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# Synthesis of α-$CF_3$-Substituted Carbonyl Compounds with Relative and Absolute Stereocontrol Using Electrophilic $CF_3$-Transfer Reagents

**Václav Matoušek,[†] Antonio Togni,*[,†] Vincent Bizet,[‡] and Dominique Cahard*[,‡]**

*Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology, ETH Zürich, CH-8093 Zürich, Switzerland, and UMR 6014 CNRS COBRA, Université et INSA de Rouen, 76130 Mont-Saint-Aignan, France*

*togni@inorg.chem.ethz.ch; dominique.cahard@univ-rouen.fr*

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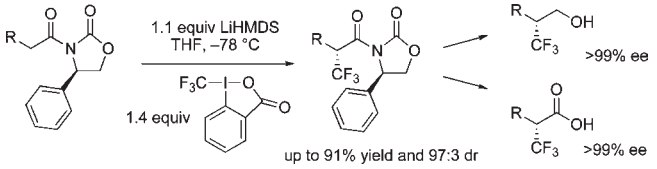
## ABSTRACT




**Evans-type chiral lithium imide enolates undergo diastereoselective α-trifluoromethylation with a hypervalent iodine−$CF_3$ reagent with up to 91% combined isolated yield and 97:3 dr. The resulting isolated diastereopure products can be further transformed into valuable products without racemization.**

The remarkable utility of organofluorine compounds in many branches of the fine chemicals industry and in life and materials science is growing in importance.[1] Indeed, the presence of highly fluorinated alkyl groups often triggers significant changes in the physical and chemical properties of molecules, such as solubility, lipophilicity, increased metabolic stability, and better bioavailability.[2] The introduction of a trifluoromethyl group, the most-sought fluorinated alkyl group, into a selected target in a reliable and effective fashion undoubtedly belongs among the most fundamental and desired transformations in fluorine chemistry.[3] Of specific interest are methodologies appropriate for late-stage trifluoromethylation in multistep syntheses, which renders them a valuable tool when juxtaposed with the classical "building block approach".[4] Early work in this field by Iseki and co-workers demonstrated that the well-established technique of diastereoselective functionalization of chiral imide enolates, originally developed by Evans,[5] can be successfully extended to radical trifluoromethylation.[6] Although high diastereomeric ratios up to 93:7 were obtained for radical trifluoromethylation,[6] a large excess of trifluoroiodomethane (a gaseous and

[†] ETH Zürich.
[‡] UMR 6014 CNRS COBRA, Université et INSA de Rouen.

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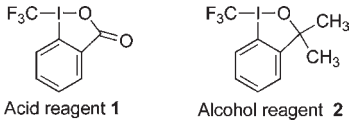
rather costly reagent) had to be employed, and $O_2$ had to be present to initiate the radical process. Later, Umemoto and co-workers showed that ate complexes obtained from potassium ketone enolates and stochiometric amounts of atropisomeric chiral boroles allow enantioselective trifluoromethylation by means of *S*-$CF_3$ dibenzothiophenium salts in up to 45% ee.[7] A related strategy was employed by Cahard and co-workers for the electrophilic trifluoromethylation of ammonium enolates of $\beta$-keto esters generated by means of cinchona alkaloids, which afforded products with up to 71% ee.[8] Even more recent work by Shibata, Cahard, and co-workers revealed that chiral guanidines also lead to enantiodiscrimination of the enolate stereofaces through H-bonding to $\beta$-keto esters.[9] Chiral imidazolidinone organocatalysts that transiently form enamines from primary aldehydes yield highly enantiopure trifluoromethylated products (in up to 99% ee) upon reaction with a large excess of trifluoroiodomethane under radical photolytic conditions.[10] In addition, a nearly equal range of substrates undergo enantioselective electrophilic trifluoromethylation with hypervalent iodine $CF_3$-transfer reagents under Lewis acid cocatalysis with practically the same ee values. However, an excess of the substrate had to be employed.[11]



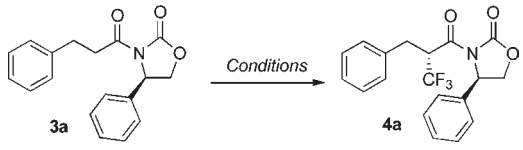
Acid reagent **1** Alcohol reagent **2**

**Figure 1.** The most prominent examples of hypervalent iodine–$CF_3$ reagents.

In the context of the newly expanding trifluoromethylation chemistry of hypervalent $CF_3$–iodine compounds developed in one of our groups,[12] we reasoned that an enantiopure enolate would undergo diastereoselective electrophilic trifluoromethylation after treatment with either of the reagents **1** or **2** (Figure 1).[13]

We focused our early efforts on the diastereoselective trifluoromethylation of chiral imide enolates by varying the nature of the metal. We began our study by reacting **1** or **2** with the (*Z*)-boron enolate of **3a** obtained using dibutyl boron triflate and Hünig's base. Disappointingly, we could not detect any desired trifluoromethylation. The zinc enolate generated from diethylzinc and **3a** analogously did not furnish any trifluoromethylated product. We speculated that a more reactive enolate might eventually serve as a more effective nucleophile in the attempted trifluoromethylation with **1** or **2**. To our delight, lithiation of **3a** with 1.1 equiv of LDA in THF at −78 °C followed by addition of 1.1 equiv of **1** led to the formation of the α-trifluoromethylated diastereomers **4a** in 60% isolated yield and 89:11 dr (Table 1). Encouraged by this promising result, we continued our screening of reaction conditions, varying parameters such as the solvent, base, counterion, and additive. As is evident from Table 1, lithium enolates show excellent reactivity and afford high dr values of the α-trifluoromethylated product **4a**. It is noteworthy that LiHMDS gave better isolated yields than LDA. Switching to the corresponding sodium enolate maintains the original dr value, but a decline in reactivity starts to become apparent. The potassium enolate shows both the worst reactivity and diastereoselectivity of all the tested alkali metal enolates. Attempted trifluoromethylation, after transmetalation of lithium enolates with Cu(I) or Zn(II) salts, resulted in the decomposition of **1**, while **2** showed itself to be practically inert toward the basic metal enolates listed in Table 1. Simple treatment of **3a** and **2** in DCM at rt in the presence of 30 mol % $CuBr \cdot Me_2S$ resulted only in

**Table 1.** Screening of Reaction Conditions



**3a** **4a**

| entry | conditions | conv (%)[a,b] | dr of **4a**[a] |
|---|---|---|---|
| 1 | 1.1 equiv of LDA, THF, −78 °C, 30 min, then 1.1 equiv of **1** at −78 °C to rt over 4 h | 100 (60) | 89:11 |
| 2 | same as 1 but with 1.1 equiv of LiHMDS | 100 (82) | 90:10 |
| 3 | same as 1 but with 1.1 equiv of NaHMDS | 90 | 88:12 |
| 4 | same as 1 but with 1.1 equiv of KHMDS | 50 | 75:25 |
| 5 | same as 2 but with transmetalation using 1.1 equiv of CuI at 0 °C 30 min prior to addition of **1** | – | – |
| 6 | same as 5 but with transmetalation using 1.1 equiv of $ZnCl_2$ at −78 °C 30 min prior to addition of **1** | – | – |

[a] Determined by $^{19}F$ NMR analysis. [b] Isolated yields are shown in parentheses.

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partial decomposition of **2** to $CF_3Br$ but no detectable trifluoromethylation. The high reactivity and selectivity of lithium enolates is explained by the strong Lewis acidity of the counterion, which is considered to lead to tighter chelation and possibly to partial $CF_3$-reagent activation.

Solvent screening was limited to ethereal solvents in which alkali metal enolates are commonly prepared. The use of diethyl ether under identical conditions revealed serious solubility problems both of substrate **3a** and reagent **1**, leading to improper mixing and resulting in sluggish reactions and low conversions. Increasing the amount of **1** to 1.4 equiv led to an 86% isolated yield of diastereomers that were separable by column chromatography. Under identical reaction conditions, Umemoto's reagent (*S*-$CF_3$ dibenzothiophenium triflate) also proved reactive toward the Li enolate of **3a**, with almost the same diastereoselectivity (89:11). However, incomplete conversion and a lower isolated yield of **4a** was observed. Further increasing the amount of LiHMDS to 1.4 equiv and the amount of **1** to 2 equiv raised the combined isolated yield of **4a** to 93%. As an acceptable compromise in terms of yield and reagent consumption, we identified the optimal conditions to be lithiation of the substrate with 1.1 equiv of

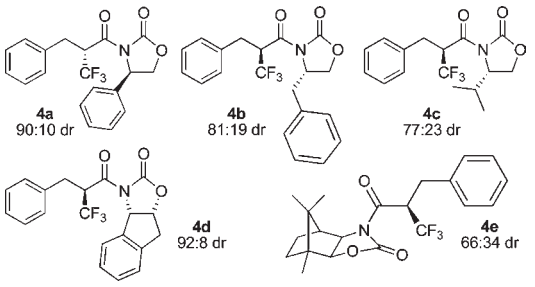


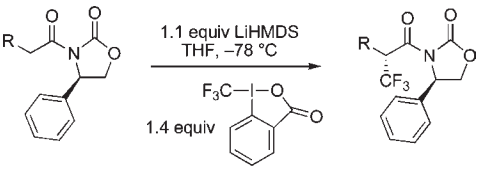

**Figure 2.** Screening of various chiral auxiliaries.

LiHMDS at −78 °C in THF followed by addition of 1.4 equiv of **1** all at once and slow warming to rt over 4 h.

Next, a screening of various chiral auxiliaries (Figure 2) led us to conclude that auxiliaries containing aromatic groups, preferably with a rigidified skeleton (**4d**) offer the best performance with regard to dr. The *cis*-aminoborneol-derived auxiliary proved to be detrimental with respect to diastereofacial discrimination of the corresponding Li enolate. Although the *cis*-aminoindanol-derived auxiliary gave the best dr, we decided to investigate the scope of (4*R*)-4-phenyl-1,3-oxazolidin-2-one, as in **4a**, because it can be more readily accessed from relatively cheap (*R*)-phenylglycine in two synthetic steps.[14] (4*R*)-4-Phenyl-1,3-oxazolidin-2-one constitutes a compromise between diastereoselectivity and easy access.

Having identified a suitable chiral auxiliary, we turned our efforts to exploring the substrate scope of the reaction.

**Table 2.** Substrate Scope




| R | product | yield (%) | dr |
|---|---|---|---|
| Bn | **4a** | 86 | 90:10 |
| Ph | **5** | 83 | 88:12 |
| 2-naphthyl | **6** | 40 | 77:23 |
| Me | **7** | 46 | 81:19 |
| *i*-Pr | **8** | 75 | 96:4 |
| *c*-hex | **9** | 91 | 94:6 |
| *t*-Bu | **10** | 83 | 97:3 |
| OBn | **11** | 74 | 86:14 |
| 2-thiophenyl | **12** | – | – |
| *N*-phth | **13** | – | – |

A survey of the substrates depicted in Table 2 delineates two evident trends: (1) With increasing steric bulk of the acyl group attached to the oxazolidinone, the isolated yield increases, culminating with the cyclohexylacetyl substituent. (2) A similar tendency can be observed in the dependence of diastereoselectivity on the steric bulk of the acyl group, as clearly demonstrated in the aliphatic series of acyl groups (**7**−**10**). The highest dr value was obtained with the most bulky *tert*-butylacetyl-substituted oxazolidinone **10**, whereas the lowest dr value was linked to the smaller propanoyl-substituted oxazolidinone **7**. We attribute the lower observed dr for **6** to the well-known propensity of arylacetic acids and their derivatives to undergo base-induced epimerization.[15] Indeed, α-trifluoromethylated product **5** was obtained with 88:12 dr under our optimized reaction conditions, but longer standing of the reaction mixture at 0 °C led to significant erosion of the product dr and partial product decomposition. Importantly, under the same reaction conditions, **4a** did not show any noticeable decrease in dr. Instead of clean α-trifluoromethylation, the attempted synthesis of **12** led to a complex mixture arising from extensive heteroaromatic trifluoromethylation. Access to compound **13** also appeared problematic because the metalation step suffered from severe complications, presumably because the freshly generated enolate can undergo facile decomposition. Attempts at α-trifluoromethylation of tertiary acylcarboxamides did not meet with any success. In all the cases where trifluoro methylation could be accomplished, the resulting diastereomeric α-trifluoromethylated products could be purified by either preparative silica gel column chromatography or crystallization, delivering diastereopure compounds. X-ray analysis of the major diastereomer of **4a** (see Figure 3) unequivocally ascertained the absolute configuration of

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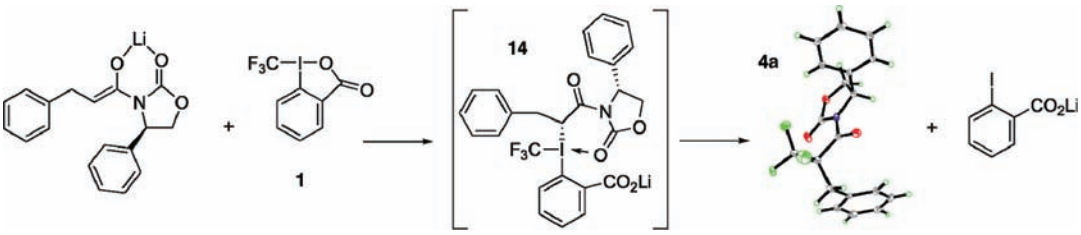


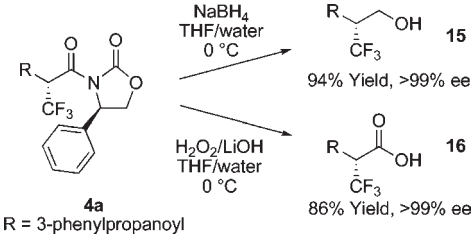

**Figure 3.** Putative mechanism of trifluoromethylation and X-ray structure of the major diastereomer of **4a**.

the newly created stereocenter to be *R*, resulting from the kinetically faster attack of the trifluoromethylating reagent **1** at the sterically less shielded *re* stereoface of the corresponding Li enolate.

It is interesting to note that there have already been attempts in our group to trifluoromethylate Li enolates of ketones and carboxylic acid esters. However, no appropriate conditions for successful α-trifluoromethylation with either **1** or **2** could be found. Evans-type acyloxazolidinones represent in this context a rather welcome exception. In an attempt to find a rationale for the success of this class of enolizable carbonyl compounds, we assume the following speculative mechanism: the Li enolate of acyl oxazolidinone **3a** is stereoselectively attacked by **1**, which leads to exchange of the internal carboxylate ligand at the hypervalent iodine center, affording α-iodanyl intermediate **14** (Figure 3) by analogy to arylation of malonates[16] and acetoxylation[17] and tosyloxylation[18] of ketones, although an alternative formation of an O–I intermediate cannot be conclusively ruled out.[19] The oxazolidinone moiety is believed to function as a weak, neutral monodentate oxygen-centered ligand, increasing the stability of intermediate **14**, which subsequently undergoes stereoretentive ligand coupling to give **4a** and lithium 2-iodobenzoate. The beneficial role of the weakly coordinating oxazolidinone[20] is also believed to lie first in increasing the steric bulk around the iodine center (thus significantly decreasing the rate of ligand exchange at the hypervalent iodine center) and second in protecting the activated α-position of the carbonyl substrate in **14** from attack by external nucleophiles. The oxazolidinone moiety thus promotes selective monosubstitution at the hypervalent iodine center, leading to productive α-trifluoromethylation and suppressing unproductive side reactions.

As an extension of the presented trifluoromethylation protocol, we explored the potential of further racemization-free synthetic transformations of diastereopure α-$CF_3$-acyloxazolidinones (Scheme 1). Reduction of pure

**Scheme 1.** Acces to Enantiopure α-$CF_3$ Alcohol and Acid Derivatives




**4a** with $NaBH_4$ in THF/water cleanly gave the corresponding product (2*R*)-2-benzyl-3,3,3-trifluoropropan-1-ol (**15**) in 94% yield with 99+% ee. Similarly, treatment of **4a** with $H_2O_2$ in the presence of 1.6 equiv of LiOH gave, after acidification, the corresponding product (2*R*)-2-benzyl-3,3,3-trifluoropropanoic acid (**16**) in 86% yield with 99+% ee, indicating full conservation of stereointegrity.

To conclude, we have successfully developed an efficient protocol, mechanistically distinct from Iseki's radical approach, for trifluoromethylation of chiral imide enolates using electrophilic $CF_3$-transfer reagents that affords isolated yields of up to 91% with diastereomeric ratios up to 97:3. The "acid reagent" appeared to show somewhat higher reactivity toward chiral lithium imide enolates than Umemoto's reagent. The oxazolidinone substituent is believed to act beneficially by suppressing the extent of unproductive side reactions, leading to clean α-trifluoromethylation. The resulting isolated diastereopure products could be further transformed into valuable products without racemization.

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**Supporting Information Available.** Experimental details and copies of $^1H$, $^{13}C$, and $^{19}F$ spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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