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Catalytic Generation of α-CF_3 Enolate: Direct Catalytic Asymmetric Mannich-Type Reaction of α-CF_3 Amide

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Supporting Information

ABSTRACT: The introduction of the CF_3 unit is a common strategy for modifying pharmacokinetic properties and slowing metabolic degradation in medicinal chemistry. A catalytic and enantioselective addition of α-CF_3 enolates allows for expeditious access to functionalized chiral building blocks with CF_3-containing stereogenicity. To date, α-CF_3 enolates have been a less explored class of nucleophiles because of rapid defluorination. The present study reveals that a designed α-CF_3 amide enables a direct asymmetric Mannich-type reaction in a cooperative catalytic system.

Organofluorine compounds have attracted considerable interest because of their particular utility in material and biological applications.[1] In the realm of medicinal chemistry, incorporation of a CF_3 group is a commonly employed strategy when seeking better drug candidates,[2] leading to significant advances in synthetic methodology for regio- and stereoselective trifluoromethylation.[3] The exploitation of α-CF_3 enolate as an active nucleophile for enantioselective C−C bond-forming reactions is a viable strategy for pursuing this end, allowing rapid access to densely functionalized chiral building blocks possessing CF_3-containing stereogenicity. Despite the considerable advances in enolate-based chemistry over the past decades,[4] α-CF_3 enolates have been only scarcely explored because of the notorious instability of α-CF_3 metal enolates. Fluoride is rapidly eliminated to give β,β-difluoro-α,β-unsaturated carbonyl compounds, which are prone to subsequent decomposition (Figure 1a).[5−9] Nakai and co-workers showed that trapping of the enolates by silylation effectively suppressed the undesired β-elimination of fluoride, and the ketene silyl acetal thus obtained could be used for subsequent C−C bond formation (Figure 1b).[5,6,10] The first successful formation of α-CF_3 metal enolates from α-CF_3 carbonyl compounds was reported by Mikami and co-workers.[7] They used stoichiometric amounts of $TiCl_4$ and Et_3N, which were applied to the *anti*-selective aldol reaction. Detailed theoretical studies revealed that the linearity of the Ti−O−C array prevented Ti−F interactions, thus inhibiting the elimination of fluoride. For the synthesis of enantioenriched products using α-CF_3 enolate, Ishihara and co-workers exploited the properties of Si enolates and Ti enolates; an imide bearing a chiral auxiliary was sequentially transformed to the corresponding Ti enolate before reacting with aldehydes to give the aldol products with decent diastereoselectivity.[8] Franck, Seon-Meniel, and Figadère independently reported a similar approach using $TiCl_4$/TMEDA.[9] Ramachandran et al.[11] documented the utility of boron enolate for the aldol reaction of α-CF_3 esters, however, there is no general method to generate α-CF_3 enolates in a truly catalytic manner. Moreover, the access to enantioenriched products relied on the use of a stoichiometric amount of a chiral source.

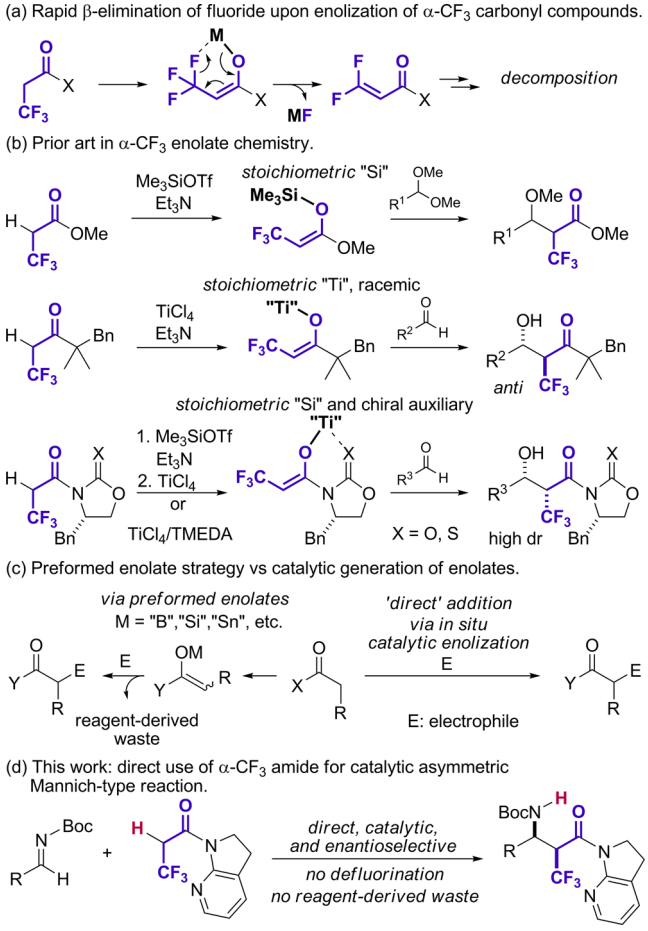

Figure 1. Overview of enolate chemistry of α-CF_3 carbonyl compounds.

Another topical issue in enolate chemistry is the direct catalytic generation of active enolate species, which are used for subsequent enantioselective C−C bond formation in a single

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flask. Historically, preformed enolates using boron, silicon, and tin reagents have been preferably utilized as nucleophiles for tractable stereocontrol with chiral Lewis acid catalysts at the C−C bond-formation stage (Figure 1c).[12] Because of the inevitable coproduction of reagent-derived waste, the "direct" use of latent enolates has gained considerable attention in the chemical community over the past two decades as a truly catalytic and atom-economical protocol to access the enantioenriched products based on enolate chemistry.[4d,13,14] α-CF_3 carbonyl compounds have until now resisted the continuing challenges of direct enolization for enantioselective C−C bond formation, despite their potential synthetic utility. Herein we report a direct catalytic asymmetric Mannich-type reaction using an α-CF_3 amide via soft Lewis acid/hard Brønsted base cooperative catalysis (Figure 1d). The α-CF_3 enolate was catalytically generated without undesirable fluoride elimination, and the Mannich products were obtained with high diastereo- and enantioselectivity. This reaction offers an expeditious protocol to access enantioenriched β-amino acid derivatives bearing a pendant α-CF_3 group.

The envisioned reaction was pursued by exploiting the 7-azaindolinylamide **1a** as a latent α-CF_3 enolate. We recently documented the utility of the α-sulfanyl 7-azaindolinylamide as a pronucleophile in a direct catalytic asymmetric aldol reaction,[15] where the facilitated catalytic enolization of the amide via a soft Lewis acid/hard Brønsted base cooperative catalyst was key to the smooth reaction.[16] Earlier theoretical studies by Mikami and co-workers suggested that interrupting the interaction of a metal with a fluorine atom is crucial to prevent the β-elimination of fluoride upon metal enolate formation.[7b,c] We reasoned that the bidentate coordination of the latent enolate to metals would fulfill this requirement and focused on the identification of suitable metal complexes and amide functionalities. 7-Azaindolinylamide **1a** and a Cu(I)/*rac*-BINAP complex emerged as a promising combination with spectroscopic evidence. Whereas **1a** was in almost exclusively the *E* conformation,[17,18] upon the addition of an equimolar amount of the Cu(I)/*rac*-BINAP complex, bidentate coordination of the *Z* conformer of **1a** to Cu(I) was observed in the solution phase by nuclear Overhauser effect (NOE) analysis, most likely because of C−N bond rotation induced by the coordination to Cu(I) (Figure 2).[19] X-ray analysis of a single crystal obtained from the solution confirmed the bidentate coordination of **1a** to Cu(I), with Cu(I) located away from the fluorine atoms of **1a**.[17]

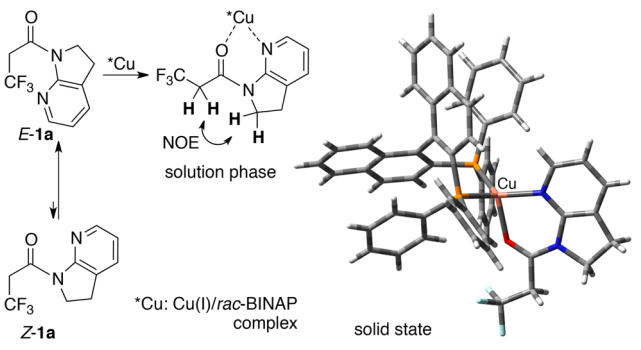
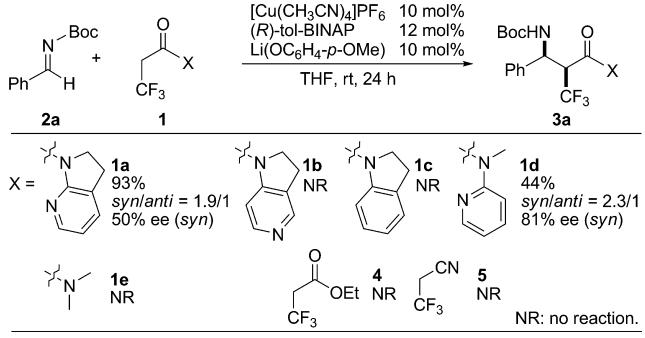


Figure 2. Preferred *E* conformation of amide **1a** and bidentate coordination to the Cu(I) complex as confirmed by NMR and X-ray crystallography. Pink, copper; orange, phosphorus; sky blue, fluorine; red, oxygen; blue, nitrogen; gray, carbon; white, hydrogen.

On the basis of these observations, catalytic deprotonation of **1a** to generate α-CF_3 enolate was examined in a Mannich-type reaction with *N*-Boc imine **2a**.[20−22] The combined use of the soft Lewis acid Cu(I)/(*R*)-tol-BINAP complex (10 mol%) and the hard Brønsted base Li(OC_6H_4-*p*-OMe) (10 mol%) afforded the desired Mannich product **3a** in 93% yield (based on **1a**) with encouraging stereoselectivity: *syn*/*anti* = 1.9/1, 50% ee (syn) (Chart 1). This preliminary result revealed that (1) the

Chart 1. Screening of α-CF_3 Amides as Pronucleophiles in the Direct Catalytic Asymmetric Mannich-Type Reaction



undesirable β-elimination of fluoride barely occurred and (2) smooth catalytic turnover was achieved even with apparently tight bidentate coordination of **1a** to Cu(I). Amide **1d** derived from 2-(methylamino)pyridine afforded the desired product in moderate yield while the isomeric amide **1b**, indolinylamide **1c**, and dimethylamide **1e** failed in the reaction, indicating that bidentate coordination is crucial for efficient enolization. Other potential α-CF_3 pronucleophiles **4** and **5** afforded no Mannich products at all, implying that the inductive effect of the α-CF_3 group is not the sole factor for facilitated deprotonation. Given the smooth α-CF_3 enolate formation of amide **1a** with the soft Lewis acid/hard Brønsted base cooperative catalytic system, chiral ligands were screened to achieve better stereocontrol (Table 1). Biaryl-type bisphosphine chiral ligands with different skeletons generally afforded the desired products in high yield, albeit with low diastereo- and enantioselectivity (entries 1−3). The alkylphosphine complex Cu(I)/(*R*,*R*)-Ph-BPE exhibited poor catalytic activity (entry 4). Ferrocene-embedded arylphosphines were beneficial to give the *syn* product predominantly, although the enantioselectivity remained low to moderate (entries 5 and 6). Biaryl-type ligands possessing bulkier aryl groups on phosphorus proved to be very effective in reaching high diastereo- and enantioselectivity (entries 7 and 8).[23] The use of Barton's base as an alternative to Li(OC_6H_4-*p*-OMe) was a viable option to give similar reaction outcomes, circumventing the need for the careful preparation of the Li base in a separate flask (entry 9). The catalyst loading was reduced to 5 mol% without any loss of stereoselectivity (entry 10).[24]

Table 2 summarizes the generality of the Mannich-type reaction with regard to the imine substrate. The reactions reached completion with catalyst loadings of 5−10 mol% at room temperature, and generally high levels of stereoselectivity were observed. Irrespective of alkyl, vinyl, methoxy, or halogen substitution on the aromatic ring, the corresponding *syn* products were obtained exclusively with high enantioselectivity (entries 1−9). The catalytic system was sufficiently robust to perform the reaction on a 1.5 g scale (entry 7). Imines bearing a *p*-TfO group afforded the *syn* product with decreased diastereoselectivity, albeit with high enantioselectivity (entry 10). Imines derived

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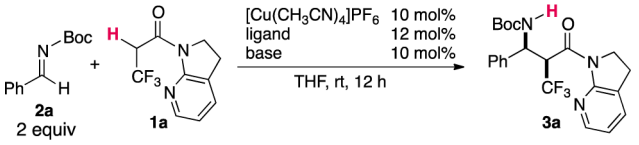
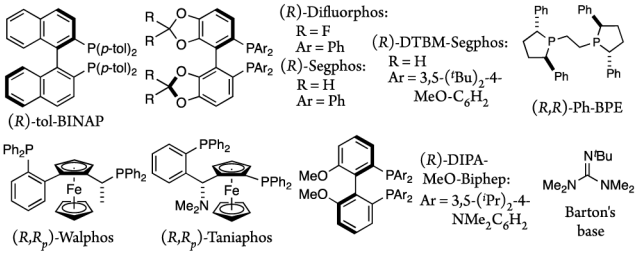
Table 1. Ligand Screening for the Direct Catalytic Asymmetric Mannich-Type Reaction of 1a and *N*-Boc Imine 2a

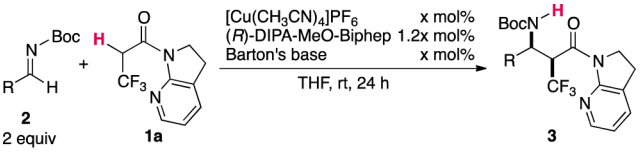


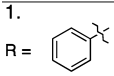
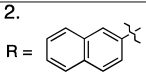
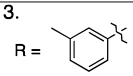
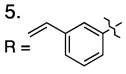
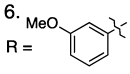
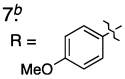
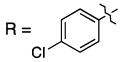
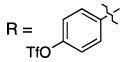
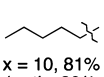
entry	ligand	base	yield (%)[a]	*syn*/*anti*[b]	ee (%)[b]
1	(*R*)-tol-BINAP	Li(OC$_6$H$_4$-*p*-OMe)	93	1.9/1	50
2	(*R*)-Segphos	Li(OC$_6$H$_4$-*p*-OMe)	95	1.8/1	23
3	(*R*)-Difluorphos	Li(OC$_6$H$_4$-*p*-OMe)	95	1.1/1	−5
4	(*R*,*R*)-Ph-BPE	Li(OC$_6$H$_4$-*p*-OMe)	13	1.4/1	39
5	(*R*,*R*$_p$)-Walphos	Li(OC$_6$H$_4$-*p*-OMe)	92	13/1	−29
6	(*R*,*R*$_p$)-Taniaphos	Li(OC$_6$H$_4$-*p*-OMe)	93	>20/1	−35
7	(*R*)-DTBM-Segphos	Li(OC$_6$H$_4$-*p*-OMe)	91	>20/1	99
8	(*R*)-DIPA-MeO-Biphep	Li(OC$_6$H$_4$-*p*-OMe)	94	>20/1	99
9	(*R*)-DIPA-MeO-Biphep	Barton's base	95	>20/1	99
10[c]	(*R*)-DIPA-MeO-Biphep	Barton's base	94	>20/1	99



[a]Isolated yields. [b]Determined by chiral-stationary-phase HPLC analysis. [c]5 mol% $[Cu(CH_3CN)_4]PF_6$ and Barton's base, and 6 mol% of ligand were used.

Table 2. Substrate Scope of the Direct Catalytic Asymmetric Mannich-Type Reaction of 1a and *N*-Boc Imines 2[a]



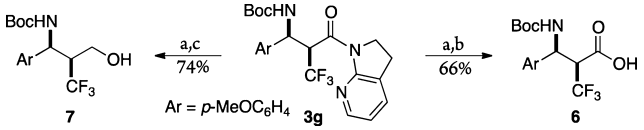
1. R =  **3a**, x = 5, 94%, *syn*/*anti*: >20/1, 98% ee	2. R =  **3b**, x = 10, 93%, *syn*/*anti*: >20/1, 95% ee	3. R =  **3c**, x = 10, 96%, *syn*/*anti*: >20/1, 97% ee	4. R =  **3d**, x = 5, 92%, *syn*/*anti*: >20/1, 99% ee
5. R =  **3e**, x = 10, 92%, *syn*/*anti*: >20/1, 96% ee	6. MeO R =  **3f**, x = 10, 90%, *syn*/*anti*: >20/1, 96% ee	7[b] R =  **3g**, x = 5, 94%, *syn*/*anti*: >20/1, 98% ee	8. R =  **3h**, x = 10, 92%, *syn*/*anti*: >20/1, 99% ee
9. R =  **3i**, x = 10, 91%, *syn*/*anti*: >20/1, 99% ee	10. R =  **3j**, x = 10, 89%, *syn*/*anti*: 5.8/1, 98% ee	11. R =  **3k**, x = 10, 94%, *syn*/*anti*: >20/1, 99% ee	12. R =  **3l**, x = 10, 95%, *syn*/*anti*: >20/1, 98% ee
13. R =  **3m**, x = 5, 91%, *syn*/*anti*: >20/1, 94% ee	14[c,d] R =  **3n**, x = 10, 77%, *syn*/*anti*: 10/1, 96% ee	15[c,e] R =  **3o**, x = 10, 81%, *syn*/*anti*: >20/1, 98% ee	16[c,e] R =  **3p**, x = 10, 85%, *syn*/*anti*: >20/1, 94% ee

[a]Isolated yields are shown. [b]1.5 g of amide **1a** was used. [c]5 equiv of imine was used. [d]At 0 °C. [e]At −20 °C.

from heteroaromatic aldehydes were also suitable substrates (entries 11−13). Of particular note is the successful application of the reaction conditions to enolization-prone aliphatic *N*-Boc imines at lower temperature, highlighting the mild reaction conditions of the present catalytic system (entries 14−16).[25]

The Mannich products can serve as versatile chiral building blocks having a CF_3-substituted stereogenic center (Scheme 1).

Scheme 1. Transformation of the Mannich Product[a]



[a]Reagents and conditions: (a) $LiAlH_4$, Et_2O, −45 °C, 1.5 h. (b) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, ^{t}BuOH/H_2O, rt, 5 h, 66% (two steps). (c) $NaBH_4$, Et_2O/MeOH, 0 °C, 1.5 h, 74% (two steps).

The 7-azaindolinylamide was readily reduced to the corresponding aldehyde with $LiAlH_4$, which was further transformed to β-amino acid **6** via Pinnick oxidation, albeit with marginal epimerization (10/1).[26,27] γ-Amino alcohol **7** was obtained via sequential hydride reduction without epimerization.

In summary, an α-CF_3 enolate of 7-azaindolinylamide was catalytically generated and integrated into the direct asymmetric Mannich-type reaction via cooperative catalysis. Both aromatic and aliphatic *N*-Boc imines were transformed into β-amino acid derivatives possessing α-CF_3 stereogenicity. Application of the present protocol to medicinal chemistry is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

Patent application submitted.

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