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Direct Catalytic Asymmetric Mannich-Type Reaction of α- and β-Fluorinated Amides

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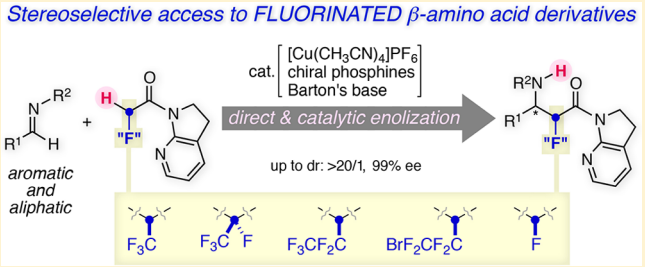
Supporting Information

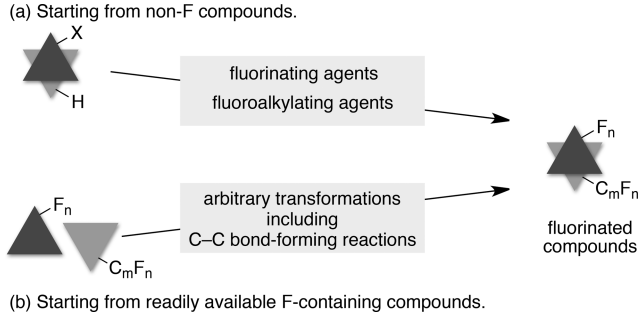
ABSTRACT: The last two decades have witnessed the emergence of direct enolization protocols providing atom-economical and operationally simple methods to use enolates for stereoselective C−C bond-forming reactions, eliminating the inherent drawback of the preformation of enolates using stoichiometric amounts of reagents. In its infancy, direct enolization relied heavily on the intrinsic acidity of the latent enolates, and the reaction scope was limited to readily enolizable ketones and aldehydes. Recent advances in this field enabled the exploitation of carboxylic acid derivatives for direct enolization, offering expeditious access to synthetically versatile chiral building blocks. Despite the growing demand for enantioenriched fluorine-containing small molecules, α- and β-fluorinated carbonyl compounds have been neglected in direct enolization chemistry because of the competing and dominating defluorination pathway. Herein we present a comprehensive study on direct and highly stereoselective Mannich-type reactions of α- and β-fluorine-functionalized 7-azaindoline amides that rely on a soft Lewis acid/hard Brønsted base cooperative catalytic system to guarantee an efficient enolization while suppressing undesired defluorination. This protocol contributes to provide a series of fluorinated analogs of enantioenriched β-amino acids for medicinal chemistry.



INTRODUCTION

Fluorine-containing compounds are of great interest because of their superior physicochemical properties in material chemistry and their favorable pharmacokinetic properties in medicinal chemistry.[1] In particular, the bioisosterism and similar van der Waals radius between fluorine atoms and hydrogen atoms renders the replacement of hydrogen atoms with fluorine atoms a common procedure in drug development and allows for retention of the biological activity, whereas the stronger C−F bond allows for increased metabolic stability and higher lipophilicity.[2] Indeed, more than 20% of small-molecule active pharmaceutical ingredients (APIs) under clinical development contain at least one fluorine atom.[2f,3] Along with the growing need for fluorine-containing compounds, chemical manipulations that allow for the introduction of fluorine atoms or fluorine-containing substituents have become a burgeoning research area. To this end, a wide variety of electrophilic and nucleophilic fluorinating (fluoroalkylating) agents have been disclosed to install fluorine atoms (fluoroalkyl groups) even in a stereoselective fashion (Scheme 1a).[4] This approach is essential for the late-stage introduction of ^{18}F atoms.[5] As a complementary method for accessing this class of high-value compounds in an enantioenriched form, the use of readily available and stable fluorinated pronucleophiles for catalytic enantioselective C−C bond-forming reactions attracted our attention (Scheme 1b).[6] The Mannich reaction is particularly attractive for this purpose because (1) the β-amino acid architecture of the Mannich product with fluorinated substituents at the α position serves as a versatile chiral building block for medicinal chemistry[7,8] and (2) the complementary approach of enantioselective electrophilic fluorination and fluoroalkylation commonly utilizes pronucleophiles without adjacent amino functionalities (e.g., aldehydes, ketones, and β-ketoesters).

Scheme 1. Complementary Approaches to High-Value Fluorine-Containing Compounds



The catalytic asymmetric Mannich reaction is a widely used C−C bond-forming reactions to construct α-stereogenic amines.[9] The initial trigger of the reaction is the generation

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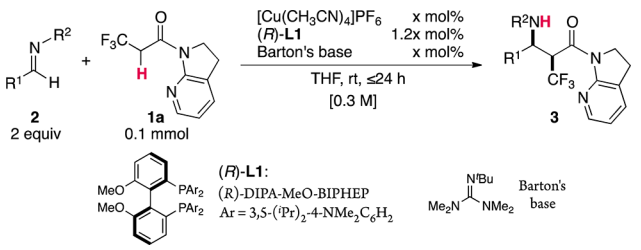
of an enolate as an active nucleophile that subsequently engages in an enantioselective addition to imines. Preformed enolates are often used for reliable stereoselectivity in the C−C bond-forming step at the expense of stoichiometric coproduction of reagent-derived waste, thereby decreasing the overall atom economy of the reaction.[10] To circumvent the undesired use of stoichiometric amounts of reagents, catalytic enolization and "direct" use of latent enolates for subsequent C−C bond formation has been a sustained topic in enolate chemistry[11,12] and for green chemistry in general.[13] The utility of a latent enolate in direct-type reactions is highly dependent on its enolization aptitude, and relatively acidic carbonyl compounds, e.g., aldehydes and ketones, are widely used.[11,12] In contrast, carboxylic acid derivatives, e.g., esters and amides, have been scarcely explored in direct Mannich-type reactions because of their reluctant enolization under catalytic conditions.[14−16] We recently demonstrated that 7-azaindoline amide serves as a privileged amide pronucleophile for the catalytic generation of active enolate in a soft Lewis acid/hard Brønsted base cooperative catalytic system.[17,18] Herein we report a comprehensive study on the enolate chemistry of fluorinated 7-azaindoline amides in a direct Mannich-type reaction to furnish fluorinated compounds of high interest for medicinal chemistry.[19] The properties of various 7-azaindoline amides in the absence and presence of a Lewis acid are documented, and chelating coordination of the amides is considered crucial to accelerate catalytic enolization and the C−C bond-forming step with imines.

RESULTS

An important and unique facet of α-CF_3 7-azaindoline acetamide **1a** is the stability of its Cu(I) enolate toward the β-elimination of fluoride, which is the major concern in the enolate chemistry of β-fluoro carbonyl compounds. A typical example is found in aldol reactions using α-CF_3 carbonyl compounds as pronucleophiles, where instantaneous defluorination is associated with their Li enolates.[20] An elegant study led by Mikami et al. revealed that the corresponding Ti enolate is sufficiently stable to engage in a subsequent C−C bond-forming reaction with an aldehyde.[21] This initial finding stimulated the enolate chemistry of β-fluoro carbonyl compounds, and the Ti-mediated reactions aided by a chiral auxiliary provided access to enantioenriched products.[22] Later, boron-mediated selective formation of *E*- and *Z*-enolates was reported,[23] but there remains room for catalytic generation of this class of enolates to avoid the use of stoichiometric amounts of reagents. A rather limited substrate scope is another drawback of this synthetic method. Furthermore, no catalytic and asymmetric protocol had been reported until our work on the Cu(I) complex.

Our previous communication on the direct Mannich-type reaction reported a unique feature of α-CF_3 7-azaindoline acetamide **1a** that imparted catalytic in situ generation of the active enolate which realized an overall reaction including a subsequent enantioselective addition step to imines in a catalytic manner.[19] The substrate scope of the reaction, including newly added examples, is shown in Table 1. Through cooperative activation with $[Cu(CH_3CN)_4]PF_6$/(*R*)-DIPA-MeO-BIPHEP ((*R*)-**L1**) as a chiral soft Lewis acid and Barton's base as a Brønsted base, Mannich-type reactions of **1a** and *N*-carbamoyl imines **2** proceeded at room temperature to afford Mannich adducts **3** with high diastereo- and enantioselectivity.[24]

Table 1. Direct Catalytic Asymmetric Mannich-Type Reaction of α-CF_3 7-Azaindoline Acetamide 1a



entry	imine 2 R¹ =		x	yield[a] (%)	*syn*/*anti*	ee (%)	entry	imine 2 R¹ =		x	yield[a] (%)	*syn*/*anti*	ee (%)
1		**2a**	5	**3a**: 94	>20/1	98	11		**2k**	10	**3k**: 92	>20/1	99
2		**2b**	5	**3b**:94	>20/1	98	12		**2l**	10	**3l**: 91	>20/1	99
3		**2c**	10	**3c**: 93	>20/1	95	13[c,d]		**2m**	10	**3m**:92	5.0/1	89
4		**2d**	10	**3d**:96	>20/1	97	14[c]		**2n**	10	**3n**: 89	5.8/1	98
5		**2e**	5	**3e**:92	>20/1	99	15		**2o**	10	**3o**: 94	>20/1	99
6		**2f**	10	**3f**: 92	>20/1	96	16		**2p**	10	**3p**: 95	>20/1	98
							17[e]		**2p**	0.75	**3p**: 93	>20/1	93
7		**2g**	10	**3g**:90	>20/1	96	18		**2q**	5	**3q**: 91	>20/1	94
8[b]		**2h**	5	**3h**:94	>20/1	98	19[c,f,g]		**2r**	10	**3r**: 77	10/1	96
9[c]		**2i**	10	**3i**: 95	2.8/1	74	20[f,h]		**2s**	10	**3s**: 81	>20/1	98
10		**2j**	10	**3j**: 86	>20/1	95	21[f,h]		**2t**	10	**3t**: 84	>20/1	94

[a]Isolated yield of *syn*-**3**. [b]A total of 1.5 g of **1a** was used. [c]Yield of diastereomixture. [d]At −60 °C. [e]Run at 2.0 M (**1a**); 0.4 mmol scale. [f]A total of 5 equiv of imine was used. [g]At 0 °C. [h]At −20 °C.

Various meta- or para-substituted aromatic imines were tolerated with high enantioselectivity, irrespective of the electronic nature of the substituents (Table 1, entries 3−8 and 10−14); however, imine **2m** bearing a *meta*-NO_2 substituent afforded lower stereoselectivity, even though the reaction was performed at −60 °C (Table 1, entry 13). *Ortho*-F-substituted aromatic imine **2i** exhibited low diastereoselectivity (Table 1, entry 9), and imines bearing a bulkier ortho-substituent resulted in lower conversions. *N*-Boc and *N*-Cbz imines exhibited comparable reactivity and stereoselectivity (Table 1, entries 1 and 2). The reaction could be conducted on a 1.5 g scale (entry 8). Heteroaromatic imines were compatible (Table 1, entries 15−18) even using as little as 0.75 mol% catalyst loading under concentrated conditions (Table 1, entry 17). Enolization-prone aliphatic *N*-Boc imines were applicable with high stereoselectivity, highlighting the mild conditions of the catalytic system and broad substrate generality (Table 1, entries 19−21). Reduction of the 7-azaindoline amide moiety of the Mannich adduct with $LiAlH_4$ gave the corresponding aldehyde, and subsequent reduction with $NaBH_4$ or Pinnick oxidation delivered γ-amino alcohol **4** and β-amino acid **5**, respectively (Scheme 2).[19]

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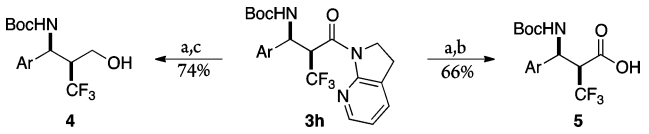
Scheme 2. Transformations of the 7-Azaindoline Moiety[a]



[a]Reagents and conditions: (a) $LiAlH_4$, Et_2O, −45 °C, 1.5 h. (b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, rt, 5 h, 66% (2 steps). (c) $NaBH_4$, Et_2O/MeOH, 0 °C, 1.5 h, 74% (2 steps). Ar = *p*-$MeOC_6H_4$.

On the basis of the catalytic enolization method with a soft Lewis acidic Cu(I) and Barton's base as a Brønsted base, other fluorinated 7-azaindoline amides were anticipated to undergo the direct Mannich-type reaction in the acid/base binary catalytic system. Given the high demand for fluorinated chiral chemical entities, we systematically investigated differently fluorinated 7-azaindoline amide for its potential utility in direct Mannich-type reactions (Figure 1). α-F-α-CF_3, α-C_2F_5, α-$BrCF_2CF_2$, and α-F 7-azaindoline acetamides **1b−e** were successfully implemented in the direct catalytic asymmetric Mannich-type reaction to provide enantioenriched β-amino acid derivatives with α-fluoro or α-fluoroalkyl groups. Amides **1f−i** bearing perfluoroalkyl or branched α substituents were not applicable. α-Branched amides **1h** and **1i** remained unchanged under the catalytic conditions, likely because an extra C-substituent at the α-carbon significantly retarded the deprotonation. This is consistent with the absence of epimerization of Mannich adducts **3** during the reaction. The ineffectiveness of α-CF_3 amides (**1aa−ae**) with different amide structures highlights the particular behavior of the 7-azaindoline amide in direct enolization chemistry. 7-Azaindole amide **1aa** was sensitive to hydrolysis and was intractable for use in the Mannich-type reaction. Isomeric 5-azaindoline acetamide **1ab**, indoline acetamide **1ac**, and amides **1ad**,**1ae** derived from 2-aminopyridine afforded no trace of the product under the optimized conditions for **1a**.[25] Other potential nucleophiles, e.g., 7-azaindoline sulfonamide **1af**, dimethylamide **1ag**, ethyl ester **1ah**, and nitrile **1ai**, failed in the reaction. Together, these results suggested that the direct Mannich-type reaction proceeds exclusively with 7-azaindoline amide.

α-F-α-CF_3 7-azaindoline acetamide **1b** is of particular interest for the construction of a stereogenic center bearing both CF_3 and F substituents that is more difficult to access via enantioselective fluorination (or trifluoromethylation).[26] The α-F-α-CF_3 carbonyl group corresponds to a fully fluorinated analog of a propionate unit, which is a common motif of a plethora of biologically active compounds. Enantioselective access to this fluorinated analog is of great interest for medicinal chemistry.[2,4,7e] These α-F-α-CF_3 carbonyl compounds, however, also readily undergo defluorination upon enolate formation using a Li base even at low temperature,[27] and indirect access via alkenyl phosphates or α-Br-α-F-α-CF_3 carbonyl compounds has been studied for the aldol reaction with aldehydes for more than 25 years.[28,29] Although a viable procedure using Bu_2BOTf/Et_3N for α-F-α-CF_3 acetamides to form *Z* enolates for aldol reactions was reported,[30] all of the examples required stoichiometric use of reagents for enolate formation, and an enantioselective variant is so far unknown. As for the Mannich-type reaction, the sole example is a Zn-mediated Reformatsky reaction using α-Br-α-F-α-CF_3 acetate and chirally decorated imines to give enantioenriched β-amino esters with α-F-α-CF_3 substituents.[31,32] In this context, a catalytic and enantioselective protocol to access β-amino acid derivatives with α-F-α-CF_3 substituents has been lacking, leading us to focus on the direct catalytic asymmetric Mannich-type reaction of α-F-α-CF_3 7-azaindoline acetamide **1b**.

Application of the previously determined optimized conditions of $[Cu(CH_3CN)_4PF_6]$/(*R*)-**L1**/Barton's base for **1a** quickly emerged as a suitable catalytic system for **1b** with slight modification of the concentration (0.5 M fo **1b** in Table 2 vs 0.3 M for **1a** in Table 1), which likely compensated for the lower nucleophilicity.[33] **1b** holds a stereogenic carbon; thus,

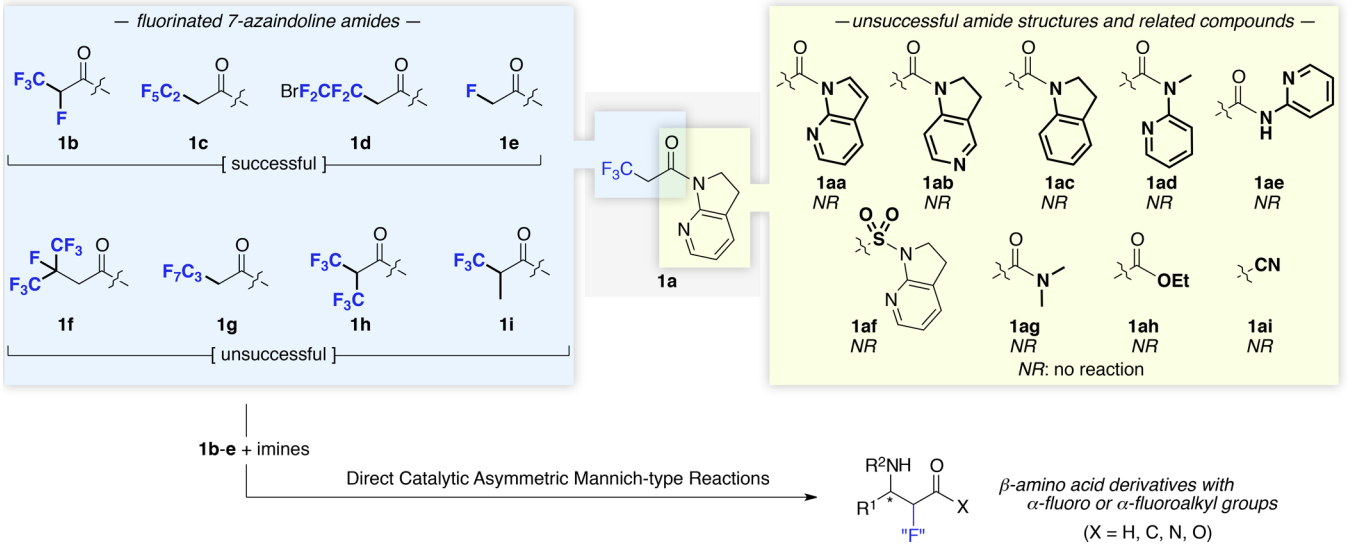


Figure 1. Schematic representation of α- and/or β-fluorinated 7-azaindoline acetamides explored in this study. On the basis of the structure of successful amide **1a**, the effects of amide structures (green background) and fluorination patterns (blue background) were systematically investigated. α-CF_3 amides without the 7-azaindoline unit (including a sulfonamide, an ester, and a nitrile) **1aa−1ai** failed in the Mannich-type reaction. (Conditions of Table 1 were applied.) α-F-α-CF_3, α-C_2F_5, α-CF_2CF_2Br, and α-F 7-azaindoline acetamides **1b−e** were successfully implemented in the Mannich-type reaction, whereas α-$CF(CF_3)_2$, α-C_3F_7, α-$CH(CF_3)_2$, and α-Me-α-CF_3 7-azaindoline acetamides **1f−i** were incompatible.

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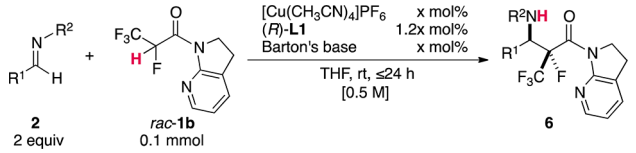
Table 2. Direct Catalytic Asymmetric Mannich-Type Reaction of α-F-α-CF_3 7-Azaindoline Acetamide 1b



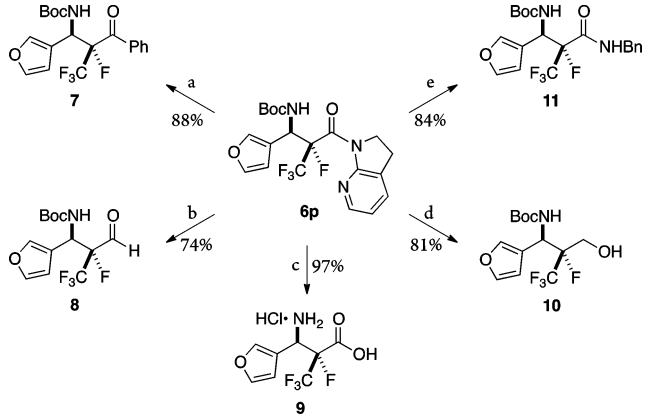
entry	imine 2 R¹ =		x	yield[a] (%)	syn/anti	ee (%)	entry	imine 2 R¹ =		x	yield[a] (%)	syn/anti	ee (%)
1		**2a**	5	**6a**: 93	>20/1	95	7[b]		**2j**	10	**6j**: 95	17/1	90
2		**2b**	10	**6b**: 88	>20/1	90	8		**2k**	10	**6k**: 91	>20/1	94
3		**2e**	10	**6e**: 90	>20/1	97	9[c]		**2m**	10	**6m**: 92	>20/1	93
4[b]		**2f**	10	**6f**: 96	20/1	92	10		**2o**	5	**6o**: 95	>20/1	97
5[b]		**2g**	5	**6g**: 97	17/1	92	11		**2p**	5	**6p**: 92	>20/1	99
							12[d]		**2p**	1.5	**6p**: 94	>20/1	94
6		**2h**	5	**6h**: 73	>20/1	99	13		**2q**	10	**6q**: 91	>20/1	97

[a]Isolated yield of *syn*-**6**. [b]Yield of diastereomixture. [c]At −40 °C. [d]Run at 1.2 M (**1b**), 0.3 mmol scale.

undesired kinetic optical resolution of racemic **1b** could occur, which may result in low conversion to the Mannich adduct (vide infra). The attempted reaction of *N*-Boc imine **2a** and a racemic mixture of amide **1b** proceeded with 5 mol% catalyst, however, to deliver almost exclusively the desired product *syn*-**6a** in 93% isolated yield with 95% ee (Table 2, entry 1).[34] Aromatic imines bearing meta or para substituents were generally applicable to afford the desired *syn*-Mannich product almost exclusively with high enantioselectivity. Various substituents with neutral as well as electron-donating and -withdrawing properties were tolerated (Table 2, entries 1−8). *Meta*-NO_2-substituted imine **2m** required cryogenic conditions to attenuate the high reactivity (Table 2, entry 9). Heteroaromatic imines were applicable: Imine **2p** derived from 3-furylaldehyde exhibited particularly high reactivity at a higher concentration (1.2 M). The reaction reached completion with 1.5 mol% catalyst loading, and a marginal loss of enantioselectivity was detected (Table 2, entry 11 vs 12). The reaction was also sensitive to steric factors; ortho-substituted aromatic imines and aliphatic imines gave no desired product. Imines derived from α,β-unsaturated aldehydes were partly reactive, albeit with low diastereoselectivity.[35]

The divergent functional group manipulation of enantio-enriched product **6** allowed for easy access to β-amino acid derivatives with an α-F-α-CF_3 tetra-substituted stereogenic center (Scheme 3). 7-Azaindoline amide behaved similarly to Weinreb amides;[36] arylation and hydride reduction of **6p** using PhMgBr and $LiAlH_4$ gave corresponding ketone **7** and aldehyde **8**, respectively, without any overarylation or over-reduction. Acidic hydrolysis of the 7-azaindoline amide smoothly proceeded with 6 N aqueous HCl at 60 °C with a concomitant removal of the Boc group, furnishing free β-amino acid hydrochloride **9**. Myers' reduction protocol of amides to primary alcohols using LDA and $BH_3{\cdot}NH_3$ worked well to afford alcohol **10**.[37] Transamidation with $BnNH_2$ was achieved

Scheme 3. Transformations of 7-Azaindoline Amide Moiety of the Mannich Adduct[a]



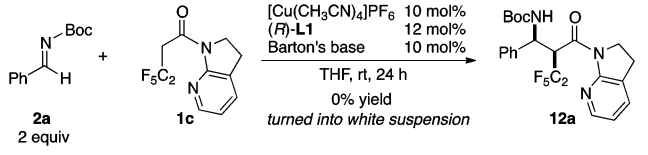
[a]Reagents and conditions: (a) PhMgBr, Et_2O, rt, 2.5 h, 88%. (b) $LiAlH_4$, Et_2O, −70 °C, 15 min, 74%. (c) 6 N aqueous HCl, THF, 60 °C, 9 h, 97%. (d) $BH_3{\cdot}NH_3$, lithium diisopropylamide (LDA), THF, 0 °C to rt, 1 h, 81%. (e) $BnNH_2$, $La(OTf)_3$, THF, rt, 1.5 h, 84%.

in the presence of a stoichiometric amount of $La(OTf)_3$ as a Lewis acid to give the corresponding benzylamide **11**.[38]

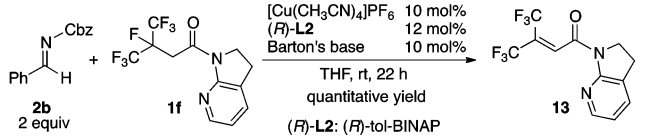
Having established α-CF_3 and α-F-α-CF_3 7-azaindoline acetamides **1a** and **1b** as privileged latent enolates, we aimed to expand the scope of accessible β-amino acid derivatives bearing fluorinated functional groups at the stereogenic α-carbon. Perfluoroalkyl groups have recently received growing attention in medicinal chemistry,[39] although reliable synthesis strategies are limited for enantioselective introduction of these groups.[40] α-C_2F_5 7-azaindoline acetamide **1c** was our obvious next target, but application of the optimal catalytic conditions for α-CF_3 amide **1a** and α-F-α-CF_3 amide **1b** to the Mannich-type reaction of **1c** and **2a** instantaneously turned the reaction mixture into a white suspension. Presumably, undesired defluorination followed by polymerization occurred, and desired product **12a** could not be isolated (Scheme 4a).[41,42]

Scheme 4. Failed Mannich-Type Reactions Using Highly Fluorinated Amides 1c and 1f

(a) Mannich-type reaction of α-C_2F_5 7-azaindoline acetamide **1c** and *N*-Boc-imine **2a**.



(b) Mannich-type reaction of α-$CF(CF_3)_2$ 7-azaindoline acetamide **1f** and *N*-Cbz-imine **2b**.



This was partly evidenced by the isolation of defluorinated product **13** from highly electron-withdrawing α-$CF(CF_3)_2$ 7-azaindoline acetamide **1f** (Scheme 4b). α,β-Unsaturated amide **13** was stable under the catalytic conditions, presumably because of the increased sterics at the β-carbon, and was isolated in quantitative yield. Because these highly fluorinated amides exhibit an enhanced defluorination aptitude, a lower reaction temperature was adopted to suppress this undesired

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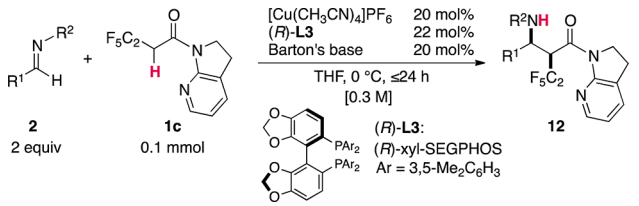
Table 3. Direct Catalytic Asymmetric Mannich-type Reaction of α-C_2F_5 7-Azaindoline Acetamide 1c

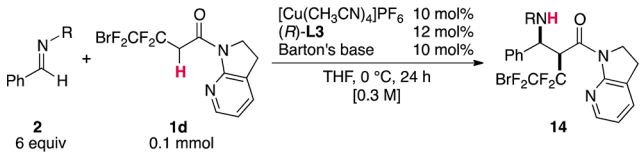


entry	imine 2 R¹ =	yield[a] (%)	syn/anti	ee (%)	entry	imine 2 R¹ =	yield[a] (%)	syn/anti	ee (%)
1	R² = Boc	**2a** **12a**: 87	>20/1	97	6	R² = Boc	**2k** **12k**: 79	>20/1	98
2	R² = Cbz	**2b** **12b**: 84	>20/1	97	7[e]	R² = Boc	**2m** **12m**: 87	13.5/1	92
3	R² = Boc	**2c** **12c**: 73	>20/1	95	8[b,c]	R² = Boc	**2o** **12o**: 88	13.5/1	99
4	R² = Boc	**2e** **12e**: 84	>20/1	93	9[b,d,e]	R² = Boc	**2s** **12s**: 83	8/1	99
5	R² = Boc	**2g** **12g**: 82	>20/1	95					

[a]Isolated yield of *syn*-**12**. [b]Reaction was run with 10 mol% $[Cu(CH_3CN)_4]PF_6$/Barton's base and 12 mol% (*R*)-**L3**. [c]At −40 °C. [d]At −20 °C; 5 equiv of imine was used. [e]Yield of diastereomixture.

pathway. Although 20 mol% catalyst loading was required to achieve high conversions, α-C_2F_5 7-azaindoline acetamide **1c** served as a viable pronucleophile to afford α-C_2F_5-β-amino acid derivatives **12** with high stereoselectivity (Table 3).[43] The use of a less sterically demanding ligand was essential to allow the in situ generated enolate to undergo C−C bond formation with imines over the undesired defluorination, and we identified (*R*)-xyl-SEGPHOS ((*R*)-**L3**) as an optimal ligand.[44] *N*-Boc and *N*-Cbz imines produced similar reaction outcomes (Table 3, entries 1 and 2). Imines bearing meta or para substituents provided the *syn*-Mannich adducts with high stereoselectivity irrespective of the electronic nature of the substituents (Table 3, entries 3−7). Ortho-substituted aromatic imines were incompatible substrates for Mannich-type reactions using amide **1c**. When highly reactive imines were used, high conversion was achieved at a temperature lower than 0 °C. The undesired defluorination pathway was likely better suppressed, allowing the reaction to proceed with reduced catalyst loading (10 mol%) (Table 3, entries 8 and 9). It is noteworthy that aliphatic imine **2s** could be exploited to give an aliphatic β-amino acid derivative bearing an α-C_2F_5 group with high enantioselectivity (Table 3, entry 9). α-CF_2CF_2Br 7-azaindoline acetamide **1d** was a partly tractable pronucleophile in this catalytic system using (*R*)-**L3** (Scheme 5). Although we observed faster defluorination for **1d**, the use of an excess of

Scheme 5. Direct Catalytic Asymmetric Mannich-Type Reaction of α-CF_2CF_2Br 7-Azaindoline Acetamide 1d

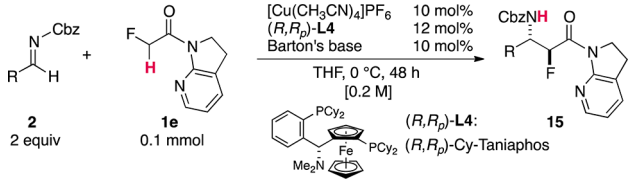


imine **2a**: R = Boc, **14a**: 97%, *syn*/*anti* >20/1, 97% ee
imine **2b**: R = Cbz, **14b**: 91%, *syn*/*anti* >20/1, 98% ee

imine (6 equiv) ensured smooth C−C bond formation from the enolate. Both *N*-Boc and *N*-Cbz imines **2a** and **2b** were compatible to afford the desired Mannich adducts **14a** and **14b** with high stereoselectivity; the C−Br bond of these can potentially be used for further elaboration.[45] Although α-C_3F_7 7-azaindoline acetamide **1g** was partly converted to the desired Mannich adduct with $[Cu(CH_3CN)_4]PF_6$/(*R*)-**L3**/Barton's base, decomposition of amide **1g** mainly occurred, which was likely triggered by defluorination upon enolization.[46]

Along with the α-perfluoroalkyl amides mentioned above, we studied the Mannich-type reaction of α-F 7-azaindoline acetamide **1e**, which provides expeditious access to chirally α-monofluorinated β-amino acid derivatives. Direct enolization of α-F carbonyl compounds has been sporadically explored in the context of direct catalytic asymmetric C−C bond-forming reactions, and the reaction using α-F ketone is the sole latent enolate developed to date.[47,48] Implementation of less acidic α-F amides for direct enolization chemistry broadens the scope of this important transformation, providing carboxylic acid derivatives bearing an α-F stereogenic center. Although efficient catalytic generation of the enolate from **1e** and decent conversion were observed with the catalytic system discussed above, biaryl-type chiral bisphosphine ligands, which served as preferred ligands for **1a−d**, afforded poor stereoselectivity, likely because of the smaller steric bias of the corresponding enolate. Ligand screening (Supporting Information) indicated that (R,R_p)-Cy-Taniaphos ((R,R_p)-**L4**) performed best, and *anti*-configured Mannich adduct **15** was obtained as the major product with good diastereoselectivity and high enantioselectivity (Table 4).[49,50] *N*-Cbz imines generally afforded higher

Table 4. Direct Catalytic Asymmetric Mannich-Type Reaction of α-F 7-Azaindoline Acetamide 1e



entry	imine 2 R¹ =	yield[a] (%)	syn/anti	ee (%)	entry	imine 2 R¹ =	yield[a] (%)	syn/anti	ee (%)
1		**2b** **15b**: 79(91)	8.9/1	91	5	MeO	**2x** **15x**: 65(80)	9.5/1	90
2[b]		**2u** **15u**: 76(90)	10.1/1	93	6	Cl	**2y** **15y**: 55(70)	6.0/1	92
3		**2v** **15v**: 70(89)	9.4/1	93	7	MeS	**2z** **15z**: 51(70)	5.7/1	90
4	MeO	**2w** **15w**: 56(75)	8.9/1	90	8	S	**2za** **15za**: 66(80)	9/1	92

[a]Isolated yield of *anti*-**15**. Conversions determined by ^{1}H NMR are shown in parentheses. [b]Reaction was run for 72 h.

diastereoselectivity than *N*-Boc imines in this specific reaction. Despite the limited substrate scope, several meta- and para-substituted imines bearing alkyl groups, heteroaromatics and halogens were tolerated (Table 4, entries 2−8). Imines with a soft Lewis basic functionality that potentially interferes with the catalysis afforded the Mannich adduct with high stereoselectivity (Table 4, entries 7 and 8).

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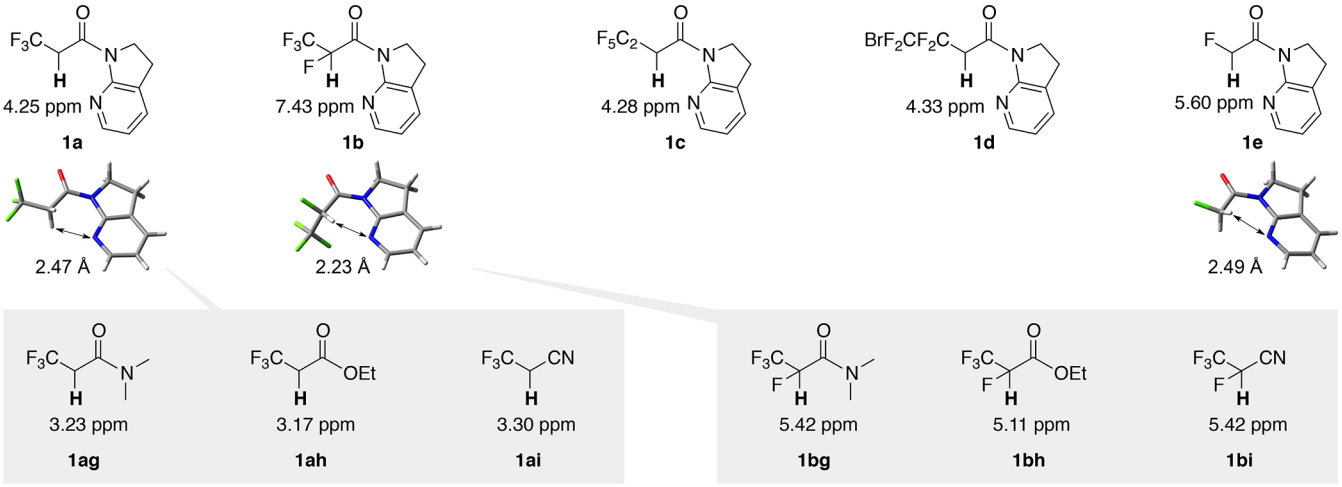

Figure 2. Solid-state structure and chemical shift of α hydrogens of fluorinated 7-azaindoline amides **1a**–**e** in $CDCl_3$. (See Supporting Information for details.) The α hydrogens of structurally related compounds **1ag**–**1ai** and **1bg**–**1bi** exhibited upfield chemical shift. Color code for X-ray structure is as follows: white, hydrogen; gray, carbon; blue, nitrogen; red, oxygen; and light green, fluorine.

DISCUSSION

The preference for the *E* amide conformation of 7-azaindoline amides **1a**–**e** was confirmed by X-ray crystallography (Figure 2). The *E* conformer was exclusive, even in solution because no *Z* conformer was observed in VT-NMR under cryogenic conditions. Along with the general tendency of tertiary amides bearing alkyl and aryl substituents,[51] this preference is enhanced because of the intramolecular hydrogen bonding of the α hydrogen and the pyridyl nitrogen of the azaindoline. Short contacts were observed for all of azaindoline amides **1a**–**e** bearing α hydrogen, and N–H distances were within the sum of van der Waals radii. Findings from the ^{1}H NMR analysis were consistent with the hydrogen-bonding interaction; the chemical shifts of α hydrogens of 7-azaindoline amides **1a**–**e** were exceptionally shifted downfield compared with spectra of structurally related compounds. For α-CF_3 and α-F-α-CF_3 7-azaindoline acetamides **1a** and **1b**, the corresponding *N*,*N*-dimethylamides **1ag** and **1bg**, ethyl esters **1ah** and **1bh**, and nitriles **1ai** and **1bi**, which lacked a proximal pyridyl nitrogen, were examined and displayed similar tendencies in their chemical shifts, which is consistent with the hydrogen-bond interaction for 7-azaindoline amides.[52] In particular, 7.43 ppm observed for **1b** was extraordinarily shifted downfield relative to that of the *N*,*N*-dimethylamide counterpart **1bg** (5.42 ppm), which is strongly indicative of intramolecular hydrogen bonding for **1b**. ^{1}H NMR and NOE analyses of **1a** and **1b** in the presence of TFA-d_1 showed complete flipping to *Z* conformation, likely because protonation of the pyridyl nitrogen renders the hydrogen bond interaction with the α proton impossible and the chelating coordination of the proton with the carbonyl group was thus favored (Supporting Information).[53]

The activation mode of 7-azaindoline amide **1a** was dissected by ^{1}H NMR analysis in solution as well as X-ray crystallographic analysis in the solid state (Figure 3).[19] The preferred *E* conformation of **1a** was switched to *Z* conformation upon coordination to Cu(I)/*rac*-BINAP (*rac*-**L5**), as evidenced by the crystal structure. The upfield shift of the α protons (protons a) *Z*-**1a**/Cu(I)/*rac*-**L5** can be ascribed to the loss of intramolecular hydrogen bonding observed for *E*-**1a**. The *Z* conformation was also validated in solution by NOE signals between α protons (protons a) and indoline protons (protons b). The amide of the chelated complex would be amenable to deprotonation by coexisiting Brønsted base catalyst to generate the corresponding enolate. Although spectroscopic evidence of the Cu(I) enolate species was not obtained, the crystal structure as well as the NMR analysis implied the formation of *Z* enolate, which is also in agreement with a literature-known boron enolate.[30]

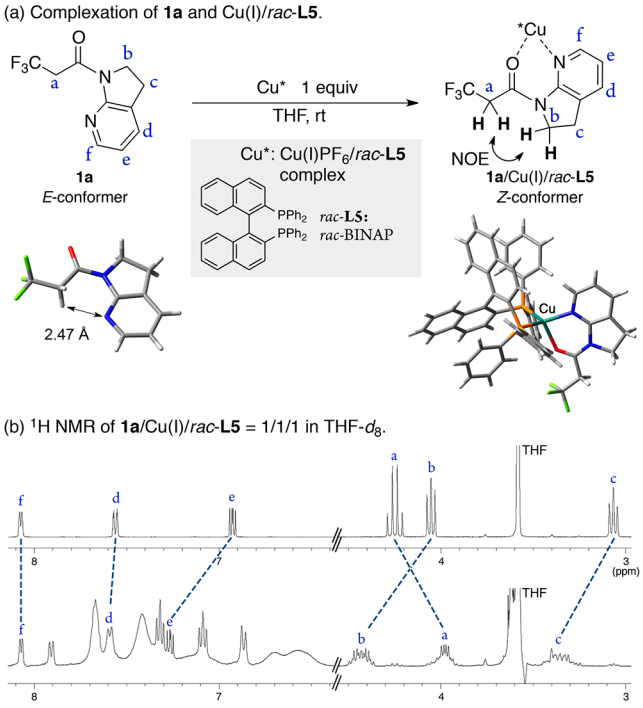

Figure 3. Single-crystal X-ray crystallographic analysis and ^{1}H NMR analysis of **1a** and the **1a**/Cu(I)/*rac*-**L5** = 1/1/1 complex. Color code for X-ray structure is as follows: white, hydrogen; gray, carbon; blue, nitrogen; red, oxygen; light green, fluorine; orange, phosphorus; and dark green, copper.

The α-F-α-CF_3 amide **1b** allowed for a more detailed mechanistic investigation of the current Mannich protocol because of its inherent chirality. The Mannich-type reaction of homochiral or racemic **1b** and imine **2a** and racemization of homochiral **1b** were traced as a function of time. The profiles of

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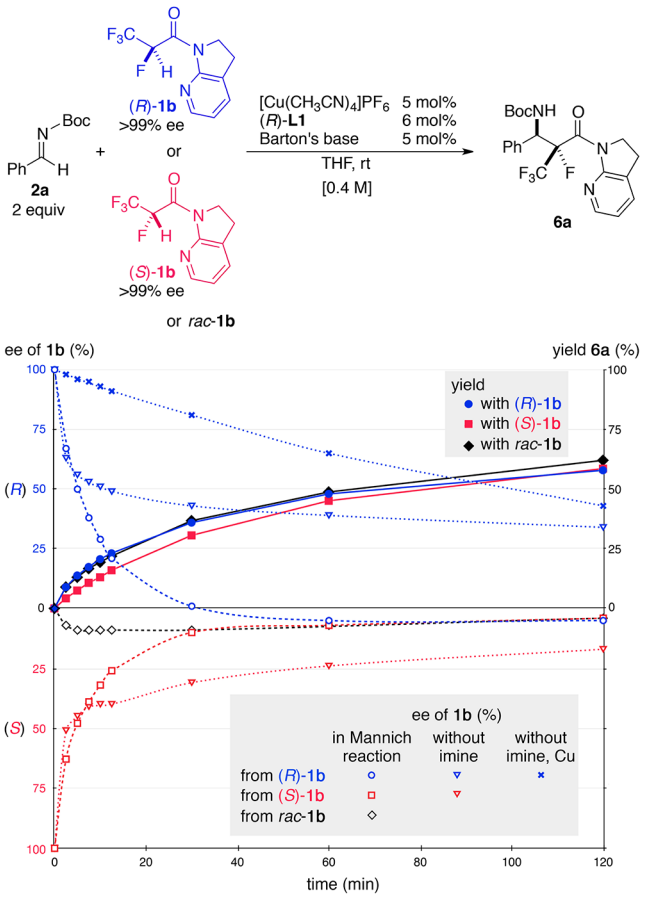

Figure 4. Reaction profile of the Mannich-type reaction promoted by the (*R*)-catalyst using homochiral **1b** ((*R*) and (*S*)) and racemic **1b**. Yield of **6a** (filled circles, squares, and diamonds with solid lines) and enantiopurity of **1b** (open circles, squares, and diamonds with dotted lines) are plotted. Open triangles represent the enantiopurity of **1b** as a function of the treatment time with the catalyst in the absence of imine **2a**. Blue crosses with a dotted line represent time-dependent racemization of (*R*)-**1b** with 5 mol% Barton's base.

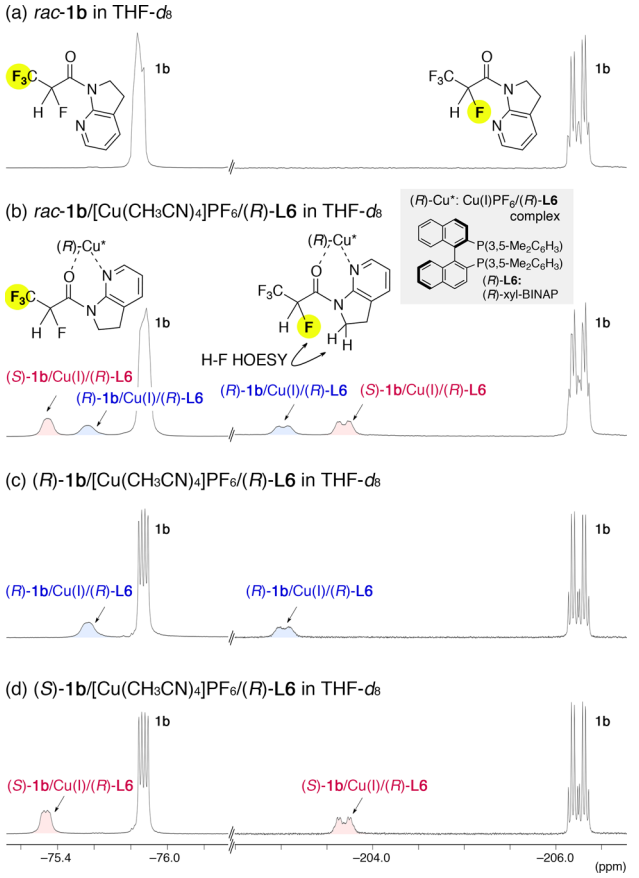

Figure 5. Partial ^{19}F NMR spectra of **1b** and its mixtures with the Cu(I)/(*R*)-**L6** complex in THF-d_8. (a) *rac*-**1b**, (b) *rac*-**1b**/[Cu-$(CH_3CN)_4]PF_6$/(*R*)-**L6** = 1/1/1, (c) (*R*)-**1b**/[$Cu(CH_3CN)_4]PF_6$/(*R*)-**L6** = 1/1/1, and (d) (*S*)-**1b**/[$Cu(CH_3CN)_4]PF_6$/(*R*)-**L6** = 1/1/1. Integration ratio of (*R*)-**1b**/[$Cu(CH_3CN)_4]PF_6$/(*R*)-**L6** complex : (*S*)-**1b**/[$Cu(CH_3CN)_4]PF_6$/(*R*)-**L6** complex : free amide is 10.1:14.5:100 for b, 21.6:0:100 for c, 0:29.5:100 for d.

the reaction progress and the enantiopurity of **1b** are summarized in Figure 4, and possible pathways are delineated in Scheme 6. The reaction rates of (*R*)-**1b** (Figure 4, blue closed circle, solid line) and (*S*)-**1b** (Figure 4, red closed square, solid line) were nearly identical, whereas at the initial stage, a marginally faster reaction was observed for (*R*)-**1b**. ^{19}F NMR analysis revealed that (1) association of **1b** with a Cu(I) complex (Cu/(*R*)-xyl-BINAP ((*R*)-**L6**)) was less favored than that of **1a** (for **1a** in Figure 3 vs for **1b** in Figure 5) and (2) stereodifferentiation of the *R* and *S* amide **1b** by the chiral complex Cu(I)/(*R*)-**L6** occurred with only a slight preference for (*S*)-**1b**/Cu/(*R*)-**L6** over (*R*)-**1b**/Cu/(*R*)-**L6** (Figure 5b–d). The marginally faster reaction of (*R*)-**1b** indicated that paths a and b in Scheme 6 are not rate-determining. H–F HOESY analyses revealed that **1b** bound to Cu(I) as a *Z* conformer and that the α-F atom is located close to the indoline, likely to minimize steric interaction between the α-CF_3 group and the indoline (Figure 5 and Supporting Information). This conformer led us to assume the preferred formation of *E*-enolate (*E*-**16**) by deprotonation of the Cu(I)–amide complex with coexisting Barton's base, and the C–C bond formation with imine **2a** proceeded from the *S* prochiral face of enolate *E*-**16** to afford (2*R*,3*R*)-**6a** via paths c and d in Scheme 6.

Rapid racemization of (*R*)-**1b** and (*S*)-**1b** was observed during the course of the Mannich-type reaction at a similar rate (blue open circle and red open square with dotted lines, Figure 4). This is indicative of the reversibility of the enolate formation and the rapid reprotonation of enolate *E*-**16** (paths c, c′, e, and e′ in Scheme 6). It is noteworthy that ca. 5–10% ee for (*S*)-**1b** was a stationary point in this catalytic system; irrespective of the *R*,*S* configuration and enantiopurity of the starting amide **1b**, the remaining **1b** comprised of a mixture of (*R*) and (*S*)-**1b** with a slight excess of (*S*)-**1b**. This can be explained by assuming that deprotonation/reprotonation from (*R*)-**1b** (paths c and c′) was kinetically favored over that from (*S*)-**1b**. From racemic **1b**, (*R*)-**1b** was consumed at a faster rate by the irreversible Mannich-type reaction of enolate *E*-**16** (path d), and (*S*)-**1b** became the major enantiomer in the reaction mixture (black diamond with a dotted line in Figure 4). When the reaction was performed with enantiopure (*R*)-**1b**, (*R*)-**1b** was partly racemized to (*S*)-**1b** via enolate *E*-**16** (paths c and e′), and (*S*)-**1b** became the major enantiomer in the reaction mixture after 30 min because of the slower deprotonation of (*S*)-**1b** (blue open circle with a dotted line, Figure 4). In the absence of imine **2a**, both (*R*)- and (*S*)-**1b** racemized at a slower rate (blue open triangle and red open triangle with

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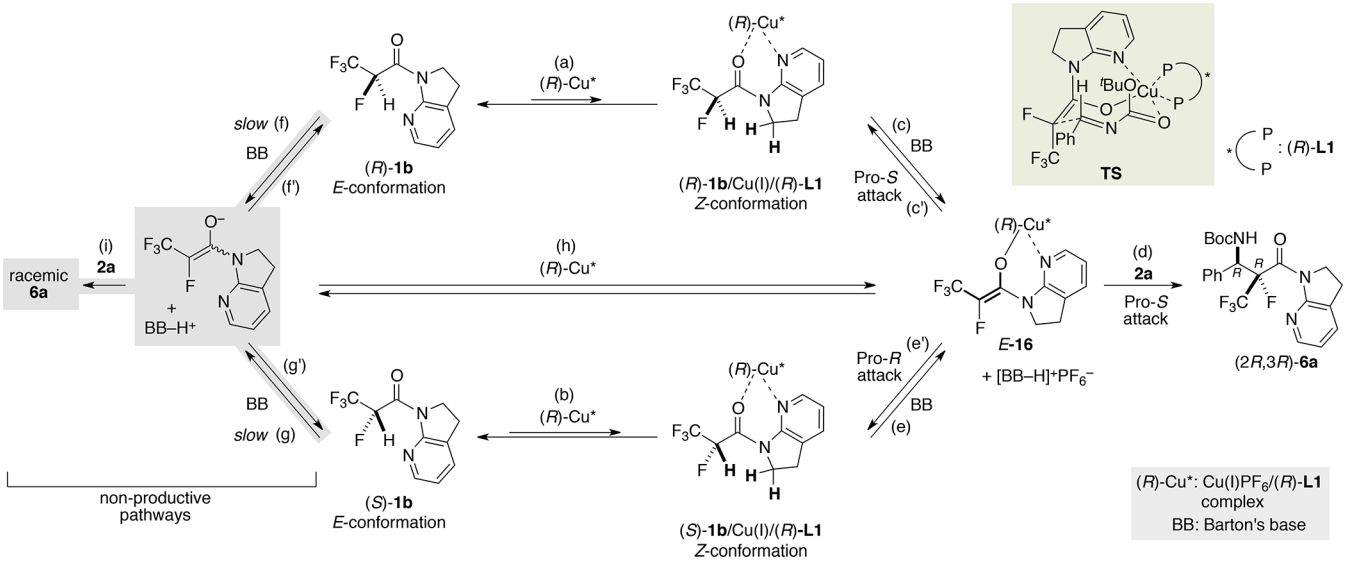
Scheme 6. Plausible Reaction Pathways of the Mannich-Type Reaction of α-F-α-CF_3 7-Azaindoline Acetamide 1b and Imine 2a



dotted lines, Figure 4). In this specific case, reprotonation was only the fate for enolate *E*-**16**. Reprotonation to (*R*)-**1b** (path c′) was faster than that to (*S*)-**1b** (path e′); thus, (*S*)-**1b** racemized at a faster rate than (*R*)-**1b**. Although (*R*)-**1b** gradually lost enantiopurity only with Barton's base (blue cross with a dotted line, Figure 4; paths f, f′, g, and g′, Scheme 6), the rate of racemization was significantly slower compared with that in the presence of the Cu(I) complex. Slow racemization with Barton's base and the absence of stereodifferentiation of the chirality of **1b** by the chiral Cu(I) complex strongly suggested that paths a−e were the main pathways and that paths f−i contribute little to the present Mannich-type reaction.

The Mannich-type reaction with only Barton's base as a catalyst failed, suggesting that the racemic reaction without the Cu(I) complex, as shown in path i, was unlikely (Scheme 6). Although **1b** was relatively acidic and slow enolization occurred only with Barton's base, the Cu(I) complex accelerated enolization and, more importantly, played a pivotal role in the C−C bond-forming process to assemble active enolate and imine in near proximity. The transient pentacoordinated Cu(I) complex (**TS**) might be involved to produce the Mannich adduct of the observed absolute configuration, where the coordination of pyridyl nitrogen of the indoline to Cu(I) was gradually replaced by the carbamoyl oxygen of the imine to activate and deliver the imine to the proximity of the enolate. However, a six-membered transition state in which the *Z*-configured imine nitrogen is coordinated to Cu(I) cannot be excluded.[54] Chelating coordination of the indoline and the enolate moiety to Cu(I) in *E*-**16** and **TS** would prevent the interaction of Cu(I) and β-fluorine atoms, which was likely beneficial for suppressing the undesired defluorination.

Hence, we conclude the following: (1) Amide **1b** was sufficiently acidic to be deprotonated only with Barton's base, and the Cu(I) complex significantly accelerated deprotonation. (This acceleration would also be true for other 7-azaindoline amides.) (2) The Cu(I) complex played a more decisive role in assembling the two substrates to achieve C−C bond formation rather than to accelerate the deprotonation, at least for more acidic amide **1b**.

CONCLUSIONS

We developed a direct catalytic asymmetric Mannich-type reaction of fluorinated amide pronucleophiles and *N*-carbamoyl imines. The use of 7-azaindoline amides in a binary catalytic system comprising of a chiral Cu(I) complex and Barton's base enabled catalytic enolization and subsequent diastereo- and enantioselective addition to imines. The *E* conformer of 7-azaindoline amide was flipped to the *Z* conformer upon coordination with the Cu(I) complex in a bidentate fashion, accelerating the catalytic enolization. Although this was not the case with some perfluorinated amides, the undesired defluorination pathway from the enolates was largely suppressed. Successful implementation of α-CF_3, α-F-α-CF_3, α-C_2F_5, α-CF_2CF_2Br, and α-F 7-azaindoline acetamides in the Mannich-type reaction allowed for an expeditious access to α-fluorinated and α-fluoroalkylated β-amino acid derivatives in a highly stereoselective manner, as evidenced by the divergent functional group transformations of the 7-azaindoline moiety of the Mannich adducts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11064.

Crystallographic information file for compound **1a**. (CIF)
Crystallographic information file for compound (rac)-**1b**. (CIF)
Crystallographic information file for compound (*S*)-**1b**. (CIF)
Crystallographic information file for compound **1e**. (CIF)
Crystallographic information file for compound **6a**. (CIF)
Crystallographic information file for compound **12a**. (CIF)
Crystallographic information file for compound **3a**. (CIF)
Crystallographic information file for compound **15b**. (CIF)

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Experimental procedures and characterization of new compounds. (PDF)
^{1}H, ^{13}C, and ^{19}F NMR spectra of the new compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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