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Highly Diastereoselective α-Hydroxylation of Fox Chiral Auxiliary-Based Amide Enolates with Molecular Oxygen

Hodney Lubin, Arnaud Tessier, Grégory Chaume, Julien Pytkowicz, and Thierry Brigaud*

Laboratoire " Synthèse Organique Sélective et Chimie bioOrganique " (SOSCO), Université de Cergy-Pontoise, 5 Mail Gay-Lussac 95000 Cergy-Pontoise Cedex, France

thierry.brigaud@u-cergy.fr

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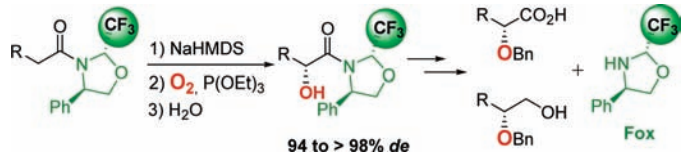
ABSTRACT



Using a trifluoromethylated oxazolidine (Fox) chiral auxiliary, the hydroxylation reaction of enolates was very efficiently performed under smooth and friendly conditions with molecular oxygen as oxidizer. This reaction occurred with an extremely high diastereoselectivity. After cleavage, the chiral auxiliary is efficiently recovered and highly valuable enantiopure oxygenated carboxylic acids and alcohols are released.

Enantiopure α-hydroxy carbonyl compounds play an important role in asymmetric synthesis as well as building blocks for total syntheses.[1] The oxidation of an enolizable carbonyl group is the most direct method to synthesize such compounds and has received a great deal of attention.[2] One of the first examples reported in the literature was the oxidation of steroidal ketone enolates by molecular oxygen followed by the reduction of the intermediate α-hydroperoxide by zinc dust.[3] This low-yielding procedure was improved in the 1960s by using trialkyl phosphite as reductant[4] and was extensively applied to different substrates mainly during the 1980s but very occasionally later for the α-hydroxylation of amide enolates.[2,5] However, the molecular oxygen oxidation of enolates suffers from several limitations such as low yields and frequent complications due to decomposition or rearrangement of the intermediate hydroperoxide.[6] Moreover, the overoxidation often limits these reactions to tertiary carbons in the α position of the carbonyl group. For these reasons, the oxidation of enolates has been more recently performed using Davis' sulfonyloxaziridine,[1a,7] Vedejs' MoOPH complex (MoO_5·HMPA·pyridine)[8] or various classical oxidizing reagents.[2] The stereoselectivity of these oxidations was mainly controlled by the chirality of the substrates. Chiral induction

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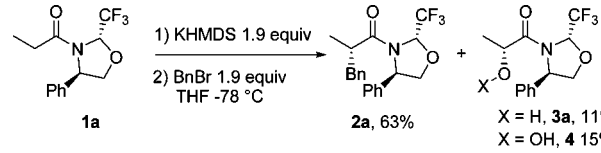
by auxiliaries,[9] chiral oxidizing reagents,[10] chiral catalysts,[11] chiral phase transfer catalysts, and enzymes[12] has also been reported. Furthermore, it appears in the literature that the most standard method extensively used in recent years is the oxidation of oxazolidinone-based chiral amide enolates with Davis' oxaziridine.[13] Intriguingly, the very attractive oxidation with molecular oxygen has not yet been developed for the synthesis of enantiopure compounds by mean of chiral auxiliaries-based methods. This is probably due to the poor stability of the intermediate hydroperoxides. To the best of our knowledge, the only example of a diastereoselective hydroxylation of a chiral amide enolate in the presence of molecular oxygen was reported by Adam et al.[14] In this pioneering work, the authors reported the autoxidation of an amide titanium enolate using (*S*)-prolinol as chiral auxiliary. The resulting chiral α-hydroxy amide was obtained in a rather good yield but with a low diastereoselectivity (34% de). Provided that the diastereoselectivity of this kind of reaction could be improved, we believe that the cheap and environmentally friendly molecular oxygen oxidation could be a very attractive alternative to onerous or toxic oxidizing agents. We report herein that fluorinated oxazolidine (Fox) chiral auxiliary presents outstanding performances to meet these requirements.

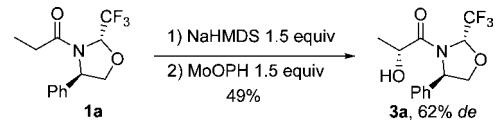
We recently reported the highly diastereoselective alkylation of fluorinated oxazolidine (Fox) derived amide enolates.[15−17] In the course of our studies, while using KHMDS as base, we were surprised to isolate two oxygenated side products in addition to the expected diastereomerically pure alkylation compound. For example, the benzylation of the potassium enolate of **1a** gave the diastereomerically pure benzylated amide **2a** in 63% isolated yield, the α-hydroxy amide **3a** in 11% yield, and the hydroperoxide **4** in 15% yield (Scheme 1). Similar oxygenated compounds were also obtained as very minor products from sodium enolates. We assumed that these oxygenated compounds were probably resulting from the enolate oxidation by residual molecular oxygen dissolved in the solvent. As these compounds were obtained as single diastereomers, we anticipated that the Fox chiral auxiliary would be an excellent chiral auxiliary for the oxygen-mediated oxidation of enolates.

Scheme 1. Unexpected Diastereoselective α-Oxidation of *N*-Acyloxazolidine **1a**



In order to characterize the α-hydroxy amide **3a** and to compare with the diastereoselectivity achieved by a standard oxidation method, the sodium enolate of **1a** was treated with Vedejs' reagent (Scheme 2).[8b,e] Under these conditions, the α-hydroxy amide **3a** was obtained in 49% yield and with only 62% de. This result shows the superiority of the molecular oxygen oxidation in term of diastereoselectivity of the reaction.

Scheme 2. Diastereoselective Hydroxylation of *N*-Acyloxazolidine **1a** with Vedejs' Reagent



As we suspected that residual molecular oxygen should be the only possible reactant able to oxidize the enolate, we decided to submit the sodium enolate of **1a** to a bubbling stream of oxygen at −78 °C. To our great delight, the hydroperoxide **4** was isolated in 85% yield and 97:3 dr after an aqueous workup (Scheme 3).[18] This result clearly indicates that the hydroperoxide is the product of the reaction whereas the α-hydroxy compound **3a** should result from its reduction. To this end, the reductions of **4** with a 2 M aqueous sodium bisulfite solution or a saturated sodium sulfite aqueous solution were attempted. Unfortunately, under these conditions, the α-hydroxy amide **3a** was only obtained in low yield and the hydroperoxide **4** mostly decomposed.

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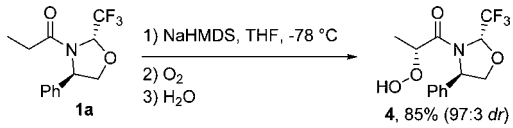
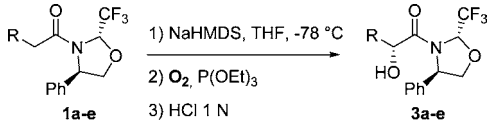
(18) The hydroperoxide **4** was conveniently isolated after aqueous workup, but it decomposed over silica gel.

Scheme 3. Diastereoselective Oxidation of *N*-Acyloxazolidine **1a** with Molecular Oxygen



In order to obtain the target α-hydroxy amide in good yield, we decided to perform the reduction of the intermediate peroxide in situ with triethyl phosphite. Under these conditions, the expected α-hydroxy amide **3a** was obtained in excellent yield (91%) and with high diastereoselectivity (94% de) (Table 1, entry 1). Moreover, the reaction turned out to be completely diastereoselective (>98% de) with more sterically hindered enolates (Table 1, entries 2 and 3). In these experiments, no trace of the minor diastereomer could be detected by ^{19}F and ^{1}H NMR in the crude reaction mixture.[19] The oxidation of the highly hindered *tert*-butyl substrate **1d** was achieved in reasonable yield without loss of stereoselectivity provided that the temperature was raised to −50 °C (Table 1, entry 4). This methodology was extended to the *β*-amino substrate **1e** allowing the preparation of the highly valuable *β*-amino-α-hydroxyl compound **3e** in a good yield and with a complete diastereoselectivity (Table 1, entry 5). In order to investigate the possible extension of this reaction to other nonfluorinated chiral auxiliaries, the oxidation of the enolate with an Evans'-type chiral auxiliary[20] was attempted. However, under our standard conditions no traces amount of the expected α-hydroxy imide[21] were detected, and a complex mixture, probably resulting from the degradation of the intermediate peroxide, was obtained. In our opinion, it seems that the Fox chiral auxiliary plays a crucial role in the stabilization of the intermediate peroxide species allowing highly selective reactions.

Table 1. α-Hydroxylation of *trans*-Fox Amide Enolates with Molecular Oxygen

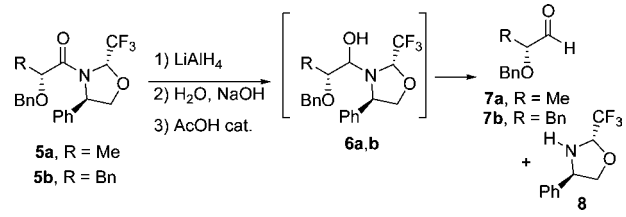


entry	R	yield[a] (%)	de[b] (%)	product
1	Me	90	94 (*R*)[c]	**3a**
2	Bn	81	>98 (*R*)	**3b**
3	*i*Pr	70	>98 (*R*)	**3c**
4	*t*Bu[d]	42	>98 (*R*)	**3d**
5	$(Bn)_2NCH_2$	75	>98 (*R*)	**3e**

[a] Yield of pure isolated product. [b] Determined by ^{19}F NMR on the crude mixture. [c] Diastereomerically pure (*R*)-**3a** was obtained after recrystallization in cyclohexane. [d] Conditions: $T = -50$ °C, 12 h. 29% of starting material was recovered.

The removal and the recovery of the Fox chiral auxiliary is a key step to justify the synthetic value of this methodology. Starting from diastereomerically pure compounds **3a** and **3b** as representative substrates, we focused our attention on the removal of the Fox chiral auxiliary in order to obtain the corresponding enantiomerically pure α-hydroxy acids and diols. The removal of the Fox chiral auxiliary of **3a** was performed by $LiAlH_4$ reduction according to our previously reported procedure.[15] Unfortunately, the expected α-hydroxy aldehyde could not be properly isolated because of its high solubility in water. Thus, we considered the protection of the hydroxyl group as a prerequisite for the reductive cleavage. The benzylation of **3a** and **3b** into **5a** and **5b** was achieved in 98% and 96% yield, respectively, using standard conditions without epimerization of the newly formed stereocenter. The benzylated hydroxy compounds **5a**,**b** were then submitted to $LiAlH_4$ reduction to give the aldehydes **7a**,**b** and the Fox chiral auxiliary **8** through the hydrolysis of the intermediate hemiaminals **6a**,**b** (Scheme 4).[22]

Scheme 4. Removal of the Fox Chiral Auxiliary **8**



At this stage, the aldehydes **7a**,**b** and the Fox chiral auxiliary **8** were not easily separated by silica gel chromatography. As we anticipated that the chiral auxiliary **8** would be stable under aldehyde oxidation and $NaBH_4$ reduction conditions, we decided to submit the amides **5a**,**b** to a two-step procedure without separation of the intermediate aldehyde/oxazolidine mixtures. According to this procedure involving the sequence $LiAlH_4$ reduction/hydrolysis/oxidation or $NaBH_4$ reduction, the enantiopure carboxylic acids **9a**,**b** and the alcohols **10a**,**b** were conveniently obtained from **5a**,**b** (Scheme 5). In each case, the chromatographic separation of the carboxylic acids or the alcohols and the oxazolidine was easily achieved and the Fox chiral auxiliary **8** was efficiently recovered (Scheme 5).

The (*R*) configurations of **9a**,**b** and **10a**,**b** were assigned by comparison of their optical rotation value with literature data.[19b,23] The enantiopurity of the carboxylic acid **9a** and the alcohol **10b** were confirmed by formation of their diastereomerically pure (*R*)-Mosher's ester and (*S*)-phenyl-

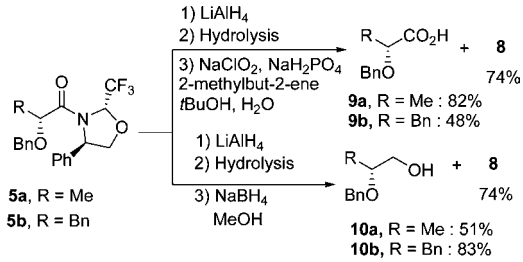
(19) These diastereoselectivities are comparable or better to those generally achieved by the alternative approach involving the chiral auxiliary-based alkylations of benzyloxyacetyl amides. (a) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165–2167, and references cited therein. (b) Chun, C. C.; Lee, G.-J.; Kim, J. N.; Kim, T H. *Tetrahedron: Asymmetry* **2005**, 2989–2992.

(20) Sodium enolate of the (*S*)-4-isopropyl-3-propionyl-1,3-oxazolidin-2-one.

(21) Kihara, N.; Ollivier, C.; Renaud, P. *Org. Lett.* **1999**, *1*, 1419–1422.

(22) For a previously reported similar reduction of SuperQuat amide into hemiaminal, see: Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 348–359.

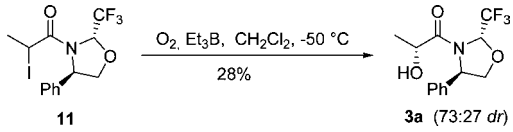
Scheme 5. Two-Step Procedure for the Synthesis of Enantiopure Carboxylic Acids **9a**,**b** and Alcohols **10a**,**b** with Efficient Recovery of the Chiral Auxiliary **8**



ethylamide derivatives. In each case, one single diastereomer was obtained.

We envisage two plausible mechanisms for this hydroxylation reaction. The first one would consist of the electrophilic addition of molecular oxygen to the enolate. The second one would involve a single electron transfer from the enolate to oxygen leading to a radical in the α position of the carbonyl group followed by the trapping of this radical by molecular oxygen. In order to discriminate these two potential mechanisms, the hydroxylation was performed according an irrefutably radical pathway. The iodinated compound **11**[24] was treated with triethylborane under oxygen atmosphere according to the procedure previously reported by Renaud et al.[21] (Scheme 6). Under these conditions, although the

Scheme 6. Radical Oxidation of the *N*-Iodoacylated Oxazolidine **11** with Molecular Oxygen



conversion of **11** was not complete (41% conversion), the α-hydroxyamide **3a** was obtained with a low diastereoselectivity (46% de). This low diastereoselectivity can be explained by the absence of chelation in the radical intermediate. These results, which are consistent with those reported by Renaud et al. with an Evans'-type chiral auxiliary,[21] allow us to propose an ionic mechanism for the molecular oxygen oxidation of the sodium enolate of **1a**.

In accordance with our previous theoretical study on the alkylation of Fox amide enolates,[16] we propose an electrophilic mechanism involving a chelated transition state presenting F···Na and O···Na interactions leading to a very highly diastereoselective *Re* face oxidation of the enolate (Figure 1).

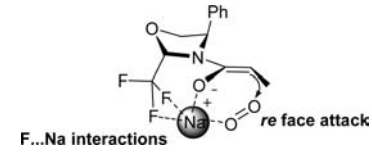


Figure 1. Postulated transition state leading to the *Re* face oxidation of the enolate.

In summary, we have reported that 2-(trifluoromethyl)oxazolidine (Fox) exhibits outstanding properties as a chiral auxiliary for amide enolates hydroxylation. The α-hydroxylation reaction of enolates using this chiral auxiliary was very efficiently performed in smooth and friendly conditions using molecular oxygen as oxidizer. The reaction is generally completely diastereoselective, and the chiral auxiliary is conveniently removed and recovered to give enantiopure oxygenated carboxylic acids and alcohols.

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Supporting Information Available: Complete experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100211S

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(24) Compound **11** was prepared by electrophilic iodination of the sodium enolate of **1a** with *N*-iodosuccinimide.