.2 (CH$_3$); **HRMS** (+ESI): *m*/*z* calcd. for $C_{26}H_{36}NO_4$ [M+H]$^+$: 426.2639, found: 426.2622.

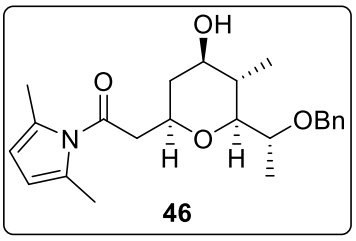
1.3.4. Acetonide removal with MeOH

A solution of acetonide amide **49** (26 mg, 0.61 µmol) and PPTS (2 mg, 10 µmol) in 3:1 DCE/MeOH (12 mL) was stirred at rt for 72 h under N_2 atmosphere. The volatiles were removed

in vacuo. ^{1}H NMR analysis of the resulting oil showed the presence of open amide **47** and cyclic amide **46** (60:40 open/cycle).

1.3.5. Acid promoted oxa-Michael[101,102]

A solution of the abovementioned open amide **47** and cyclic amide **46** (60:40 open/cycle) (0.61 mmol) and CSA (3 mg, 12 µmol, 20 mol %) in DCE (1,3 mL) was stirred at rt for 2 h under N_2 atmosphere. Then, it was heated at 60 °C for 48 h until total compsumption of open amide. The volatiles were removed in vacuo. The residue was purified by column chromatography (hexanes/EtOAc 70:30) to afford 12 mg (0.32 mmol, 52% yield) of cyclic amide **46**.



46

***N*-[2-(2*R*,4*R*,5*S*,6*S*)-[6-[(*S*)-1-Benzyloxyethyl]-4-hydroxy-5-methyltetrahydro-2*H*-pyran-2-yl]acetyl]-2,5-dimethylpyrrole (46)**. Brown oil. **R_f** (CH_2Cl_2/EtOAc 85:15) = 0.5; **$[\alpha]^{20}_D$** = +9.1 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3424 (br), 3031, 2965, 2930, 2870, 1708, 1540, 1451, 1388, 1359, 1315, 1264, 1242, 1160, 1049 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30–7.25 (5H, m, ArH), 5.81 (2H, s, CH=CN), 4.68 (1H, d, *J* = 12.1 Hz, $PhCH_xH_y$), 4.37 (1H, d, *J* = 12.1 Hz, $PhCH_xH_y$), 4.05–3.97 (1H, m, CH_2CHO), 3.65 (1H, qd, *J* = 6.4, 2.2 Hz, CHOBn), 3.46–3.32 (1H, m, CHOH), 3.20 (1H, dd, *J* = 16.3, 7.5 Hz, CH_xH_yCON), 2.92 (1H, dd, *J* = 10.0, 2.1 Hz, CHCHOBn), 2.83 (1H, dd, *J* = 16.3, 5.0 Hz, CH_xH_yCON), 2.38 (6H, s, 2 × $ArCH_3$), 2.08 (1H, ddd, *J* = 12.1, 4.8, 1.8 Hz, $CHOHCH_xH_y$), 1.75 (1H, tq, *J* = 10.0, 6.5 Hz, $CHOHCHCH_3$), 1.47–1.37 (1H, m, $CHOHCH_xH_y$), 1.24 (3H, d, *J* = 6.4 Hz, CH_3CHOBn), 0.80 (1H, d, *J* = 6.5 Hz, $CHOHCHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.1 (C), 138.3 (C), 130.3 (C), 128.3 (CH), 128.1 (CH), 127.6 (CH), 111.4 (CH), 84.0 (CH), 73.7 (CH), 72.8 (CH), 72.0 (CH), 70.7 (CH_2), 44.9 (CH_2), 40.5 (CH_2), 39.4 (CH), 16.5 (CH_3), 15.4 (CH_3), 12.1 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{23}H_{32}NO_4$ $[M+H]^+$: 386.2329, found: 386.2329; $C_{23}H_{31}NNaO_4$ $[M+Na]^+$: 408.2145, found 408.2147.

1.3.6. One-pot: Acid promoted acetonide removal and Oxa-Michael

A solution of acetonide amide **49** (45 mg, 0.10 mmol), MeOH (162 µL, 4 mmol), and CSA (5 mg, 20 µmol, 20 mol %) in DCE (2 mL) was stirred at rt for 6 h under N_2 atmosphere. Then, it was heated at 60 °C for 48 h until total consumption of open amide. The volatiles were removed in vacuo. The residue was purified by column chromatography (hexanes/EtOAc 70:30) to isolate 10 mg of cylic amide **46** (26 µmol, 26% yield) and 14 mg of cyclic methyl ester **50** (43 µmol, 43% yield). Spectroscopic data of amide **46** is shown in section 1.3.5.

1.3.7. One-pot: Acid promoted acetonide removal, oxa-Michael, and amide to ester transformation

A solution of acetonide amide **49** (78 mg, 0.18 mmol), EtOH (0.84 mL, 14.4 mmol,), and CSA (4 mg, 0.18 µmol, 10%, or 8 mg, 36 µmol, 20 mol %) in DCE (9 mL) was stirred at rt for 6 h

under N_2 atmosphere. The mixture was heated at 70 °C for 24 h and then, a second portion of CSA (4 mg, 0.18 µmol, 10 mol %, or 8 mg, 36 µmol, 20 mol %) was added and the reaction was heated at 70 °C for further 24h. The volatiles were removed in vacuo. The residue was purified by column chromatography (CH_2Cl_2/EtOAc 85:15) to isolate cyclic amide **46** and cyclic ethyl ester **44c**. Results are summarised in Table 38 and spectroscopic data of the amide is shown in section 1.3.5 and for ester in section 1.3.9.

Entry	% CSA	Yield Amide 46 (%)[a]	Yield Ester 44c (%)[a]	Overall (%)[a]
1	10 + 10	20	30	50
2	20 +20	8	43	51

[a] Isolated overall yield after column chromatography.

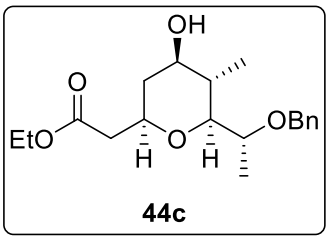
Table 38

1.3.8. One-pot: Acid promoted acetonide removal and oxa-Michael

A solution of acetonide amide **49** (390 mg, 0.91 mmol), EtOH (0.8 mL, 13.7 mmol), and CSA (20 mg, 91 µmol, 10 mol %) in DCE (9 mL) was stirred at rt for 6 h under N_2 atmosphere. Then, it was heated at 60 °C for 16 h. The volatiles were removed in vacuo. The residue was purified by column chromatography (CH_2Cl_2/EtOAc 85:15) to isolate 204 mg of cyclic amide **46** (0.53 mmol, 58% yield) and 69 mg of cyclic ethyl ester **44c** (0.21 mmol, 23% yield). Spectroscopic data of the amide is shown in section 1.3.5 and for ester in section 1.3.9.

1.3.9. Amide to ester transformation wih NaOEt[101]

A freshly prepared 0.5 M solution of NaOEt (0.6 mL, 0.3 mmol) (Na in EtOH) was added to a solution of amide **46** (92 mg, 0.26 mmol) in CH_2Cl_2 (3 mL) at –25 °C under N_2 atmosphere. The reaction mixture was stirred at 0 °C and, after 15 h, it was quenched by addition of sat. NH_4Cl (3 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (CH_2Cl_2/EtOAc 85:15) to afford 79 mg of ethyl ester **44c** (0.23 mmol, 90% yield).



44c

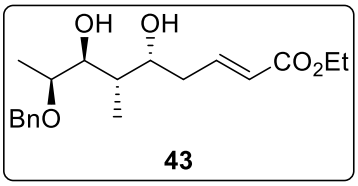
Ethyl 2-[(2*R*,4*R*,5*S*,6*S*)-6-((*S*)-1-benzyloxyethyl)-tetrahydro-4-hydroxy-5-methyl-2*H*-pyran-2-yl]acetate (44c) . Colourless oil. **R_f** (CH_2Cl_2/EtOAc 85:15) = 0.2; **IR** (ATR) ν 3427 (br), 2971, 2931, 2871, 1730, 1058, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.28 (5H, m, ArH), 4.69 (1H, d, *J* = 12.1 Hz, $PhCH_xH_y$), 4.38 (1H, d, *J* = 12.1 Hz, $PhCH_xH_y$), 4.19–4.08 (2H, m, CH_2CH_3), 3.81–3.72 (1H, m, CH_2CHO), 3.65 (1H, qd, *J* = 6.3, 2.1 Hz, CHOBn), 3.36 (1H, td, *J* = 10.5, 4.7 Hz, CHOH), 2.88 (1H, dd, *J* = 10.0, 2.1 Hz, CHCHOBn), 2.68 (1H, dd, *J* = 15.4, 8.1 Hz, $CH_xH_yCO_2Et$), 2.42 (1H, dd, *J* = 15.4, 5.2 Hz, $CH_xH_yCO_2Et$), 1.99 (1H, ddd, *J* = 12.2, 4.7, 1.6 Hz, $CHOHCH_xH_y$), 1.85–1.67 (1H, m, $CHOHCHCH_3$), 1.41–1.32 (1H, m, $CHOHCH_xH_y$), 1.25 (3H, t, *J* = 7.0 Hz, CH_2CH_3),

1.24 (3H, d, *J* = 6.3 Hz, C<u>H</u>$_3$CHOBn), 0.79 (3H, d, *J* = 6.5 Hz, CHOHCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.2 (C), 138.4 (C), 128.2 (CH), 128.1 (CH), 127.6 (CH), 83.8 (CH), 73.7 (CH), 72.7 (CH), 72.1 (CH), 70.5 (CH_2), 60.4 (CH_2), 40.9 (CH_2), 40.4 (CH_2), 39.3 (CH), 15.3 (CH_3), 14.2 (CH_3), 12.0 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{19}H_{29}O_5$ $[M+H]^+$: 337.2010, found: 337.2008.

1.4. Ethyl acrylate aproach

1.4.1. Cross metathesis of **42** with ethyl acrylate[82,84,210]

A solution of Hoveyda–Grubbs II catalyst (11 mg, 18 μmol, 2.5 mol %), diol **42** (192 mg, 0.72 mmol,) and ethyl acrylate (237 μL, 2.16 mmol) in CH_2Cl_2 (3.6mL) was stirred at rt for 8 h under N_2 atmosphere. Then, a second portion of the catalyst (11 mg, 18 μmol, 2.5 mol %) was added and the reaction mixture was stirred for further 16 h. It was filtered on Celite®, eluted with CH_2Cl_2 (3 × 10 mL) and concentrated. The residue (248 mg, 0.72 mmol) of ethyl (2*E*,5*R*,6*S*,7*S*,8*S*) 8-benzyloxy-5,7-dihydroxy-6-methyl-2-nonenoate (**43**) as a mixture of diastereomers (dr 94:6, E/Z ≥ 97:3) was used in the next step without further purification.

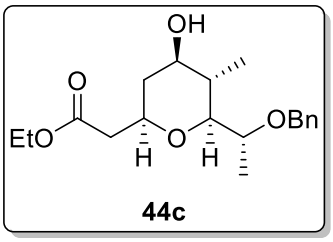


43

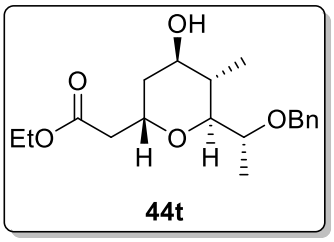
Ethyl (2*E*,5*R*,6*S*,7*S*,8*S*)-8-benzyloxy-5,7-dihydroxy-6-methyl-2-nonenoate (43). Colourless oil. **R_f** (Hexanes/EtOAc 60:40) = 0.3; **$[\alpha]^{20}_D$** = +54.6 (*c* 1.0, $CHCl_3$, dr 94:6, E/Z ≥ 97:3); **IR** (film) ν 3417 (br), 2976, 2934, 1716, 1652, 1563, 1455 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.27 (5H, m, Ar<u>H</u>), 7.02–6.89 (1H, m, CH_2C<u>H</u>=CH), 5.91 (1H, d, *J* = 15.7 Hz, CH_2CH=C<u>H</u>), 4.70 (1H, d, *J* = 11.5 Hz, PhC<u>H$_x$H$_y$</u>), 4.43 (1H, d, *J* = 11.5 Hz, PhCH$_x$<u>H$_y$</u>), 4.19 (2H, q, *J* = 7.1 Hz, C<u>H</u>$_2$CH$_3$), 4.07–4.00 (1H, m, C<u>H</u>OHCH$_2$), 3.66 (1H, p, *J* = 6.2 Hz, C<u>H</u>OBn), 3.47–3.43 (1H, m, CHOBnC<u>H</u>OH), 3.41 (1H, d, *J* = 2.4 Hz, CH$_2$CHO<u>H</u>), 3.01 (1H, d, *J* = 3.6 Hz, CHOBnCHO<u>H</u>), 2.52–2.41 (1H, m, CHOHC<u>H$_x$H$_y$</u>), 2.29–2.19 (1H, m, CHOHCH$_x$<u>H$_y$</u>), 1.77–1.68 (1H, m, CHOHC<u>H</u>CH$_3$), 1.28 (3H, t, *J* = 7.1 Hz, CH$_2$C<u>H</u>$_3$), 1.20 (3H, d, *J* = 6.2 Hz, C<u>H</u>$_3$CHOBn), 0.99 (3H, d, *J* = 7.1 Hz, CHOHCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 166.4 (C), 145.7 (CH), 137.9 (C), 128.5 (2 × CH), 127.9 (CH), 127.8 (CH), 123.3 (CH), 79.7 (CH), 75.7 (CH), 71.0 (CH_2), 70.6 (CH), 60.2 (CH_2), 37.4 (2 × CH), 37.1 (CH_2), 15.7 (CH_3), 14.2 (CH_3), 11.1 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{19}H_{29}O_5$ $[M+H]^+$: 337.2010, found: 337.2012.

1.4.2. *t*-BuOK-mediated oxa-Michael cyclization of **43**[83]

A mixture alkenediol **43** (248 mg, 0.72 mmol) and *t*-BuOK (13 mg, 0.12 mmol, 20 mol %) in THF (12 mL) was stirred at rt for 2 h under N_2 atmosphere. The reaction was quenched by addition of sat. NH_4Cl (12 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The residue (209 mg, 0.59 mmol) as a mixture of pyranes **44c/44t** (dr 2:1) was used in the next step without further purification.



44c



44t

Colourless oil. $\mathbf{R_f}$ (55:45 hexane/EtOAc) = 0.4; **IR** (ATR) ν 3427 (br), 2971, 2931, 2871, 1730, 1058, 1027 cm^{-1}; **HRMS** (+ESI): *m/z* calcd. for $C_{19}H_{29}O_5$ $[M+H]^+$: 337.2010, found: 337.2008.

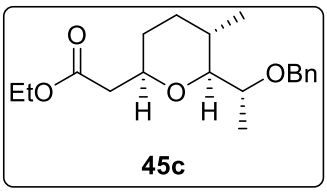
1.4.3. Barton-McCombie deoxygenation

1.4.3.1. Thionocarbonate formation[211]

O-Phenyl chlorothionoformate (120 µL, 0.89 mmol) and pyridine (84 µL, 1.03 mmol) were added to a solution of alcohols **44c/44t** (209 mg, 0.59 mmol, dr 1.8:1) in CH_2Cl_2 (1.4 mL) at 0 °C under N_2 atmosphere. The resulting bright yellow solution was stirred at 0 °C for 30 min and then at rt for 15 h. The reaction was quenched by addition of MeOH (25 µL) and stirred at rt for 15 min. The mixture was diluted with CH_2Cl_2 (30 mL), washed with 1 M HCl (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. ^{1}H NMR analysis of the resulting oil showed complete conversion affording a mixture of thionocarbonate diastereomers (dr 2:1), which was used in the next reaction without further purification.

1.4.3.2. Radical reduction[91,93]

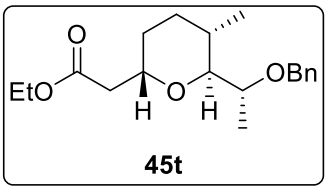
To a solution of the abovementioned diastereomeric mixture of thionocarbonates (dr 2:1) and AIBN (21.0 mg, 0.14 mmol, 20 mol %) in degassed (with N_2) toluene (13 mL) was added $(TMS)_3SiH$ (420 µL, 1.36 mmol) at rt under N_2 atmosphere, and the resulting mixture was stirred at 100 °C for 2 h and at 0 °C for 5 min. It was diluted with Et_2O (80 mL), washed with 1 M NaOH (5 × 40 mL), dried ($MgSO_4$), filtered, and concentrated. ^{1}H NMR analysis of the resulting oil showed the presence of **45c** and **45t** diastereomers (dr 3.8:1), which were separated by column chromatography (hexanes/EtOAc 96:4 to 90:10) to isolate 119 mg of tetrahydropyran **45c** (0.37 mmol, 62% yield over 2 steps) and 21 mg of **45t** (66 µmol, 11% yield over 2 steps) in a 73% overall.



45c

Ethyl 2-[(2*R*,5*S*,6*S*)-6-((*S*)-1-Benzyloxyethyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl]acetate (45c). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = +27.5 (*c* 1.0, $CHCl_3$) [lit.[76] $\mathbf{[\alpha]^{20}_D}$ = +29.4 (*c* 1.97, $CHCl_3$)]; **IR** (ATR) ν 2970, 2927, 1737, 1367, 1229, 1217, 1202, 1084, 1029 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.25 (5H, m, Ar<u>H</u>), 4.69 (1H, d, *J* = 12.2 Hz, PhC<u>H</u>$_x$H$_y$), 4.39 (1H, d, *J* = 12.2 Hz, PhCH$_x$<u>H</u>$_y$), 4.19–4.07 (2H, m, $CO_2C\underline{H}_2CH_3$), 3.72–3.65 (1H, m, $CH_2C\underline{H}O$), 3.63 (1H, qd, *J* = 6.5, 2.2 Hz, C<u>H</u>OBn), 2.85 (1H, dd, *J* = 9.5, 2.2 Hz, C<u>H</u>CHOBn), 2.63 (1H, dd, *J* = 15.2, 8.1 Hz, C<u>H</u>$_x$H$_y$CO$_2$Et), 2.39 (1H, dd, *J* = 15.2, 5.3 Hz, CH$_x$<u>H</u>$_y$CO$_2$Et), 1.87–1.75 (2H, m, C<u>H</u>$_x$H$_y$C<u>H</u>CH$_3$), 1.65–1.58 (1H, m, C<u>H</u>$_x$H$_y$CHCH$_2$CO$_2$Et), 1.43–1.32 (1H, m, CH$_x$<u>H</u>$_y$CHCH$_2$CO2Et), 1.25 (3H, t, *J* = 7.1 Hz,

$CO_2CH_2C\underline{H}_3$), 1.25–1.15 (1H, m, $CH_x\underline{H}_yCHCH_3$), 1.22 (3H, d, *J* = 6.5 Hz, $C\underline{H}_3CHOBn$), 0.64 (3H, d, *J* = 6.3 Hz, $CH_2CHC\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.7 (C), 138.8 (C), 128.2 (CH), 128.1 (CH), 127.4 (CH), 86.3 (CH), 75.2 (CH), 72.6 (CH), 70.5 (CH_2), 60.2 (CH_2), 41.3 (CH_2), 32.9 (CH_2), 31.5 (CH_2), 30.3 (CH), 17.0 (CH3), 15.1 (CH_3), 14.2 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{19}H_{29}O_4$ $[M+H]^+$: 321.2060, found: 321.2065.



45t

Ethyl 2-[(2*S*,5*S*,6*S*)-6-((*S*)-1-Benzyloxyethyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl]acetate (45t). Colourless oil. **R_f** (Hexanes/EtOAc 90:10) = 0.2; **$[\alpha]^{20}_D$** = +58.0 (*c* 0.6, $CHCl_3$); **IR** (ATR) ν 2927, 2850, 1733, 1454, 1369, 1276, 1196, 1162, 1084, 1068, 1028 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.24 (5H, m, Ar$\underline{H}$), 4.68 (1H, d, *J* = 12.1 Hz, $PhC\underline{H}_xH_y$), 4.56–4.49 (1H, m, $CH_2C\underline{H}O$), 4.39 (1H, d, *J* = 12.1 Hz, $PhCH_x\underline{H}_y$), 4.20–4.06 (2H, m, $CO_2C\underline{H}_2CH_3$), 3.65 (1H, qd, *J* = 6.3, 2.4 Hz, $C\underline{H}OBn$), 3.13 (1H, dd, *J* = 9.2, 2.4 Hz, $C\underline{H}CHOBn$), 2.83 (1H, dd, *J* = 14.1, 9.5 Hz, $C\underline{H}_xH_yCO_2Et$), 2.36 (1H, dd, *J* = 14.1, 5.7 Hz, $CH_x\underline{H}_yCO_2Et$), 1.96–1.80 (2H, m, $C\underline{H}_xH_yCHCH_2CO_2Et$, $CH_2C\underline{H}CH_3$), 1.69–1.61 (1H, m, $C\underline{H}_xH_yCHCH_3$), 1.50–1.44 (1H, m, $CH_x\underline{H}_yCHCH_2CO_2Et$), 1.25 (3H, t, *J* = 7.2 Hz, $CO_2CH_2C\underline{H}_3$), 1.35–1.23 (1H, m, $CH_x\underline{H}_yCHCH_3$), 1.18 (3H, d, *J* = 6.3 Hz, $C\underline{H}_3CHOBn$), 0.71 (3H, d, *J* = 6.6 Hz, $CH_2CHC\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.4 (C), 138.8 (C), 128.2 (CH), 128.1 (CH), 127.4 (CH), 78.6 (CH), 72.7 (CH), 70.7 (CH_2), 69.8 (CH), 60.4 (CH_2), 36.8 (CH_2), 30.4 (CH), 28.0 (CH_2), 27.3 (CH_2), 17.6 (CH_3), 15.3 (CH_3), 14.2 (CH_3); **HRMS** (+ESI): *m/z* calcd. for $C_{19}H_{29}O_4$ $[M+H]^+$: 321.2060, found: 321.2054.

1.4.4. *t*-BuOK-mediated isomerization of **45t** to **45c**[83]

A mixture of tetrahydropyran **45t** (21 mg, 6.6 µmol) and *t*-BuOK (2.9 mg, 26 µmol, 40 mol %) in THF (1.3 mL) was stirred at rt for 24 h under N_2 atmosphere. The reaction was quenched by addition of sat. NH_4Cl (5 mL) and the mixture was partitioned with Et_2O (20 mL) and H_2O (10 mL) and the organic layer was washed with brine (10 mL), dried ($MgSO_4$), filterd, and concentrated. The resulting oil was purified by column chromatography (hexanes/EtOAc 95:5 to 90:10) to afford 15 mg (47 µmol, 71% yield) of **45c** as a single diastereomer. Spectroscopic data of the amide is shown in section 1.4.3.2.

Preparation of starting materials for Chapters 3 and 4

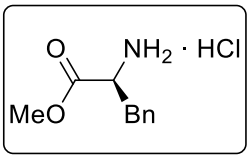
STARTING MATERIALS FOR CHAPTERS 3 AND 4
TABLE OF CONTENTS

1. Preparation of chiral auxiliaries

1.1. (*S*)-4-Benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (59)[142]

1.1.1. Methyl (*S*)-phenylalaninate hydrochloride

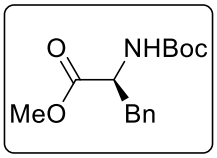
Chlorotrimethylsilane (42.0 mL, 330 mmol) was added to a solution of L-phenylalanine (9.91 g, 60 mmol) in methanol (100 mL) at rt under N_2 atmosphere. The resulting mixture was heated at reflux for 3 h. Then it was allowed to cool to rt and the volatiles were removed in vacuo to afford 12.94 g (60 mmol, 100%) of methyl (*S*)-phenylalaninate hydrochloride, which was used in the next step without further purification.



Methyl (*S*)-phenylalaninate hydrochloride. White solid, **Mp** = 157–158 °C; **IR** (KBr) ν 3300–2800, 2623, 1747 cm^{-1}; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.38–7.25 (5H, m, ArH), 4.35–4.32 (1H, m, COCH), 3.78 (3H, s, CH_3O), 3.26 (1H, dd, *J*= 14.3, 6.3 Hz, CH_xH_yPh), 3.19 (1H, dd, *J* = 14.3, 7.2 Hz, CH_xH_yPh); **^{13}C NMR** (100.6 MHz, CD_3OD) δ 169.0, 133.9, 129.0, 128.7, 127.5, 53.8, 52.2, 36.0.

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

Et_3N (6.6 mL, 47 mmol) was added dropwise to a solution of methyl (*S*)-phenylalaninate hydrochloride (10.22 g, 47 mmol) in CH_2Cl_2 (75 mL) at 0 °C under N_2 atmosphere and the resulting mixture was stirred for 10 min. A solution of Boc_2O (10.35 g, 47 mmol) in CH_2Cl_2 (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) and brine (80 mL), dried ($MgSO_4$), filtered, and concentrated to afford 12.72 g (45 mmol, 96% yield) of methyl (*S*)-*N*-*tert*-butoxycarbonylphenylalaninate.

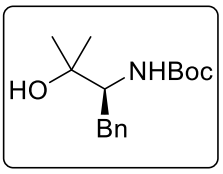


Methyl (*S*)-*N*-*tert*-butoxycarbonylphenylalaninate. Yellow oil. **R_f** (CH_2Cl_2) = 0.5; **IR** (ATR) ν 3370, 1760, 1719, 1499 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.12 (5H, m, ArH), 4.97 (1H, br d, *J* = 8.5 Hz, NH), 4.61–4.54 (1H, m, CHCO), 3.71 (3H, s, CH_3O), 3.12 (1H, br dd, *J* = 14.0, 6.0 Hz, CH_xH_yPh), 3.04 (1H, br dd, *J* = 14.0, 6.0 Hz, CH_xH_yPh), 1.42 (9H, s, $C(CH_3)_3$); **^{13}C NMR** (75.4 MHz, $CDCl_3$) δ 172.3, 155.1, 136.0, 129.3, 128.5, 127.0, 79.9, 54.4, 52.2, 38.4, 28.3.

1.1.3. (*S*)-3-amino-*N*-*tert*-butyloxocarbonyl-2-methyl-4-phenyl-2-butanol

A 3 M solution of MeMgBr in Et_2O (40 mL, 0.3 mol) was added dropwise to a solution of methyl (*S*)-*N*-*tert*-butoxycarbonylphenylalaninate (8.38 g, 30 mmol) in THF (100 mL) at 0 °C under N_2 atmosphere and the resulting mixture was stirred at rt for 2.5 days. The reaction was quenched at 0 °C with 40 mL of methanol (CAUTION: slow addition, release of gas) and a few

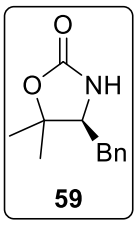
minutes later water (15 mL). The mixture was filtered through Celite® and eluted with EtOAc (50 mL). The solvent of the filtrate was evaporated under reduced pressure and the residue was dissolved in Et_2O (50 mL). The solution was dried ($MgSO_4$) and filtered through Celite®. The solvent of the filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 (50 mL), dried again ($MgSO_4$), filtered, and concentrated to afford 7.69 g (0.28 mmol, 92% yield) of (*S*)-3-amino-*N*-tert-butyloxocarbonyl-2-methyl-4-phenyl-2-butanol.



(*S*)-*N*-*tert*-Butyloxocarbonyl-3-amino-2-methyl-4-phenyl-2-butanol. White solid. **Mp** = 95–99°C; **R_f** (CH_2Cl_2/MeOH98:2) = 0.40; **IR** (KBr) ν br 3487, 3380, 2976, 1668, 1531 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.29–7.17 (5H, m, ArH), 4.55 (1H, d, *J* = 9.2 Hz, NH), 3.72–3.66 (1H, m, CHN), 3.09 (1H, dd, *J* = 14.2, 3.3 Hz, CH_xH_yPh), 2.60 (1H, dd, *J* = 14.2, 11.8 Hz, CH_xH_yPh), 2.47 (1H, br s, OH), 1.30 (6H, s, CCH_3), 1.29 (9H, s, $C(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 156.4, 139.0, 129.1, 128.3, 126.1, 79.2, 72.9, 60.4, 36.0, 28.2, 27.5, 26.5.

1.1.4. (*S*)-4-Benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (**59**)

Solid *t*-BuOK (4.46 g, 40 mmol) was added quickly 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 under N_2 atmosphere. The resulting mixture was stirred at 0 °C for 30 min and quenched with 20 mL of sat. NH_4Cl (slow addition). The mixture was concentrated under reduced pressure and the residue was partitioned in 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), dried ($MgSO_4$), filtrated, and concentrated. The crude was purified by chromatography (hexanes/EtOAc 50:50) to afford 6.37 g (38 mmol, 94% yield) of (*S*)-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (**59**).



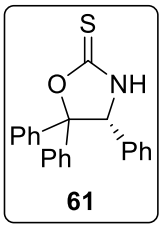
59

(*S*)-4-Benzyl-5,5-dimethyl-1,3-oxazolidin-2-one (59). White solid. **Mp** = 60–62°C; **R_f** (Hexanes/EtOAc 50:50) = 0.5; **$[\alpha]^{20}_D$** = –98.9 (*c* 1.0, $CHCl_3$), [lit.[142] **$[\alpha]^{20}_D$** = –103.5 (*c* 1.0, $CHCl_3$)]; **IR** (KBr) ν 3262, 2976, 1734 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.36–7.17 (5H, m, ArH), 5.18 (1H, br s, NH), 3.70 (1H, dd, *J* = 10.5, 4.1 Hz, CHN), 2.83 (1H, dd, *J* = 13.4, 4.1 Hz, CH_xH_yPh), 2.69 (1H, dd, *J* = 13.4, 10.5 Hz, CH_xH_yPh), 1.46 (3H, s, CCH_3), 1.45 (3H, s, CCH_3); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 158.0 (C), 136.9 (C), 129.0 (2 × CH), 128.8 (2 × CH), 127.1 (CH), 83.2 (C), 63.1 (CH), 37.1 (CH_2), 27.5 (CH_3), 21.9 (CH_3).

1.2. (*R*)-4,5,5-Triphenyl-1,3-oxazolidine-2-thione (61)[140]

Neat CS_2 (0.53 mL, 8.75 mmol) was added to a solution of (*R*)-2-amino-1,1,2-triphenyl-1-ethanol (506 mg, 1.75 mmol) in THF (7 mL) at rt under N_2 atmosphere. The solution became yellow. After 5 min, Et_3N (0.98 mL, 7 mmol) was added. The the resultant solution was heated to reflux for one day after which it became reddish brown. After cooling, the volatiles were removed

in vacuo and the residue was partitioned in water and CH_2Cl_2 (50 mL each). The aqueous layer was extracted with further CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentreated. The resulting brown oil was purified by column chromatography (CH_2Cl_2) to afford 552 mg (1.7 mmol, 95% yield) of (*R*)-4,5,5-triphenyl-1,3-oxazolidine-2-thione (**61**).



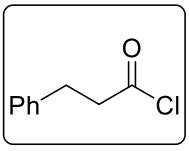
61

(*R*)-4,5,5-Triphenyl-1,3-oxazolidine-2-thione (61). White solid. **Mp** = 236–237 °C; $\mathbf{R_f}$ (Hexanes/CH_2Cl_2 60:40) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = +260.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3208, 3063, 3027, 2974, 1492, 1444, 1232, 1185, 1150 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66–7.63 (2H, m, ArH), 7.44–7.35 (3H, m, ArH), 7.18–7.11 (3H, m, ArH), 7.05–6.97 (7H, m, ArH), 5.76 (1H, s, CHPh); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 188.5 (C), 141.7 (C), 137.9 (C), 135.5 (C), 129.0 (CH), 128.9 (2 × CH), 128. 6 (2 × CH), 128.0 (2 × CH), 127.8 (CH), 127.7 (2 × CH), 126.8 (2 × CH), 126.3 (2 × CH), 97.4 (C), 69.2 (CH); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{18}NOS$ $[M+H]^+$: 332.1104, found: 332.1105.

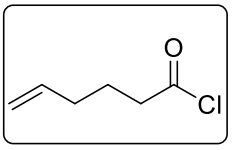
1.3. Acylation of chiral auxiliaries

1.3.1. Preparation of acyl chlorides

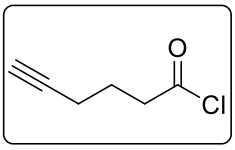
Two drops of DMF and oxalyl chloride (0.61 mL, 7.2 mmol) were added dropwise to a solution of the corresponding carboxylic acid (6.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at rt for 2 h. The volatiles were removed in vacuo obtaining acyl chlorides quantitatively. The products were used in the next step without further purification.



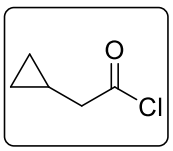
3-Phenylpropanoyl chloride. Yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.19 (5H, m, ArH), 3.21 (2H, t, *J* = 7.5 Hz, $COCH_2$), 3.02 (2H, t, *J* = 7.5 Hz, $PhCH_2$).



5-Hexenoyl chloride. Yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.75 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, $CH=CH_2$), 5.09–5.01 (2H, m, $CH=CH_2$), 2.90 (2H, t, *J* = 7.3 Hz, $COCH_2$), 2.13 (2H, q, *J* = 7.0 Hz, $CH_2CH=CH_2$), 1.82 (2H, p, *J* = 7.3 Hz, $COCH_2CH_2$).



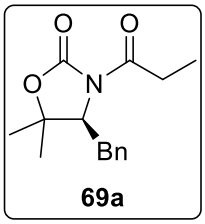
5-Hexynoyl chloride. Yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.97 (2H, t, *J* = 7.3 Hz, $COCH_2$), 2.21 (2H, td, *J* = 6.6, 2.7 Hz, $CH_2C{\equiv}CH$), 1.93 (1H, t, *J* = 2.7 Hz, $CH_2C{\equiv}CH$), 1.82 (2H, p, *J* = 7.1 Hz, $CH_2CH_2C{\equiv}CH$).



2-cyclopropylacetyl chloride. Yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.78 (2H, d, *J* = 7.0 Hz, $COCH_2$), 1.18–1.08 (1H, m, $COCH_2CH$), 0.68–0.63 (2H, m, $CHCH_2$), 0.27–0.23 (2H, $CHCH_2$).

1.3.2. (*S*)-4-Benzyl-5,5-dimethyl-*N*-propanoyl-1,3-oxazolidin-2-one (**69a**)[147]

A 2.5 M solution of *n*-BuLi in hexanes (4.6 mL, 11.6 mmol) was added dropwise to a solution of oxazolidinone **59** (2.14 g, 10.5 mmol) in THF (50 mL) at –78 °C under N_2 atmosphere. The solution was stirred for 15 min and propionyl chloride (1.2 mL, 13.7 mmol) was added dropwise. The resulting mixture was stirred at –78 °C for 20 min, allowed to warm to rt and stirred for 1 h. The reaction mixture was quenched with sat. NH_4Cl (20 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), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 2.48 g (10.1 mmol, 96% yield) of (*S*)-4-benzyl-5,5-dimethyl-*N*-propanoyl-1,3-oxazolidin-2-one (**69a**).

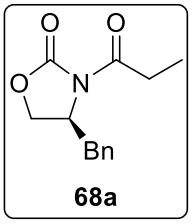


69a

(*S*)-4-Benzyl-5,5-dimethyl-*N*-propanoyl-1,3-oxazolidin-2-one (69a). White solid. **Mp** = 62–63 °C, [lit.[212] **Mp** = 62–63 °C]; $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = –40.0 (*c* 1.1, $CHCl_3$), [lit.[212] $\mathbf{[\alpha]^{25}_D}$ = –39.8 (*c* 1.0, $CHCl_3$)]; **IR** (KBr) ν 2991, 1771, 1707 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.20 (5H, m, Ar<u>H</u>), 4.51 (1H, dd, *J* = 9.5, 4.0 Hz, C<u>H</u>N), 3.15 (1H, dd, *J* = 14.2, 4.0 Hz, C<u>H</u>$_x$H$_y$Ph), 2.93 (2H, q, *J* = 7.3 Hz, C<u>H</u>$_2$CH$_3$), 2.88 (1H, dd, *J* = 14.2, 9.5 Hz, CH$_x$<u>H</u>$_y$Ph), 1.37 (3H, s, CC<u>H</u>$_3$), 1.36 (3H, s, CC<u>H</u>$_3$), 1.14 (3H, t, *J* = 7.3 Hz, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.2 (C), 152.6 (C), 136.9 (C), 129. (2 × CH), 128.5 (2 × CH), 126.7 (CH), 82.1 (C), 63.5 (CH), 35.3 (CH_2), 29.3 (CH_2), 28.5 (CH_3), 22.2 (CH_3), 8.3 (CH_3); **MS** (+ESI): *m*/*z* calcd. for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438, found: 262.1440.

1.3.3. (*S*)-4-Benzyl-*N*-propanoyl-1,3-oxazolidin-2-one (**68a**)

The experimental procedure described in section 1.3.2 was followed starting from (*S*)-4-benzyl-1,3-oxazolidin-2-one (**58**) (1.03 g, 5 mmol) and propionyl chloride (565 µL, 6.5 mmol). The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 1.25 g (4.8 mmol, 96% yield) of (*S*)-4-benzyl-*N*-propanoyl-1,3-oxazolidin-2-one (**68a**).

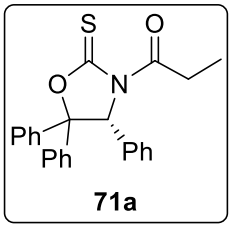


68a

(*S*)-4-Benzyl-*N*-propanoyl-1,3-oxazolidin-2-one (68a). White solid. **Mp** = 44-45 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = +55.6 (*c* 1.3, $CHCl_3$); **IR** (KBr) ν 3063, 2981, 2882, , 1779, 1699 1455 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.21 (5H, m, Ar<u>H</u>), 4.71–4.66 (1H, m, C<u>H</u>N), 4.21 (1H, dd, *J* = 9.0, 7.5 Hz, OC<u>H</u>$_x$H$_y$), 4.17 (1H, dd, *J* = 9.0, 3.5 Hz, OCH$_x$<u>H</u>$_y$), 3.31 (1H, dd, *J* = 13.5, 3.5 Hz, C<u>H</u>$_x$H$_y$Ph), 3.04-2.89 (2H, m, C<u>H</u>$_2$CH$_3$), 2.88 (1H, dd, *J* = 13.5, 9.5 Hz, CH$_x$<u>H</u>$_y$Ph), 1.21 (3H, t, *J* = 7.5 Hz, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.3 (C), 153.7 (C), 135.5 (C), 129.6 (2 × CH), 129.1 (2 × CH), 127.5 (CH), 66.4 (CH_2), 55.3 (CH), 38.1(CH_2), 29.4 (CH_2), 8.5 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{13}H_{15}NNaO_3$ $[M+Na]^+$: 256.0944, found: 256.0957.

1.3.4. (*R*)-4,5,5-Triphenyl-*N*-propanoyl-1,3-oxazolidine-2-thione (**71a**)

The experimental procedure described in section 1.3.2 was followed starting from oxazolidinethione **61** (250 mg, 0.75 mmol) and propionyl chloride (85 µL, 0.98 mmol). The residue was purified by column chromatography (hexanes/CH_2Cl_2 60:40) to afford 271 mg (0.70 mmol, 93% yield) of (*R*)-4,5,5-triphenyl-*N*-propanoyl-1,3-oxazolidine-2-thione (**71a**).

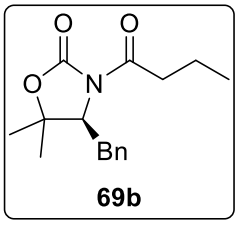


71a

(*R*)-4,5,5-Triphenyl-*N*-propanoyl-1,3-oxazolidine-2-thione (71a). White solid. **Mp** = 56–58 °C; **R_f** (Hexanes/CH_2Cl_2 60:40) = 0.30; **$[\alpha]_D$** +283.5 (*c* 1.0, $CHCl_3$); **IR** (film) ν 3056, 3024, 2974, 2936, 1704, 1489, 1444, 1400, 1337, 1299, 1197, 1150 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64–7.61 (2H, m, ArH), 7.45–7.35 (3H, m, ArH), 7.14–6.98 (10H, m, ArH), 6.44 (1H, s, NCHPh), 3.33 (1H, dq, *J* = 18.4, 7.2 Hz, CH_xH_y), 3.19 (1H, dq, *J* = 18.4, 7.2 Hz, CH_xH_y), 1.07 (3H, t, *J* = 7.2 Hz, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 184.2 (C), 174.3 (C), 141.2 (C), 137.3 (C), 135.5 (C), 129.0 (2 × CH), 128.9 (CH), 128.4 (2 × CH), 128.3 (CH), 127.7 (2 × CH), 127.6 (CH), 127.5 (2 × CH), 126.4 (2 × CH), 125.9 (2 × CH), 93.2 (C), 69.8 (CH), 31.4 (CH_2), 8.3 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{24}NO_2S$ $[M+H]^+$: 354.1522, found: 354.1528.

1.3.5. (*S*)-4-Benzyl-*N*-butanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (**69b**)

The experimental procedure described in section 1.3.2 was followed starting from oxazolidinone **59** (1.03 g, 5.0 mmol) and butyryl chloride (0.67 mL, 6.5 mmol). The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 1.28 g (4.7 mmol, 93% yield) of (*S*)-4-benzyl-*N*-butanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (**69b**).

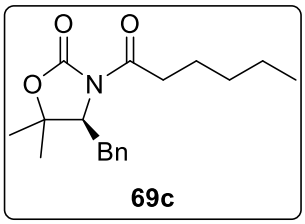


69b

(*S*)-4-Benzyl-*N*-butanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (69b). White solid. **Mp** = 69–71 °C; **R_f** (Hexanes/EtOAc 90:10) = 0.3; **$[\alpha]^{20}_D$** = –41.2 (*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), 137.0 (C), 129.0 (2 × CH), 128.6 (2 × CH), 126.8 (CH), 82.1 (C), 63.4 (CH), 37.5 (CH_2), 35.4 (CH_2), 28.5 (CH_3), 22.3 (CH_3), 17.8 (CH_2), 13.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{16}H_{21}NNaO_3$ $[M+Na]^+$: 298.1414, found: 298.1419.

1.3.6. (*S*)-4-Benzyl-*N*-hexanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (**69c**)

The experimental procedure described in section 1.3.2 was followed starting from oxazolidinone **59** (308 mg, 1.5 mmol) and hexanoyl chloride (0.27 mL, 2.0 mmol). The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 423 mg (1.4 mmol, 92% yield) of (*S*)-4-benzyl-*N*-hexanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (**69c**).

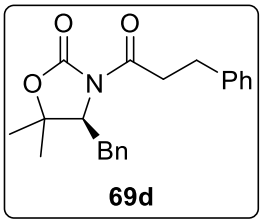


69c

(*S*)-4-Benzyl-*N*-hexanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (69c). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.4; $\mathbf{[\alpha]^{20}_D}$ = –34.5 (*c* 1.05, $CHCl_3$); **IR** (ATR) ν 2954, 2927, 2874, 2851, 1779, 1694, 1378, 1347, 1089 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.21(5H, m, ArH), 4.51 (1H, dd, *J* = 9.5, 3.9 Hz, CHN), 3.14 (1H, dd,*J* = 14.4, 3.9 Hz, CH_xH_yPh), 2.92–2.85 (3H, m, CH_xH_yPh, $COCH_2$), 1.67–1.59 (2H, m, $COCH_2CH_2$), 1.37 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 1.35–1.30 (4H, m, $CH_2CH_2CH_3$), 0.90 (3H, t, *J* = 7.0 Hz, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.8 (C), 152.8 (C), 137.1 (C), 129.2 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 82.2 (CH), 63.6 (C), 35.8 (CH_2), 35.5 (CH_2), 31.4 (CH_2), 28.7 (CH_3), 24.2 (CH_2), 22.6 (CH_3), 22.4 (CH_2), 14.1 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{25}NNaO_3$ $[M+Na]^+$: 326.1727, found: 326.1735.

1.3.7. (*S*)-4-Benzyl-5,5-dimethyl-*N*-(3-phenylpropanoyl)-1,3-oxazolidin-2-one (**69d**)

The experimental procedure described in section 1.3.2 was followed starting from oxazolidinone **59** (308 mg, 1.5 mmol) and 3-phenylpropanoyl chloride (505 mg, 3 mmol). The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 506 mg (1.5 mmol, 98% yield) of (*S*)-4-benzyl-5,5-dimethyl-*N*-(3-phenylpropanoyl)-1,3-oxazolidin-2-one (**69d**).

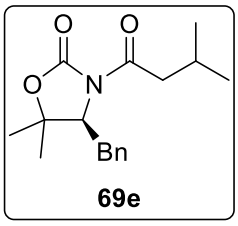


69d

(*S*)-4-Benzyl-5,5-dimethyl-*N*-(3-phenylpropanoyl)-1,3-oxazolidin-2-one (69d). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.4; $\mathbf{[\alpha]^{20}_D}$ = –27.1 (*c* 1.05, $CHCl_3$); **IR** (film) 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), 152.6 (C), 140.4 (C), 136.9 (C), 129.1 (2 × CH), 128.6 (2 × CH), 128.5 (CH), 128.4 (CH), 126.8 (CH), 126.2 (CH), 82.2 (C), 63.4 (CH), 37.2 (CH_2), 35.3 (CH_2), 30.5 (CH_2), 28.5 (CH_3), 22.3 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found: 338.1753.

1.3.8. (*S*)-4-Benzyl-5,5-dimethyl-*N*-(3-methylbutanoyl)-1,3-oxazolidin-2-one (**69e**)

The experimental procedure described in section 1.3.2 was followed starting from oxazolidinone **59** (1.03 g, 5.0 mmol) and isovaleryl chloride (0.79 mL, 6.5 mmol). The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 1.39 g (4.8 mmol, 96% yield) of (*S*)-4-benzyl-5,5-dimethyl-*N*-(3-methylbutanoyl)-1,3-oxazolidin-2-one (**69e**).

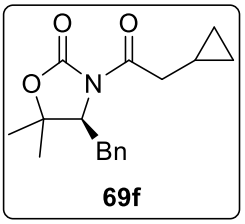


69e

(*S*)-4-Benzyl-5,5-dimethyl-*N*-(3-methylbutanoyl)-1,3-oxazolidin-2-one (69e). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = –33.9 (*c* 1.1, $CHCl_3$); **IR** (film) 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), 2.81 (1H, d, *J* = 6.9 Hz, $COCH_xH_y$), 2.81 (1H, d, *J* = 7.0 Hz, $COCH_xH_y$), 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 172.8 (C), 152.6 (C), 136.9 (C), 129.0 (2 × CH), 128.6 (2 × CH), 126.7 (CH), 81.9 (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), 22.2 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{17}H_{24}NO_3$ $[M+H]^+$: 290.1751, found: 290.1751.

1.3.9. (*S*)-4-Benzyl-*N*-(2-cyclopropylacetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**69f**)

The experimental procedure described in section 1.3.2 was followed starting from oxazolidinone **59** (616 mg, 3.0 mmol), and 2-cyclopropylacetyl chloride (367 mg, 3.1 mmol). The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 337 mg (1.2 mmol 39% yield) of (*S*)-4-benzyl-*N*-(2-cyclopropylacetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**69f**).

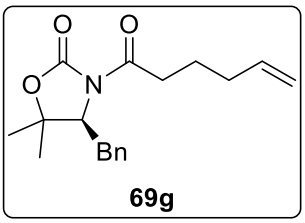


69f

(*S*)-4-Benzyl-*N*-(2-cyclopropylacetyl)-5,5-dimethyl-1,3-oxazolidin-2-one (69f). Colourless oil. $\boldsymbol{R_f}$ (Hexanes/EtOAc 80:20) = 0.5; $\mathbf{[\alpha]^{20}_D}$ = –32.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) 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, CHN), 3.17 (1H, dd, *J* = 14.4, 3.8 Hz, CH_xH_yPh), 2.89 (1H, dd, *J* = 14.4, 9.5 Hz, CH_xH_yPh), 2.85 (1H, dd, *J* = 16.4, 8.7 Hz, $COCH_xH_y$), 2.81 (1H, dd, *J* = 16.4, 7.1 Hz, $COCH_xH_y$), 1.38 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 1.14–1.04 (1H, m, $COCH_2CH$), 0.57–0.55 (2H, m, $CHCH_2$), 0.21–0.17 (2H, m, $CHCH_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.1 (C), 152.7 (C), 136.9 (C), 129.0 (2 × CH), 128.6 (2 × 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 (2 × CH_2); **HRMS** (+ESI): *m*/*z* calcd. for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found: 288.1598.

1.3.10. (*S*)-4-Benzyl-*N*-(5-hexenoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**69g**)

The experimental procedure described in section 1.3.2 was followed starting from oxazolidinone **59** (308 mg, 1.5 mmol) and 5-henexoyl chloride (259 mg, 2.0 mmol). The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 415 mg (1.4 mmol, 92% yield) of (*S*)-4-benzyl-*N*-(5-hexenoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**69g**).

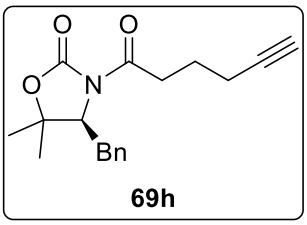


69g

(*S*)-4-Benzyl-*N*-(5-hexenoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (69g). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = –30.9 (*c* 1.7, $CHCl_3$); **IR** (film) 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), 2.92 (2H, td, *J* = 7.2, 1.3 Hz, 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 (2 × CH), 128.6 (2 × CH), 126.8 (CH), 115.2 (CH_2), 82.1 (C), 63.4 (CH), 35.4 (CH_2), 34.9 (CH_2), 33.0 (CH_2), 28.5 (CH_3), 23.4 (CH_2), 22.3 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found: 302.1753.

1.3.11. (*S*)-4-Benzyl-*N*-(5-hexynoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**69h**)

The experimental procedure described in section 1.3.2 was followed starting from oxazolidinone **59** (410 mg, 2.0 mmol) and 5-hexynyl chloride (391 mg, 3.0 mmol). The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 557 mg (1.9 mmol, 93% yield) of (*S*)-4-benzyl-*N*-(5-hexynoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**69h**).

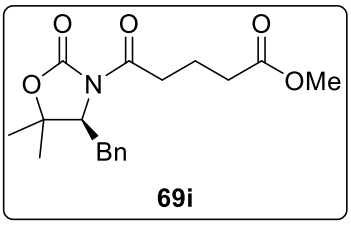


69h

(*S*)-4-Benzyl-*N*-(5-hexynoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (69h). White solid. **Mp** = 61–62 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = –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), 2.26 (2H, td, *J* = 6.9, 2.7 Hz, CH_2C≡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. 7 (C), 152.6 (C), 136.9 (C), 129.0 (2 × CH), 128.7 (2 × CH), 126.8 (CH), 83.4 (C), 82.3 (C), 69.2 (CH), 63.4 (CH), 35.4 (CH_2), 34.4 (CH_2), 28.5 (CH_3), 22.9 (CH_2), 22.2 (CH_3), 17.7 (CH_2); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{21}NO_3$ $[M+H]^+$: 322.1414, found: 322.1426.

1.3.12. (*S*)-4-Benzyl-*N*-(5-methoxy-5-oxopentanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**69i**)

The experimental procedure described in section 1.3.2 was followed starting from oxazolidinone **59** (308 mg, 1.5 mmol) and methyl glutaryl chloride (0.27 mL, 2.0 mmol). The residue was purified by column chromatography (hexanes/EtOAc 80:20) to afford 483 mg (1.5 mmol, 97% yield) of (*S*)-4-benzyl-*N*-(5-methoxy-5-oxopentanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**69i**).

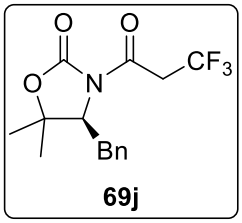


69i

(*S*)-4-Benzyl-*N*-(5-methoxy-5-oxopentanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (69i). White solid. **Mp** = 54–56 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = –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 173.3 (C), 172.5 (C), 152.6 (C), 136.8 (C), 129.0 (2 × CH), 128.6 (2 × CH), 126.7 (CH), 82.2 (C), 63.4 (CH), 51.5 (CH_3), 35.3 (CH_2), 34.7 (CH_2), 32.9 (CH_2), 28.4 (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.

1.3.13. (*S*)-4-Benzyl-5,5-dimethyl-*N*-(3,3,3-trifluoropropanoyl)-1,3-oxazolidin-2-one (69j)

A mixture of 3,3,3-trifluoropropanoic acid (180 μL, 2.0 mmol), pivaloyl chloride (270 μL, 2.2 mmol), and Et_3N (310 μL, 2.2 mmol) in THF (10 mL) was stirred for 15 min at –78 °C and 45 min at –15 °C. At the same time, A 2.5 M solution of *n*-BuLi in hexanes (1.8 mL, 4.4 mmol) was added to a solution of oxazolidinone **59** (821 mg, 4.0 mmol) in THF (40 mL) at –78 °C. The resultant red solution was stirred at –78 °C for 15 min and was then added to the former solution via cannula. The reaction mixture was stirred for 1 h at 0 °C and was quenched by addition of sat. NH_4Cl (15 mL). The mixture was concentrated in vacuo and the residue was extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexanes/EtOAc 80:20) to afford 165 mg (0.52 mmol, 26% yield) of (*S*)-4-benzyl-5,5-dimethyl-*N*-(3,3,3-trifluoropropanoyl)-1,3-oxazolidin-2-one (**69j**).



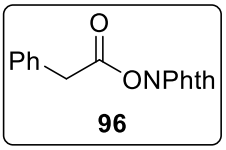
69j

(*S*)-4-Benzyl-5,5-dimethyl-*N*-(3,3,3-trifluoropropanoyl)-1,3-oxazolidin-2-one (69j). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.4; $\mathbf{[\alpha]^{20}_D}$ = –22.8 (*c* 1.5, $CHCl_3$); **IR** (KBr) ν 2982, 2925, 1773, 1709, 1405, 1356, 1274, 1239, 1210, 1160, 1116, 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, CHN), 3.94 (1H, dq, *J* = 17.0, 9.8 Hz, $COCH_xH_yCF_3$), 3.81 (1H, dq, *J* = 17.0, 9.8 Hz, $COCH_xH_yCF_3$), 3.18 (1H, dd, *J* = 14.4, 4.0 Hz, $PhCH_xH_y$), 2.91 (1H, dd, *J* = 14.4, 9.5 Hz, $PhCH_xH_y$),1.41 (3H, s, CCH_3), 1.38 (3H, s, CCH_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 (2 × CH), 128.8 (2 × 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.

2. Preparation of phtalimido esters[213]

2.1. *N*-(3-Phenylacetyloxy)phthalimide (96)

Solid EDC·HCl (2.12 g, 10.5 mmol) was added to a solution of phenylacetic acid (2.72 g, 20 mmol). hydrocinnamic acid (1.05 g, 7.0 mmol) and *N*-hydroxyphthalimide (4.89 g, 30 mmol) in CH_2Cl_2 (40 mL) ar rt under N_2 atmosphere. The resulting mixture was stirred for 16 h at rt. Then, it was diluted with CH_2Cl_2 (30 mL), washed with 2 M HCl (30 mL), sat. of $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by recrystallization in hot hexanes/CH_2Cl_2 to afford 4.773 g (85% yield) of *N*-(3-phenylacetyloxy)phthalimide (**96**).

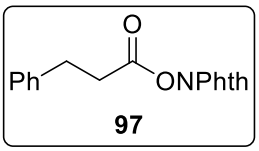


96

***N*-(3-Phenylacetyloxy)phthalimide (96)**. White soild. **Mp** = 133–135 °C; **IR** (KBr) ν 3134, 2959, 1775, 1730 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91–7.86 (2H, m, Phth$\underline{H}_A H_B$), 7.81–7.76 (2H, m, Phth$H_A\underline{H}_B$), 7.39–7.30 (5H, Ar$\underline{H}$), 4.00 (2H, s, COC$\underline{H}_2$). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 163.5, 134.4, 133.7, 129.9, 129.3, 128.9, 128.5, 123.5, 39.9.

2.2. *N*-(3-Phenylpropanoyloxy)phthalimide (97)

The experimental procedure described in section 2.1 was followed starting from hydrocinnamic acid (1.05 g, 7.0 mmol) and *N*-hydroxyphthalimide (1.71 g, 10.5 mmol). The residue was purified by column chromatography (hexanes/EtOAc 90:10) to afford 1.85 g (6.3 mmol, 90% yield) of *N*-(3-phenylpropanoyloxy)phthalimide (**97**).



97

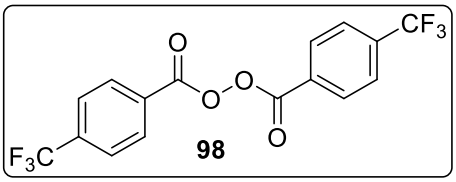
***N*-(3-Phenylpropanoyloxy)phthalimide (97)**. White solid. **Mp** = 84–85 °C; **R_f** (Hexanes/EtOAc 80:20) = 0.3; **IR** (KBr) ν 3130, 2950, 1789, 1740 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92–7.87 (2H, m, Phth$\underline{H}_A H_B$), 7.82–7.77 (2H, m, Phth$H_A\underline{H}_B$), 7.36–7.23 (5H, Ar$\underline{H}$), 3.11 (2H, t, *J* = 8.2 Hz, PhC$\underline{H}_2$), 2.99 (2H, t, *J* = 8.2 Hz, COC$\underline{H}_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.9, 161.9, 139.2, 134.8, 128.9, 128.7, 128.3, 126.7, 123.9, 32.7, 30.6.

3. Preparation of diacyl peroxides[184,190,214]

3.1. 4-Trifluoromethylbenzoyl peroxide (98)

30% Hydrogen peroxide (100 µL, 1.0 mmol) was added to a solution of 4-trifluoromethylbenzoic acid (510 mg, 3.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 atmosphere. The resultant solution was 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 stirred at 0 °C for 2 h. After

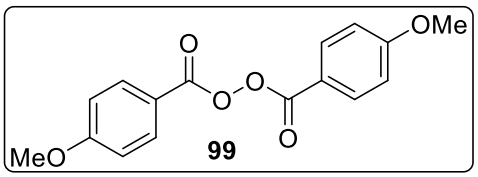
the addition of hexanes (50 mL) to precipitate as much urea as posible, the mixture was filtered, dried ($MgSO_4$), and concentrated. The residue was analysed by ^{1}H NMR and purified by column chromatography (hexanes/CH_2Cl_2 60:40) to afford 481 mg (1.3 mmol, 76% yield) of 4-trifluoromethylbenzoyl peroxide (**98**).



4-triFluoromethylbenzoyl peroxide (98). White solid. **R_f** (Hexanes/EtOAc 80:20) = 0.5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (4H, 2 × ArH AA'BB'), 7.81 (4H, 2 × ArH AA'BB'); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 161.9, 136.2, 135.9, 130.4, 126.2 (q, J_{CF} = 3.7 Hz).

3.2. 4-Methoxybenzoyl peroxide (99)

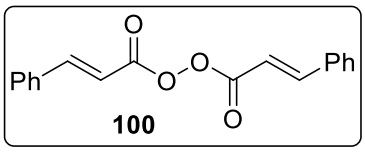
The experimental procedure described in section 3.1 was followed starting from 4-methoxybenzoic acid (403 µL, 3.4 mmol). The residue was purified by column chromatography (hexanes/CH_2Cl_2 50:50) to afford 359 mg (1.2 mmol, 70% yield) of 4-methoxybenzoyl peroxide **(99)**.



4-Methoxybenzoyl peroxide (99). White solid. **R_f** (Hexanes/CH_2Cl_2 50:50) = 0.3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (4H, 2 × ArH AA'BB'), 6.99 (4H, 2 × ArH AA'BB'), 3.86 (6H, s, 2 × CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 165.3, 163.6, 132.5, 118.3, 115.0, 56.4.

3.3. (*E*)-3-Phenyl-2-propenoyl peroxide (100)

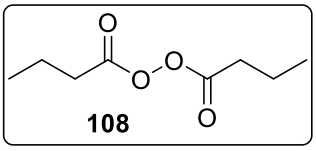
The experimental procedure described in section 3.1 was followed starting from cinnamic acid (740 mg, 5.0 mmol). Crude product of 443 mg of (*E*)-3-phenyl-2-propenoyl peroxide (**100**) was used without further purification.



(*E*)-3-Phenyl-2-propenoyl peroxide (100). Colourless oil. No characterised due to the poor stability of the peroxide.

3.4. Butanoyl peroxide (108)

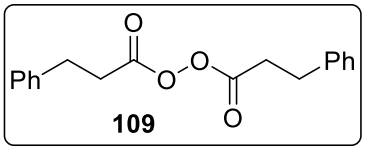
The experimental procedure described in section 3.1 was followed starting from butanoic acid (311 µL, 3.4 mmol). The residue was purified by column chromatography (hexanes/CH_2Cl_2 70:30) to afford 179 mg (1.0 mmol, 59% yield) of butanoyl peroxide (**108**).



Butanoyl peroxide (108). Colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (4H, t, J = 7.3 Hz, 2 × $COCH_2$), 1.59–1.52 (4H, m, 2 × $COCH_2CH_2$), 0.88 (6H, t, J = 6.7 Hz, 2 × CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.5, 33.2, 20.3, 13.6.

3.5. 3-Phenylpropanoyl peroxide (109)

The experimental procedure described in section 3.1 was followed starting from hydrocinnamic acid (510 mg, 3.4 mmol). The residue was purified by column chromatography (hexanes/CH_2Cl_2 60:40) to afford 443 mg (1.5 mmol, 87% yield) of 3-phenylpropanoyl peroxide (**109**).

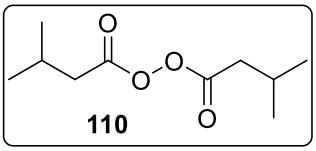


109

3-Phenylpropanoyl peroxide (109). White solid. $\mathbf{R_f}$ (Hexanes/CH_2Cl_2 60:40) = 0.5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.20 (10H, m, Ar<u>H</u>), 3.03 (4H, t, *J* = 7.8 Hz, 2 × C<u>H</u>$_2$Ph) 2.74 (4H, t, *J* = 7.8 Hz, 2 × COC<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.4, 139.3, 128.7, 128.3, 126.7, 31.7, 30.7.

3.6. 3-Metylbutanoyl peroxide (110)

The experimental procedure described in section 3.1 was followed starting from isovaleric acid (1.1 mL, 10 mmol). The residue was purified by column chromatography (hexanes/CH_2Cl_2 70:30) to afford 960 mg (4.7 mmol, 95% yield) of 3-metylbutanoyl peroxide (**110**).

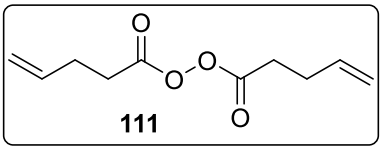


110

3-Metylbutanoyl peroxide (110). Colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.31 (4H, d, *J* = 7.1 Hz, 2 × COC<u>H</u>$_2$), 2.24–2.11 (2H, m, 2 × CH$_2$C<u>H</u>), 1.03 (12H, d, *J* = 6.6 Hz, 4 × C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.6, 39.0, 26.1, 22.4.

3.7. 4-Pentenoyl peroxide (111)

The experimental procedure described in section 3.1 was followed starting from 4-pentenoic acid (347 µL, 3.4 mmol). The residue was purified by column chromatography (hexanes/CH_2Cl_2 70:30) to afford 247 mg (1.2 mmol, 73% yield) of 4-pentenoyl peroxide (**111**).

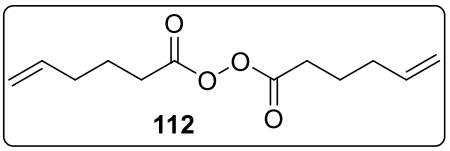


111

4-Pentenoyl peroxide (111). Colourless oil. $\mathbf{R_f}$ (Hexanes/CH_2Cl_2 50:50) = 0.5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 (2H, ddt, *J* = 16.8, 10.2, 6.3 Hz, 2 × C<u>H</u>=CH$_2$), 5.14–5.05 (4H, m, 2 × CH=C<u>H</u>$_2$), 2.56–2.52 (4H, m, 2 × COC<u>H</u>$_2$), 2.49–2.44 (4H, m, 2 × COCH$_2$C<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.5, 135.4, 116.5, 29.4, 28.6.

3.8. 5-Hexenoyl peroxide (112)

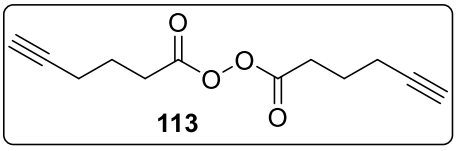
The experimental procedure described in section 3.1 was followed starting from 5-hexenoic acid (403 µL, 3.4 mmol). The residue was purified by column chromatography (hexanes/CH_2Cl_2 70:30) to afford 364 mg (1.6 mmol, 94% yield) of 5-hexenoyl peroxide (**112**).



5-Hexenoyl peroxide (112). Colourless oil. $\mathbf{R_f}$ (Hexanes/CH_2Cl_2 60:40) = 0.5; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (2H, ddt, *J* = 17.0, 10.2, 6.7 Hz, 2 × C<u>H</u>=CH_2), 5.09–5.00 (4H, m, 2 × CH=C<u>H</u>$_2$), 2.44 (4H, t, *J* = 7.4 Hz, 2 × COC<u>H</u>$_2$), 2.19–2.13 (4H, m, 2 × C<u>H</u>$_2$CH=CH_2), 1.82 (4H, p, *J* = 7.4 Hz, 2 × $COCH_2$C<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.2, 137.0, 116.1, 32.8, 29.3, 24.0.

3.9. 5-Hexynoyl peroxide (113)

The experimental procedure described in section 3.1 was followed starting from 5-hexynoic acid (375 µL, 3.4 mmol). The residue was purified by column chromatography (hexanes/CH_2Cl_2 60:40) to afford 266 mg (1.2 mmol, 71% yield) of 5-hexynoyl peroxide (**113**).

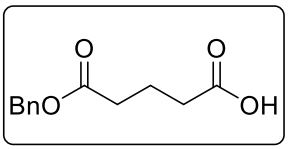


5-Hexynoyl peroxide (113). Colourless oil. $\mathbf{R_f}$ (Hexanes/CH_2Cl_2 50:50) = 0.3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.60 (4H, t, *J* = 7.3 Hz, 2 × COC<u>H</u>$_2$), 2.33 (4H, td, *J* = 7.3, 2.6 Hz, 2 × C<u>H</u>$_2$C≡CH), 2.01 (2H, t, *J* = 2.6 Hz, 2 × C≡C<u>H</u>), 1.94 (4H, p, *J* = 7.3 Hz, 2 × $COCH_2$C<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 168.8, 82.6, 69.8, 28.8, 23.6, 17.8.

3.10. 5-Benzyloxy-5-oxopentanoyl peroxide (114)

3.10.1. <u>*O*-Benzylglutaric acid</u>[215]

To a solution of glutaric anhydride (1.14 g, 10.0 mmol) and benzyl alcohol (0.94 mL, 9.1 mmol) in DMF (4 mL) at rt under N_2 atmosphere, *i*-Pr_2NEt (1.9 mL, 11.0 mmol) was added. The resulting mixture was stirred for 16 h at rt. Then, it was diluted with EtOAc (20 mL), washed with 2 M HCl (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (CH_2Cl_2/MeOH 98:2) to afford 1.41 g (6.3 mmol, 70% yield) of *O*-benzylglutaric acid.

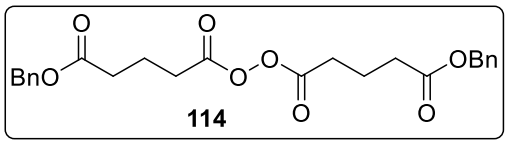


***O*-Benzylglutaric acid**. $\mathbf{R_f}$ (CH_2Cl_2/MeOH 98:2) = 0.2; **IR** (ATR) ν 3125 (br), 3066, 2992, 2867, 1740, 1715, 1588 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.30 (5H, m, Ar<u>H</u>), 5.12 (2H, s, C<u>H</u>$_2$Ph), 2.45 (2H, t, *J* = 7.3 Hz, COC<u>H</u>$_2$), 2.43 (2H, t, *J* = 7.3 Hz, COC<u>H</u>$_2$), 1.98 (2H, p, *J* = 7.3 Hz, $COCH_2$C<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 179.2, 172.8, 136.0, 128.7, 128.4, 128.4, 66.5, 33.3, 33.1, 19.9.

3.10.2. <u>5-Benzyloxy-5-oxopentanoyl peroxide (**114**)</u>

The experimental procedure described in section 3.1 was followed starting from *O*-benzylglutaric acid (755 mg, 3.4 mmol). The residue was purified by column chromatography

(hexanes/EtOAc 80:20) to afford 544 mg (1.2 mmol, 72% yield) of 5-benzyloxy-5-oxopentanoyl peroxide (**114**).

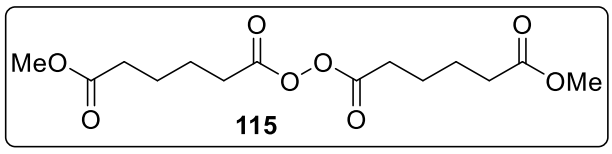


114

5-Benzyloxy-5-oxopentanoyl peroxide (114). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.35 (10H, m, Ar<u>H</u>), 5.13 (4H, s, 2 × C<u>H</u>$_2$Ph), 2.52 (4H, t, *J* = 7.3 Hz, 2 × COC<u>H</u>$_2$), 2.50 (4H, t, *J* = 7.3 Hz, 2 × COC<u>H</u>$_2$), 2.06 (4H, p, *J* = 7.3 Hz, 2 × COCH$_2$C<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.3, 168.5, 135.9, 128.6, 128.3, 128.3, 66.4, 32.8, 29.1, 20.1.

3.11. 6-Methoxy-6-oxohexanoyl peroxide (115)

The experimental procedure described in section 3.1 was followed starting from *O*-methyladipic acid (741 µL, 5.0 mmol). The residue was purified by column chromatography (hexanes/EtOAc 70:30) to afford 639 mg (2.0 mmol, 81% yield) of 6-methoxy-6-oxohexanoyl peroxide (**115**).

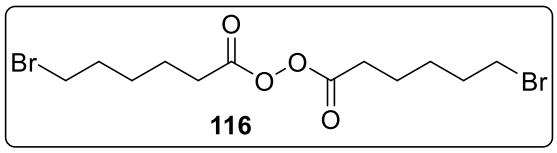


115

6-Methoxy-6-oxohexanoyl peroxide (115). White solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.68 (6H, s, 2 × C<u>H</u>$_3$), 2.48–2.44 (8H, m, 4 × COC<u>H</u>$_2$), 2.37–2.34 (8H, m, 4 × COCH$_2$C<u>H</u>$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.6, 168.9, 51.7, 33.5, 29.8, 24.3, 24.2.

3.12. 6-Bromohexanoyl peroxide (116)

The experimental procedure described in section 3.1 was followed starting from 6-bromohexanoic acid (975 mg, 5.0 mmol). The residue was purified by column chromatography (hexanes/CH_2Cl_2 50:50) to afford 767 mg (2.0 mmol, 80% yield) of 6-bromohexanoyl peroxide (**116**).

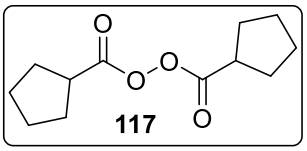


116

6-Bromohexanoyl peroxide (116). Colourless oil. $\mathbf{R_f}$ (Hexanes/CH_2Cl_2 50:50) = 0.3; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.41 (4H, t, *J* = 6.7 Hz, 2 × C<u>H</u>$_2$Br), 2.46 (4H, *J* = 7.4 Hz, 2 × COC<u>H</u>$_2$), 1.93–1.86 (4H, m, 2 × C<u>H</u>$_2$CH$_2$Br), 1.79–1.72 (4H, m, 2 × COCH$_2$C<u>H</u>$_2$), 1.59–1.51 (4H, m, COCH$_2$CH$_2$C<u>H</u>$_2$; **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 169.0, 33.3, 32.3, 29.9, 27.5, 24.1.

3.13. Peroxide from cyclopentanecarboxylic acid (117)

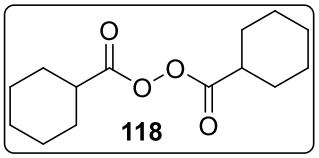
The experimental procedure described in section 3.1 was followed starting from cyclopentanecarboxylic acid (571 mg, 5.0 mmol). The residue was purified by filtration through a short pad of alumina (CH_2Cl_2) to afford 413 mg (1.8, mmol, 73% yield) of (**117**).



Peroxide from cyclopentanecarboxylic acid (117). Colourless 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>$_2$)$_4$).

3.14. Peroxide from cyclohexanecarboxylic acid (118)

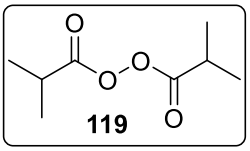
The experimental procedure described in section 3.1 was followed starting from cyclohexanecarboxylic acid (1.28 g, 10.0 mmol). The residue was purified by filtration through a short pad of alumina (CH_2Cl_2) to afford 796 mg (3.1 mmol, 63% yield) of (**118**).



Peroxide from Cyclohexanecarboxylic acid (118). Colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.49–2.41 (2H, m, 2 × COC<u>H</u>), 1.97–1.27 (20H, m, 2 × CH(C<u>H</u>$_2$)$_5$).

3.15. 2-Methylpropanoyl peroxide (119)

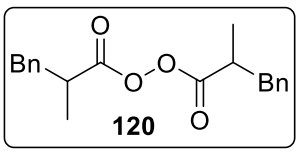
The experimental procedure described in section 3.1 was followed starting from 2-methylpropanoyl acid (1.47 g, 16.7 mmol). The residue was purified by filtration through a short pad of alumina (CH_2Cl_2) to afford 738 mg (4.2 mmol, 50% yield) of 2-methylpropanoyl peroxide (**119**).



2-Methylpropanoyl peroxide (119). Colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.74 (2H, h, *J* = 7.0 Hz, 2 × COC<u>H</u>), 1.29 (12H, d, *J* = 7.0 Hz, 4 × CHC<u>H</u>$_3$).

3.16. 2-Methyl-3-phenylpropanoyl peroxide (120)

The experimental procedure described in section 3.1 was followed starting from 2-methyl-3-phenylpropanoic acid (1.64 g, 10 mmol). The residue was purified by filtration through a short pad of alumina (CH_2Cl_2) to afford 488 mg (1.5 mmol, 30% yield) of a 1:1 mixture of diastereomers of 2-methyl-3-phenylpropanoyl peroxide (**120**).

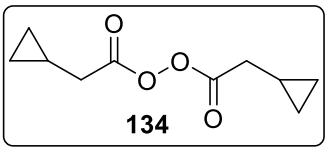


2-Methyl-3-phenylpropanoyl peroxide (120). Colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.11 (10H, m, Ar<u>H</u>), 3.16–3.09 (2H, m, 4 × C<u>H</u>$_x$H$_y$Ph) 2.91–2.86 (2H, m, 4 × CH$_x$<u>H</u>$_y$Ph), 2.76–2.71 (2H, m, 4 × COC<u>H</u>), 1.27 (6H, d, *J* = 5.6 Hz, 2 × C<u>H</u>$_3$ diast 1), 1.25 (6H, d, *J* = 5.6 Hz, 2 × C<u>H</u>$_3$ diast 2).

3.17. Cyclopropylacetyl peroxide (134)

The experimental procedure described in section 3.1 was followed starting from cyclopropylacetic acid (680 µL, 7 mmol) at –20 °C. The residue was purified by filtration through

a very short pad of silica gel (CH_2Cl_2) to afford 416 mg (2.1 mmol, 60% yield) of cyclopropylacetyl peroxide (**134**).



134

Cyclopropylacetyl peroxide (134). Colourless oil. No characterised due to the poor stability of the peroxide.

CHAPTER 3

Oxidations with TEMPO and Oxygen

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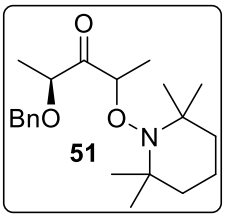
1. Aminoxylations with TEMPO

1.1. Aminoxylation of 1 with TEMPO

Neat $TiCl_4$ (120 µL, 1.1 mmol) was added dropwise to a solution of ketone **1** (192 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at –78 °C under N_2 atmoshpere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (192 µL, 1.1 mmol) was added dropwise and the ensuing dark red solution was stirred for 30 min at –78 °C. Then, TEMPO (2.1 mmol) was added and the resultant mixture was stirred at –78 °C for 3 h.

The reaction was quenched by the addition of sat. NH_4Cl (5 mL) at rt with vigorous stirring. The mixture was partitioned in Et_2O (50 mL) and water (30 mL), and the organic layer was washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^1H NMR and purified by column chromatography (hexanes/EtOAc 95:5) to afford 112 mg (0.33 mmol, 33% yield) of (2*S*)-2-(benzyloxy)-4-(2,2,6,6-tetramethylpiperidinyloxy)-3-pentanone (**51**) as a 75:25 mixture of diastereomers.



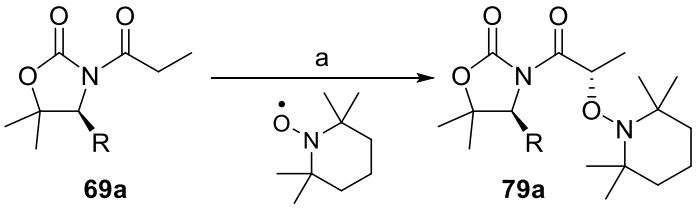
(2*S*)-2-(Benzyloxy)-4-(2,2,6,6-tetramethylpiperidinyloxy)-3-pentanone (**51**) (dr 75:25). Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.3; **IR** (KBr) ν 3030, 2976, 2915, 2880, 1720, 1150, 1015 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.38–7.29 (5H, m, ArH), 4.73 (1H, q, *J* = 7.0 Hz, COCHON), 4.60 (1H, d, *J* = 11.7 Hz, CH_xH_yPh), 4.52 (1H, d, *J* = 11.7 Hz, CH_xH_yPh), 4.33 (1H, q, *J* = 6.7 Hz, COCHOBn), 1.45–1.05 (12H, m, $N(C(CH_3)_2)_2$, $(CH_2)_3$), 1.40 (3H, d, *J* = 7.0 Hz, CH_3CHON), 1.35 (3H, d, *J* = 6.7 Hz, CH_3CHOBn), 1.14 (6H, s, $N(C(CH_3)_2)_2$), **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 211.5 (C), 137.7 (C), 128.3 (2 × CH), 127.8 (2 × CH), 127.7 (CH), 83.2 (CH), 77.5 (CH), 71.4 (CH_2), 60.1 (C), 59.4 (C), 40.2 (CH_3), 34.2 (CH_2), 33.9 (CH_2), 20.4 (CH_2), 17.4 (CH_2), 17.1 (CH_3), 16.4 (CH_3); **MS** (+ESI): *m*/*z* calcd. for $C_{21}H_{34}NO_3$ $[M+H]^+$: 348.2533, found: 348.2493.

1.2. Optimisation studies of the aminoxylation with TEMPO

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, n eq of TEMPO were added and the resultant mixture was stirred at **T** for **t**.

The reaction was quenched by the addition of sat. NH_4Cl (2 mL) at rt with vigorous stirring. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting crude mixtures were analysed analysed by ^1H NMR and

purified by column chromatography. Results were summarised in Table 39 and spectroscopic data is shown in section 1.4.



a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) n eq TEMPO, T, t.

Entry	R^1, R^2	TEMPO (eq)	T (°C)	Time (h)	dr[a]	Yield[b] (%)
1	Me, Bn	1.2	rt	2	94:6	46
2	Me, Bn	2.1	0	0.5	94:6	93
3	Me, Bn	2.1	0	1	94:6	93
4	Me, Bn	2.1	rt	2	94:6	94

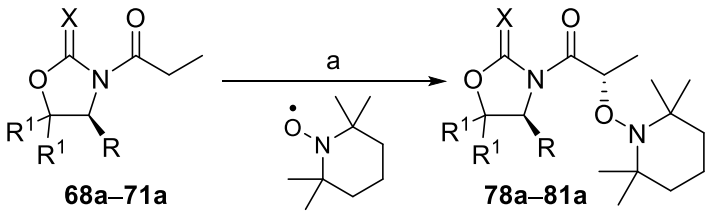
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Overall isolated yield after column chromatography. Pure isolated diastereomer into brackets.

Table 39

1.3. Aminoxylations with TEMPO. General procedure

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a the corresponging *N*-acylated chiral auxiliary (0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, TEMPO (164 mg, 1.05 mmol) was added and the resultant mixture was stirred at 0 °C for 1 h.

The reaction was quenched by the addition of sat. NH_4Cl (2 mL) at rt with vigorous stirring. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results were summarised in Table 40 and spectroscopic data is shown in section 1.4.



68a–71a **78a–81a**

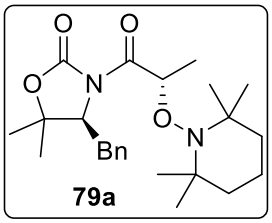
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 2.1 eq TEMPO, 0 °C, 1 h.

Entry	Substrate	X	R^1, R^2	R	dr[a]	Yield[b] (%)
1	**69a**	O	Me, Bn	Me	94:6	93
2[c]	**69a**	O	Me, Bn	CF_3	> 95:5	65
3	**68a**	O	H, Bn	Me	75:25	93
4	**81a**	S	Ph, Ph	Me	90:10	62(56)

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Overall isolated yield after column chromatography. Pure isolated diastereomer into brackets.
[c] Reaction performed from –78 °C to –20 °C

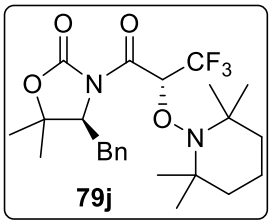
Table 40

1.4. Spectroscopic data of aminoxylated adducts



79a

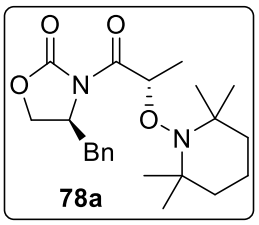
(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*S*)-2-(1-(2,2,6,6-tetramethylpiperidinyloxy)propanoyl]-1,3-oxazolidin-2-one (**79a**) was prepared according to the procedure described in section 1.3 from *N*-propanoyl oxazolidinone **69a** (131 mg, 0.5 mmol) at 0 °C for 1 h. Purification of the residue by column chromatography (hexanes/EtOAc 85:15) afforded **79a** (194 mg, 0.47 mmol, 93% yield) as a white solid. **Mp** = 94–96 °C. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.4: $\mathbf{[\alpha]^{20}_D}$ = –61.6 (*c* 2.2, $CHCl_3$, dr 94:6). **IR** (ATR) ν 2972, 2929, 1778, 1712, 1456, 1375, 1360, 1276, 1240, 1209, 1182, 1133, 1099 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.20 (5H, m, ArH), 5.68 (1H, q, *J* = 6.8 Hz, CHON), 4.49 (1H, dd, *J* = 10.8, 2.5 Hz, CHN), 3.34 (1H, dd, *J* = 14.5, 2.5 Hz, CH_xH_yPh), 2.80 (1H, dd, *J* = 14.5, 10.8 Hz, CH_xH_yPh), 1.55–1.28 (6H, m, $(CH_2)_3$), 1.46 (3H, d, *J* = 6.8 z, $CHCH_3$), 1.32 (3H, s, CCH_3), 1.30 (3H, s, CCH_3), 1.28–1.00 (12H, m, $N(C(CH_3)_2)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.5 (C), 152.1 (C), 137.1 (C), 128.9 (CH), 128.6 (CH), 126.7 (CH), 82.4 (C), 80.2 (CH), 63.8 (CH), 59.5 (2 × C), 40.2 (2 × CH_2), 34.8 (CH_2), 33.9 (CH_3), 33.4 (CH_3), 28.7 (CH_3), 22.4 (CH_3), 20.1 (2 × CH_3), 19.0 (CH_3), 17.1 (CH_2); **HRMS** (+ESI): *m*/*z* calcd. for $C_{24}H_{37}N_2O_4$ $[M+H]^+$: 417.2748, found: 417.2748.



79j

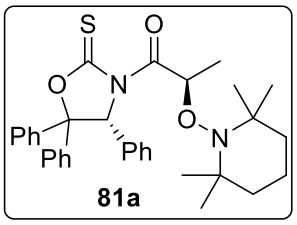
(*S*)-4-Benzyl-5,5-dimethyl-*N*-((*R*)-2-(2,2,6,6-tetramethylpiperidinyloxy)-3,3,3-trifluoropropanoyl)-1,3-oxazolidin-2-one (**79j**) was prepared according to the procedure described in section 1.3 from *N*-(3,3,3-trifluoropropanoyl oxazolidinone **69j** (79 mg, 0.25 mmol) from –78 °C to –20 °C for 1.5 h. Purification of the residue by column chromatography (hexanes/EtOAc 85:15) afforded **79j** (78 mg, 0.17 mmol, 65% yield) as a white solid. **Mp** = 122–124°C; $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.5; $\mathbf{[\alpha]^{20}_D}$ = –65.9 (*c* 1.0, $CHCl_3$, dr 94:6); **IR** (ATR) ν 2949, 2911, 1788, 1709, 1374 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$)

δ 7.34–7.22 (5H, m, ArH), 6.61 (1H, q, J_{HF} = 6.4 Hz, CHON), 4.56 (1H, dd, J = 10.8, 2.7 Hz, CHN), 3.28 (1H, dd, J = 14.5, 2.7 Hz, CH_xH_yPh), 2.86 (1H, dd, J = 14.5,10.8 Hz, CH_xH_yPh), 1.52–1.03 (12H, m, $N(C(CH_3)_2)_2$), 1.52–1.03 (6H, m, $(CH_2)_3$), 1.34 (3H, s, CCH_3), 1.33 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 166.5 (q, J_{CF} = 2.7 Hz, C), 152.1 (C), 136.7 (C), 128.9 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 122.4 (q, J_{CF} = 285.7 Hz, C), 83.2 (C), 80.1 (q, J_{CF} = 29.6 Hz, CH), 64.2 (CH), 61.1 (C), 60.5 (C), 40.6 (CH_2), 34.8 (CH_2), 33.6 (CH_3) 32.8 (CH_3), 28.5 (CH_3), 22.3 (CH_3), 20.1 (2 × CH_3), 16.9 (2 × CH_2).**^{19}F NMR** (376 MHz, $CDCl_3$) δ –69.8 (d, J_{FH} = 6.4 Hz); **HRMS** (+ESI): *m*/*z* calcd. for $C_{24}H_{34}F_3N_2O_4$ $[M+H]^+$: 471.2465, found: 471.2469.



78a

(*S*)-4-Benzyl-*N*-[(*S*)-2-(1-(2,2,6,6-tetramethylpiperidinyloxy)propanoyl]-1,3-oxazolidin-2-one (**78a**) was prepared according to the general procedure described in section 1.3 from *N*-propanoyl oxazolidinone **68a** (233 mg, 1.0 mmol) at 0 °C for 1 h. Purification of the residue by column chromatography (hexanes/EtOAc 90:10) afforded **78a** (361 mg, 0.93 mmol, 93% yield) as a white solid (dr 78:22). **R_f** (Hexanes:EtOAc 85:15) = 0.3; **IR** (ATR) ν 2929, 1777, 1708, 1453, 1375, 1344, 1209, 1131, 958, 700 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H), 5.67 (1H, q, J = 6.8 Hz, COCHON), 4.67 (1H, ddd, J = 14.1, 7.1, 3.6 Hz, CHN), 4.26–4.13 (2H, m, CH_2CHBn), 3.49 (1H, dd, J = 13.2, 3.4 Hz, CH_xH_yPh), 2.60 (1H, dd, J = 13.2, 10.6 Hz, CH_xH_yPh), 1.45 (3H d, J = 6.8 Hz, $CHCH_3$), 1.48–0.99 (18H, m, $N(C(CH_3)_2)_2$, $(CH_2)_3$). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.3 (C), 153.1 (C), 135.6 (C), 129.5 (2 × CH), 129.1 (2 × CH), 127.4 (CH), 80.2 (CH), 66.3 (CH_2), 59.8 (2 × C), 55.5 (CH), 40.4 (2 × CH_2), 38.2 (CH_2), 34.1 (CH_3), 33.7 (CH_3), 20.4 (CH_3), 19.0 (CH_2), 17.3 (CH_3); **HRMS** (ESI) *m*/*z* calcd. for $C_{22}H_{33}N_2O_4$ $[M+H]^+$: 389.2435, found: 389.2439.



81a

(*R*)-5,5,4-triphenyl-*N*-[(*S*)-2-(1-(2,2,6,6-tetramethylpiperidinyloxy)propanoyl]-1,3-oxazolidine-2-thione (**81a**) was prepared according to the general procedure described in section 1.3 from *N*-propanoyl oxazolidinonethione **71a** (96 mg, 0.25 mmol) at 0 °C for 1h. Purification of the residue by column chromatography (hexanes/CH_2Cl_2 60:04) afforded **81a** (75 mg, 0.14 mmol, 56% yield) as a white solid. **Mp** = 176–177 °C. **R_f** (Hexanes/CH_2Cl_2 60:40) = 0.2; **$[\alpha]^{20}_D$** = +180,8 (*c* 0.75, $CHCl_3$); **IR** (film) ν 3062, 3002, 2993, 2958, 2926, 2860, 2844, 1694, 1448, 1337, 1302, 1172 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58–7.55 (2H, m, ArH), 7.43–7.34 (3H, m, ArH), 7.10–7.02 (10H, m, ArH), 6.49 (1H, q, J = 6.9 Hz, CHON), 6.39 (1H, s, CHPh), 1.18 (3H, d, J = 6.9 Hz, $CHCH_3$), 1.49–0.60 (18H, m, $(CH_2)_3$), $N(C(CH_3)_2)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 183.9 (C), 175.3 (CH), 140.9 (C), 137.0 (C), 134.9 (C), 129.0 (CH), 128.9 (2 × CH), 128.2 (CH), 128.1 (2 × CH), 127.7 (2 × CH), 127.7 (CH), 127.7 (2 × CH), 126.5 (2 × CH), 126.0 (2 × CH), 93.5 (C), 80.2 (CH), 69.6 (CH), 59.5 (2 × C), 40.2 (2 × CH_2), 34.0 (CH_3), 33.2 (CH_3), 20.1 (2 × CH_3), 18.8 (CH_3), 17.1 (CH_2); **HRMS** (+ESI) *m*/*z* calcd. for $C_{33}H_{39}N_2O_3S$ $[M+H]^+$: 543.2676, found: 543.2677.

2. Hydroxylation with oxygen

2.1. Preliminary studies

2.1.1. Enolization with $TiCl_4$ and bubbled oxygen

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, the reaction was bubbled with H_2SO_4 dried O_2 for 15 min at 0 °C and stirring was continued at rt until the enolate colour was extinguished (2 h).

The reaction was quenched by the addition of sat. NH_4Cl (2 mL) at rt with vigorous stirring. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^1H NMR and purified by column chromatography (hexanes/EtOAc 80:20) to afford 39 mg (0.14 mmol, 28% yield) of (*S*)-4-benzyl-*N*-[(*S*)-2-hydroxypropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86a**). Spectroscopic data is shown in section 2.3.

2.1.2. Enolization with $TiCl_4$ and purgued oxygen

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, the reaction flask was purged with H_2SO_4 dried O_2 for 5 min and stirring was continued at rt until the enolate colour was extinguished (2 h).

The reaction was quenched and treated as in section 2.1.1. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. The residue was analysed by ^1H NMR and purified by column chromatography (hexanes/EtOAc 80:20) to afford 62 mg (0.22 mmol, 45% yield) of (*S*)-4-benzyl-*N*-[(*S*)-2-hydroxypropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86a**). Spectroscopic data is shown in section 2.3.

2.1.3. Enolization with *n*-Bu_2BOTf[147]

A 1 M solution of *n*-Bu_2BOTf in CH_2Cl_2 (220 µL, 0.22 mmol) and *i*-Pr_2NEt (42 µL, 0.24 mmol) were added to a solution of *N*-propanonyl oxazolidinone **69a** (52 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) under N_2 atmosphere at 0 °C. The resulting yellowish solution was stirred at 0 °C for 40 min. Then, the reaction flask was purged with H_2SO_4 dried O_2 for 5 min at 0 °C and stirring was continued at 0 °C for 16 h.

The reaction was quenched by the addition of pH 7 phosphate buffer solution (3 mL) at rt with vigorous stirring. The solvent was removed, and the product was dissolved in MeOH (3 mL) and 30% H_2O_2 (1mL) at 0 °C and stirred for 1 h. Methanol was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^{1}H NMR, which showed that it was essentially starting material.

2.1.4. Enolization with NaHMDS[216]

A solution of *N*-propanonyl oxazolidinone **69a** (52 mg, 0.2 mmol) in THF (0.25 mL) was added via cannula (2 × 0.25 mL) to a 1 M solution of NaHMDS (220 µL, 0.22 mmol) in THF (1 mL) at –78 °C, and the solution was stirred at –78 °C for 40 min. Then, the reaction flask was purged with H_2SO_4 dried O_2 for 5 min at –78 °C and stirring was continued at –78 °C for 4 h and at –20 °C for further 16 h.

The reaction was quenched by the addition of sat. $NaHCO_3$ (2 mL) at rt with vigorous stirring. The mixture was partitioned in Et_2O (50 mL) and water (30 mL), and the organic layer was washed with a 1 M HCl (10 mL), sat. $NaHCO_3$ (10 mL), and brine (10 mL). The organic fraction was dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^{1}H NMR, which showed that it was essentially starting material.

2.1.5. Enolization with LDA[216]

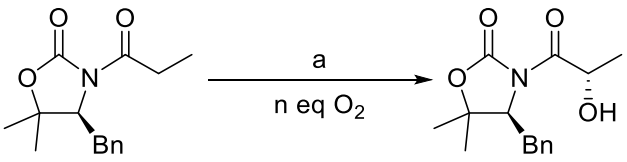
A solution of *N*-propanonyl oxazolidinone **69a** (52 mg, 0.2 mmol) in THF (0.25 mL) was added via cannula (2 × 0.25 mL) to a 2 M solution of LDA (110 µL, 0.22 mmol) in THF (1 mL) at –78 °C, and the solution was stirred at –78 °C for 40 min. Then, the reaction flask was purged with H_2SO_4 dried O_2 for 5 min at –78 °C and stirring was continued at –78 °C for 4 h and at –20 °C for further 16 h.

The reaction was quenched by the addition of sat. $NaHCO_3$ (2 mL) at rt with vigorous stirring. The mixture was partitioned in Et_2O (50 mL) and water (30 mL), and the organic layer was washed with a 1 M HCl (10 mL), sat. $NaHCO_3$ (10 mL), and brine (10 mL). The organic fraction was dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^{1}H NMR, which showed that it was essentially starting material.

2.1.6. Quantity of oxygen

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, H_2SO_4 dried O_2 (n eq) was injected through a syringe at 0 °C and stirring was continued at rt until the enolate colour was extinguished (2 h).

The reaction was quenched and treated as in section 2.1.1. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatography. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatography. Results were summarised Table 41 and spectroscopic data is shown in section 2.3.



69a **86a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) n eq O_2 at 0 °C, then rt until colour changes to yellow-orange.

Entry	O_2 (eq)[a]	dr[b]	Yield (%)[c]
1	2.5	≥ 97:3	45
2	1.3	≥ 97:3	45
3	0.6	≥ 97:3	40

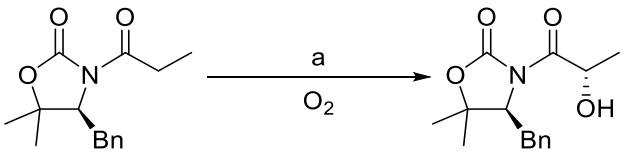
[a] Estimated amount of O_2 based on the equivalence 1 mmol ≈ 22.4 L
[b] Determined by ^{1}H NMR and HPLC analysis of the crude mixture.
[c] Isolated yield after column chromatography.

Table 41

2.1.7. Lewis acids screening for the hydroxylation with oxygen

The corresponding Lewis acid (0.55 mmol) was added dropwise to a solution of *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, the reaction was bubbled with H_2SO_4 dried O_2 for 15 min at 0 °C and stirring was continued at rt until the enolate colour was extinguished (2 h).

The reaction was quenched by the addition of sat. NH_4Cl (2 mL) at rt with vigorous stirring. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatograpy. Results were summarised Table 42 and spectroscopic data is shown in section 2.3.



69a **86a**

a) (i) 1.1 eq ML_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) O_2 bubbling for 15 min at 0 °C, then rt until colour changes to yellow-orange.

Entry	ML_4	dr[a]	Yield (%)[b]
1	$TiCl_4$	≥ 97:3	28
2	$TiCl_3$(*i*-PrO)	≥ 97:3	33
3	$TiCl_2$(*i*-PrO)$_2$	≥ 97:3	(4)
4	TiCl(*i*-PrO)$_3$	≥ 97:3	(3)
5	$TiBr_4$	≥ 97:3	(5)
6	$ZrCl_4$	-	-
7[c]	$ZrCl_4$	≥ 97:3	18

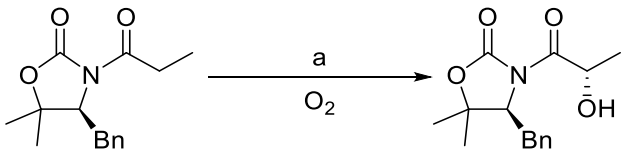
[a] Determined by ^{1}H NMR and HPLC analysis of the crude mixture.
[b] Isolated yield after column chromatography. NMR conversion into brackets.
[c] Performed with 3.5 eq of NEt_3.

Table 42

2.1.8. Optimisation studies of the hydroxylation with oxygen

The corresponding TiL_4 Lewis acid (0.55 mmol) was added dropwise to a solution of *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, the reaction flask was purged with H_2SO_4 dried O_2 for 5 min at 0 °C and stirring was continued at **T** until the enolate colour was extinguished (2 h).

The reaction was quenched and treated as in section 2.1.1. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatography. Results were summarised Table 43 and spectroscopic data is shown in section 2.3.



69a **86a**

a) (i) 1.1 eq TiL_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) O_2 atm for 5 min at T (0 °C when T = rt), then T until colour changes to yellow-orange.

Entry	TiL_4	T (°C)	Concentration (M)	dr[a]	Yield (%)[b]
1	$TiCl_4$	–50	0.25	–	> 5
2	$TiCl_4$	–20 → rt	0.25	≥ 97:3	44
3	$TiCl_4$	0	0.25	≥ 97:3	38
4	$TiCl_4$	rt	0.25	≥ 97:3	44
5	$TiCl_4$	rt	0.05	≥ 97:3	45
6	$TiCl_4$	rt	0.025	≥ 97:3	44
7	2 × $TiCl_4$	rt	0.25	≥ 97:3	41
8	$TiCl_3$(*i*-PrO)	0	0.25	≥ 97:3	41
9	$TiCl_3$(*i*-PrO)	rt	0.25	≥ 97:3	29
10	$TiCl_3$(*i*-PrO)	0	0.025	≥ 97:3	37
11	2 × $TiCl_3$(*i*-PrO)	0	0.25	≥ 97:3	(38)

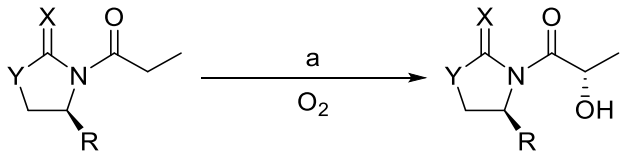
[a] Determined by ^1H NMR and HPLC analysis of the crude mixture.
[b] Isolated yield after column chromatography. NMR conversion into brackets.

Table 43

2.1.9. Scaffold screening for the direct hydroxylation with oxygen

The corresponding TiL_4 Lewis acid (0.55 mmol) was added dropwise to a solution of the corresponding *N*-propanonyl chiral auxiliary (0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at °C or 0 °C. Then, the reaction flask was purged with H_2SO_4 dried O_2 for 5 min at 0 °C and stirring was continued at **T** for 16 h.

The reaction was quenched and treated as in section 2.1.1. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results were summarised in Table 44.



68a, **63a**, **64a** **91a–93a**

a) (i) 1.1 eq TiL_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii)) O_2 atm for 5 min at T, then T overnight.

Entry	Substrate	X	Y	R	TiL_4	T (°C)	Product	dr[a]	Yield (%)[b]
1	**68a**	O	O	Bn	$TiCl_4$	rt	**91a**	≥ 97:3	42[c]
2	**68a**	O	O	Bn	$TiCl_3$(*i*-PrO)	rt	**91a**	≥ 97:3	27[c]
3	**63a**	S	O	*i*-Pr	$TiCl_4$	0	**92a**	-	-
4	**63a**	S	O	*i*-Pr	$TiCl_3$(*i*-PrO)	–20	**92a**	-	-
5	**64a**	S	S	*i*-Pr	$TiCl_3$(*i*-PrO)	–50 → rt	**93a**	-	-

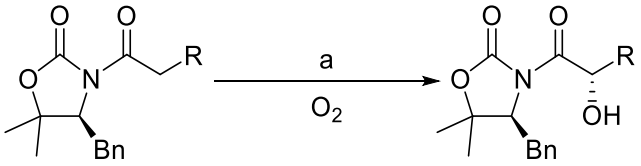
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Impure isolated yield.

Table 44

2.2. Direct hydroxylation with oxygen. General procedure

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of the corresponding *N*-acyl oxazolidinone (0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, the reaction flask was purged with H_2SO_4 dried O_2 for 5 min at 0 °C and stirring was continued at rt for 3–5 h.

The reaction was quenched and treated as in section 2.1.1. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results were summarised Table 45 and spectroscopic data is shown in section 2.3.



69a–i **86a–i**

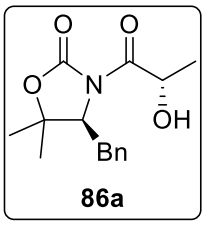
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) O_2 atm for 5 min at 0 °C, then rt for 2–5 h.

Entry	Substrate	R	Product	dr[a]	Yield[b] (%)
1	**69a**	Me	**86a**	≥ 97:3	45
2[c]	**69a**	Me	**86a**	≥ 97:3	41
3	**69b**	Et	**86b**	≥ 97:3	43
4[c]	**69b**	Et	**86b**	≥ 97:3	34
5	**69c**	Bu	**86c**	≥ 97:3	30
6	**69d**	Bn	**86d**	≥ 97:3	34
7[c]	**69d**	Bn	**86d**	≥ 97:3	23
8	**69e**	*i*-Pr	**86e**	≥ 97:3	31
9[c]	**69e**	*i*-Pr	**86e**	≥ 97:3	30
10	**69f**	Cyclopopyl	**86f**	≥ 97:3	32
11	**69g**	$(CH_2)_2CH=CH_2$	**86g**	≥ 97:3	32
12	**69h**	$(CH_2)_2C\equiv CH$	**86h**	≥ 97:3	32
13	**69i**	$(CH_2)_2CO_2Me$	**86i**	≥ 97:3	33

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Performed with 1.1 eq. of $TiCl_3(Oi\text{-}Pr)$ at 0 °C for 16 h.

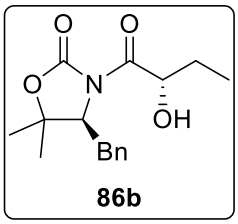
Table 45

2.3. Spectroscopic data of hydroxylation adducts



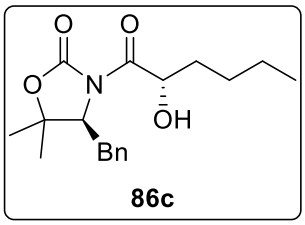
86a

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxypropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (131 mg, 0.5 mmol). Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **86a** (62 mg, 0.22 mmol, 45% yield) as a white solid; **Mp** = 45–47 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.2; $\mathbf{[\alpha]^{20}_D}$ = –36.5 (*c* 1.1, $CHCl_3$); **IR** (ATR) ν 3451, 2982, 2930, 1771, 1694, 1392, 1354, 1275, 1100 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, ArH), 5.04 (1H, p, *J* = 6.9 Hz, CHOH), 4.49 (1H, dd, *J* = 9.5, 3.8 Hz, CHN), 3.74 (1H, d, *J* = 6.9 Hz, OH), 3.18 (1H, dd, *J* = 14.5, 3.8 Hz, CH_xH_yPh), 2.93 (1H, dd, *J* = 14.5, 9.5 Hz, CH_xH_yPh), 1.42 (3H, d, *J* = 6.9 Hz, $CHCH_3$),1.40 (3H, s, CCH_3) 1.39 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.2, 152.7, 136.5, 129.0, 128.7, 126.9, 83.6, 67.1, 64.0, 35.1, 28.5, 22.2, 19.7; **HRMS** (+ESI): *m*/*z* calcd. for $C_{15}H_{20}NO_4$ $[M+H]^+$: 278.1387, found: 278.1392



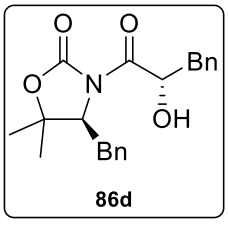
86b

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxybutanoyl]-5,5-dimethyl-oxazolidin-2-one (**86b**) was prepared according to the general procedure described in section 2.2 from *N*-butyl oxazolidinone **69b** (137 mg, 0.5 mmol). Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **86b** (63 mg, 0.22 mmol, 43% yield) as a white solid; **Mp** = 67–68 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = –30.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3412, 2967, 2927, 2874, 1770, 1672, 1352 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, Ar<u>H</u>), 4.95 (1H, td, *J* = 7.6, 3.8 Hz, C<u>H</u>OH), 4.47 (1H, dd, *J* = 9.6, 3.6 Hz, C<u>H</u>N), 3.44 (1H, d, *J* = 7.6 Hz, O<u>H</u>), 3.20 (1H, dd, *J* = 14.5, 3.6 Hz, C<u>H</u>$_x$H$_y$Ph), 2.93 (1H, dd, *J* = 14.5, 9.6 Hz, CH$_x$<u>H</u>$_y$Ph), 1.91–1.81 (1H, m, C<u>H</u>$_x$H$_y$CH$_3$) 1.68–1.57 (1H, m, CH$_x$<u>H</u>$_y$CH$_3$), 1.39 (3H, s, CC<u>H</u>$_3$) 1.39 (3H, s, CC<u>H</u>$_3$), 1.03 (3H, t, *J* = 7.4 Hz, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.1, 152.4, 136.6, 129.0, 128.8, 127.0, 83.5, 71.8, 64.1, 35.1, 28.5, 27.3, 22.2, 9.5; **HRMS** (+ESI): *m*/*z* calcd. for $C_{16}H_{21}NNaO_4$ $[M+Na]^+$: 314.1363, found: 314.1373.



86c

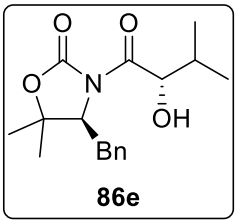
(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxyhexanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86c**) was prepared according to the general procedure described in section 2.2 from *N*-hexanoyl oxazolidinone **69c** (106 mg, 0.35 mmol). Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **86c** (31 mg, 0.10 mmol, 28% yield) as a white solid; **Mp** = 83–85 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.4; $\mathbf{[\alpha]^{20}_D}$ = –29.0 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3417, 2954, 2927, 2856, 1775, 1685, 1352, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, Ar<u>H</u>), 4.99 (1H, td, *J* = 7.8, 3.6 Hz, C<u>H</u>OH), 4.47 (1H, dd, *J* = 9.6, 3.5 Hz, C<u>H</u>N), 3.43 (1H, d, *J* = 7.8 Hz, O<u>H</u>), 3.20 (1H, dd, *J* = 14.5, 3.5 Hz, C<u>H</u>$_x$H$_y$Ph), 2.93 (1H, dd, *J* = 14.5, 9.6 Hz, CH$_x$<u>H</u>$_y$Ph), 1.83–1.75 (1H, m, COHC<u>H</u>$_x$H$_y$), 1.63–1.30 (5H, m, CH$_x$<u>H</u>$_y$(C<u>H</u>$_2$)$_2$CH$_3$), 1.39 (3H, s, CC<u>H</u>$_3$) 1.39 (3H, s, CC<u>H</u>$_3$), 0.91 (3H, t, *J* = 7.1 Hz, CH$_2$C<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.3, 152.4, 136.6, 129.0, 128.7, 126.9, 70.8, 64.1, 35.1, 33.9, 28.5, 27.3, 22.4, 22.2, 14.0; **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{25}NNaO_4$ $[M+Na]^+$: 342,1676, found: 342.1689.



86d

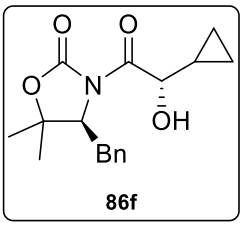
(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-3-phenylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86d**) was prepared according to the general procedure described in section 2.2 from *N*-(3-phenyl-propanoyl) oxazolidinone **69d** (60 mg, 0.5 mmol) for 5 h. Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **86d** (276 mg, 0.17 mmol, 34% yield) as a white solid; **Mp** = 98–99 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = –17.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3425, 3056, 3025, 2994, 2972, 2914, 1792, 1677, 1352, 1330, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.23 (10H, m, Ar<u>H</u>), 5.28 (1H, td, *J* = 7.9, 4.0 Hz, C<u>H</u>OH), 4.46 (1H, dd, *J* = 9.7, 3.7 Hz, C<u>H</u>N), 3,46 (1H, d, *J* = 7.9 Hz, O<u>H</u>), 3.20 (1H, dd, *J* = 14.2, 3.7 Hz, NCHC<u>H</u>$_x$H$_y$Ph), 3.16 (1H, dd, *J* = 13.8, 4.0 Hz, CHOHC<u>H</u>$_x$H$_y$Ph), 2.92 (1H, dd, *J* = 14.2, 9.7 Hz, NCHCH$_x$<u>H</u>$_y$Ph), 2.88 (1H, dd, *J* = 13.8, 7.9 Hz, CHOHC<u>H</u>$_x$H$_y$Ph), 1.40 (3H, s, CC<u>H</u>$_3$), 1.37 (3H, s,

CCH$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.2, 152.4, 136.8, 136.6, 129.6, 129.0, 128.8, 128.4, 126.9, 126.8, 83.6, 71.7, 64.0, 40.3, 35.0, 28.6, 22.3; **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{24}NO_4$ $[M+H]^+$: 354.1700, found: 354.1715.



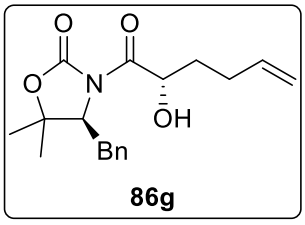
86e

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-3-methylbutanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86e**) was prepared according to the general procedure described in section 2.2 from *N*-[3-methylbutanoyl] oxazolidinone **69e** (145 mg, 0.5 mmol). Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **86e** (43 mg, 0.14 mmol, 28% yield) as a white solid; **Mp** = 65–66 °C; **R_f** (Hexanes/EtOAc 80:20) = 0.3; **$[\alpha]^{20}_D$** = –18.0 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3430, 2972, 2923, 2869, 1766, 1694, 1672, 1347 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, ArH), 4.98 (1H, dd, *J* = 8.3, 3.3 Hz, CHOH), 4.46 (1H, dd, *J* = 9.7, 3.5 Hz, CHN), 3.21 (1H, dd, *J* = 14.5, 3.5 Hz, CH$_x$H$_y$Ph), 3.19 (1H, d, *J* = 8.3 Hz, OH), 2.94 (1H, dd, *J* = 14.5, 9.7 Hz, CH$_x$H$_y$Ph), 2.12–2.04 (1H, m, CH(CH$_3$)$_2$), 1.38 (6H, s, 2 × CCH$_3$), 1.09 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_2$), 0.84 (3H, d, *J* = 6.8 Hz, CH(CH$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 175.1, 152.2, 136.7, 129.0, 128.8, 126.9, 83.4, 74.7, 64.2, 35.1, 31.4, 28.4, 22.1, 19.7, 15.1; **HRMS** (+ESI): *m*/*z* calcd. for $C_{17}H_{23}NNaO_4$ $[M+Na]^+$: 328.1519, found: 328.1529.



86f

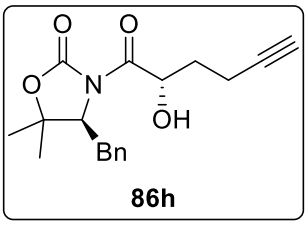
(*S*)-4-Benzyl-*N*-[(*S*)-2-cyclopropyl-2-hydroxyacetyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86f**) was prepared according to the general procedure described in section 2.2 from *N*-(2-cyclopropylacetyl) oxazolidinone **69f** (99 mg, 0,35 mmol) at rt for 3 h. Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **86f** (32 mg, 0.11 mmol, 32% yield) as a white solid; **Mp** = 106–108°C; **R_f** (Hexanes/EtOAc 80:20) = 0.2; **$[\alpha]^{20}_D$** = –30.9 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3404, 2963, 2918, 2851, 1780, 1668, 1352, 1160, 1094 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, ArH), 4.82 (1H, dd, *J* = 8.0, 6.1 Hz, CHOH), 4.49 (1H, dd, *J* = 9.6, 3.6 Hz, CHN), 3.39 (1H, d, *J* = 8.0 Hz, OH), 3.21 (1H, dd, *J* = 14.5, 3.6 Hz, CH$_x$H$_y$Ph), 2.95 (1H, dd, *J* = 14.5, 9.6 Hz, CH$_x$H$_y$Ph), 1.41 (3H, s, CCH$_3$), 1.40 (3H, s, CCH$_3$), 1.29–1.22 (1H, m, CH(CH$_2$)$_2$), 0.61–0.39 (4H, m, CH(CH$_2$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 173.8, 152.6, 135.8, 128.1, 127.9, 126.0, 82.8, 70.5, 63.4, 34.3, 27.6, 21.3, 12.9, 0.7, 0.0; **HRMS** (+ESI): *m*/*z* calcd. for $C_{17}H_{21}NNaO_4$ $[M+Na]^+$: 326.1363, found: 326.1359.



86g

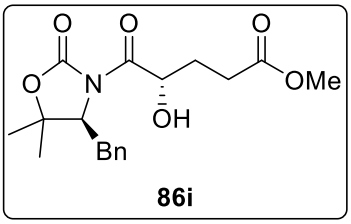
(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-5-hexenoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86g**) was prepared according to the general procedure described in section 2.2 from *N*-(5-hexenoyl) oxazolidinone **69g** (150 mg, 0.5 mmol) for 16 h. Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **86g** (51 mg, 0.16 mmol, 32% yield) as a white solid; **Mp** = 90–92 °C; **R_f** (Hexanes/EtOAc 80:20) = 0.3; **$[\alpha]^{20}_D$** = –15.1 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3448, 2994, 2972, 2940, 2990, 2851, 1766, 1703, 1361, 1281 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, ArH), 5.84—5.71 (1H, m,

C<u>H</u>OH), 5.07 (1H, dq, *J* = 17.1, 1.6 Hz, C=C<u>H</u>$_Z$H$_E$), 5.01–4.95 (2H, m, C<u>H</u>=CH$_Z$<u>H</u>$_E$), 4.47 (1H, dd, *J* = 9.6, 3.7 Hz, C<u>H</u>N), 3.52 (1H, d, *J* = 7.6 Hz, O<u>H</u>), 3.19 (1H, dd, *J* = 14.5, 3.7 Hz, C<u>H</u>$_x$H$_y$Ph), 2.93 (1H, dd, *J* = 14.5, 9.6 Hz, CH$_x$<u>H</u>$_y$Ph), 2.29–2.24 (2H, m, C<u>H</u>$_2$CH=CH$_2$), 1.94–1.85 (1H, m, CHOHC<u>H</u>$_x$H$_y$), 1.71–1.62 (1H, m, CHOHCH$_x$<u>H</u>$_y$), 1.40 (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 174.9, 152.4, 137.5, 136.6, 129.0, 128.8, 126.9, 115.4, 83.6, 70.3, 64.0, 35.1, 33.2, 29.4, 28.6, 22.2; **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{23}NNaO_4$ [M+Na]$^+$: 340.1519, found: 340.1532.



86h

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-5-hexynoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86h**) was prepared according to the general procedure described in section 2.2 from *N*-(5-hexynoyl) oxazolidinone **69h** (149 mm, 0.5 mmol) for 16 h. Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **86h** (51 mg, 0.16 mmol, 32% yield) as a white solid; **Mp** = 106–108 °C; **R$_f$** (Hexanes/EtOAc 80:20) = 0.3; **[α]$^{20}_D$** = –16.4 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3466, 3292, 2949, 2918, 1761, 1699, 1352, 1107 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, Ar<u>H</u>), 4.99 (1H, ddd, *J* = 8.6, 7.1, 3.6 Hz, C<u>H</u>OH), 4.49 (1H, dd, *J* = 9.4, 3.9 Hz, C<u>H</u>N), 3.77 (1H, d, *J* = 7.1 Hz, O<u>H</u>), 3.18 (1H, dd, *J* = 14.5, 3.9 Hz, C<u>H</u>$_x$H$_y$Ph), 2.93 (1H, dd, *J* = 14.5, 9.4 Hz, CH$_x$<u>H</u>$_y$Ph), 2.42 (2H, td, *J* = 7.3, 2.6 Hz, C<u>H</u>≡CH), 2.10–2.01 (1H, m, COHC<u>H</u>$_x$H$_y$), 1.97 (1H, t, *J* = 2.6 Hz, C≡C<u>H</u>), 1.87–1.78 (1H, m, COHCH$_x$<u>H</u>$_y$), 1.41 (3H, s, CC<u>H</u>$_3$), 1.40 (3H, s, CC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.0, 152.7, 136.5, 129.0, 128.8, 126.9, 83.8, 83.4, 69.6, 69.0, 64.0, 35.1, 32.2, 28.6, 22.2, 14.4; **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{21}NNaO_4$ [M+Na]$^+$: 338.1363, found: 338.1377.

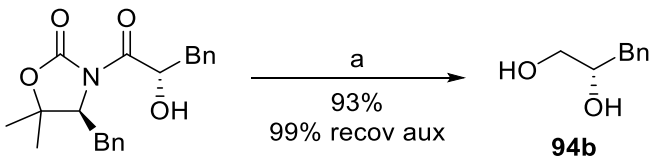


86i

(*S*)-4-Benzyl-*N*-[(*S*)-2-hydroxy-5-methoxy-5-oxopentanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**86i**) was prepared according to the general procedure described in section 2.2 from *N*-(5-methoxy-5-oxopentanoyl) oxazolidinone **69i** (166 mg, 0.5 mmol). Purification of the crude product by column chromatography (hexanes/EtOAc 80:20) afforded **86i** (53 mg, 0.15 mmol, 30% yield) as a white solid; **Mp** = 91–93 °C; **R$_f$** (Hexanes/EtOAc 80:20) = 0.2; **[α]$^{20}_D$** = –21.0 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3466, 2972, 2918, 2851, 1757, 1703, 1352, 1245 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.22 (5H, m, Ar<u>H</u>), 4.97 (1H, td, *J* = 7.8, 3.9 Hz, C<u>H</u>OH), 4.48 (1H, dd, *J* = 9.5, 3.8 Hz, C<u>H</u>N), 3.68 (3H, s, OC<u>H</u>$_3$), 3.68 (1H, d, *J* = 7.8 Hz, O<u>H</u>), 3.18 (1H, dd, *J* = 14.5, 3.8 Hz, C<u>H</u>$_x$H$_y$Ph), 2.92 (1H, dd, *J* = 14.5, 9.5 Hz, CH$_x$<u>H</u>$_y$Ph), 2.61–2.47 (2H, m, C<u>H</u>$_2$CO$_2$Me), 2.18–2.10 (1H, m, COHC<u>H</u>$_x$H$_y$) 2.00–1.91 (1H, m, COHCH$_x$<u>H</u>$_y$), 1.42 (3H, s, CC<u>H</u>$_3$), 1.40 (3H, s, CC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.2, 173.7, 152.6, 136.6, 129.0, 128.7, 126.9, 83.7, 69.7, 64.0, 51.6, 35.1, 29.5, 28.6, 28.5, 22.3; **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{23}NNaO_6$ [M+Na]$^+$: 372.1418, found: 372.1430.

2.4. Transformations of 86b

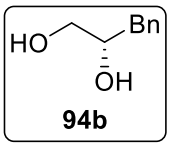
2.4.1. Reduction to diol[144]



86b **94b**

a) $NaBH_4$, THF/H_2O, 0 °C, 1 h.

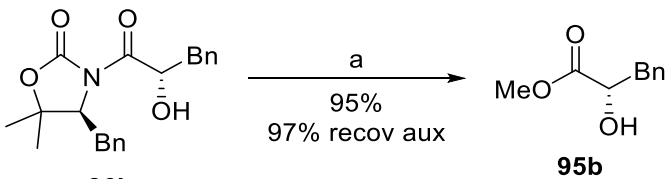
Solid $NaBH_4$ (34 mg, 0.9 mmol) was added to a mixture of $THF:H_2O$ (3:1, 2.2 mL) at 0 ˚C and stirred for 2 min. In a separate flask, alcohol **86b** (53 mg, 0.15 mmol) was dissolved in THF (1.0 mL) and added to reaction vessel via cannula (2 × 0.25 mL). After 50 min stiring at 0 ˚C, the reaction was quenched by dropwise addition of 2M HCl/brine solution until bubbling ceased. The organic layer was separated, and the aqueous layer extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (10 mL), and brine extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (hexanes/EtOAc 40:60 to 20:80) afforded 21 mg (0.14 mmol, 95 %) of (*S*)-3-phenyl-1,2-propanediol (**94b**) and 30 mg (0.15 mmol, 97 %) of oxazolidinone **59**.



94b

(*S*)-3-Phenyl-1,2-propanediol (94b). White caramel solid. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.2, $\mathbf{[\alpha]^{20}_D}$= –18.3 (*c* 1.3, $CHCl_3$) [lit.[122] $\mathbf{[\alpha]^{20}_D}$= –18.6 (*c* 1.3, $CHCl_3$) for *S* enantiomer]; **IR** (ATR) ν 3221, 3024, 2917, 2850, 1495, 1451, 1070, 1036 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, ArH), 3.95–3.89 (1H, m, CHOH), 3.66 (1H, dd, *J* = 11.2, 2.7 Hz, CH_xH_yOH), 3.49 (1H, dd, *J* = 11.2, 7.0 Hz, CH_xH_yOH), 2.80–2.70 (2H, m, CH_2Ph), 2.39 (2H, br s, OH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 137.9 (C), 129.5 (2 × CH), 128.8 (2 × CH), 126.7 (CH), 73.2 (CH), 66.1 (CH_2), 39.9 (CH_2); **HRMS** (+ESI): *m*/*z* calcd. for $C_9H_{16}NO_2[M+NH_4]^+$: 170.1176, found: 170.1176.

2.4.2. Formation of methyl ester[110,144]

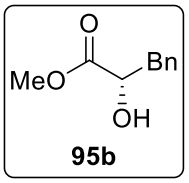


86b **95b**

a) MeMgBr, $MeOH/CH_2Cl_2$, 0 °C, 5 min.

Methylmagnesium bromide 3.0M in diethyl ether (103 µL, 0.31 mmol) was added to anhydrous methanol (1.0 mL) and stirred at 0 ˚C for 10 min. A solution of alcohol **86b** (0.53 g, 0.15 mmol) in CH_2Cl_2:MeOH (3:1, 1.5 mL) was added to the suspension at 0 ˚C. After 5 min at 0˚C, reaction was quenched with pH 7 phosphate buffer solution (1mL). The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with

CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (hexanes/EtOAc 85:15) afforded 25 mg (0.14 mmol, 93 %) of (*S*)-methyl-phenyllactate (**95b**) and 31 mg (0.15 mmol, 99 %) of oxazolidinone **59**.



95b

(*S*)-Methyl-phenyllactate (95b). White solid. **Mp** = 47–48 °C; $\mathbf{R_f}$ (Hexanes/EtOAc 40:60) = 0.5; $\mathbf{[\alpha]^{20}_D}$ = –12.1 (*c* 1.1, CH_2Cl_2) [lit.[110] $\mathbf{[\alpha]^{20}_D}$ = –13.7 (*c* 1.1, CH_2Cl_2) for *S* enantiomer]; **IR** (ATR) ν 3271, 3018, 2945, 2838, 1748, 1726, 1425, 1273, 1251, 1087 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, Ar<u>H</u>), 4.45 (1H, ddd, *J* = 6.8, 6.1, 4.4 Hz, COC<u>H</u>), 3.77 (3H, s, OC<u>H_3</u>), 3.12 (1H, dd, *J* = 13.9, 4.4 Hz, C<u>H</u>$_x$H$_y$Ph), 2.96 (1H, dd, *J* = 13.9, 6.8 Hz, CH$_x$<u>H</u>$_y$Ph), 2.74 (1H, d, *J* = 6.1 Hz, O<u>H</u>); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 174.7 (C), 136.4 (C), 129.6 (2 × CH), 128.6 (2 × CH), 127.0 (CH), 71.4 (CH), 52.6 (CH_3), 40.7 (CH_2); **HRMS** (+ESI): *m*/*z* calcd. for $C_{10}H_{16}NO_3$ $[M+Na]^+$: 198.1125, found: 198.1116.

CHAPTER 4

Alkylations

EXPERIMENTAL SECTION FOR CHAPTER 4
TABLE OF CONTENTS

1. Alkylations

1.1. Attemts in photoredox induced reactivity

Neat $TiCl_4$ (37 µL, 0.33 mmol) was added dropwise to a solution *N*-propanonyl oxazolidinone **69a** (79 mg, 0.30 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (58 µL, 0.33 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, the corresponding photoredox catalyst (1 mol %), n eq of *i*-Pr_2NEt, n eq of Hantzch ester additives and radical source (0.45 mmol) were added and the resultant mixture was stirred at rt for 16 h under a 20 W cold compact fluorescent lightbulb.

The reaction was quenched by the addition of sat. NH_4Cl (2 mL) at rt with vigorous stirring. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The resulting crude mixtures were analysed analysed by ^1H NMR. Results were summarised in Table 46.

Entry	Source	Photocatalyst	*i*-Pr_2NEt (eq)	Hantzch (eq)	Yield[a] (%)
1	$BnCO_2NPhth$	$Ru(PPh_3)_3Cl_2$	-	-	-
2	$BnCO_2NPhth$	benzophenone	-	-	-
3	$BnCO_2NPhth$	$Ru(bpy)_3(PF_6)_2$	-	-	-
4	$BnCO_2NPhth$	$Ru(bpy)_3(PF_6)_2$	1.5	-	-
5	$BnCO_2NPhth$	$Ru(bpy)_3(PF_6)_2$	2.2	10%	-
6	$BnCH_2CO_2NPhth$	$Ru(bpy)_3(PF_6)_2$	2.2	10%	-
7	$BnCO_2NPhth$	$Ru(bpy)_3(PF_6)_2$	2.2	1.5	-
8	$BnCH_2CO_2NPhth$	$Ru(bpy)_3(PF_6)_2$	2.2	1.5	-
9	$BnCO_2NPhth$	$Ir(ppy)_3$	-	-	-
10	$BnCH_2CO_2NPhth$	$Ir(ppy)_3$	-	-	-
11	$BnCO_2NPhth$	$Ir(ppy)_3$	2.2	1.5	-
12	$BnCH_2CO_2NPhth$	$Ir(ppy)_3$	2.2	1.5	-
13	PhI	$Ir(ppy)_3$	-	-	-
14	Propyll	$Ir(ppy)_3$	-	-	-
15	[*p*-$BrPhN_2$]BF_4	$Ru(bpy)_3(PF_6)_2$	-	-	-

[a] Determined by ^1H NMR analysis of the crude mixture.

Table 46

1.2. Screening of potential reagents

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added

dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, the corresponding reagent (1.1 mmol) was added and the resultant mixture was stirred at **T** for 16 h.

The reaction was quenched and treated as in section 1.1. The resulting crude mixtures were analysed by ^{1}H NMR. Results are summarised in Table 47.

Entry	Reagent	T (°C)	dr[a]	Yield[a] (%)
1	TMS-acetophenone enol	rt	-	-
2	B_2Pin_2	rt	-	-
3	B_2Pin_2	60	-	-
4	Sn_2Me_6	rt	-	-
5	Sn_2Me_6	60	-	-
6	$Zn(SO_2CF_3)_2$	rt	-	-
7	$BnBF_3^-K^+$	rt	-	-
8	$BrPhN_2^+BF_4^-$	rt	-	Complex mixture
9	$BnCH_2CO_2NPhth$	rt	-	-
10	Benzoyl Peroxide	rt	80:20	(65)

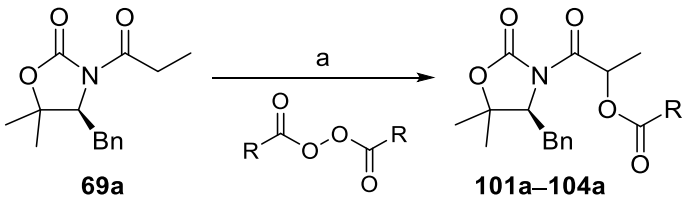
[a] Determined by ^{1}H NMR analysis of the crude mixture.

Table 47

1.3. Reaction with aromatic peroxides

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, a solution of the corresponding aromatic peroxide (n eq) in CH_2Cl_2 was dried (MgSO4), filtered, concentrated and added to the enolate and the resultant mixture was stirred at rt for 2 h.

The reaction was quenched and treated as in section 1.1. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatography. Results are summarised in Table 48 spectroscopic data is shown in section 1.4.



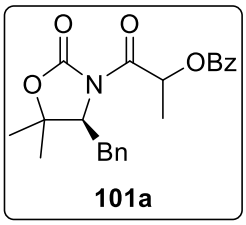
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) n eq diacyl peroxide, rt, 16 h.

Entry	Peroxide	R	Peroxide (eq)	Product	dr[a]	Conversion (%)[a]	Yield (%)[b]
1	**BPO**	Ph	1.1	**101a**	80:20	65	nd
2	**BPO**	Ph	1.5	**101a**	80:20	75	55
3	**BPO**	Ph	3.1	**101a**	80:20	76	nd
4[c]	**BPO**	Ph	1.5	**101a**	80:20	37	nd
5	**98**	*p*-CF_3Ph	1.5	**102a**	74:26	62	50
6	**99**	*p*-OMePh	1.5	**103a**	86:14	17	nd
7	**100**	CH=CHPh	1.5	**104a**	84:16	31	22

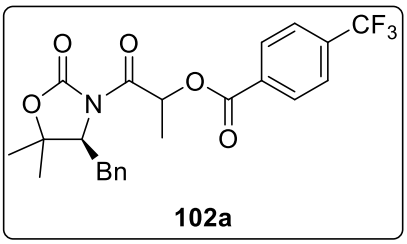
[a] Determined by ^{1}H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Performed with 1.1 eq of $TiCl_3$(*i*-PrO).

Table 48

1.4. Spectroscopic data of acyloxylated compounds 101a–104a

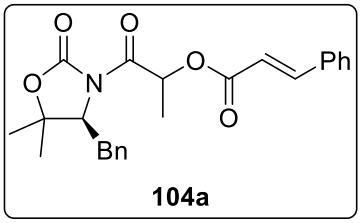


(*S*)-4-Benzyl-*N*-(2-benzoyloxypropanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**101a**) was prepared according to the procedure described in section 1.3 from *N*-acyl oxazolidinone **69a** (131 mg, 0.5 mmol) and 70% benzoyl peroxide (260 mg, 0.75 mmol). Purification of the residue by chromatography (hexanes/EtOAc 85:15) afforded **101a** (106 mg, 0.28 mmol, 55% yield) as an 80:20 mixture of diastereomers. White solid. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.4; **IR** (ATR) 3028, 2972, 2930, 1766, 1703, 1601, 1452, cm^{-1}; Major diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24–7.04 (10H, m, ArH), 6.24 (1H, q, *J* = 6.8 Hz, COCH), 4.50 (1H, dd, *J* = 10.4, 2.7 Hz, NCH), 3.31 (1H, dd, *J* = 14.8, 2.7 Hz, $PhCH_xH_y$), 2.96 (1H, dd, *J* = 14.8, 10.4 Hz, $PhCH_xH_y$), 1.68 (3H, d, *J* = 6.8 Hz, $CHCH_3$), 1.38 (3H, s, CCH_3), 1.37 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 171.7 (C), 166.0 (C), 152.1 (C), 137.0 (C), 133.3 (C), 129.9 (2 × CH), 129.0 (2 × CH), 128.6 (2 × CH), 128.6 (2 × CH), 128.3 (CH), 126.6 (CH), 83.1 (C), 69.8 (CH), 64.0 (CH), 34.6 (CH_2), 28.8 (CH_3), 22.4 (CH_3), 16.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{22}H_{23}NNaO_5$ $[M+Na]^+$: 404.1468, found: 404.1468.



(*S*)-4-Benzyl-*N*-(2-(4-trifluoromethyl)-benzoyloxypropanoyl)-5,5-dimethyl-1,3-oxazolidin-2-one (**102a**) was prepared according to the procedure described in section 1.3 from *N*-acyl oxazolidinone **69a** (79 mg, 0.3 mmol) and 4-trifluoromethylbenzoyl peroxide (170 mg, 0.45 mmol). Purification of the residue by

chromatography (hexanes/EtOAc 85:15) afforded **102a** (57 mg, 0.13 mmol, 42% yield) as a 74:26 mixture of diastereomers impurified with chlorinated by-product. White solid. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.3; Major diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21–8.15 (2H, m, ArH), 7.72–7.69 (2H, m, ArH), 7.32–7.19 (5H, m, ArH), 6.27 (1H, q, *J* = 6.7 Hz, COCH), 4.50 (1H, dd, *J* = 10.5, 2.5 Hz, NCH), 3.38 (1H, dd, *J* = 14.8, 2.5 Hz, PhCH_xH_y), 2.96 (1H, dd, *J* = 14.8, 10.5 Hz, PhCH_xH_y), 1.69 (3H, d, *J* = 6.7 Hz, CHCH_3), 1.39 (3H, s, CCH_3), 1.38 (3H, s, CCH_3).



104a

(*S*)-4-Benzyl-*N*-(2-cinnamoyloxy)propanoyl-5,5-dimethyl-1,3-oxazolidin-2-one (**104a**) was prepared according to the procedure described in section 1.3 from *N*-acyl oxazolidinone **69a** (131 mg, 0.5 mmol) and 3-phenyl-2-propenoyl peroxide (220 mg, 0.75 mmol). Purification of the residue by chromatography (hexanes/EtOAc 85:15) afforded **104a** (46 mg, 0.11 mmol, 22% yield) as an 84:16 mixture of diastereomers. Colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.4; Major diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 16.9 Hz, PhCH=CH), 7.52–7.20 (10H, m, ArH), 6.51(1H, d, *J* = 16.9 Hz, PhCH=CH), 6.14 (1H, q, *J* = 6.7 Hz, COCH), 4.50 (1H, dd, *J* = 10.4, 2.4 Hz, NCH), 3.30 (1H, dd, *J* = 14.8, 2.4 Hz, PhCH_xH_y), 2.96 (1H, dd, *J* = 14.8, 10.4 Hz, PhCH_xH_y), 1.62 (3H, d, *J* = 6.7 Hz, CHCH_3), 1.37 (3H, s, CCH_3), 1.36 (3H, s, CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 172.0 (C), 166.4 (C), 152.2 (C), 146.2 (CH), 137.2 (C), 134.4 (C), 130.6 (CH), 129.1 (2 × CH), 129.0 (2 × CH), 128.8 (2 × CH), 128.3 (2 × CH), 126.8 (CH), 117.1 (CH), 83.3 (C), 69.5 (CH), 64.1 (CH), 34.7 (CH_2), 28.9 (CH_3), 22.5 (CH_3), 16.7 (CH_3).

2. Decarboxylative alkylation with diacyl peroxides

2.1. Preliminary studies

2.1.1. Enolization with $TiCl_4$

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, lauroyl peroxide (219 mg, 0.55 mmol) was added and the resultant mixture was stirred at rt for further 16 h.

The reaction was quenched by the addition of sat. NH_4Cl (2 mL) at rt with vigorous stirring. The mixture was partitioned with CH_2Cl_2 (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^{1}H NMR and purified by column chromatography (hexanes/EtOAc 90:10) to afford 110 mg (0.26 mmol, 54% yield) of (*S*)-4-benzyl-5,5-dimethyl-*N*-(*R*)-(2-methyltridecanoyl)-1,3-oxazolidin-2-one (**106a**). Spectroscopic data is shown in section 2.3.

2.1.2. Enolization with *n*-Bu_2BOTf[147]

A 1 M solution of *n*-Bu_2BOTf in CH_2Cl_2 (220 µL, 0.22 mmol) and *i*-Pr_2NEt (42 µL, 0.24 mmol) were added to a solution of *N*-propanonyl oxazolidinone **69a** (52 mg, 0.2 mmol) in CH_2Cl_2 (1 mL) under N_2 atmosphere at 0 °C. The resulting yellowish solution was stirred at 0 °C for 40 min. Then, lauroyl peroxide (247 mg, 0.62 mmol) was added and the resultant mixture was stirred at 0 °C for 16 h.

The reaction was quenched by the addition of pH 7 phosphate buffer solution (5 mL) at rt with vigorous stirring. The solvent was removed, and the product was dissolved in MeOH (3 mL) and 30% H_2O_2 (1mL) at 0 °C and stirred for 1 h. Methanol was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^1H NMR, which showed that it was essentially starting material.

2.1.3. Enolization with NaHMDS[216]

A solution of *N*-propanonyl oxazolidinone **69a** (52 mg, 0.2 mmol) in THF (0.25 mL) was added via cannula (2 × 0.25 mL) to a 1 M solution of NaHMDS (220 µL, 0.22 mmol) in THF (1 mL) at –78 °C, and the solution was stirred at –78 °C for 40 min. Then, lauroyl peroxide (247 mg, 0.62 mmol) was added and the resultant mixture was stirred at –78 °C for 4 h and at –20 °C for further 16 h.

The reaction was quenched by the addition of sat. $NaHCO_3$ (2 mL) at rt with vigorous stirring. The mixture was partitioned in Et_2O (50 mL) and water (30 mL), and the organic layer was washed with a 1 M HCl (10 mL), sat. $NaHCO_3$ (10 mL), and brine (10 mL). The organic fraction was dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^1H NMR, which showed that it was essentially starting material.

2.1.4. Enolization with LDA[216]

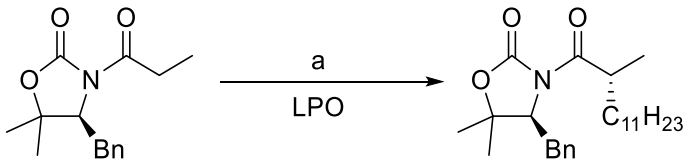
A solution of *N*-propanonyl oxazolidinone **69a** (52 mg, 0.2 mmol) in THF (0.25 mL) was added via cannula (2 × 0.25 mL) to a 2 M solution of LDA (110 µL, 0.22 mmol) in THF (1 mL) at –78 °C, and the solution was stirred at –78 °C for 40 min. Then, lauroyl peroxide (247 mg, 0.62 mmol) was added and the resultant mixture was stirred at –78 °C for 4 h and at 0 °C for further 16 h.

The reaction was quenched by the addition of sat. $NaHCO_3$ (2 mL) at rt with vigorous stirring. The mixture was partitioned in Et_2O (50 mL) and water (30 mL), and the organic layer was washed with a 1 M HCl (10 mL), sat. $NaHCO_3$ (10 mL), and brine (10 mL). The organic fraction was dried ($MgSO_4$), filtered, and concentrated. The residue was analysed by ^1H NMR, which showed that it was essentially starting material.

2.1.5. Optimisation of the alkylation with lauroyl peroxide

Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-propanonyl oxazolidinone **69a** (0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, lauroyl peroxide (n eq) was added and the resultant mixture was stirred at rt until the enolate colour was extinguished (2 h).

The reaction was quenched and treated as in section 2.1.1. The resulting crude mixtures were analysed by ^1H NMR and purified by column chromatography. Results were summarised Table 49 and spectroscopic data is shown in section 2.3.



69a **106a**

a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) n eq LPO, T, 2 h to 16 h.

Entry	TiL_4	LPO (eq)	dr[a]	Yield[b] (%)
1	$TiCl_4$	0.66	≥ 97:3	(35) (53)[c]
2	$TiCl_4$	1.1	≥ 97:3	54 (58)
3	$TiCl_4$	1.5	≥ 97:3	60 (66)
4	$TiCl_4$	2.1	≥ 97:3	66 (73)
5	$TiCl_4$	3.1	≥ 97:3	76% (80)
6	$TiCl_4$	6.1	≥ 97:3	73% (86)
7[d]	$TiCl_4$	3.1	≥ 97:3	(66)
8[e]	$TiCl_4$	3.1	≥ 97:3	(15)
9[f]	$TiCl_4$	3.1	≥ 97:3	(43)

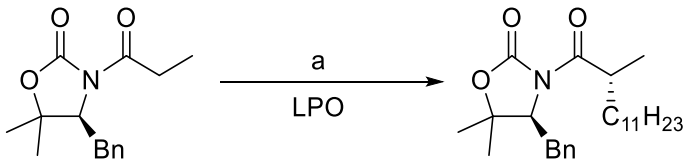
[a] Determined by ^1H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography. NMR conversion into brackets.
[c] Conversion to LPO. d Performed at 0 °C for 16 h.
[d] Performed at –20 °C for 16 h. f Performed at 0.02M.

Table 49

2.1.6. Lewis acids screening for the alkylation with lauroyl peroxide

The corresponding Lewis acid (0.55 mmol) was added dropwise to a solution of *N*-propanonyl oxazolidinone **69a** (131 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, lauroyl peroxide (617 mg, 1.55 mmol) was added and the resultant mixture was stirred at rt for further 2 h.

The reaction was quenched and treated as in section 2.1.1. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatography. Results were summarised Table 50 and spectroscopic data is shown in section 2.3.



69a **106a**

a) (i) 1.1 eq TiL_4, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 3.1 eq LPO, rt, 2 h.

Entry	TiL_4	dr[a]	Conversion (%)[a]
1	$TiCl_4$	≥ 97:3	76[b]
2	2 × $TiCl_4$	≥ 97:3	32
3	0,5 × $TiCl_4$	≥ 97:3	34
4	$TiCl_3$(*i*-PrO)	≥ 97:3	31
5	$TiBr_4$	≥ 97:3	< 10

[a] Determined by ^{1}H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.

Table 50

2.1.7. Alkylation of *N*-propanoyl oxazolidinone **68a**

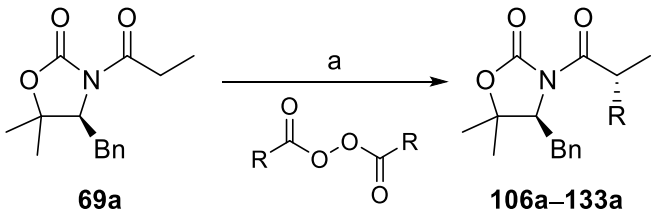
Neat $TiCl_4$ (61 µL, 0.55 mmol) was added dropwise to a solution of *N*-propanonyl oxazolidinone **68a** (117 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Then, *i*-Pr_2NEt (96 µL, 0.55 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, lauroyl peroxide (617 mg, 1.55 mmol) was added and the resultant mixture was stirred at rt for 2 h.

The reaction was quenched and treated as in section 2.1.1. The residue was analysed by ^{1}H NMR and purified by column chromatography **(**hexanes/EtOAc 90:10) to afford 95 mg (0.25 mmol, 49% yield) of (*S*)-4-Benzyl-*N*-[(*R*)-2-methyltridecanoyl]-1,3-oxazolidin-2-one (**107a**). Spectroscopic data is shown in section 2.3.

2.2. Decarboxylative alkylation with diacyl peroxides. General procedure

Neat $TiCl_4$ (37 µL, 0.33 mmol) was added dropwise to a solution of *N*-propanonyl oxazolidinone **69a** (79 mg, 0.30 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C under N_2 atmosphere and the resultant yellow suspension was stirred for 5 min. Anhydrous *i*-Pr_2NEt (58 µL, 0.33 mmol) was added dropwise and the ensuing dark solution was stirred for 40 min at 0 °C. Then, the corresponding freshly prepared diacyl peroxyde (0.93 mmol) was added and the resultant mixture was stirred at rt for 2 h.

The reaction was quenched and treated as in section 2.1.1. The resulting crude mixtures were analysed by ^{1}H NMR and purified by column chromatography. Results were summarised Table 51 and spectroscopic data is shown in section 2.3.



69a **106a–133a**

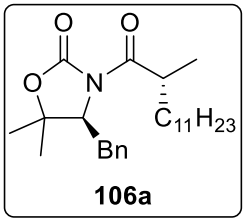
a) (i) 1.1 eq $TiCl_4$, 1.1 eq *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 40 min; (ii) 3.1 eq peroxide, rt, 2 h.

Entry	Peroxide	R	Product	dr[a]	Yield (%)[b]
1	**108**	Pr	**121a**	≥ 97:3	87
2	**109**	CH_2Bn	**122a**	≥ 97:3	85
3	**LPO**	$C_{11}H_{23}$	**106a**	≥ 97:3	76
4[c]	**LPO**	$C_{11}H_{23}$	**107a**	≥ 97:3	49
5	**110**	*i*-Bu	**123a**	≥ 97:3	71
6	**111**	$(CH_2)_2CH=CH_2$	**124a**	≥ 97:3	87
7	**112**	$(CH_2)_3CH=CH_2$	**125a**	≥ 97:3	81
8	**113**	$(CH_2)_3CH\equiv CH$	**126a**	≥ 97:3	72
9	**114**	$(CH_2)_3CO_2Bn$	**127a**	≥ 97:3	45
10	**115**	$(CH_2)_4CO_2Me$	**128a**	≥ 97:3	54
11	**116**	$(CH_2)_4CH_2Br$	**129a**	≥ 97:3	84
12	**117**	C_5H_9	**130a**	≥ 97:3	64
13	**118**	C_6H_{11}	**131a**	≥ 97:3	60
14	**119**	*i*-Pr	**132a**	≥ 97:3	78
15	**120**	CH(Me)Bn	**133a**	65:35[d]	70
16	**134**	C_4H_7	**124a**	≥ 97:3	65

[a] Determined by ^{1}H NMR analysis of the crude mixture.
[b] Isolated yield after column chromatography.
[c] Performed with (*S*)-4-Benzyl-N-propanoyl-1,3-oxazolidin-2-one (**68a**).
[d] Diastereomeric ratio of the second chiral center formed.

Table 51

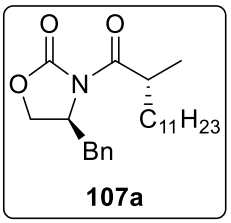
2.3. Spectroscopic data of alkylation adducts



106a

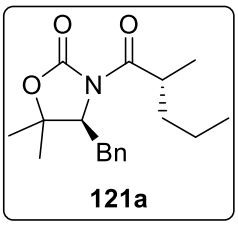
(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methyltridecanoyl]-1,3-oxazolidin-2-one (**106a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (131 mg, 0.5 mmol) and lauroyl peroxide (617 mg, 1.55 mmol). Purification of the residue by chromatography (hexanes/EtOAc 95:5) afforded **106a** (158 mg, 0.38 mmol, 76% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.35; $\mathbf{[\alpha]^{20}_D}$ = –46.4 (*c* 1.0, $CHCl_3$) ; **IR** (ATR) ν 2925, 1771, 1696, 1605 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, C$\underline{H}_x$H$_y$Ph), 2.87 (1H, dd, *J* = 14.3, 9.7 Hz, CH$_x\underline{H}_y$Ph), 1.74–1.66 (1H, m, COCHC$\underline{H}_x$H$_y$), 1.36 (3H, s, CC$\underline{H}_3$), 1.34 (3H, s, CC$\underline{H}_3$), 1.25 (19H, br s, COCHCH$_x\underline{H}_y$(C$\underline{H}_2$)$_9$), 1.15 (3H, d, *J* = 6.8 Hz, CHC$\underline{H}_3$), 0.87 (3H, t, *J* = 6.8 Hz, CH$_2$C$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.7 (C), 152.3 (C), 137.0 (C), 129.1 (2 × CH), 128.6 (2 × CH), 126.7 (CH), 81.8 (C), 63.7 (CH), 37.6 (CH), 35.4 (CH_2), 33.8 (CH_2), 31.9 (CH_2), 29.6 (2 × CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.6 (CH_3), 27.0 (CH_2), 22.7 (CH_2), 22.3 (CH_3), 16.8 (CH_3), 14.1 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{26}H_{41}NO_3$ $[M+H]^+$: 416.3159, found: 416.3165.



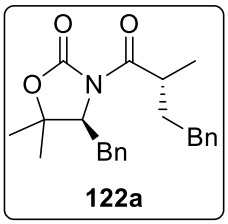
107a

(*S*)-4-Benzyl-*N*-[(*R*)-2-methyltridecanoyl]-1,3-oxazolidin-2-one (**107a**) was prepared according to the procedure described in section 2.1.7 from *N*-propanoyl oxazolidinone **68a** (117 mg, 0.5 mmol) and lauroyl peroxide (617 mg, 1.55 mmol). Purification of the residue by chromatography (hexanes/EtOAc 90:10) afforded **107a** (95 mg, 0.25 mmol, 49% yield) as a colourless oil. **R_f** (Hexanes/EtOAc 90:10) = 0.3; **$[\alpha]^{20}_D$** = –23.8 (*c* 1.0, $CHCl_3$); **IR** (ATRl) ν 3031, 2920, 2850, 1777, 1695 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.21 (5H, m, Ar$\underline{H}$), 4.69 (1H, ddt, *J* = 9.8, 7.0, 3.4 Hz, C$\underline{H}$N), 4.19–4.12 (2H, m, C$\underline{H}_2$CHBn) 3.74 (1H, sext, *J* = 6.7 Hz, COC$\underline{H}$), 3.30 (1H, dd, *J* = 13.3, 3.4 Hz, C$\underline{H}_x$H$_y$Ph), 2.73 (1H, dd, *J* = 13.3, 9.8 Hz, CH$_x\underline{H}_y$Ph), 1.82–1.73 (1H, m, COCHC$\underline{H}_x$H$_y$), 1.48–1.40 (1H, m, COCHCH$_x\underline{H}_y$), 1.37–1.25 (18H, br s, COCHCH$_2$(C$\underline{H}_2$)$_9$), 1.17 (3H, d, *J* = 6.8 Hz, CHC$\underline{H}_3$), 0.87 (3H, t, *J* = 6.7 Hz, CH$_2$C$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.6 (C), 153.2 (C), 135.5 (C), 129.6 (2 × CH), 129.1 (2 × CH), 127.5 (CH), 66.1 (CH_2), 55.5 (CH), 38.2 (CH_2), 37.7 (CH), 34.0 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 27.2 (CH_2), 22.8 (CH_2), 16.9 (CH_3), 14.3 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{24}H_{38}NO_3$ $[M+H]^+$: 388.2846, found: 388.2849.



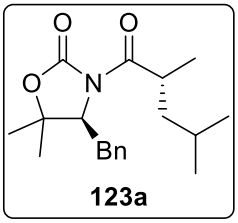
121a

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methylpentanoyl]-1,3-oxazolidin-2-one (**121a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and butanoyl peroxide (162 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/EtOAc 90:10) afforded **121a** (79 mg, 0.26 mmol, 87% yield) as a colourless oil. **R_f** (Hexanes/EtOAc 90:10) = 0.3; **$[\alpha]_D$** = –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, Ar$\underline{H}$), 4.53 (1H, dd, *J* = 9.7, 3.7 Hz, C$\underline{H}$N), 3.77 (1H, sext, *J* = 6.7 Hz, COC$\underline{H}$), 3.12 (1H, dd, *J* = 14.4, 3.7 Hz, C$\underline{H}_x$H$_y$Ph), 2.87 (1H, dd, *J* = 14.4, 9.7 Hz, CH$_x\underline{H}_y$Ph), 1.74–1.66 (1H, m, COCHC$\underline{H}_x$H$_y$), 1.38–1.27 (3H, m, COCHCH$_x\underline{H}_y$, C$\underline{H}_2$CH$_3$), 1.36 (3H, s, CC$\underline{H}_3$), 1.34 (3H, s, CC$\underline{H}_3$), 1.15 (3H, d, *J* = 6.8 Hz, COCHC$\underline{H}_3$), 0.90 (3H, t, *J* = 7.1 Hz, CH$_2$C$\underline{H}_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.8 (C), 152.5 (C), 137.1 (C), 129.2 (2 × CH), 128.8 (2 × CH), 126. 9 (CH), 82.0 (C), 63.8 (CH), 37.6 (CH), 36.1 (CH_2), 35.6 (CH_2), 28.7 (CH_3), 22.5 (CH_2), 20.4 (CH_2), 16.9 (CH_3), 14.2 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{26}NO_3$ $[M+H]^+$: 304.1907, found: 304.1914.



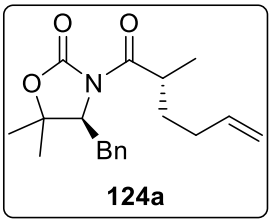
122a

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methyl-4-phenylbutanoyl]-1,3-oxazolidin-2-one (**122a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and hydrocinnamyl peroxide (277 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/CH_2Cl_2 40:60) afforded **122a** (95 mg, 0.26 mmol, 87% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/CH_2Cl_2 40:60) = 0.3; $\mathbf{[\alpha]^{20}_D}$ = –53.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 2924, 2854, 1777, 1696 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, sext, *J* = 6.8 Hz, COCH), 3.09 (1H, dd, *J* = 14.4, 3.8 Hz, NCHCH$_x$H$_y$Ph), 2.86 (1H, dd, *J* = 14.4, 9.6 Hz, NCHCH$_x$H$_y$Ph), 2.67–2.52 (2H, m, CH_2CH_2Ph), 2.10–2.01 (1H, m, CH$_x$H$_y$$CH_2$Ph), 1.70–2.61 (1H, m, CH$_x$H$_y$$CH_2$Ph), 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), 136.92 (C), 129.1 (2 × CH), 128.7 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 126.8 (CH), 125.9 (CH), 81.9 (C), 63.7 (CH), 37.8 (CH), 35.7 (CH_2), 35.4 (CH_2), 33.6 (CH_2), 28.6 (CH_3), 22.3 (CH_3), 17.0 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{23}H_{28}NO_3$ $[M+H]^+$: 366.2064, found: 366.2056.



123a

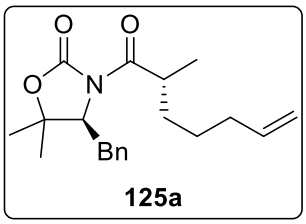
(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2,4-dimethylpentanoyl]-1,3-oxazolidin-2-one (**123a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and 3-methylbutanoy) peroxide (162 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/EtOAc 95:5 to 90:10) afforded **123a** (67 mg, 0.21 mmol, 71% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.5; $\mathbf{[\alpha]_D}$ = –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$_x$H$_y$Ph), 2.88 (1H, dd, *J* = 14.4, 9.7 Hz, CH$_x$H$_y$Ph), 1.64 (1H, dt, *J* = 12.9, 6.9 Hz , COCHCH$_x$H$_y$), 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$_x$H$_y$), 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 (2 × CH), 128.6 (2 × 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.



124a

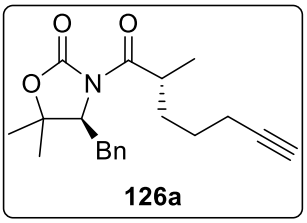
(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-(2-methyl-5-hexenoyl]-1,3-oxazolidin-2-one (**124a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and 4-pentenoyl peroxide (184 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/EtOAc 95:5 to 90:10) afforded **124a** (82 mg, 0.26 mmol, 87% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.4; $\mathbf{[\alpha]_D}$ = –53.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3060, 2024, 2971, 2932, 1767, 1692 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, Ar<u>H</u>), 5.80 (1H, ddt, *J* = 16.8, 10.0, 6.7 Hz, C<u>H</u>=CH_2), 5.07–4.98 (1H, m, CH=C<u>H</u>$_x$H$_y$), 4.97–4.93 (1H, m, CH=CH$_x$<u>H</u>$_y$), 4.53 (1H, dd, *J* = 9.7, 3.8 Hz, C<u>H</u>N), 3.77 (1H, sext, *J* = 6.8 Hz, COC<u>H</u>), 3.13 (1H, dd, *J* = 14.4, 3.8 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), 2.11–2.01 (2H, m, C<u>H</u>$_2$CH=CH_2), 1.85 (1H, ddt, *J* = 13.6, 8.7, 6.8 Hz, COCHC<u>H</u>$_x$H$_y$), 1.50–1.41 (1H, m, COCHCH$_x$<u>H</u>$_y$), 1.37 (3H, s, CC<u>H</u>$_3$), 1.34 (3H, s, CC<u>H</u>$_3$), 1.17 (3H, d, *J* = 6.8 Hz, COCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.5 (C), 152.4 (C), 138.2 (CH), 137.1 (C), 129.2 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 115.1 (CH_2), 82.1 (C), 63.8 (CH), 37.4 (CH), 35.6 (CH_2), 33.0 (CH_2), 31.4 (CH_2), 28.7 (CH_3), 22.4 (CH_3), 17.0 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1907, found: 316.1914.



125a

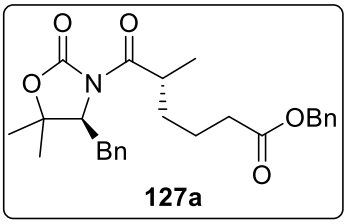
(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-(2-methyl-6-heptenoyl]-1,3-oxazolidin-2-one (**125a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and 5-hexenoyl peroxide (210 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/EtOAc 95:5 to 90:10) afforded **125a** (79 mg, 0.24 mmol, 81% yield) as a colourless oil. **R_f** (Hexanes/EtOAc 90:10) = 0.4; **[α]$_D$** = –57.2 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3065, 3027, 2977, 2929, 2856, 1770, 1691 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.20 (5H, m, Ar<u>H</u>), 5.79 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz, C<u>H</u>=CH_2), 5.04–4.98 (1H, m, CH=C<u>H</u>$_x$H$_y$), 4.97–4.93 (1H, m, CH=CH$_x$<u>H</u>$_y$), 4.53 (1H, dd, *J* = 9.6, 3.8 Hz, C<u>H</u>N), 3.75 (1H, sext, *J* = 6.6 Hz, COC<u>H</u>), 3.11 (1H, dd, *J* = 14.3, 3.8 Hz, C<u>H</u>$_x$H$_y$Ph), 2.88 (1H, dd, *J* = 14.3, 9.6 Hz, CH$_x$<u>H</u>$_y$Ph), 2.08–2.02 (2H, m, C<u>H</u>$_2$CH=CH_2), 1.76–1.68 (1H, m, COCHC<u>H</u>$_x$H$_y$), 1.47–1.37 (3H, m, COCHCH$_x$<u>H</u>$_y$, C<u>H</u>$_2$CH$_2$CH=CH_2), 1.37 (3H, s, CC<u>H</u>$_3$), 1.34 (3H, s, CC<u>H</u>$_3$), 1.15 (3H, d, *J* = 6.8 Hz, COCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.6 (C), 152.5 (C), 138.6 (CH), 137.1 (C), 129.2 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 114.8 (CH_2), 82.0 (C), 63.8 (CH), 37.7 (CH), 35.6 (CH_2), 33.8 (CH_2), 33.4 (CH_2), 28.7 (CH_3), 26.4 (CH_2), 22.4 (CH_3), 17.0 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{28}NO_3$ $[M+H]^+$: 330.2064, found: 330.2071.



126a

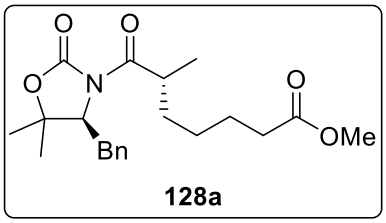
(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-(2-methyl-6-heptynoyl]-1,3-oxazolidin-2-one (**126a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and 5-hexynoyl peroxide (206 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/CH_2Cl_2 30:70) afforded **126a** (71 mg, 0.22 mmol, 72% yield) as a colourless oil. **R_f** (Hexanes/CH_2Cl_2 30:70) = 0.3; **[α]$_D$** = –49.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3284, 3069, 3027, 2974, 2929, 2863, 1767, 1694 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–7.20 (5H, m, Ar<u>H</u>), 4.53 (1H, dd, *J* = 9.5, 4.0 Hz, C<u>H</u>N), 3.79–3.73 (1H, m, COC<u>H</u>), 3.11 (1H, dd, *J* = 14.3, 4.0 Hz, C<u>H</u>$_x$H$_y$Ph), 2.89 (1H, dd, *J* = 14.3, 9.5 Hz, CH$_x$<u>H</u>$_y$Ph), 2.21–2.16 (2H, m, C<u>H</u>$_2$C≡CH), 1.95 (1H, t, *J* = 2.7 Hz, C≡C<u>H</u>), 1.82–1.75 (1H, m, COCHC<u>H</u>$_x$H$_y$), 1.55–1.47 (3H, m, COCHCH$_x$<u>H</u>$_y$C<u>H</u>$_2$), 1.38 (3H, s, CC<u>H</u>$_3$), 1.35 (3H, s, CC<u>H</u>$_3$), 1.17 (3H, d, *J* = 6.8 Hz, COCHC<u>H</u>$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.3 (C), 152.5 (C), 137.0 (C), 129.2 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 84.2 (C), 82.1 (C), 68.7 (CH),

63.8 (CH), 37.4 (CH), 35.6 (CH_2), 33.0 (CH_2), 28.7 (CH_3), 26.1 (CH_2), 22.4 (CH_3), 18.6 (CH_2), 17.0 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{26}NO_3$ $[M+H]^+$: 328.1907, found: 328.1911.



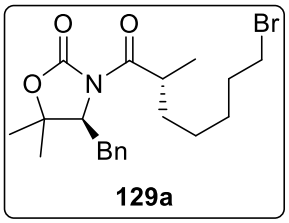
127a

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-2-methyl-6-benzyloxy-6-oxohexanoyl]-1,3-oxazolidin-2-one (**127a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and 5-benzyloxy-5-oxopentanoyl peroxide (411 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/EtOAc 90:10) afforded **127a** (59 mg, 0.13 mmol, 45% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 80:20) = 0.4; $\mathbf{[\alpha]_D}$ = –41.7 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3062, 3027, 2974, 2926, 2866, 1770, 1732, 1691 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.19 (10H, m, ArH), 5.13 (1H, d, *J* = 12.3 Hz, OCH_xH_yPh), 5.09 (1H, d, *J* = 12.3 Hz, OCH_xH_yPh), 4.51 (1H, dd, *J* = 9.6, 3.9 Hz, CHN), 3.74 (1H, sext, *J* = 6.7 Hz, COCH), 3.10 (1H, dd, *J* = 14.4, 3.9 Hz, CH_xH_yPh), 2.86 (1H, dd, *J* = 14.4, 9.6 Hz, CH_xH_yPh), 2.43–2.30 (2H, m, CH_2CO_2Bn), 1.78–1.55 (3H, m, $COCHCH_xH_yCH_2$), 1.44–1.36 (1H, m, $COCHCH_xH_y$), 1.36 (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 177.2 (C), 173.2 (C), 152.4 (C), 137.1 (C), 136.2 (C), 129.2 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.3 (2 × CH), 128.3 (CH), 126.9 (CH), 82.1 (C), 66.3 (CH_2), 63.8 (CH), 37.5 (CH), 35.5 (CH_2), 34.2 (CH_2), 33.2 (CH_2), 28.7 (CH_3), 22.5 (CH_3), 22.4 (CH_2), 16.9 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{26}H_{32}N_2O_5$ $[M+NH_4]^+$: 455.2540, found: 455.2545.



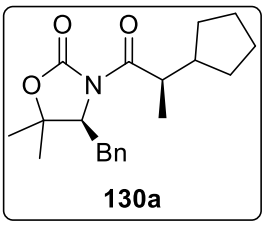
128a

(*S*)-4-Benzyl-5,5-dimethyl-*N*-(*R*)-(2-methyl-7-benzyloxy-7-oxoheptanoyl)-1,3-oxazolidin-2-one (**128a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and 6-methoxy-6-oxohexanoyl peroxide (411 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/EtOAc 85:15) afforded **128a** (60 mg, 0.16 mmol, 54% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 85:15) = 0.3; $\mathbf{[\alpha]_D}$ = –43.8 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2974, 2936, 2856, 1770, 1733, 1695 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, p, *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 177.5 (C), 174.2 (C), 152.5 (C), 137.1 (C), 129.2 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 82.1 (C), 63.8 (CH), 51.6 (CH_3), 37.6 (CH), 35.6 (CH_2), 34.0 (CH_2), 33.4 (CH_2), 28.7 (CH_3), 26.6 (CH_2), 25.0 (CH_2), 22.4 (CH_3), 16.9 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{30}NO_5$ $[M+H]^+$: 376.2118, found: 376.2123.



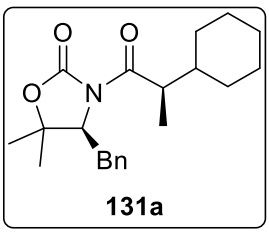
129a

(*S*)-4-Benzyl-*N*-[(*R*)-(7-bromo2-methyl-heptanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**129a**) was prepared according to the general procedure described in section 2.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and di-6-bromohexanoyl peroxide (361 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/CH_2Cl_2 50:50 to 30:70) afforded **129a** (104 mg, 0.25 mmol, 84% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/CH_2Cl_2 40:60) = 0.3; $\mathbf{[\alpha]_D}$ = –54.9 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3059, 3027, 2970, 2929, 2850, 1770, 1688 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, $CH_2CH_2CH_2$Br), 1.37 (3H, s, CCH_3), 1.35 (3H, s, CCH_3), 1.35–1.13 (3H, m, COCHC$H_xH_yCH_2$), 1.15 (3H, d, *J* = 6.8 Hz, COCHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.4 (CH), 152.3 (C), 136.9 (C), 129.1 (2 × CH), 128.6 (2 × CH), 126.8 (CH), 81.9 (C), 63.6 (CH), 37.5 (CH), 35.5 (CH_2), 33.8 (CH_2), 33.5 (CH_2), 32.6 (CH_2), 28.6 (CH_3), 28.1 (CH_2), 26.2 (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.



130a

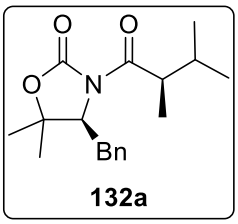
(*S*)-4-Benzyl-*N*-[(*R*)-(2-cyclopentylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**130a**) was prepared according to the general procedure described in section 5.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and peroxide from cyclopentanecarboxylic acid (210 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/EtOAc 95:5) afforded **130a** (63 mg, 0.19 mmol, 64% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.2; $\mathbf{[\alpha]_D}$ = –55.5 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3027, 2945, 2857, 1770, 1688 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 178.0 (C), 152.6 (C), 137.2 (C), 129.2 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 81.9 (C), 63.9 (CH), 43.6 (CH), 42.6 (CH), 35.4 (CH_2), 31.0 (CH_2), 30.0 (CH_2), 28.8 (CH_3), 25.4 (CH_2), 25.2 (CH_2), 22.5 (CH_3), 16.3 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{20}H_{28}NO_3$ $[M+H]^+$: 330.2064, found: 330.2072.



131a

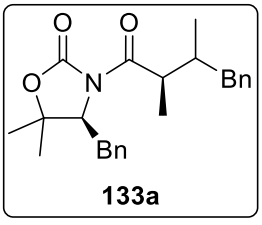
(*S*)-4-Benzyl-*N*-[(*R*)-2-cyclohexylpropanoyl]-5,5-dimethyl-1,3-oxazolidin-2-one (**131a**) was prepared according to the general procedure described in section 5.2 from *N*-propanoyl oxazolidinone **69a** (131 mg, 0.5 mmol) and peroxide from cyclohexanecarboxylic acid (406 mg, 1.55 mmol). Purification of the residue by chromatography (hexanes/EtOAc 90:10) afforded **131a** (102 mg, 0.30 mmol, 60% yield) as a colourless oil. $\mathbf{R_f}$ (Hexanes/EtOAc 90:10) = 0.4; $\mathbf{[\alpha]_D}$ = –71.3 (*c* 1.0, $CHCl_3$); **IR** (ATR) ν 3059,

3028, 2970, 2923, 2850, 1767, 1688 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, p, *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 177.7 (C), 152.6 (C), 137.2 (C), 129.2 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 81.9 (C), 63.9 (CH), 42.7 (CH), 40.9 (CH), 35.6 (CH_2), 31.4 (CH_2), 28.8 (CH_2), 28.7 (CH_3), 26.4 (CH_2), 26.5 (CH_2), 26.5 (CH_2), 22.5 (CH_3), 13.7 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{21}H_{30}NO_3$ $[M+H]^+$: 344.2220, found: 344.2222.



132a

(*S*)-4-Benzyl-5,5-dimethyl-*N*-[(*R*)-(2,3-dimethylbutanoyl]-1,3-oxazolidin-2-one (**132a**) was prepared according to the general procedure described in section 5.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and of 2-methylpropanoyl peroxide (165 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/EtOAc 95:5 to 90:10) afforded **132a** (71 mg, 0.23 mmol, 78% yield) as a colourless oil. **R_f** (Hexanes/EtOAc 90:10) = 0.3; **$[\alpha]_D$** = –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, CHN), 3.65 (1H, p, *J* = 6.8 Hz, COCH), 3.16 (1H, dd, *J* = 14.4, 3.5 Hz, CH_xH_yPh), 2.85 (1H, dd, *J* = 14.4, 10.0 Hz, CH_xH_yPh), 2.03 (1H, sext, *J* = 6.8 Hz, COCHCH), 1.35 (3H, s, CCH_3), 1.33 (3H, s, CCH_3), 1.11 (3H, d, *J* = 6.8 Hz, COCHCH_3), 0.96 (3H, d, *J* = 6.8 Hz, CH$(CH_3)_2$), 0.87 (3H, d, *J* = 6.8 Hz, CH$(CH_3)_2$);**^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.6 (C), 152.5 (C), 137.2 (C), 129.1 (2 × CH), 128.8 (2 × CH), 126.9 (CH), 81.8 (C), 63.8 (CH), 43.5 (CH), 35.5 (CH_2), 31.0 (CH), 28.8 (CH_3), 22.6 (CH_3), 21.2 (CH_3), 18.3 (CH_3), 13.1 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{18}H_{26}NO_3$ $[M+H]^+$: 304.1907, found: 304.1914.



133a

(*S*)-4-Benzyl-5,5-dimethyl-*N*-(2*R*)-(2,3-dimethyl-3-phenylpronanoyl)-1,3-oxazolidin-2-one (**133a**) was prepared according to the general procedure described in section 5.2 from *N*-propanoyl oxazolidinone **69a** (79 mg, 0.3 mmol) and 2-methyl-3-phenylpropanoyl peroxide (210 mg, 0.93 mmol). Purification of the residue by chromatography (hexanes/EtOAc 95:5 to 90:10) afforded **133a** (80 mg, 0.21 mmol, 70% yield) as a 70:30 mixture of diastereomers. Colourless thick oil. **R_f** (Hexanes/EtOAc 90:10) = 0.3; **IR** (ATR) ν 3027, 2964, 2932, 2869, 1777, 1696 cm^{-1}; Major diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31–7.11 (10H, m, ArH), 4.57 (1H, dd, *J* = 9.8, 3.7 Hz, CHN), 3.80 (1H, m, COCH), 3.11 (1H, dd, *J* = 14.4, 3.7 Hz, NCHCH_xH_yPh), 2.84 (1H, dd, *J* = 14.4, 9.8 Hz, NCHCH_xH_yPh), 2.77 (1H, dd, *J* = 12.9, 3.9 Hz CH_xH_yPh), 2.35 (1H, dd, *J* = 12.9, 10.2 Hz CH_xH_yPh), 2.27–2.13 (1H, m, CHCH_2Ph), 1.35 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.15 (3H, d, *J* = 6.9 Hz, COCHCH_3), 0.74 (3H, d, *J* = 6.8 Hz, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 177.2 (C), 152.5 (C), 140.9 (C), 137.1 (C), 129.4 (2 × CH), 129.1 (2 × CH)1, 128.8 (2 × CH), 128.3 (2 × CH), 126.9 (CH), 126.1

(CH), 82.0 (C), 63.8 (CH), 42.8 (CH), 42.0 (CH_2), 37.6 (CH), 35.6 (CH_2), 28.8 (CH_3), 22.6 (CH_3), 14.3 (CH_3), 12.4 (CH_3); Minor diastereomer: **^{1}H NMR** 7.31–7.11 (10H, m, ArH), 4.57 (1H, dd, *J* = 9.8, 3.7 Hz, CHN), 3.83 (1H, m, COCH), 3.18 (1H, dd, *J* = 14.3, 3.3 Hz, NCHCH_xH_yPh), 2.89–2.82 (2H, m, NCHCH_xH_yPh, CH_xH_yPh), 2.27–2.13 (2H, m, CH_xH_yPh, CHCH_2Ph), 1.36 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 1.25 (3H, d, *J* = 6.9 Hz, COCHCH_3), 0.85 (3H, d, *J* = 6.3 Hz, CHCH_3); **^{13}C NMR** 177.3 (C), 152.5 (C), 140.9 (C), 137.1 (C), 129.3 (2 × CH), 129.1 (2 × CH)1, 128.8 (2 × CH), 128.4 (2 × CH), 126.9 (CH), 126.0 (CH), 91.9 (C), 64.0 (CH), 42.9 (CH), 38.9 (CH_2), 38.1 (CH), 35.5 (CH_2), 28.8 (CH_3), 22.6 (CH_3), 17.4 (CH_3), 13.6 (CH_3); **HRMS** (+ESI): *m*/*z* calcd. for $C_{24}H_{30}NO_3$ $[M+H]^+$: 380.2220, found: 380.2225.

ACRONYMS AND ABBREVIATIONS

AIBN	2,2′-Azobisisobutyronitrile
ATR	Attenuated total reflectance
aux	auxiliary
BHT	Butylated hydroxytoluene
BINOL	1,1’-Binaphthol
BNAH	1-Benzyl-1,4-dihydronicotinamide
Boc	*tert*-Butyloxycarbonyl
BPO	Benzoyl peroxide
bpy	2,2′-Bipyridine
CAN	Ceric ammonium nitrate
cat	Catalyst or catalytic amount
Cat	Catechol
Cp	Cyclopentadienyl
CS	Closed shell
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N′-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DIBALH	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
dtbbpy	4,4′-Di-*tert*-butyl-2,2′-bipyridine
E	Electrophile
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
EDG	Electron donating group
ee	Enantiomeric excess
ent	Enantiomer
EPR	Electron paramagnetic resonance
eq	Equivalent
ESI	Electrospray ionization
EWG	Electron withdrawing group
hν	Light
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HG-II	Hoveyda-Grubbs Catalyst 2nd Generation
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HQ	Hydroquinone
HRMS	High-resolution mass spectrometry
IR	Infrared
ISC	Intersystem crossing
L	Ligand
LA	Lewis acid
LDA	Lithium diisopropylamide
lit.	Literature
LPO	Lauroyl peroxide
M	Metal
Mes	Mesityl
MLCT	Metal-Ligand-Charge-Transfer
Mp	Melting point
MS	Molecular sieve
NaHMDS	Sodium bis(trimethylsilyl)amide
nd	Not determined
NHPI	N-Hydroxyphthalimide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
OS	Open shell
Piv	Pivaloyl
PMB	*p*-MethoxybenzylPPTS Pyridinium *p*-toluenesulfonate
ppy	2-Phenylpyridine
pyr	Pyridine
R_f	Retention factor
rt	Room temperature
Salen	((R,R)-N,N’-Bis(3,5-di-*tert*-butylsali-cylidene)-1,2-cyclohexanediamine
sat.	Saturated

SCE	Saturated calomel electrode
SET	Single electron transfer
SOMO	Singly occupied molecular orbital
T	Temperature
t	Time
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
Tc	Thiophene-2-carboxylate
TEMPO	2,2,6,6-tetramethylpiperidine-1-yl)oxyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPP	Tetraphenylporphyrin
Ts	*p*-Toluenesulfonyl
TS	Transition state
TTMSS	Tris(trimethylsilyl)silane
UV	Ultraviolet

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