Direct Catalytic Asymmetric Aldol Addition of an \( \alpha \)-CF\(_3\) Amide to Arylglyoxal Hydrates

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Supporting Information

ABSTRACT: Direct asymmetric aldol addition of an \( \alpha \)-CF\(_3\) amide to arylglyoxal hydrates was promoted by a chiral catalyst comprising a soft Lewis acidic Cu(I), a chiral bisphosphine ligand, and DBU. The 7-azaindoline moiety of the amide facilitates its enolization and stabilizes the thus-generated Cu enolate, furnishing enantioenriched aldol adducts.

Fluorine-containing chiral building blocks are widely utilized in numerous fields of chemistry, including medicinal chemistry.\(^1\) Given the well-established enolate chemistry, \( \alpha \)-CF\(_3\)-substituted carbonyl compounds are attractive starting materials for constructing stereogenic carbon centers bearing trifluoromethyl groups.\(^2\) Nevertheless, \( \alpha \)-CF\(_3\) enolates have been sporadically exploited in the literature due to their high aptitude for \( \beta \)-fluoride elimination triggered by strong metal–fluorine interactions (Scheme 1a).\(^3\) So far, silicon, titanium, and boron-based \( \alpha \)-CF\(_3\) enolates have been successfully prepared upon \( \alpha \)-deprotonation and employed in carbon–carbon bond-forming reactions (e.g., aldol reactions).\(^4\) Although these pioneering works established the foundation of this important research area, they required stoichiometric amounts of metal/base and relied on a chiral auxiliary-based approach to asymmetric synthesis. Thus, development of catalytic enantioselective methodologies has been anticipated for further applications in this area.\(^5\)

Over the decades, the chemistry community has been keen on directly exploiting catalytically generated active enolate species instead of preforming enolates or their equivalents using stoichiometric amounts of activators.\(^6\) In particular, harnessing less \( \alpha \)-acidic but synthetically more versatile carboxylate-type donors is a subject of ongoing research.\(^7\) As a part of our continuous research program on direct enolization chemistry,\(^8\) we recently devised a solution to the instability problem associated with \( \alpha \)-CF\(_3\) enolates by employing a chelating unit that prevents direct metal contact with the fluorine atoms of the trifluoromethyl group. The designed 7-azaindoline amides\(^9\) were successfully employed in Cu(I)-catalyzed direct Mannich-type reactions\(^10\) and allylic alkylations,\(^11\) where the stabilized amide Cu enolate generated by a catalytic amount of Brønsted base underwent subsequent asymmetric reactions to construct a stereogenic carbon bearing a CF\(_3\) moiety. We envisioned that a similar approach would enable the development of a direct catalytic asymmetric aldol reaction of the \( \alpha \)-CF\(_3\) carbonyl compound (Scheme 1b). This paper describes our efforts toward this goal.

At the outset, various catalysts were screened for aldol additions to benzaldehyde or isobutyraldehyde, but all attempts led to unsatisfactory results. Subsequently, we turned our attention to glyoxals as aldol acceptors. Arylglyoxals are usually unstable sticky oils or semisolids that readily undergo oligomerization, whereas their hydrates are commercial, stable solids that are easier to handle.\(^12\) The majority of reported metal-based asymmetric catalysis, however, employed anhydrous aldehydes as substrates due to the moisture-sensitive nature of the catalysts.\(^13\) Because Cu(I)-based nucleophiles are less sensitive to protonolysis,\(^14\) we expected Cu(I)-catalyzed aldol addition to aryglyoxal hydrates to be unaffected by in situ generated water. This notion proved correct, and aldol product 3a was smoothly formed with a promising ee in the presence of a Cu-aryloxide and bisphosphine ligand L1 in THF at \(-40 \, ^\circ C\).
Table 1. Screening Conditions for Direct Catalytic Asymmetric Aldol Addition of α-CF₃ Amide

<table>
<thead>
<tr>
<th>Cu(I) source</th>
<th>Brønsted base</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield (%)b</th>
<th>anti/synb</th>
<th>Ee (%)c</th>
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<tbody>
<tr>
<td>1</td>
<td>CuOAr⁶</td>
<td>L₁</td>
<td>THF</td>
<td>97</td>
<td>62/38</td>
<td>−57</td>
</tr>
<tr>
<td>2</td>
<td>CuOAr⁶</td>
<td>L₂</td>
<td>THF</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>CuOAr⁶</td>
<td>L₃</td>
<td>THF</td>
<td>65</td>
<td>81/19</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>CuOAr⁶</td>
<td>L₃</td>
<td>Toluene</td>
<td>55</td>
<td>82/18</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>CuOAr⁶</td>
<td>L₃</td>
<td>DMF</td>
<td>98</td>
<td>66/34</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>CuOAr⁶</td>
<td>L₃</td>
<td>DMF</td>
<td>4</td>
<td>ND</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>[Cu(CH₃CN)₄]PF₆</td>
<td>L₃</td>
<td>Toluene</td>
<td>0</td>
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<td>ND</td>
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<tr>
<td>8</td>
<td>[Cu(CH₃CN)₄]PF₆</td>
<td>L₃</td>
<td>Toluene</td>
<td>60</td>
<td>92/8</td>
<td>95</td>
</tr>
<tr>
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<td>[Cu(CH₃CN)₄]PF₆</td>
<td>L₃</td>
<td>Toluene</td>
<td>72</td>
<td>93/7</td>
<td>93</td>
</tr>
</tbody>
</table>

“1a (0.2 mmol), 2 (0.1 mmol). −40 °C, 18 h. bYield and diastereomer ratio were determined by 1H NMR analysis of unpurified reaction mixture. cEnantiomeric excess of the anti isomer was determined with normal-phase HPLC on a chiral support. dMesCu (10 mol %), ArOH (10 mol %). eReaction time was 30 min. f1.1 equiv of 1a was used. Yield values refer to isolated yield. ND: not determined.

(Table 1, entry 1). Whereas bulky ligand L2 completely retarded the reaction, ferrocene-based bisphosphine ligand L3 afforded the product with improved dr and ee (entries 2 and 3). Extensive solvent screening revealed that greater stereoselectivity was achieved in toluene (entry 4); generally higher ee values were obtained in nonpolar, hydrocarbon solvents than in ethereal ones, but most reactions in the former solvents suffered from low reproducibility due to the low solubility of 1a.16 Conversely, DMF provided ideal solubility, but 3a was formed in only 8% ee (entry 5). This low enantioselectivity was partially caused by a fast retro-aldol reaction in this medium, as the product was obtained in much higher ee at an earlier stage of the reaction (entry 6).17 Alkoxide bases did not promote the reaction, but the use of DBU as a Brønsted base improved both diastereo- and enantioselectivities (entries 7 and 8), allowing the amount of 1a to be reduced to 1.1 equiv (entry 9).

We encountered the solubility issue again when examining the scope and limitations of the aldol reaction under the optimized conditions in Table 1. Further solvent screening identified that the addition of a small amount of DMF reproducibly afforded the addition products without diminishing selectivity, and hence, various glyoxal hydrates were evaluated under these modified conditions (Table 2).18 Although aldol adduct 3b was obtained in the same yield as 3a, the reaction was rather sensitive to the electronic nature of substituents attached to the aromatic ring; 3c and 3d were obtained in slightly lower yields and good selectivity. Both meta- and ortho-substituents were tolerated, affording products with excellent selectivity (3e, 3f). Potentially detrimental Lewis basic heteroaromatics had little effect on the reaction outcome (3g). This aldol protocol was not applicable to aliphatic substrates, presumably due to a competitive enolization of the electrophiles by the relatively strong Brønsted base.

On a gram scale, 5 mol % of the Cu(I) catalyst was sufficient to afford aldol adduct 3a without compromising stereoselectivity. The relative and absolute configurations of 3a were determined by X-ray diffraction after conversion into a TBS ether (Scheme 2). The stereochemistry of other products was assigned by analogy.

In order to gain insights into the role of the 7-azaindoline moiety, pKₐ values of a series of acetamides 5–8 in DMSO were calculated using a DFT method (Figure 1a).19,20 Furthermore, structurally related amides 9–11 were subjected to an aldol reaction with phenylglyoxal hydrate 1a under otherwise identical conditions (Figure 1b). As expected, aromatic amides (5–7) showed enhanced acidity compared to their archetypal aliphatic counterparts (8), and 7-azaindyl amide 5 is the least acidic among the aromatic amides in the absence of a metal cation. Notably, possessing more acidic α-protons than 7-azaindoline amides, α-CF₃ amides 9 and 10 failed to afford the aldol product, although they were not decomposed. These results support the bifunctional role of the 7-azaindoline moiety:
Infrared (IR) spectra were recorded on a HORIBA FT210 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL ECS-400, a Bruker AVANCE III HD 400, or a Bruker AVANCE III 500. Chemical shifts (δ) are given in parts per million relative to residual solvent peaks. Data for H NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), q (quartet), m (multiplet), br (broad). For 19F NMR, chemical shifts were reported in the scale relative to PhCF3 (δ = -62.7680 ppm in CDCl3) as an external reference. Single-crystal X-ray data were collected on a Rigaku R-Axis Rapid II imaging plate area detector with graphite-monochromated Cu Kα radiation. Optical rotation was measured using a 1.0 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. High-resolution mass spectra (ESI TOF (+)) were measured on a Thermo Fisher Scientific LTQ-Orbitrap XL.

Anhydrous MTBE, PhCF3, PhCl, m-xylene, and pyridine were purchased from commercial suppliers. THF, EtO, CPME, CH3Cl, toluene, n-hexane, EtOAc, and DME were purified by passing through a solvent purification system (Glass Contour). Glyoxal derivatives and their hydrates were either purchased or synthesized. All other starting materials and chiral ligands were used as supplied by commercial vendors or prepared by the method described in the corresponding reference.

All quantum chemical calculations were performed using the Gaussian 09 program. Structural optimizations were conducted with very tight optimization parameters, and DFT calculations employed an ultrafine integration grid (99 radial shells, 590 angular points). Frequency calculations confirmed the identity of geometry minima (no imaginary frequencies).

General Procedure for Table 1. To a flame-dried test tube equipped with a magnetically stirred chip and a three-way stopcock were charged [Cu(CH3CN)4]PF6 (3.7 mg, 0.01 mmol, 10 mol %) and L3 (6.7 mg, 0.01 mmol, 10 mol %) in a glovebox. To this were added glyoxal hydrate (0.11 mmol, 1.1 equiv), amide (2.3 mg, 0.1 mmol, 1.0 equiv), DMF (50 mL), and toluene (1.95 mL). Then the mixture was cooled to −40 °C, and DBU solution in toluene (0.05 mL, 0.01 mmol, 10 mol %) was slowly added down the side of the tube via a syringe. After the addition of saturated aqueous NH4Cl at −40 °C, the mixture was diluted with EtOAc. The aqueous phase was extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over Na2SO4, filtered, and removed under reduced pressure. The resulting residue was submitted to 1H NMR analysis to determine the diastereoselectivity. The crude material was purified by preparative TLC (n-hexane:acetonitrile = 3:1, then toluene:acetonitrile = 6:1).

**EXPERIMENTAL SECTION**

General Experimental Methods. Unless otherwise noted, all reactions were carried out in oven-dried glassware fitted with a three-way glass stopcock under an argon atmosphere and were stirred with Teflon-coated magnetic stir bars. All workup and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Thin layer chromatography (TLC) was performed on Merck TLC plates (0.25 mm) precoated with silica gel 60 F254 and visualized by UV quenching and staining with ninhydrin, KMnO4, anisaldehyde, or ceric ammonium molybdate solution. Flash column chromatography was performed on a Teledyne Combiflash Rf 200 or a Biotage Isolera Spectra One.
9.5, 5.2 Hz, 1H), 7.51–7.55 (m, 1H), 7.69 (dd, J = 5.0, 1.1 Hz, 8.06–8.09 (m, 2H)); 13C NMR (100 MHz, CDCl3) δ 23.9, 46.1, 46.6 (q, Jc–F = 26 Hz), 73.9, 119.5, 124.7 (q, Jc–F = 280 Hz), 126.5, 128.3, 134.2, 135.0, 135.2, 140.7, 146.1, 154.5, 165.5, 191.2; 15N NMR (376 MHz, CDCl3) δ −63.74 (d, JF–H = 8.7 Hz); [δF]d −170.1 (c 0.12, CHCl3, 88% ee sample); HRMS (EI) m/z calc for C37H40N3F3Si [M + H]+ 537.0764, found 537.0767.

HPLC conditions: CHIRALPAK IC-3 (0.46 cm × 25 cm), n-hexane/IPA = 4/1, detection at 254 nm, flow rate 1.0 mL/min, tf = 25.8 min (major). 27.9 min (minor).

**Gram Scale Synthesis of 3a (Scheme 2).** To a flame-dried 50 mL flask equipped with a magnetic stirrer chip were added amide 2 (1.14 g, 5.0 mmol, 1.0 equiv) and phenylglyoxal hydrate 1a (837 mg, 5.5 mmol, 1.1 equiv). In a glovebox, [Cu(CnCN)2]PF6 (93 mg, 0.25 mmol, 5 mol%) and LiCl (172 mg, 0.25 mmol, 5 mol%) were added to the flask. After it was taken from the glovebox, toluene (48 mL) was added. The solution was stirred for 5 min at rt and 20 min at −40 °C before the addition of the solution of DBU (2.5 mL, 0.2 M in toluene, 0.50 mmol, 10 mol%). After the addition of saturated aqueous NH4Cl at −40 °C, the solution was diluted with ETOAc. The aqueous phase was extracted with ETOAc (3×). The combined organic phases were washed with brine, dried over Na2SO4, filtered, and removed under reduced pressure. The crude material was purified by silica gel column chromatography (n-hexane/acetonitrile = 95/5 to 70/30) to give aldo product 3a (1.28 g, 70%).

(2R,3S)-2-((tert-Butylidimethylsilyloxy)oxy)-4,2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1H-heterobicycle on a preparative h.p.l.c. column, eluting with n-hexane/IPA 25/75, flow rate 1.0 mL/min, tf = 11.9 min (major).

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01381.
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Details for the optimization studies, copies of HPLC traces and NMR spectra, and computational data (PDF) X-ray data (CCDC 1545444) for compound 4 (CIF)

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REFERENCES


