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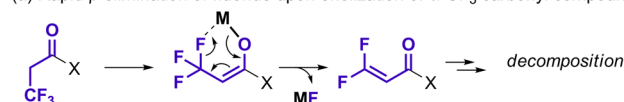
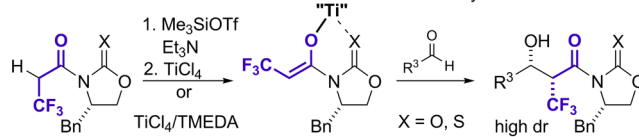
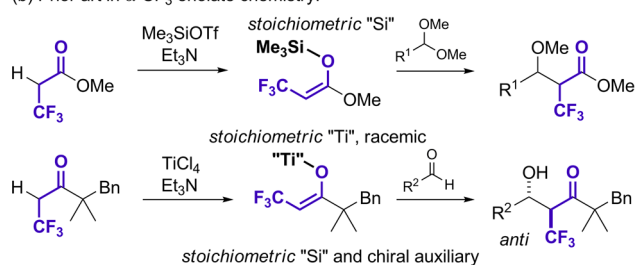
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Catalytic Generation of  $\alpha$ -CF<sub>3</sub> Enolate: Direct Catalytic Asymmetric Mannich-Type Reaction of  $\alpha$ -CF<sub>3</sub> AmideLiang Yin,<sup>†</sup> Lennart Brewitz,<sup>†</sup> Naoya Kumagai,<sup>\*,†</sup> and Masakatsu Shibasaki<sup>\*,†,‡</sup><sup>†</sup>Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan<sup>‡</sup>ACT-C, Japan Science and Technology Agency (JST), 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

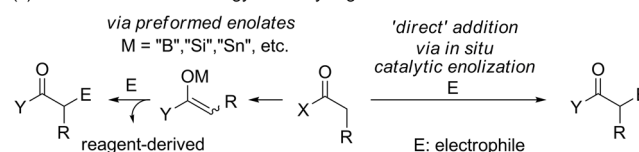
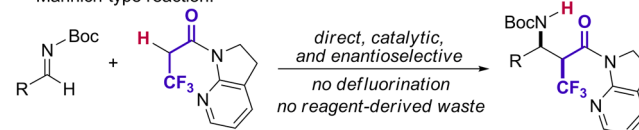
## Supporting Information

**ABSTRACT:** The introduction of the CF<sub>3</sub> unit is a common strategy for modifying pharmacokinetic properties and slowing metabolic degradation in medicinal chemistry. A catalytic and enantioselective addition of  $\alpha$ -CF<sub>3</sub> enolates allows for expeditious access to functionalized chiral building blocks with CF<sub>3</sub>-containing stereogenicity. To date,  $\alpha$ -CF<sub>3</sub> enolates have been a less explored class of nucleophiles because of rapid defluorination. The present study reveals that a designed  $\alpha$ -CF<sub>3</sub> 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.<sup>1</sup> In the realm of medicinal chemistry, incorporation of a CF<sub>3</sub> group is a commonly employed strategy when seeking better drug candidates,<sup>2</sup> leading to significant advances in synthetic methodology for regio- and stereoselective trifluoromethylation.<sup>3</sup> The exploitation of  $\alpha$ -CF<sub>3</sub> 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<sub>3</sub>-containing stereogenicity. Despite the considerable advances in enolate-based chemistry over the past decades,<sup>4</sup>  $\alpha$ -CF<sub>3</sub> enolates have been only scarcely explored because of the notorious instability of  $\alpha$ -CF<sub>3</sub> metal enolates. Fluoride is rapidly eliminated to give  $\beta,\beta$ -difluoro- $\alpha,\beta$ -unsaturated carbonyl compounds, which are prone to subsequent decomposition (Figure 1a).<sup>5–9</sup> Nakai and co-workers showed that trapping of the enolates by silylation effectively suppressed the undesired  $\beta$ -elimination of fluoride, and the ketene silyl acetal thus obtained could be used for subsequent C–C bond formation (Figure 1b).<sup>5,6,10</sup> The first successful formation of  $\alpha$ -CF<sub>3</sub> metal enolates from  $\alpha$ -CF<sub>3</sub> carbonyl compounds was reported by Mikami and co-workers.<sup>7</sup> They used stoichiometric amounts of TiCl<sub>4</sub> and Et<sub>3</sub>N, 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  $\alpha$ -CF<sub>3</sub> 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.<sup>8</sup> Franck, Seon-Meniel, and Figadère independently reported a

(a) Rapid  $\beta$ -elimination of fluoride upon enolization of  $\alpha$ -CF<sub>3</sub> carbonyl compounds.(b) Prior art in  $\alpha$ -CF<sub>3</sub> enolate chemistry.

(c) Preformed enolate strategy vs catalytic generation of enolates.

(d) This work: direct use of  $\alpha$ -CF<sub>3</sub> amide for catalytic asymmetric Mannich-type reaction.**Figure 1.** Overview of enolate chemistry of  $\alpha$ -CF<sub>3</sub> carbonyl compounds.

similar approach using TiCl<sub>4</sub>/TMEDA.<sup>9</sup> Ramachandran et al.<sup>11</sup> documented the utility of boron enolate for the aldol reaction of  $\alpha$ -CF<sub>3</sub> esters, however, there is no general method to generate  $\alpha$ -CF<sub>3</sub> enolates in a truly catalytic manner. Moreover, the access to enantioenriched products relied on the use of a stoichiometric amount of a chiral source.

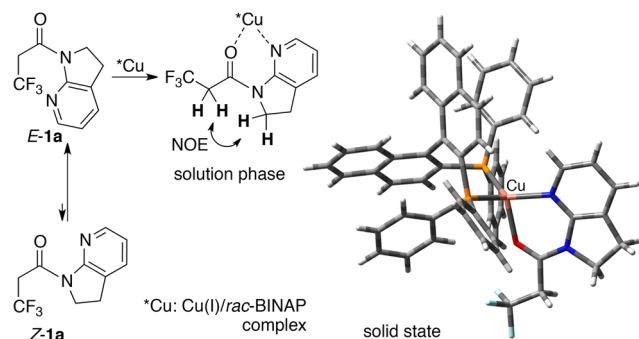
Another topical issue in enolate chemistry is the direct catalytic generation of active enolate species, which are used for subsequent enantioselective C–C bond formation in a single

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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).<sup>12</sup> 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.<sup>4d,13,14</sup>  $\alpha$ -CF<sub>3</sub> 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  $\alpha$ -CF<sub>3</sub> amide via soft Lewis acid/hard Brønsted base cooperative catalysis (Figure 1d). The  $\alpha$ -CF<sub>3</sub> 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  $\beta$ -amino acid derivatives bearing a pendant  $\alpha$ -CF<sub>3</sub> group.

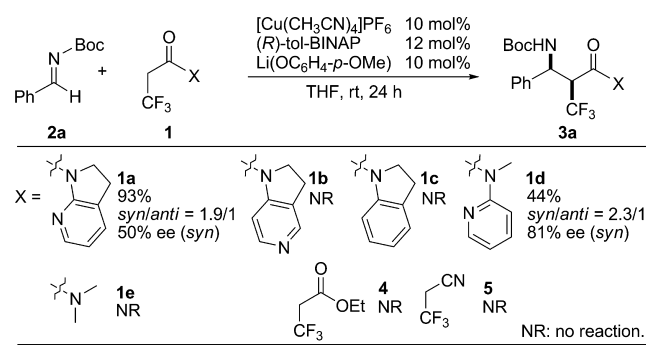
The envisioned reaction was pursued by exploiting the 7-azaindolylamide **1a** as a latent  $\alpha$ -CF<sub>3</sub> enolate. We recently documented the utility of the  $\alpha$ -sulfonyl 7-azaindolylamide as a pronucleophile in a direct catalytic asymmetric aldol reaction,<sup>15</sup> where the facilitated catalytic enolization of the amide via a soft Lewis acid/hard Brønsted base cooperative catalyst was key to the smooth reaction.<sup>16</sup> 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  $\beta$ -elimination of fluoride upon metal enolate formation.<sup>7b,c</sup> 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-Azaindolylamide **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,<sup>17,18</sup> 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).<sup>19</sup> 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**.<sup>17</sup>



**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.

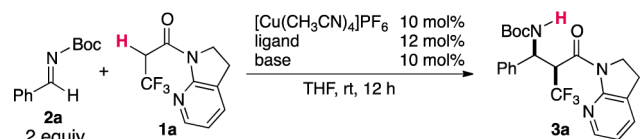
On the basis of these observations, catalytic deprotonation of **1a** to generate  $\alpha$ -CF<sub>3</sub> enolate was examined in a Mannich-type reaction with *N*-Boc imine **2a**.<sup>20–22</sup> The combined use of the soft Lewis acid Cu(I)/(*R*)-tol-BINAP complex (10 mol%) and the hard Brønsted base Li(OC<sub>6</sub>H<sub>4</sub>-*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  $\alpha$ -CF<sub>3</sub> Amides as Pronucleophiles in the Direct Catalytic Asymmetric Mannich-Type Reaction

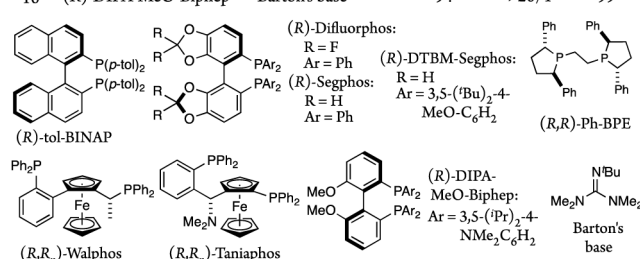


undesirable  $\beta$ -elimination of fluoride barely occurred and (2) smooth catalytic turnover was achieved even with apparently tight bidentate coordination of **1a** to Cu(I). Amide **1d** derived from 2-(methylamino)pyridine afforded the desired product in moderate yield while the isomeric amide **1b**, indolylamide **1c**, and dimethylamide **1e** failed in the reaction, indicating that bidentate coordination is crucial for efficient enolization. Other potential  $\alpha$ -CF<sub>3</sub> pronucleophiles **4** and **5** afforded no Mannich products at all, implying that the inductive effect of the  $\alpha$ -CF<sub>3</sub> group is not the sole factor for facilitated deprotonation. Given the smooth  $\alpha$ -CF<sub>3</sub> 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).<sup>23</sup> The use of Barton's base as an alternative to Li(OC<sub>6</sub>H<sub>4</sub>-*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).<sup>24</sup>

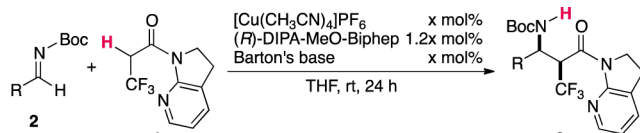
Table 2 summarizes the generality of the Mannich-type reaction with regard to the imine substrate. The reactions reached completion with catalyst loadings of 5–10 mol% at room temperature, and generally high levels of stereoselectivity were observed. Irrespective of alkyl, vinyl, methoxy, or halogen 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

















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


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



<sup>a</sup>Isolated yields. <sup>b</sup>Determined by chiral-stationary-phase HPLC analysis. <sup>c</sup>5 mol% [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> 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<sup>a</sup>**


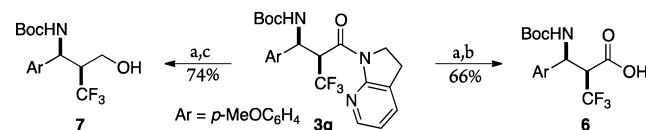
1. R =  <b>3a</b> , x = 5, 94% syn/anti: >20/1 98% ee	2. R =  <b>3b</b> , x = 10, 93% syn/anti: >20/1 95% ee	3. R =  <b>3c</b> , x = 10, 96% syn/anti: >20/1 97% ee	4. R =  <b>3d</b> , x = 5, 92% syn/anti: >20/1 99% ee
5. R =  <b>3e</b> , x = 10, 92% syn/anti: >20/1 96% ee	6. R =  <b>3f</b> , x = 10,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

<sup>a</sup>Isolated yields are shown. <sup>b</sup>1.5 g of amide 1a was used. <sup>c</sup>5 equiv of imine was used. <sup>d</sup>At 0 °C. <sup>e</sup>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).<sup>25</sup>

The Mannich products can serve as versatile chiral building blocks having a CF<sub>3</sub>-substituted stereogenic center (Scheme 1).

**Scheme 1. Transformation of the Mannich Product<sup>a</sup>**

<sup>a</sup>Reagents and conditions: (a) LiAlH<sub>4</sub>, Et<sub>2</sub>O, –45 °C, 1.5 h. (b) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O, 2-methyl-2-butene, <sup>t</sup>BuOH/H<sub>2</sub>O, rt, 5 h, 66% (two steps). (c) NaBH<sub>4</sub>, Et<sub>2</sub>O/MeOH, 0 °C, 1.5 h, 74% (two steps).

The 7-azaindolinyllamide was readily reduced to the corresponding aldehyde with LiAlH<sub>4</sub>, which was further transformed to β-amino acid 6 via Pinnick oxidation, albeit with marginal epimerization (10/1).<sup>26,27</sup> γ-Amino alcohol 7 was obtained via sequential hydride reduction without epimerization.

In summary, an α-CF<sub>3</sub> enolate of 7-azaindolinyllamide 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<sub>3</sub> 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.

## ■ ACKNOWLEDGMENTS

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