ChemPubSoc Europe

DOI: 10.1002/chem.201402127

CHEMISTRY A European Journal Full Paper

Synthetic Methods

Stereoselective Aminoxylation of Biradical Titanium Enolates with TEMPO

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Abstract: A highly efficient and straightforward aminoxylation of titanium(IV) enolates from (*S*)-*N*-acyl-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-ones with TEMPO has been developed. A wide array of functional groups on the acyl moiety, including alkyl and aryl substituents, olefins, esters, or α-cyclopropyl, as well as α-trifluoromethyl groups, are well tolerated. This transformation can therefore produce the α-aminoxylated adducts in excellent yields with high diastereomeric ratios (d.r.). In turn, parallel additions to the α,β-unsaturated *N*-acyl counterparts give the corresponding γ-adducts with complete regioselectivity in moderate to good yields. Removal of the piperidinyl moiety or the chiral auxiliary converts the resultant adducts into enantiomerically pure α-hydroxy carboxyl derivatives, alcohols, or esters in high yields under mild conditions. Finally, a new mechanistic model based on the biradical character of the titanium(IV) enolates has been proposed.

Introduction

The development over the last decades of highly chemo-, regio-, and stereoselective procedures for the enolization of carbonyl compounds has meant that metal enolates are now among the most important carbon nucleophiles. This has paved the way for the use of metal enolates in a wide array of organic transformations and, nowadays, a significant number of stereoselective bond-forming reactions can only be understood through considering the contribution of lithium, boron, titanium(IV), or tin(II) enolates as structurally defined and very reactive nucleophilic species.[1] Running parallel to this heterolytic profile, attention has also been focused on the exploitation of the homolytic reactivity of α-carbonyl radicals (enolyl radicals), which can participate in highly stereoselective transformations.[2] To date, α-halo carbonyl compounds have commonly been used as the source of such intermediates. For instance, Sibi disclosed highly stereocontrolled radical alkylations of chiral α-bromo *N*-acyl oxazolidinones,[3] and Porter reported related transformations promoted by chiral Lewis acids.[4] In turn, Guindon has developed a general strategy for polypropionate synthesis based on a sequence of a Mukaiyama aldol reaction followed by stereoselective free radical reduction of the resultant α-bromo or α-seleno esters.[5] Apart from this reaction path, the classical dimerization of metal enolates[6–8] has recently been updated and some ingenious methods based on the oxidation of metal enolates and subsequent homo- as well as heterocoupling of the resultant enolyl radicals have been devised.[9] This radical chemistry was further advanced through the introduction by MacMillan's group of SOMO-organocatalysis concepts, whereby one-electron oxidation of a transient chiral enamine derived from an aldehyde provides a cation radical that can undergo highly enantioselective transformations.[10] Despite the tremendous advancement in asymmetric synthesis facilitated by these ideas, the requirement of a stoichiometric amount of an oxidant to generate the reactive intermediate is a major drawback in terms of atom economy.[11] This hurdle has occasionally been overcome by merging photoredox catalysis with organocatalysis.[12] Indeed, upon irradiation, ruthenium(II) photoredox catalysts trigger the formation of the enamine cation radical, which then reacts with other radical intermediates produced by the ruthenium(I) species. Such an ingenious combination of two independent catalytic cycles permits the enantioselective intermolecular α-alkylation of aldehydes without the need for an additional oxidant.[13,14]

In this context, we revealed the unconventional biradical character of the titanium(IV) enolates,[15] which might mean that they can participate *directly* in homolytic transformations without any additional reagents in a highly economic manner. Zakarian proved the feasibility of this new reaction paradigm by developing the radical haloalkylation of the titanium(IV) enolates of chiral *N*-acyl oxazolidinones catalyzed by ruthenium(II) complexes.[16a] Later, the method was expanded to zirconium(IV) enolates,[16b] and it was also found that it could be carried out using catalytic amounts of $TiCl_4$.[16c] Thus, the biradi-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402127.

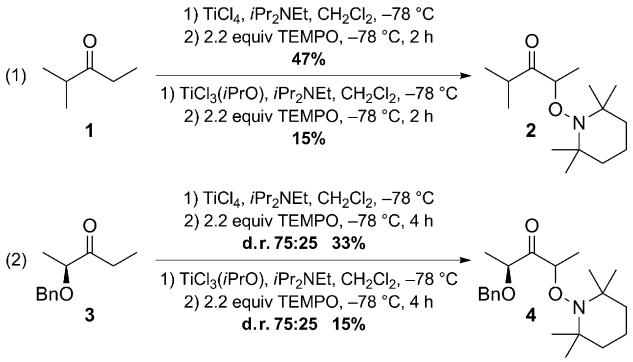
cal character of titanium(IV) enolates could be an excellent platform from which to take advantage of the radical chemistry of enolyl-like intermediates.[17]

These precedents and our ongoing interest in the reactivity of the titanium(IV) enolates[18] led us to explore new stereoselective transformations in which they could act as radicals.[19] Initially, we chose the 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO), a commercially available stable free radical,[20] to probe this new reactivity that might deliver α-oxygenated carbonyl compounds in a straightforward and stereocontrolled manner. α-Hydroxylated carbonyl compounds are traditionally prepared by treating the corresponding enolates with a variety of oxidizing reagents, including oxygen, peroxides, hypervalent iodine complexes, and chiral *N*-sulfonyloxazaridines.[21] More recently, this set of procedures has been enlarged through the addition of several enantioselective organocatalytic methods based on oxidation with nitrosobenzene,[22,23] peroxides,[24] oxygen,[25] and TEMPO.[26] Unfortunately, these methods can only be applied to aldehydes, so the quest for more general and efficient methods for the synthesis of α-hydroxy carbonyl compounds remains active.

The direct oxidation of enolates with TEMPO could meet these challenges, but α-aminoxylation of metal enolates with TEMPO usually requires the generation of *N*-oxoammonium salts in situ through the use of an external oxidant.[27–29] Renaud and Studer overcame this constraint by using ketone-derived catecholboron enolates, the reaction of which with TEMPO gave the corresponding α-carbonyl radicals, which could then be trapped with a second equivalent of TEMPO to provide the α-aminoxylated carbonyl products.[30] Jahn has convincingly proved that the single-electron oxidation of lithium enolates from ketones, esters, and amides with ferrocenium hexafluorophosphate (Cp_2FePF_6) affords the desired enolyl radicals, which then couple with TEMPO in a straightforward manner.[31] Finally, Li has recently proposed that copper-catalyzed α-aminoxylation of α-alkoxy ketones with TEMPO may also proceed through enolyl radicals.[32] All of these methods provide the α-aminoxylated derivatives in good yields, but their lack of stereocontrol thwarts advanced synthetic applications. This restriction has been successfully addressed by Zakarian, who has reported the asymmetric radical addition of TEMPO to titanium(IV) enolates from chiral oxazolidinones.[33] This very recent advance has prompted us to disclose herein our findings, which confirm Zakarian's results and show that titanium(IV) enolates from a wide range of carbonyl and carboxyl compounds react under very mild conditions with TEMPO to provide the corresponding α-aminoxylated compounds in good yields and with moderate to excellent diastereoselectivities.

Results and Discussion

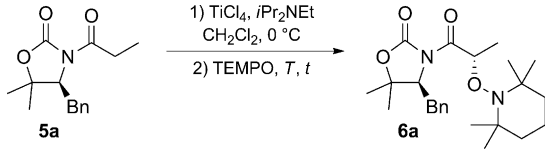
Our experience with substrate-controlled aldol reactions[18,34] initially led us to assess the addition of TEMPO to different titanium(IV) enolates of 2-methyl-3-pentanone (**1**). We were pleased to observe that the addition occurred and produced the desired α-aminoxylated adduct **2** in 15–47% yield, depending on the use of $TiCl_3(i\text{PrO})$ or $TiCl_4$ as the titanium(IV) Lewis acids, respectively (Eq. (1) in Scheme 1). Encouraged by these findings, we then applied the same experimental conditions to (*S*)-2-benzyloxy-3-pentanone (**3**), a lactate-derived chiral ketone (Eq. (2) in Scheme 1). Unfortunately, this substrate-controlled transformation yielded only small amounts of α-aminoxylated adduct **4** and, most significantly, with only moderate diastereoselectivity (d.r. 75:25). None of our efforts to improve these results were successful. Nevertheless, the study demonstrated the feasibility of the reaction and indicated that electron-donating ligands bound to the metal atom lower the reactivity of the resultant enolates and should therefore be avoided. Moreover, the moderate 1,3-asymmetric induction observed for α-benzyloxy ketone **3** suggested that the reaction proceeds through an open transition state in which the C1-methyl group hardly differentiates between the two faces of the enolate.[35]



Scheme 1. α-Aminoxylation of titanium enolates from ethyl ketones.

It was thus clear that the asymmetric α-aminoxylation of titanium enolates represented a genuine opportunity, provided that sufficiently reactive and structurally rigid enolates were used. These two requirements led us to center our attention on titanium enolates from *N*-propanoyl oxazolidinone **5a** (see Table 1), because they had already permitted highly stereocon-

Table 1. Preliminary studies of the addition of TEMPO to the titanium enolate of *N*-propanoyl oxazolidinone, **5a**.



	TEMPO[a]	T [°C]	t [h]	d.r. [b]	Yield [%][c]
1	1.2	20	2	94:6	46
2	1.2	20	15	93:7	41
3	1.7	20	2	94:6	77
4	2.2	20	2	94:6	94
5	2.2	−78	2	92:8	58
6	2.2	−20	2	94:6	90
7	2.2	0	2	94:6	94
8	2.1	0	1	94:6	93
9	2.1	0	0.5	94:6	91

[a] Equivalents of TEMPO. [b] Established by ^{1}H NMR analysis of the reaction mixture. [c] Overall isolated yield.

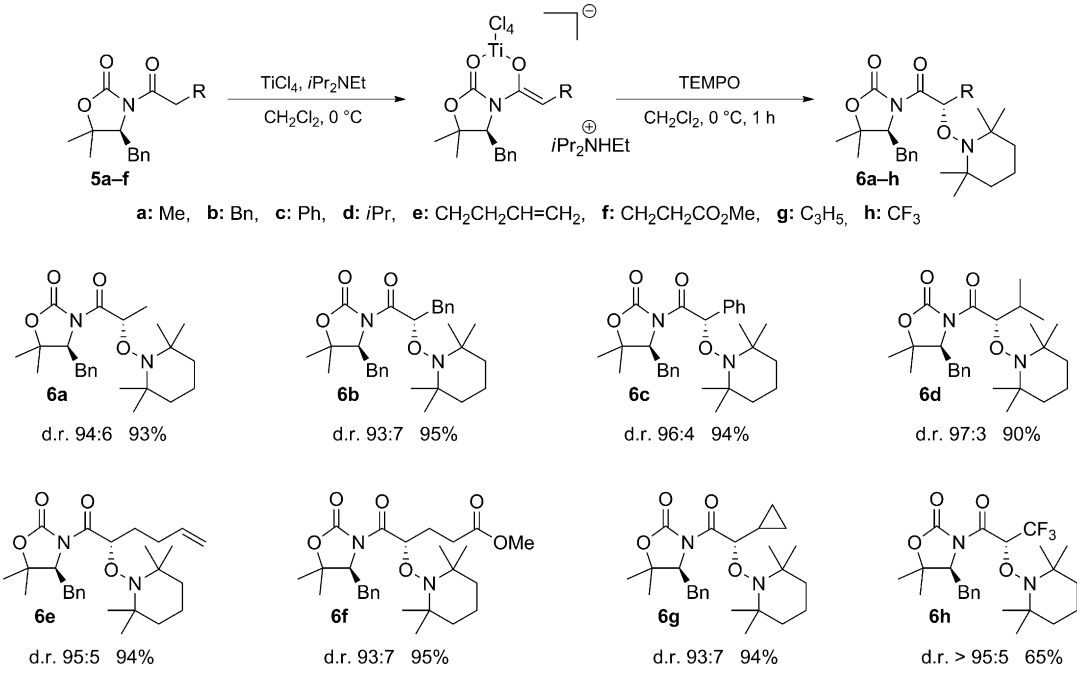
trolled additions of radicals to putative enolyl intermediates.[3,16,36] Exploratory experiments confirmed that our choice was right. Indeed, treatment of the $TiCl_4$-mediated enolate of **5a** with 1.2 equivalents of TEMPO at room temperature for 2 h afforded α-aminoxylated adduct **6a** in 46% yield with a 94:6 diastereomeric ratio (see entry 1 in Table 1). Remarkably, the conversion proved to be closely related to the amount of TEMPO used, and it was finally established that an additional equivalent is necessary to obtain **6a** in a yield up to 94% (compare entries 1–4 in Table 1). Low temperatures did not improve the diastereoselectivity, and **6a** was consistently obtained with an excellent diastereomeric ratio at both room temperature and −78 °C (compare entries 4–7 in Table 1) whereas the addition progressed very rapidly at 0 °C to the point that **6a** was isolated in 91–94% yield after 0.5–2 h (compare entries 7–9 in Table 1).[37] In light of these results and taking into account the need for a general procedure, we chose the conditions summarized in entry 8 as optimal; **6a** was obtained in a highly stereocontrolled manner (d.r. 94:6) in 93% yield by treating the $TiCl_4$-enolate of **5a** with 2.1 equivalents of TEMPO for 1 h at 0 °C.

Next, we examined the scope of the reaction by applying the optimal conditions to a wide range of *N*-acyl oxazolidinones **5**. The results, summarized in Scheme 2, show that α-aminoxylated adducts **6** were consistently obtained in a highly chemoselective and stereoselective manner. Indeed, *N*-acyl oxazolidinones **5a–d** produced excellent yields and diastereoselectivities, irrespective of the steric bulk of R. Moreover, the presence of functional groups such as an olefin, a methyl ester, or a cyclopropyl ring in oxazolidinones **5e–g** was well tolerated, and the corresponding adducts **6e–g** were isolated in 94–95% yield with diastereomeric ratios higher than 93:7 (Scheme 2). Conversely, *N*-trifluoropropanoyl oxazolidinone **5h** did not produce the desired adduct under the general conditions, probably because of the instability of the titanium enolate at 0 °C.[38] Thus, we were pleased to isolate adduct **6h** in 65% yield as a single diastereomer (d.r. > 95:5)[39] by carrying out the enolization at −78 °C and allowing the reaction mixture to slowly warm for 1 h. This provides new and enantioselective access to small chiral fragments containing a trifluoromethyl group that could be very useful in medicinal chemistry.[40]

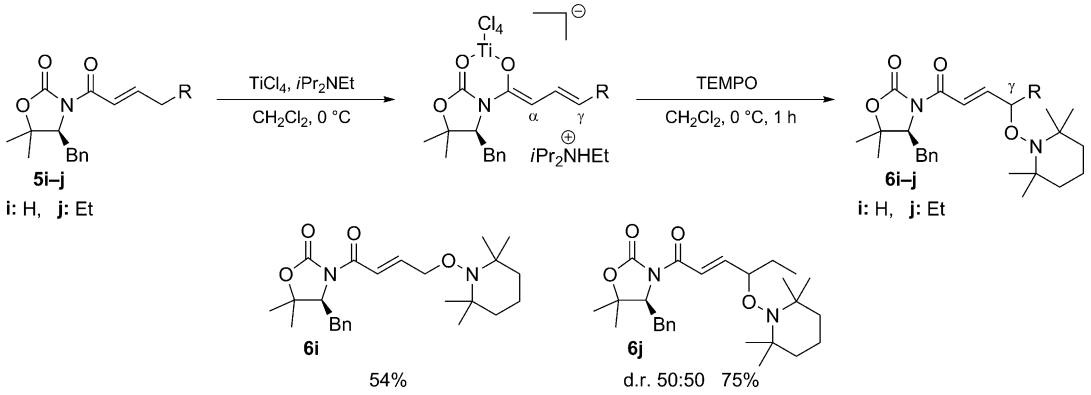
Moreover, the reactions of α,β-unsaturated *N*-acyl oxazolidinones **5i** and **5j** turned out to be completely regioselective and the γ-adducts **6i** and **6j** were isolated in moderate to good yields without observing the formation of the alternative α-OTEMP adducts (Scheme 3).[41] Unfortunately, the γ-aminoxylated adduct **6j** was obtained as a 1:1 mixture of (*E*)-α,β-unsaturated diastereomers.[42] This lack of stereocontrol may be due to the conformational flexibility of the β,γ-conjugated enolate or the inability of the C4-benzyl group to shield the upper face of the π-system at the γ-position.

The configuration of these α-aminoxylated adducts was established through X-ray analysis of **6b** (Figure 1).[43] It was later confirmed by removal of the chiral auxiliary from **6a** and the correlation of the resultant alcohol (see ref. [53]).

Having applied the asymmetric addition of TEMPO to a wide range of *N*-acyl oxazolidinones, **5**, we next studied the origin of this successful transformation. Initially, we surveyed other common chiral auxiliaries to gain a better understanding of the structural elements that determine the stereochemical outcome of the process. We were especially interested in determining the influence of geminal methyl groups at C5 and the outcome of the reaction using a sulfur-based chiral auxiliary. Therefore, we evaluated the additions of TEMPO to the titanium enolates from chiral *N*-propanoyl oxazolidinone **7** and



Scheme 2. Additions of TEMPO to the titanium enolates of *N*-acyl oxazolidinones **5a–h**.



Scheme 3. Additions of TEMPO to the titanium enolates of α,β-unsaturated *N*-acyl oxazolidinones **5i,j**.

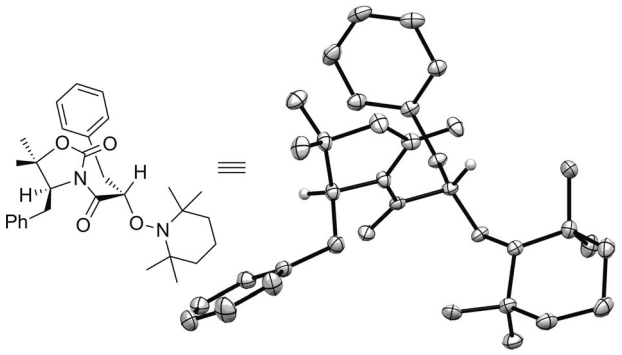
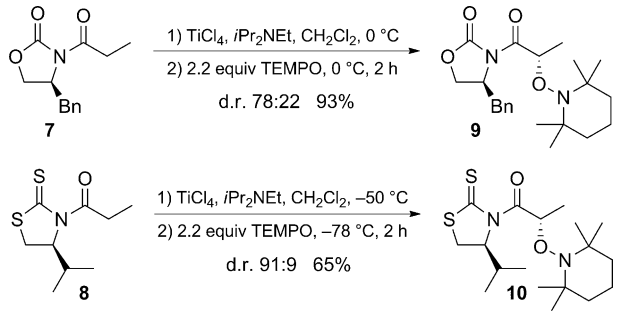


Figure 1. X-ray crystal structure of **6b**. Hydrogen atoms at non-stereogenic centers have been removed for clarity.



Scheme 4. Additions of TEMPO to titanium enolates from **7** and **8**.

thiazolidinethione **8** (Scheme 4). The former gave the α-aminoxylated adduct **9** in 93% yield, but in a less stereocontrolled manner (d.r. 78:22) than **5a**. This proves the key role played by the geminal methyl groups at C5. In turn, thiazolidinethione **8** produced the corresponding adduct **10** in similar yield and with comparable diastereoselectivity to **5a** (see entry 5 in Table 1). Thus, replacement of the oxygen-based chiral auxiliary by a sulfur-based moiety did not modify the outcome of the addition. Hence, the thiazolidinethione chiral auxiliary represents an appealing alternative because of its easy removal under very mild conditions.[44]

As for ketones, all of these results suggest that the α-aminoxylation of the titanium enolates from *N*-acyl oxazolidinones **5** proceeds through a transition state in which the benzyl group at the chiral auxiliary hinders the α-approach of TEMPO to the *Re* face of the corresponding chelated titanium enolate. Moreover, the absolute regioselectivity observed for the aminoxylation of **5i** and **5j** suggests orbital-controlled addition, as occurs in Lewis acid-mediated vinylogous additions of electrophiles to conjugated silyl enol ethers.[45] Without detracting from the importance of these features, the crux of such additions is the titanium atom.[46] In this context, the poor oxidative capacity of titanium(IV) complexes[47] and the need for two equivalents of TEMPO indicate that it is unlikely that the titanium enolates from **5** would oxidize TEMPO to generate the corresponding oxoammonium salt. In contrast, this addition might proceed through a radical pathway in which the biradical character of titanium enolates represented by **II** (Figure 2) would play a crucial role.

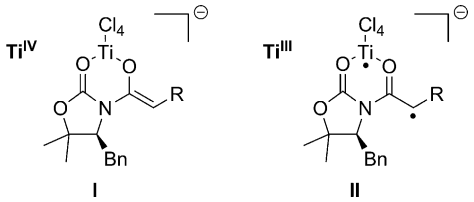
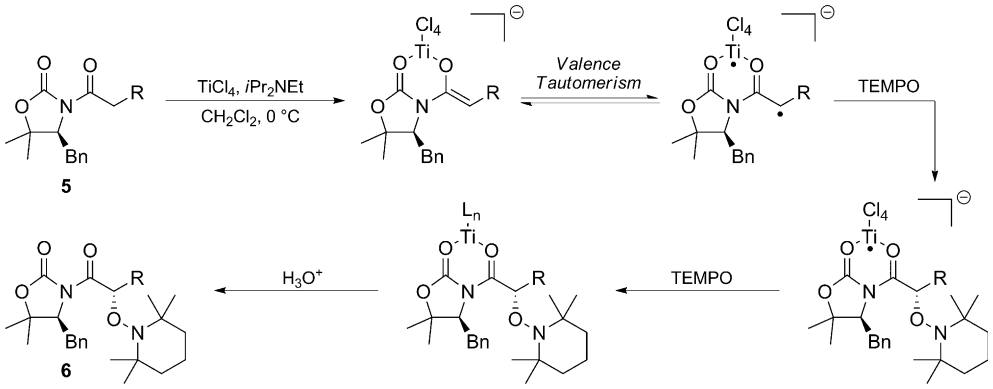


Figure 2. Titanium enolate derived from **5**.

The way the enolate form **II** acts cannot be understood by overlapping the reactivity of two radicals; rather, we require a valence tautomeric[17,48,49] paradigm that interweaves the Ti^{III}/Ti^{IV} and the enolyl-like chemistries. One of the crucial issues related to this model involves the beginning of the reaction sequence. This might take advantage of the reducing capacity of Ti^{III} to produce an enolyl radical, which would subsequently be trapped by a TEMPO radical in the classical way. Conversely, the initial attack of a TEMPO radical at the α-position (or the γ-position in α,β-unsaturated *N*-acyl oxazolidinones) of **II** might be followed by the trapping of the resultant Ti^{III} complex with a second molecule of TEMPO. Zakarian favored the former pathway based on its mechanistic similarity with catecholboron enolate oxidation by TEMPO, as reported by Studer and

Renaud,[30] together with indirect experimental evidence, primarily isolation of enolate dimerization by-products from certain reactions.[33] We have never observed the titanium enolates from **5** to induce such dimerizations. In fact, when the titanium enolate from **5a** was stirred at 0 °C for one day, quenched, and analyzed, the starting material was quantitatively recovered and the ^{1}H NMR spectrum was completely clear without any other peak. Furthermore, crude reaction mixtures from **5g** bearing a cyclopropyl ring (*radical clock*)[50] also produced clear spectra. Had classical radicals been involved in these transformations, other aminoxylated isomers would have been observed.[51]

All together, these results suggest that α-carbonyl radicals are not true intermediates in the process. Instead, experimental evidence supports a sequence as described in Scheme 5, in



Scheme 5. Plausible mechanism for the addition of TEMPO to titanium enolates derived from **5**.

which the initial Cα addition of TEMPO is followed by the interaction of the resultant Ti^{III} complex with a second molecule of TEMPO. The initial addition of TEMPO appears to be very fast and involves a low activation barrier that prevents us from improving the diastereoselectivity by carrying out the reaction at low temperatures. In turn, the fate of the resultant titanium(III) complex is at present unknown. We speculate that it may involve a single-electron transfer to produce the corresponding anion of the hydroxylamine form or the formation of a new formal Ti^{IV} complex in which TEMPO acts as a ligand.

Finally, we examined the removal of the piperidine moiety and the chiral auxiliary. Regarding the first issue, we applied a common procedure reported in the literature, based on the use of zinc in hot AcOH or 3:1:1 AcOH/THF/H_2O.[52] These conditions turned out to be too harsh for model **6a**, producing a remarkable Cα-epimerization and partial hydrolysis of the resultant hydroxy derivative **11a** (see entries 1 and 2 in Table 2). Instead, the reduction proceeded smoothly over 6 h in AcOH/THF/H_2O (3:1:1) at room temperature, which permitted us to isolate diastereomerically pure **11a** in 78% yield and certain amounts of the chiral auxiliary (compare entries 3 and 4 in Table 2).

Simultaneously, we focused our efforts on the removal of the chiral auxiliary from adducts **6**. Thereby, the treatment of **6a** with $NaBH_4$ in THF/H_2O at room temperature for 4 h afforded alcohol **12a** in 63% yield in addition to a 93% recovery of the chiral auxiliary **13** (Scheme 6).[53] Unfortunately, such conditions were unsuitable for more hindered adducts such as **6b**, and long reaction times were necessary to attain moderate yields. Eventually, $LiAlH_4$ turned out to be the most appropriate reducing agent, affording both **12b** and **13** in quantitative yields (Scheme 6). In turn, treatment of **6a** with NH_3/MeOH provided methyl ester **14a** in 92% yield in a straightforward manner under very mild conditions (Scheme 6).[54]

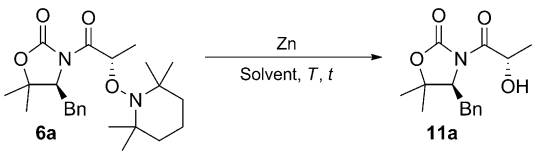
Conclusion

The aminoxylation of titanium(IV) enolates with TEMPO is a general transformation that proceeds under mild conditions. In particular, chiral *N*-acyl-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-ones are an appealing platform for obtaining α-aminoxylated adducts in excellent yields and diastereomeric ratios. Acyl components containing olefin, ester, cyclopropyl, or trifluoromethyl groups are well tolerated, which confers this reaction with a broad chemoselective profile. Furthermore, the α,β-unsaturated *N*-acyl counterparts afford the corresponding γ-aminoxylated adducts with outstanding regioselectivity in moderate to good yields. Therefore, the addition of TEMPO to the $TiCl_4$-enolates from a wide array of *N*-acyl-4-benzyl-5,5-dimethyl-1,3-oxazolidin-2-ones produces the aminoxylated adducts in a highly efficient and straightforward manner.

Both the piperidine moiety and the chiral auxiliary can be removed to provide enantioselectively pure α-hydroxy *N*-acyl oxazolidinones, alcohols, or esters in high yields.

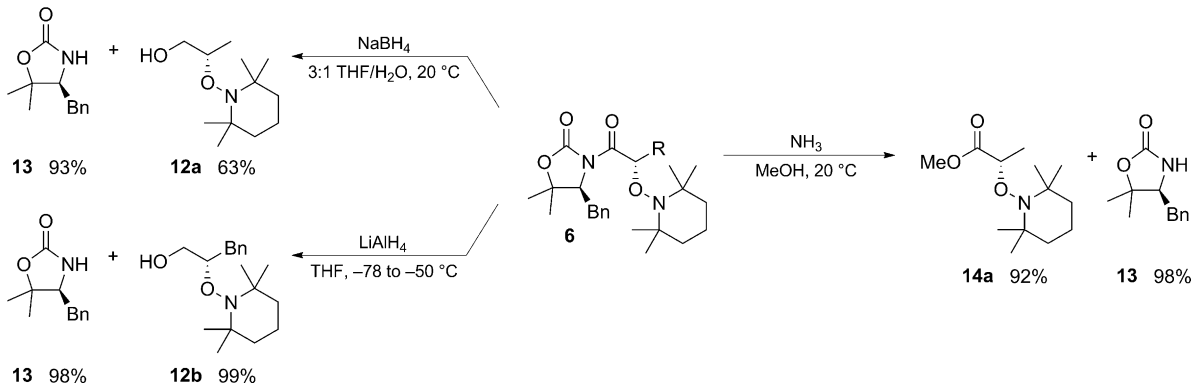
Finally, a mechanistic model based on the biradical character of titanium enolates has been proposed to account for the

Table 2. Reduction of the O–N bond in **6a**.



	Solvent	*T* [°C]	*t* [h]	d.r. [a]	Yield [%][b]
1	AcOH	50	1.5	42:58	27 (37)
2	3:1:1 AcOH/THF/H_2O	50	1.5	32:68	20 (44)
3	3:1:1 AcOH/THF/H_2O	20	19	93:7	66 (6)[c]
4	3:1:1 AcOH/THF/H_2O	20	6	94:6	78 (7)[d]

[a] Established by ^{1}H NMR analysis of the reaction mixture. [b] Isolated yield of **11a**. In parentheses, isolated yield of the other diastereomer. [c] 12% of the chiral auxiliary was isolated. [d] 5% of the chiral auxiliary was isolated.



Scheme 6. Removal of the chiral auxiliary from **6**.

outcomes of these additions, which might be an example of a new reaction paradigm.

Experimental Section

General procedure: Neat $TiCl_4$ (60 μL, 0.55 mmol) was added dropwise to a solution of *N*-acyl oxazolidinone **5** (0.50 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. The resulting mixture was stirred for 5 min and then anhydrous iPr_2NEt (96 μL, 0.55 mmol) was added dropwise. The resulting solution was stirred for 40 min at 0 °C. A solution of TEMPO (164 mg, 1.05 mmol) in CH_2Cl_2 (0.25 mL) was then added via a cannula (1×0.25 mL) and stirring was continued for 1 h at 0 °C. The reaction was then quenched by the addition of saturated aqueous NH_4Cl solution (2 mL) and the mixture was vigorously stirred at rt for 10 min. It was then partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was analyzed by ^1H NMR and purified by flash column chromatography to afford the aminoxylated adduct **6**.

Acknowledgements

Financial support from the Spanish Ministerio de Economía y Competitividad (Grant No. CTQ2012–31034) and the Generalitat de Catalunya (2009SGR825) as well as doctorate studentships to M.P. and J.M.R. (FPU, Ministerio de Educación) are acknowledged.

Keywords: aminoxylation · asymmetric synthesis · radical reactions · TEMPO · titanium

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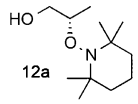

12a $[\alpha]^{20}_D$ –29.3(*c* 1.3, $CHCl_3$, *ee* 88%)
Maruoka[26b] ***ent*-12a** $[\alpha]^{20}_D$ +31.9(*c* 1.3, $CHCl_3$, *ee* 90%)

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Received: February 11, 2014
Published online on July 7, 2014