
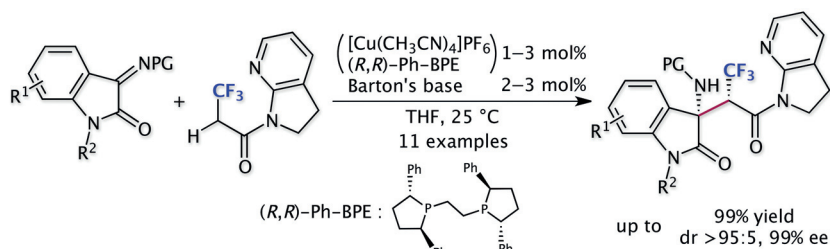


# Direct Catalytic Asymmetric Mannich-Type Reaction of an $\alpha$ -CF<sub>3</sub> Amide to Isatin Imines

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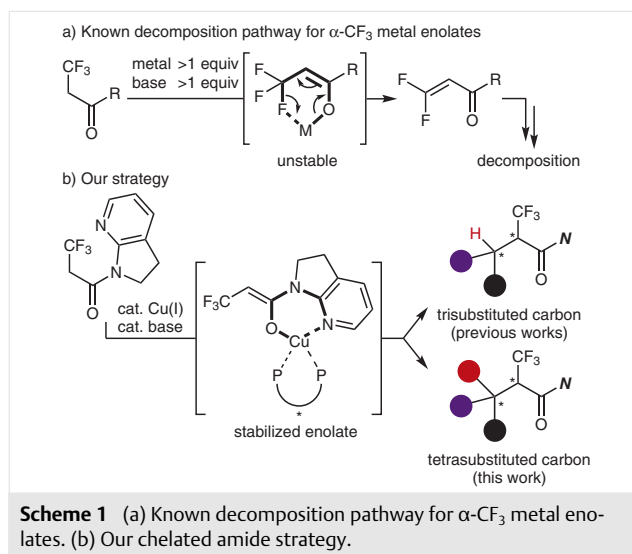
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**Abstract** An  $\alpha$ -CF<sub>3</sub> amide underwent direct asymmetric Mannich-type reaction to isatin imines in the presence of a chiral catalyst comprising a soft Lewis acid Cu(I), a chiral bisphosphine ligand, and Barton's base. The Mannich adduct was converted in one step into a unique tricycle bearing a trifluoromethylated chiral center and an  $\alpha$ -tertiary amine moiety.

**Key words** asymmetric catalysis, copper catalysis, fluorine, Mannich reaction, heterocycle

Organofluorine compounds generally exhibit distinctive chemical properties compared to their corresponding non-fluorinated analogues owing to the strong C–F bond and high electronegativity of fluorine.<sup>1</sup> The altered attributes are often beneficial for medicinal and agrochemical applications.<sup>2</sup> Therefore, the incorporation of fluorine and perfluoroalkyl groups such as CF<sub>3</sub> into organic molecules has been a topic of the intensive research.<sup>3</sup> In addition to fluorinated aromatics, recent effort has also been dedicated to the preparation of fluorine-containing aliphatic compounds in enantioenriched form.<sup>4</sup> Two strategies exist for this purpose: fluorination/fluoroalkylation and building block approaches. Given the broad utility of enolate-based chemical transformations,  $\alpha$ -CF<sub>3</sub> enolates would seem one of the most ideal building blocks for the construction of a trifluoromethylated stereogenic carbon. Nevertheless, only limited chemistry has been explored with this class of nucleophiles due to their notorious instability associated with the high aptitude for  $\beta$ -fluoride elimination from the corresponding metal enolates (Scheme 1, a).<sup>5,6</sup>



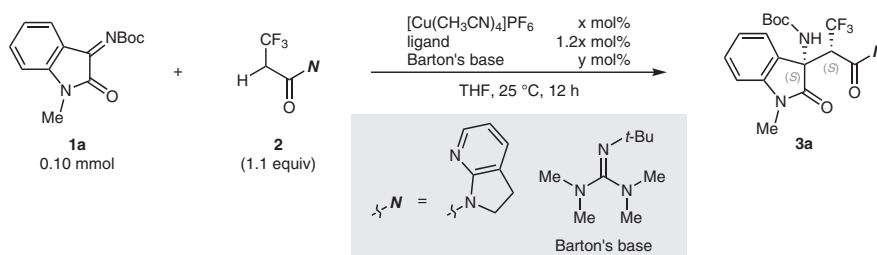
As a part of our research program in direct enolization chemistry,<sup>7</sup> we have recently devised a chelated enolate strategy to tame otherwise unstable  $\alpha$ -CF<sub>3</sub> metal enolates (Scheme 1, b).<sup>8</sup> The designed pronucleophile<sup>9</sup> contains a 7-azaindoline amide as a bidentate chelating unit that prevents unfavorable metal–fluorine interactions. The thus generated  $\alpha$ -CF<sub>3</sub> enolate has proven effective in the construction of CF<sub>3</sub>-containing stereogenic carbons in a wide range of Cu(I)-catalyzed asymmetric transformations.<sup>10</sup> The applications have, however, been limited to the construction of trisubstituted stereocenters at the  $\beta$ -position of the amide carbonyl group.<sup>11,12</sup> Facile Mannich addition of the  $\alpha$ -CF<sub>3</sub> amide to Boc-aldimines<sup>8</sup> prompted us to examine activated ketimines as potential reaction partners. Herein, we report the successful implementation of this strategy for

the preparation of tetrasubstituted carbons by means of a direct catalytic asymmetric Mannich-type reaction to isatin imines.<sup>13</sup>

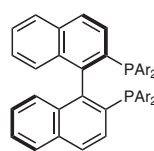
Our experience with 7-azaindoline amides has established a combined soft Lewis acid/Brønsted base system comprising Cu(I)/chiral bisphosphine ligand/Barton's base as a particularly effective catalyst for direct enolization chemistry.<sup>8,14</sup> A recent systematic study has also found that the Ph-BPE ligand exhibits consistently high catalytic competency for a broad range of  $\alpha$ -substituents of the amides including N<sub>3</sub>, Cl, and alkyl groups, but not fluoroalkyl groups such as CF<sub>3</sub>; biaryl-type phosphine ligands are preferred for the  $\alpha$ -CF<sub>3</sub> amide.<sup>15</sup> With these factors in mind,

our optimization studies for the Mannich-type reaction of amide **2** to isatin imine **1a** commenced with screening various biaryl-type ligands (Table 1). A quick examination revealed that the desired product was indeed formed in the presence of 5 mol% Cu(I)/chiral biaryl ligand complex, although the enantioselectivities were low to moderate (Table 1, entries 1–4). Hence, we turned our attention to different ligand backbones, and surprisingly, Ph-BPE (**L8**) was found to perform the best among the ligands evaluated (Table 1, entries 5–8). The catalyst loading was reduced to as little as 1 mol% without sacrificing the reactivity and selectivities (Table 1, entry 9).

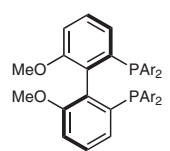
**Table 1** Optimization Studies<sup>a</sup>



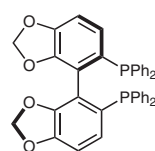
Entry	Ligand	x (mol%)	y (mol%)	Yield (%) <sup>b</sup>	dr <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>L1</b>	5	5	93	91:9	-69
2	<b>L2</b>	5	5	70	60:40	21
3	<b>L3</b>	5	5	90	92:8	-49
4	<b>L4</b>	5	5	80	90:10	-23
5	<b>L5</b>	5	5	59	89:11	-95
6	<b>L6</b>	5	5	95	94:6	-70
7 <sup>d</sup>	<b>L7</b>	5	5	88	88:12	31
8 <sup>d</sup>	<b>L8</b>	5	5	98	>95:5	99
9 <sup>d</sup>	<b>L8</b>	1	2	98	>95:5	99



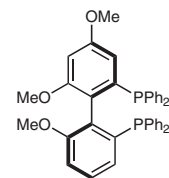
Ar = 4-Me-C<sub>6</sub>H<sub>4</sub>  
**L1**: (*R*)-tol-BINAP



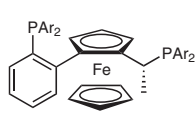
Ar = 3,4,5-(MeO)<sub>3</sub>-C<sub>6</sub>H<sub>2</sub>  
**L2**: (*R*)-BIPHEP-type



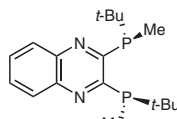
**L3**: (*R*)-Segphos



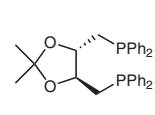
**L4**: (*R*)-Garphos



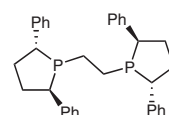
Ar = 3,5-Me<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>  
**L5**: (*R,R<sub>p</sub>*)-Walphos-type



**L6**: (*R,R*)-QuinoxP\*



**L7**: (*S,S*)-DIOP



**L8**: (*R,R*)-Ph-BPE

<sup>a</sup> Reaction conditions: **1a** (0.10 mmol), **2** (0.11 mmol), THF (0.1 M).

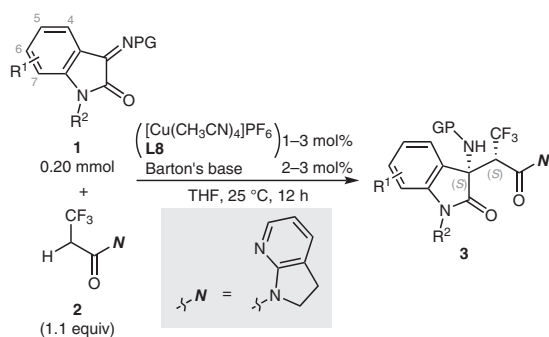
<sup>b</sup> Yield and diastereomeric ratio were determined by <sup>1</sup>H NMR analysis of the unpurified reaction mixture using 3,4,5-trichloropyridine as an internal standard.

<sup>c</sup> Enantiomeric excess of (*S,S*)-isomer was determined with normal-phase HPLC on a chiral support.

<sup>d</sup> The reaction was performed on a 0.2 mmol scale in THF (0.2 M), and isolated yield was reported.

After the identification of a highly selective ligand for this transformation, a series of isatin imines **1** was evaluated with either 1 mol% or 3 mol% Cu catalyst (Table 2). The Cbz-protected imine also proved suitable for this catalytic system, affording the corresponding product with almost the same level of selectivities (Table 2, entries 1, 2). Both electron-donating and electron-withdrawing substituents at the 5-position were tolerated (Table 2, entries 3–7). Positional isomers of **3d** bearing a chlorine atom at different positions were obtained in comparable diastereo- and enantioselectivities (Table 2, entries 8, 9). Substituents on the oxindole nitrogen other than Me were also examined. While the PMB-protected substrate exhibited slightly lower reactivity and selectivities (Table 2, entry 10), the allyl-protected compound afforded results close to those of the Me-substituted one (Table 2, entry 11). The relative and absolute configurations of **3e** were determined by X-ray diffraction, and those of the other compounds were assigned by analogy.<sup>16</sup>

**Table 2** Substrate Scope of the Mannich-Type Reaction of  $\alpha$ -CF<sub>3</sub> Amide **2**<sup>a</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	PG	Product	Yield (%) <sup>b</sup>	er <sup>c</sup>	ee (%) <sup>d</sup>
1	H	Me	Boc	<b>3a</b>	98	>95:5	99
2	H	Me	Cbz	<b>3b</b>	91	>95:5	99
3	5-F	Me	Boc	<b>3c</b>	86	94:6	99
4	5-Cl	Me	Boc	<b>3d</b>	89	92:8	99
5	5-Br	Me	Boc	<b>3e</b>	90	>95:5	99
6	5-Me	Me	Boc	<b>3f</b>	99	>95:5	98
7	5-MeO	Me	Boc	<b>3g</b>	81	>95:5	99
8	6-Cl	Me	Boc	<b>3h</b>	86	>95:5	99
9	7-Cl	Me	Boc	<b>3i</b>	90	>95:5	96
10	H	PMB	Boc	<b>3j</b>	66	86:14	92
11	H	Allyl	Boc	<b>3k</b>	97	>95:5	97

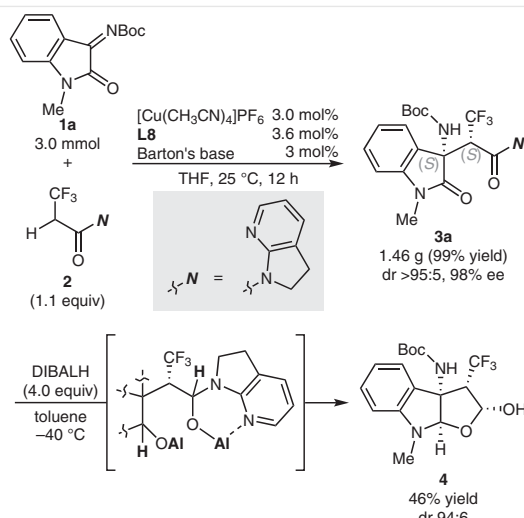
<sup>a</sup> Reaction conditions: **1** (0.20 mmol), **2** (0.22 mmol), THF (0.2 M). For entries 1–4, [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> (1.0 mol%), L8 (1.2 mol%), Barton's base (2.0 mol%). For entries 5–11, [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> (3.0 mol%), L8 (3.6 mol%), Barton's base (3.0 mol%).

<sup>b</sup> Yield values refer to isolated yield.

<sup>c</sup> Diastereomer ratio was determined by <sup>1</sup>H NMR and <sup>19</sup>F NMR analysis of the unpurified reaction mixture.

<sup>d</sup> Enantiomeric excess of (S,S)-isomer was determined with normal-phase HPLC on a chiral support.

The reaction proceeded smoothly on a 3.0 mmol scale, producing 1.46 g of Mannich adduct **3a** with almost perfect stereoselectivities, albeit a slightly higher catalyst loading was necessary for full consumption of the substrates (Scheme 2).<sup>17,18</sup> We have previously shown that 7-azaindoline amides can provide an in situ chelating group when treated with an organometallic reagent in a manner similar to Weinreb amides, and thus prevent further sequential addition of the reagent.<sup>8b,9,11b,14b</sup> Mannich adduct **3a** was reduced by the action of DIBALH to form a masked aldehyde accompanied by the formation of an aluminum alkoxide derived from reduction of the oxindole moiety, which cyclized presumably during the workup. This triple-bond-forming process (two reductions and one cyclization) furnished highly decorated tricycle **4** in 46% yield with excellent diastereoselectivity.<sup>19</sup>



**Scheme 2** A large scale reaction and the transformation of its product into a tricyclic skeleton.

In summary, we developed the direct catalytic Mannich-type reaction of an  $\alpha$ -CF<sub>3</sub> amide to isatin imines. Enolization was promoted without decomposition by a proficient soft Lewis acidic Cu(I)/bisphosphine/Barton's base catalytic system, and the generated enolate underwent a highly stereoselective addition, producing an  $\alpha$ -tertiary amine with an adjacent trifluoromethylated stereogenic carbon. The Mannich adduct was smoothly transformed into a tricyclic framework by harnessing a unique property of the 7-azaindoline as a chelating unit in the reduction step.

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611642>.

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- (16) See the Supporting Information for details. CCDC 1874483 contains the supplementary crystallographic data for **3e**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/getstructures](http://www.ccdc.cam.ac.uk/getstructures).
- (17) With 1 mol% catalyst, **3a** was obtained in 55% yield with the high selectivities retained (dr >95:5, 98% ee).
- (18) **Compound 3a**  
A flame-dried 30 mL flask equipped with a magnetic stirring bar and 3-way glass stopcock were charged with imine **1a** (781 mg, 3.0 mmol, 1.0 equiv), and  $\alpha$ -CF<sub>3</sub> amide **2** (760 mg, 3.3 mmol, 1.1 equiv), followed by the addition of anhydrous THF (9.6 mL, 0.2 M) via syringe with a stainless steel needle under an Ar atmosphere. After being stirred at 25 °C for 5 min, a solution of the catalyst in THF (4.5 mL) containing a chiral copper(I) complex (0.090 mmol, 3.0 mol%), which was prepared from [Cu(CH<sub>3</sub>CN)<sub>4</sub>]PF<sub>6</sub> (33.5 mg, 0.090 mmol) and (R,R)-Ph-BPE L8 (54.7 mg, 0.11 mmol, 3.6 mol%), and a solution of Barton's base (0.1 M in THF, 0.90 mL, 0.09 mmol, 3.0 mol%) were sequentially added via a syringe with a stainless steel needle. After stirring at 25 °C for 12 h, the reaction mixture was filtered through a pad of silica gel and washed with EtOAc, then concentrated *in vacuo* to afford the crude residue. <sup>1</sup>H NMR analysis of the crude

residue showed that the dr was >95:5. The combined crude residue was then purified by silica gel column chromatography (5% to 80% EtOAc in hexane) to afford product **3a** (1.46 g, 99% yield). IR (thin film):  $\nu = 3371, 2943, 1721, 1653, 1426, 1256, 1164, 754 \text{ cm}^{-1}$ .  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.93\text{--}7.92$  (m, 1 H), 7.51–7.49 (m, 1 H), 7.44 (d,  $J = 7.2 \text{ Hz}$ , 1 H), 7.35–7.31 (m, 1 H), 7.08–7.04 (m, 2 H), 6.91 (dd,  $J = 7.6 \text{ Hz}, 5.2 \text{ Hz}$ , 1 H), 6.84 (d,  $J = 7.6 \text{ Hz}$ , 1 H), 6.31 (q,  $J = 8.8 \text{ Hz}$ , 1 H), 4.31–4.10 (m, 2 H), 3.15–2.99 (m, 2 H), 2.96 (s, 3 H), 1.20 (s, 9 H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 174.6, 163.4, 154.8, 153.8, 145.2, 143.2, 134.3, 129.3, 127.2, 126.8, 125.4$  (d,  $J = 2.5 \text{ Hz}$ ), 124.3 (q,  $J = 281.1 \text{ Hz}$ ), 122.2,

119.0, 108.1, 80.0, 61.2, 48.9 (q,  $J = 26.1 \text{ Hz}$ ), 46.0, 27.9, 26.1, 23.7.  $^{19}\text{F NMR}$  (376 MHz,  $\text{CDCl}_3$ ):  $\delta = -57.98$  (d,  $J = 8.5 \text{ Hz}$ ). HRMS (ESI):  $m/z$  calcd for  $\text{C}_{24}\text{H}_{25}\text{O}_4\text{N}_4\text{F}_3\text{Na}$   $[\text{M} + \text{Na}]^+$ : 513.1720; found: 513.1724.  $[\alpha]_{\text{D}}^{24} -48.0$  ( $c = 1.00, \text{CHCl}_3$ ). Enantiomeric excess of the product was determined to be 98% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H ( $\phi$  0.46 cm  $\times$  25 cm), 2-propanol/*n*-hexane = 1:4, flow rate 1.0 mL/min, detection at 254 nm,  $t_{\text{R}} = 5.9 \text{ min}$  (major), 13.2 min (minor)).

(19) The stereochemistry of **4** was assigned by NOE analysis. See the Supporting Information for details.