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# Direct Catalytic Asymmetric Mannich-Type Reaction of an α-$CF_3$ Amide to Isatin Imines

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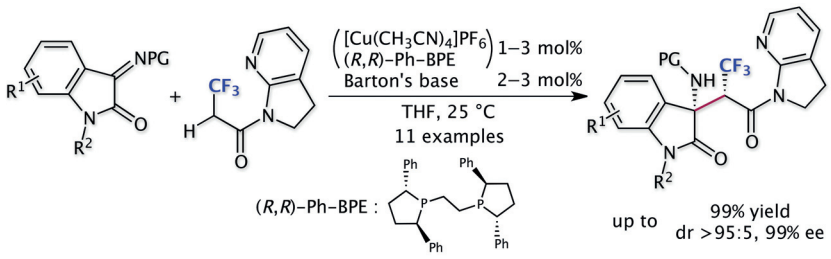


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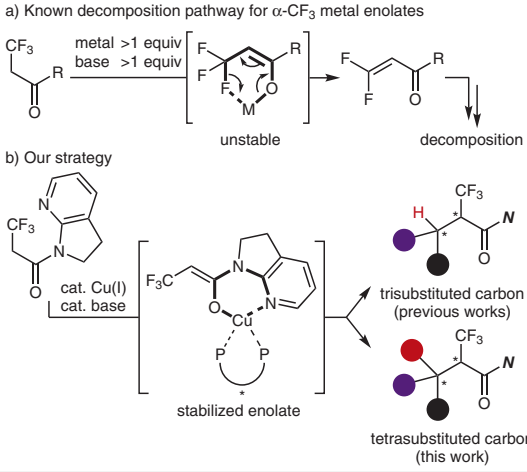
**Abstract** An α-$CF_3$ amide underwent direct asymmetric Mannich-type reaction to isatin imines in the presence of a chiral catalyst comprising a soft Lewis acid Cu(I), a chiral bisphosphine ligand, and Barton's base. The Mannich adduct was converted in one step into a unique tricycle bearing a trifluoromethylated chiral center and an α-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.[1] The altered attributes are often beneficial for medicinal and agrochemical applications.[2] Therefore, the incorporation of fluorine and perfluoroalkyl groups such as $CF_3$ into organic molecules has been a topic of the intensive research.[3] In addition to fluorinated aromatics, recent effort has also been dedicated to the preparation of fluorine-containing aliphatic compounds in enantioenriched form.[4] Two strategies exist for this purpose: fluorination/fluoroalkylation and building block approaches. Given the broad utility of enolate-based chemical transformations, α-$CF_3$ 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 β-fluoride elimination from the corresponding metal enolates (Scheme 1, a).[5,6]



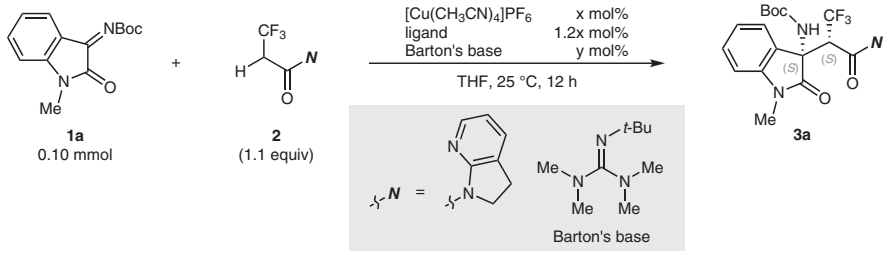

**Scheme 1** (a) Known decomposition pathway for α-$CF_3$ metal enolates. (b) Our chelated amide strategy.

As a part of our research program in direct enolization chemistry,[7] we have recently devised a chelated enolate strategy to tame otherwise unstable α-$CF_3$ metal enolates (Scheme 1, b).[8] The designed pronucleophile[9] contains a 7-azaindoline amide as a bidentate chelating unit that prevents unfavorable metal–fluorine interactions. The thus generated α-$CF_3$ enolate has proven effective in the construction of $CF_3$-containing stereogenic carbons in a wide range of Cu(I)-catalyzed asymmetric transformations.[10] The applications have, however, been limited to the construction of trisubstituted stereocenters at the β-position of the amide carbonyl group.[11,12] Facile Mannich addition of the α-$CF_3$ amide to Boc-aldimines[8] prompted us to examine activated ketimines as potential reaction partners. Herein, we report the successful implementation of this strategy for

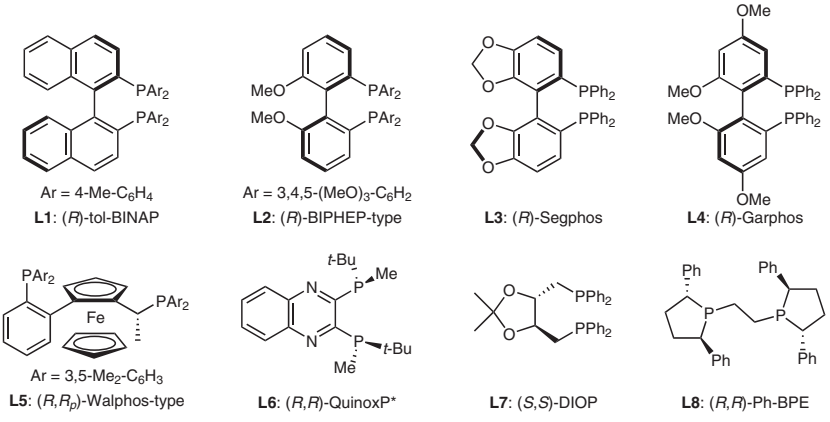
the preparation of tetrasubstituted carbons by means of a direct catalytic asymmetric Mannich-type reaction to isatin imines. [13]

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.[8,14] A recent systematic study has also found that the Ph-BPE ligand exhibits consistently high catalytic competency for a broad range of α-substituents of the amides including $N_3$, Cl, and alkyl groups, but not fluoroalkyl groups such as $CF_3$; biaryl-type phosphine ligands are preferred for the α-$CF_3$ amide.[15] 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[a]



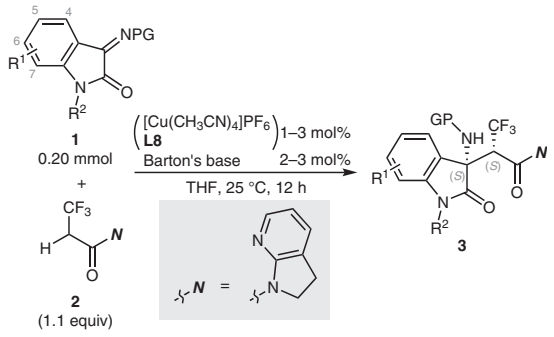

| Entry | Ligand | x (mol%) | y (mol%) | Yield (%)[b] | dr[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **L1** | 5 | 5 | 93 | 91:9 | –69 |
| 2 | **L2** | 5 | 5 | 70 | 60:40 | 21 |
| 3 | **L3** | 5 | 5 | 90 | 92:8 | –49 |
| 4 | **L4** | 5 | 5 | 80 | 90:10 | –23 |
| 5 | **L5** | 5 | 5 | 59 | 89:11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




[a] Reaction conditions: **1a** (0.10 mmol), **2** (0.11 mmol), THF (0.1 M).
[b] Yield and diastereomeric ratio were determined by $^1$H NMR analysis of the unpurified reaction mixture using 3,4,5-trichloropyridine as an internal standard.
[c] Enantiomeric excess of (*S*,*S*)-isomer was determined with normal-phase HPLC on a chiral support.
[d] 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.[16]

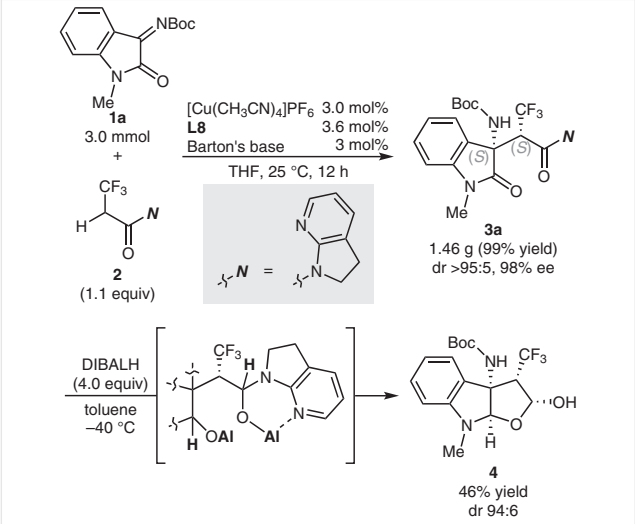
**Table 2** Substrate Scope of the Mannich-Type Reaction of α-$CF_3$ Amide **2**[a]




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

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.22 mmol), THF (0.2 M). For entries 1–4, [Cu($CH_3CN$)]$PF_6$ (1.0 mol%), **L8** (1.2 mol%), Barton's base (2.0 mol%). For entries 5–11, [Cu($CH_3CN$)]$PF_6$ (3.0 mol%), **L8** (3.6 mol%), Barton's base (3.0 mol%).
[b] Yield values refer to isolated yield.
[c] Diastereomer ratio was determined by $^1H$ NMR and $^{19}F$ NMR analysis of the unpurified reaction mixture.
[d] 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).[17,18] 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.[8b,9,11b,14b] 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.[19]




**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 α-$CF_3$ 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 α-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.

## Funding Information

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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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(11) In Cu(I)-catalyzed aldol reactions, the reactivity of the α-$CF_3$ enolate is somewhat lower than those with other substituents: While α-alkyl, vinyl, and $N_3$ 7-azaindoline amides smoothly undergo aldol additions to simple aldehydes, α-$CF_3$ amide **2** only reacts with activated arylglyoxal hydrates. (a) Weidner, K.; Sun, Z.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 6236. (b) Liu, Z.; Takeuchi, T.; Pluta, R.; Arteaga, F. A.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2017**, *19*, 710. (c) Takeuchi, T.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2018**, *83*, 5851. (d) Matsuzawa, A.; Noda, H.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2017**, *82*, 8304.

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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.

(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 α-$CF_3$ 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 $[Cu(CH_3CN)_4]PF_6$ (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. $^1$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): ν = 3371, 2943, 1721, 1653, 1426, 1256, 1164, 754 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.93–7.92 (m, 1 H), 7.51–7.49 (m, 1 H), 7.44 (d, *J* = 7.2 Hz, 1 H), 7.35–7.31 (m, 1 H), 7.08–7.04 (m, 2 H), 6.91 (dd, *J* = 7.6 Hz, 5.2 Hz, 1 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 6.31 (q, *J* = 8.8 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). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 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 Hz), 124.3 (q, *J* = 281.1 Hz), 122.2, 119.0, 108.1, 80.0, 61.2, 48.9 (q, *J* = 26.1 Hz), 46.0, 27.9, 26.1, 23.7. $^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –57.98 (d, *J* = 8.5 Hz). HRMS (ESI): *m/z* calcd for $C_{24}H_{25}O_4N_4F_3Na$ $[M + Na]^+$: 513.1720; found: 513.1724. $[\alpha]_D^{24}$ –48.0 (*c* = 1.00, $CHCl_3$). Enantiomeric excess of the product was determined to be 98% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46 cm × 25 cm), 2-propanol/*n*-hexane = 1:4, flow rate 1.0 mL/min, detection at 254 nm, $t_R$ = 5.9 min (major), 13.2 min (minor)).

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