

Stereoselective Decarboxylative Alkylation of Titanium(IV) Enolates with Diacyl Peroxides

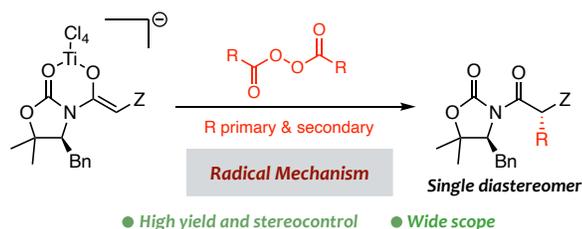
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Supporting Information Placeholder



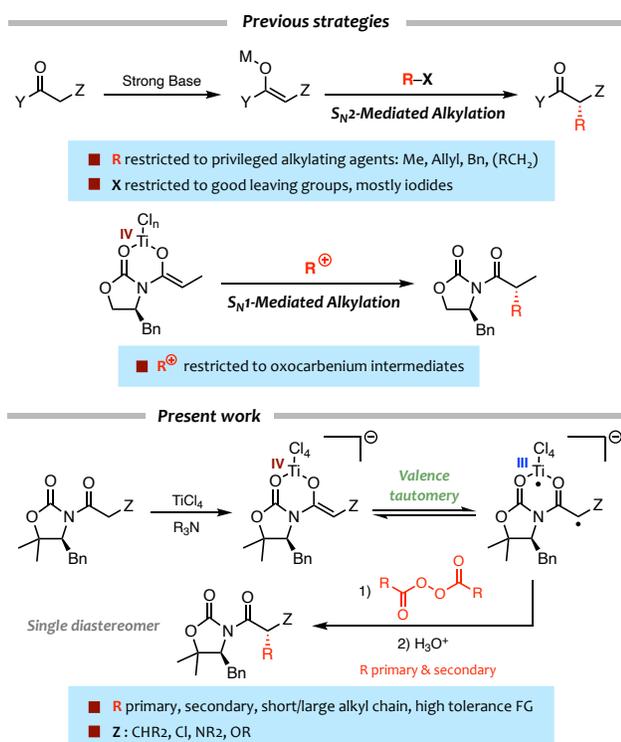
ABSTRACT: Simple treatment of chiral titanium(IV) enolates with diacyl peroxides produces highly diastereoselective decarboxylative alkylations to efficiently deliver the corresponding adducts, most of which are not accessible through any of the current alkylating procedures. Such an unprecedented alkylation proceeds through a SET process that triggers the decomposition of the peroxide into a carbon-centered radical that finally combines with the resulting C α radical. The procedure has been applied to the enantioselective synthesis of arundic acid.

The stereocontrolled construction of the carbon backbone of chiral molecules is at the core of asymmetric synthesis.¹ One of the simplest approaches to meet such challenge hinges on the alkylation of the C α position of carbonyl compounds.² Indeed, the alkylation of alkaline enolates of chiral *N*-acyl oxazolidinones³ and pseudoephedrine^{4,5} hold a prominent position among the carbon–carbon bond forming reactions and usually remain the method of choice for the synthesis of natural products.^{6,7} These, as well as related methods,^{8–10} proceed through a S_N2 mechanism so their scope is restricted to a set of privileged electrophiles (Scheme 1). Furthermore, Evans reported that titanium(IV) enolates of chiral *N*-acyl oxazolidinones may undergo stereoselective S_N1-like alkylations with certain oxocarbenium intermediates (Scheme 1).¹¹ Therefore, and despite the undeniable success of such approaches, there is still a need for a wide breadth of C α alkylating methods that enable the stereoselective introduction of any alkyl group without requiring strong bases in the enolization step that may thwart their application to sensitive substrates. A compelling manner to address such a challenge involves the use of radical intermediates that undergo homolytic reactions.^{12–14} Unfortunately, carbon-centered radicals are highly reactive species, which can only be produced from a small number of substrates.¹⁵

Herein, we disclose a *different concept* to overcome the abovementioned limitations. This calls for the unprecedented stereoselective alkylation of titanium(IV) enolates with diacyl peroxides through a homolytic mechanism. Indeed, a single electron transfer from the enolate to the peroxide triggers a mesolytic cleavage and consequent decarboxylation, which leads to the formation of a carbon-centered radical that combines with the enolate. As represented in Scheme 1, this new approach relies on the diradical character of titanium enolates^{16–19} and the weak oxygen–oxygen bond of peroxides. Synthetically, it allows the straightforward and stereoselective alkylation of chiral imides including their α -chloro, α -amino, and α -hydroxy counterpart with a large variety of R groups. Therefore, this method combines simplicity and robustness, which makes possible the highly chemo and stereoselective introduction of primary and secondary alkyl groups that are not easily amenable to any other current alkylation method.

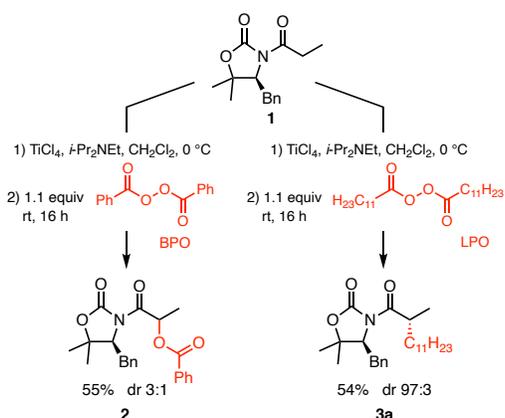
In our search for new reactivity of titanium(IV) enolates based on their diradical character, we envisaged that diacyl peroxides might be a suitable source for carbon-centered radicals.^{20,21} Initially, we explored the stereoselective alkylation of titanium(IV) enolates of chiral *N*-propanoyl oxazolidinone **1**²² with commercially available benzoyl peroxide (BPO) and lauroyl peroxide (LPO) shown in Scheme 2. Benzoyl peroxide did

Scheme 1. Stereoselective Alkylations



not undergo the desired carbon–carbon bond forming reaction and afforded instead α -benzoyloxy adduct **2** in acceptable yields but moderate diastereoselectivity. Otherwise, lauroyl peroxide (LPO) proceeded as expected and produced a single undecyl–derived diastereomer **3a** (Scheme 2).

Scheme 2. Reactions of Titanium(IV) Enolate from **1** with Diacyl Peroxides



A detailed examination of the reaction showed the benefits of working with an excess of LPO. Increasing amount of peroxide provided higher yields and kinetic rates up to a point in which the alkylation of **1** was completed in less than 2 h and afforded 76% of **3a** with 3 equivalents of LPO. Larger quantities of LPO resulted superfluous (Table S1). With the optimal amount of peroxide determined, we also established that changes in the temperature or concentration, as well as the use of other titanium(IV) Lewis acids or a less bulky oxazolidinone did not improve the outcome of the alkylation (Table S2). Interestingly, we observed along these studies the formation of traces of **I** and

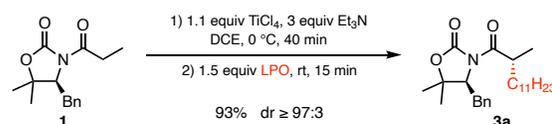
significant amounts (5–10%) of dichloromethyl derivative **II** (Figure 1), which further suggested the involvement of radicals in the alkylating pathway. Thus, we decided to evaluate the influence of other chlorinated solvents.



Figure 1. By-products of the Decarboxylative Alkylation

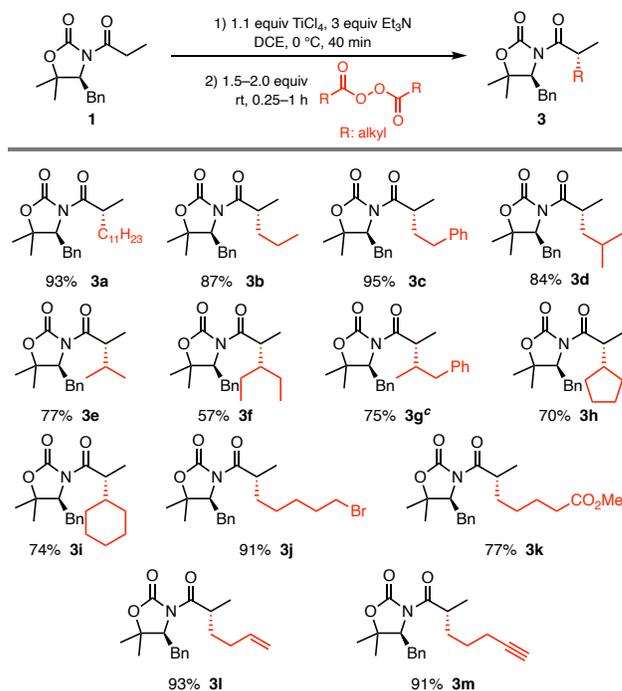
Gratifyingly, the solvent had a dramatic impact on the alkylation. Indeed, CCl₄ and CHCl₃ proved to be completely unsuitable, 1,1,2,2-tetrachloroethane (TCE) gave similar results to CH₂Cl₂, but 1,2-dichloroethane (DCE) afforded **3a** in a higher yield without being contaminated by the corresponding analog of **II** (Table S3). Then, following a comprehensive survey of the alkylation in DCE (Table S4)¹⁶ we established that the use of 3 equivalents of Et₃N and just 1.5 equivalents of LPO allowed us to isolate diastereomerically pure **3a** with a 93% yield (Scheme 3).

Scheme 3. Optimized Alkylation of **1** with LPO



Having improved the experimental procedure, we assessed the scope of the reaction by applying the optimized conditions to other diacyl peroxides.²³ The results summarized in Scheme 4 show that our protocol affords a single diastereomer (dr \geq 97:3) in yields of up to 95%. Noteworthy, this is not only limited to primary alkyl groups **3a–3d** but may also be applied to

Scheme 4. Scope of the Alkylation of **1**^{a,b}

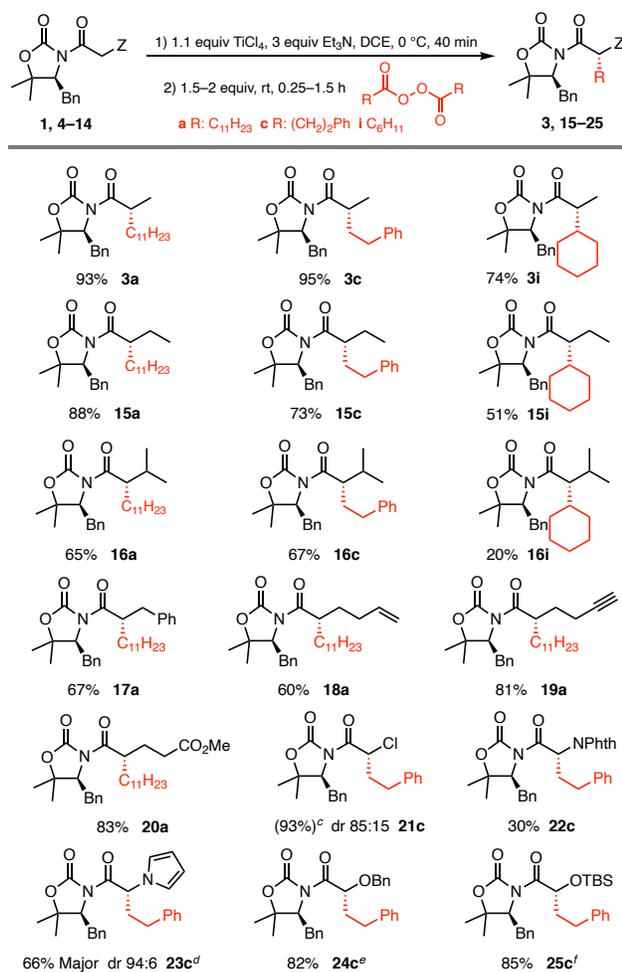


^aIsolated yield. ^bdr \geq 97:3. ^cdr 2:1 at C β

secondary alkyl groups **3e–3i**. Indeed, the method permits the introduction of isopropyl (**3e**), 3-pentyl (**3f**), 1-phenyl-2-propyl (**3g**), cyclopentyl (**3h**), or cyclohexyl (**3i**) groups in high yields, a range of substrates that had proven elusive to other alkylation procedures. Finally, we were delighted to observe that the alkylation with diacyl peroxides containing halides, esters, double, and triple bonds also led to the isolation of a single diastereomer of adducts **3j–3m** in high to excellent yields. Furthermore, the tolerance of these functional groups is remarkable and highlights the outstanding chemoselectivity of the process.

In view of such results, we next examined the robustness of the acyl group. As summarized in Scheme 5, the alkylation of increasingly sterically hindered substrates both at the C α acyl group (Z) and the radical (R) is possible. Indeed, substrates **1** and **4** containing unhindered acyl groups (Z: Me, Et) react with diacyl peroxides **a** and **c** to give **3a**, **3c**, **15a**, and **15c** as a single diastereomer (dr \geq 97:3) in excellent yields (73–95%), whereas parallel reactions with the more bulky diacyl peroxide **i** provided adducts **3i** and **15i** in good yields (51–74%). Likewise, alkylation of a more hindered substrate **5** (Z: *i*-Pr) with diacyl peroxides **a**, **c**, and **i** also gave adducts **16a**, **16c**, and **16i** with notable efficiency (20–67%). At this point, configuration of the

Scheme 5. Scope of the Alkylation of *N*-Acyl Oxazolidinones^{a,b}

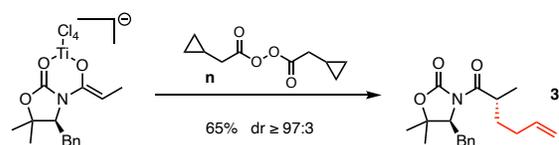


^aIsolated yield. ^bdr \geq 97:3. ^cOverall yield. ^dReaction at -20 °C. ^eReaction at 0 °C. ^fReaction at -10 °C

C α chiral center was firmly established by X-ray analysis of **16c**.²⁴ Importantly, substrates containing phenyl, alkene, alkyne, or ester groups proved suitable and gave adducts **17a–20a** with a 60–83% yield. Furthermore, the alkylation resulted compatible with C α heteroatoms. Thereby, alkylation of *N*-chloroacetyl oxazolidinone (Z: Cl) with diacyl peroxide **c** produced the α -chlorinated adduct **21c** as an 85:15 diastereomeric mixture with a 92% overall yield. Even the alkylation of α -nitrogenated substrates resulted feasible and pyrrole-derived oxazolidinone (Z: pyrrole) afforded a 94:6 diastereomeric mixture from which **23c** was isolated in a 66% yield. Eventually, α -hydroxy substrates (Z: OBn, OTBS) were also found to be appropriate and produced adducts **24c** and **25c** in an 82–85% yield. All together, these results show that the appropriate choice of the Z group may give a straightforward access to a remarkable range of enantiomerically pure α -halo, α -amino, and α -hydroxy acids.²⁵

Having demonstrated the wide scope and the robustness of the alkylation, we focused our attention on its mechanism. Our working hypothesis revolved around the diradical character of the titanium(IV) enolates^{16,17} of **1**. The isolation of small quantities of dichloromethyl derivative **II** (Figure 1) supported such a hypothesis, but further proof was required. In this context, the alkylation with the diacyl peroxide from 2-cyclopropylacetic acid (**n**) was crucial. Importantly, we only observed the formation of the open-chain adduct **3I** (Scheme 6), which is strong evidence that the decarboxylative alkylation proceeds through the addition of radicals to the titanium(IV) enolates.²⁶

Scheme 6. Mechanistic Studies

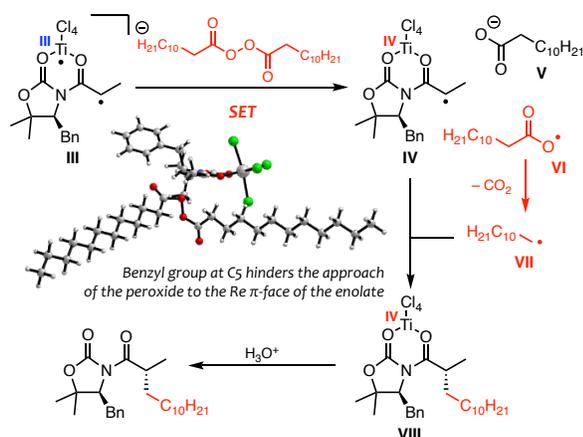


In parallel, we carried out a computational analysis to gain insight into the mechanistic details of the process. Keeping in mind the diradical character of the titanium(IV) enolates,^{16,17} we thoroughly examined the addition of the titanium(IV) enolate from **1** to the model dilauroyl peroxide (Scheme 7). Thereby, it was found that the reaction proceeds through an electron transfer from the α -carbon in **III** to the σ^* orbital of the O–O bond in a Single Electron Transfer (SET) *redox reaction*, which gives radical **IV**, causes the cleavage of the O–O bond into a carboxylate anion and a radical (**V** and **VI** respectively). Then, the spontaneous decarboxylation of **VI** produces a carbon-centered radical **VII** that may combine with **IV** to form the C–C bond. At this point, we cannot rule out the possibility that the key C–C bond can be formed by reaction of the alkyl radical **VII** with **III** (instead of **IV**) in a radical chain reaction, more complex than the depicted in Scheme 7 (for further details, see the Supporting Information).

In any case, a SET mechanism may account for the experimental results. Indeed, this involves alkyl radical intermediates, which explains the occurrence of compounds like **3I** and by-product **II**. Remarkably, the overall transformation is energetically feasible ($\Delta G = -16.6$ kcal mol⁻¹). Furthermore, the reagents must approach to a short distance for the electron transfer to occur, and due to the bulkiness of **III** and the diacyl peroxides

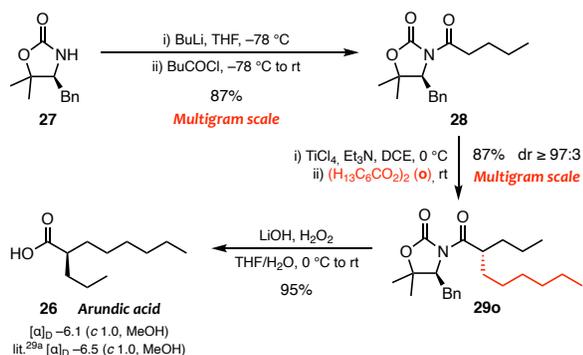
a good diastereoselectivity is ensured (Scheme 7). Thereby, a remarkable minimum energy difference of at least 3.5 kcal mol⁻¹ for the approach to both π -faces in the electron transfer structure at C–O distances ranging from 1.8 to 4 Å in distinct conformations was calculated, which corresponds to a dr > 99:1. Therefore, the proposal depicted in Scheme 7 accounts for both the observed reactivity and stereoselectivity, since carbon-centered alkyl radicals are involved in the reaction and the stereochemical outcome of the alkylation depends on the approach of the entire diacyl peroxide to the less sterically shielded *Si* face of the enolate.

Scheme 7. Mechanistic Hypothesis



Finally, we considered the opportunity to apply the new method to the synthesis of arundic acid (**26** in Scheme 8), a chiral carboxylic acid with potential neuroprotective activity.²⁸ The synthesis commenced with a standard acylation of **27** to produce *N*-pentanoyl oxazolidinone **28**.²⁹ Then, treatment of the titanium(IV) enolate of **28** with diheptanoyl peroxide (**o**) provided a single diastereomer of the alkylated adduct **29o** with an 87% yield at multigram scale. Next, removal of the chiral auxiliary afforded enantiomerically pure arundic acid **26** in 95% yield and complete recovery of **27**.³⁰ Therefore, arundic acid has been prepared with a 70% overall yield in a three-step sequence that involves the decarboxylative alkylation previously developed.

Scheme 8. Enantioselective Synthesis of Arundic Acid



In summary, a highly stereoselective decarboxylative alkylation of the titanium(IV) enolates from a wide array of chiral *N*-

acyl oxazolidinones with diacyl peroxides from primary and secondary aliphatic carboxylic acids is described. Experimental evidence and theoretical calculations indicate that the reaction takes advantage of the diradical character of the titanium(IV) enolate and proceeds through a SET step that triggers the decomposition of the diacyl peroxide. This proves for the first time that titanium(IV) enolates may behave as *reducing agents* and thus take part in radical transformations to afford enantiomerically pure alkylated products. Furthermore, this method has been applied to the enantioselective synthesis of the arundic acid at a multigram scale.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, compound characterization, and copies of ¹H and ¹³C NMR spectra (PDF)

Crystallographic data for **16c** (CIF)

Details of theoretical calculations (PDF)

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Notes

The authors declare no competing financial interest.

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