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C_2-Symmetric Chiral Bisoxazolines as Hydrogen-Bond-Acceptor Catalysts in Enantioselective Aldol Reaction of *β*-Carbonyl Acids with Trifluoroacetaldehyde Hemiacetals

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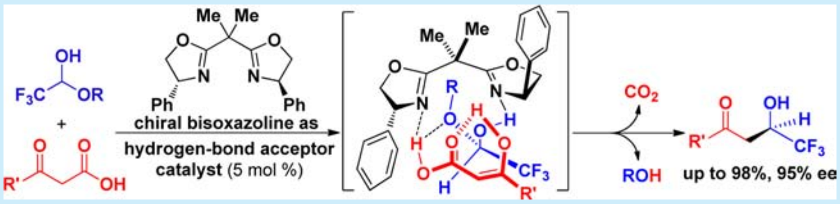
Ⓢ *Supporting Information*



ABSTRACT: A simple C_2-symmetric chiral bisoxazoline is demonstrated to use hydrogen bonding to catalyze an important family of aldol reactions of trifluoroacetaldehyde hemiacetals with various *β*-carbonyl acids. This reaction is highly enantioselective, delivering chiral nonracemic trifluoromethylated alcohols with excellent optical purity and good isolated yields. This concept of relaying chiral information via a chiral hydrogen-bond acceptor should be applicable to a vast number of organocatalytic processes.

Hydrogen bonding is a special type of electrostatic attraction between the hydrogen atom bonded to the donor and the lone electron pair on the acceptor.[1] In biological systems, hydrogen bonding is one of the most dominant forces for molecular interaction and recognition, such as protein folding, DNA base-pairing, receptor−ligand binding, and enzyme catalysis.[2] In addition to the eminent importance of hydrogen bonding for the intricate architecture and functionality of biological molecules, the potential benefits that hydrogen bonding offers in asymmetric catalysis have been appreciated by organic chemists in recent years. Accordingly, a great number of hydrogen-bond donors[3] have been invented as small organic molecule catalysts and demonstrated useful levels of enantioselectivity for a wide range of different asymmetric transformations. The unique characteristic of hydrogen-bonding catalysis is that the catalyst not only activates the reactants and stabilizes the transition states through hydrogen-bonding interactions but also orients them in close proximity with the desired relative geometry, and therefore, the reaction is often facilitated in a synergistic way, in a manner similar to that of enzymatic catalysis. In addition to a hydrogen donor, an acceptor with a lone electron pair is another partner in hydrogen bonding. However, no example has emerged of asymmetric catalysis using chiral hydrogen-bond acceptors as organocatalysts[4] to promote chemical reactions.

Over the past several decades C_2-symmetric chiral bisoxazolines have proved to be one of the most successful and commonly used classes of ligand structures for asymmetric catalysis because of their ready accessibility and modular nature. A myriad of chiral metal complexes of bisoxazolines have spawned countless asymmetric reaction classes, thereby dramatically expanding the synthetic toolbox available to researchers in the chemical and biological sciences (Figure 1a).[5] In contrast, little progress has made in the direct use of C_2-symmetric bisoxazolines as chiral organocatalysts for enantioselective synthesis, and only one report by Göbel and co-workers has addressed a bisoxazoline-catalyzed Diels−Alder reaction of N-substituted maleimides with anthrones through ion-pair intermediates.[6] The design of chiral bisoxazolines was originally inspired by the ligand framework of vitamin B_{12}. Therefore, every now and then chiral bisoxazolines would be prepared, but usually only as metal ligands on the road toward

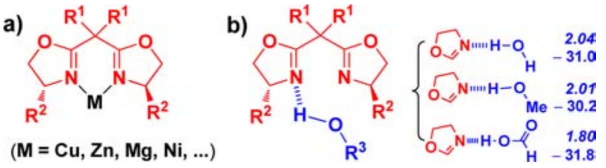


Figure 1. Use of C_2-symmetric chiral bisoxazolines (a) as ligands in metal complexes and (b) as acceptors in hydrogen-bonding complexes. Calculated hydrogen-bond lengths L (N···H−O−R^3) [Å] and interaction energies ΔE [kcal/mol] for complexes of oxazoline with H_2O, MeOH, and HCO_2H are also shown (see SI-Figure 1).

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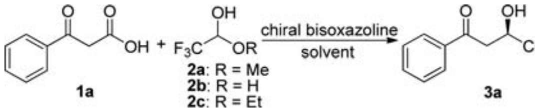
more efficient and hopefully unpatented metal complexes. In point of fact, oxazolines are typical weak bases, and the nitrogen atom of oxazolines can act as a hydrogen-bond acceptor (Figure 1b).[7] Thus, we envisioned that chiral bisoxazolines should program the assembly of reaction partners with appropriately oriented hydrogen bonds that are activated toward useful chemical transformations.

Here we report an implementation of this strategy using C_2-symmetric chiral bisoxazolines as small-molecule hydrogen-bond-acceptor catalysts. Specifically, the aldol reaction between trifluoroacetaldehyde hemiacetals and β-carbonyl acids was employed as an ideal platform to test the catalytic ability of chiral bisoxazolines.[8,9] Because of the unique physicochemical and biological properties of organofluorine compounds, stereoselective construction of chiral fluorine-containing molecules under mild reaction conditions has been highly desirable in organic synthesis, medicinal chemistry, and materials science.[10] It was recognized that the accompanying aldol products with a trifluoromethyl group have been established as important chiral synthons for several biologically active compounds of medicinal and agrochemical interest.[11,12]

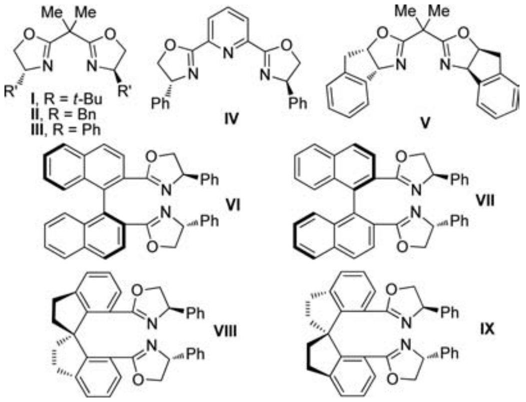
The studies were initiated by evaluating the catalytic activity of a series of readily accessible chiral bisoxazoline catalysts **I**–**IX**[13] in the aldol reaction of 3-oxo-3-phenylpropanoic acid (**1a**) and trifluoroacetaldehyde methyl hemiacetal (**2a**) in dichloromethane. Under these reaction conditions, the aldol product **3a** was obtained in high yield with variable enantioselectivity (Table 1, entries 1–9), with catalyst **III** giving the best performance (entry 3). These results clearly validated the strategy and suggested that additional improvement of the enantioselectivity might be feasible through further optimization of the conditions. The solvent was found to have an important effect on the reactivity (entries 10–15). Among the solvents tested, toluene was found to be the solvent of choice for this reaction with respect to both catalytic activity and asymmetric induction (entries 14 and 15), whereas the use of methanol did not furnish the desired product (entry 12). Under the standard reaction conditions, the catalyst loading was lowered to 5 mol % without deteriorating the yield and enantioselectivity (entry 16). Even at a loading of 1 mol %, catalyst **III** still delivered comparable results (90% yield with 90% ee) when the reaction was run with a prolonged reaction time (entry 17). With an increase in temperature, significant amounts of byproduct acetophenone, formed from a competing decarboxylation pathway, was recovered during the course of the reaction (entries 18 and 19). To corroborate further the reactivity and enantioselectivity of the bisoxazoline catalyst **III**, trifluoroacetaldehyde hydrate (**2b**) and trifluoroacetaldehyde ethyl hemiacetal (**2c**) were also tested under the optimized reaction conditions. The target product **3a** was also obtained in high yield and enantioselectivity (entries 20 and 21).

Table 1. Optimization of the Organocatalytic Aldol Reaction[a]

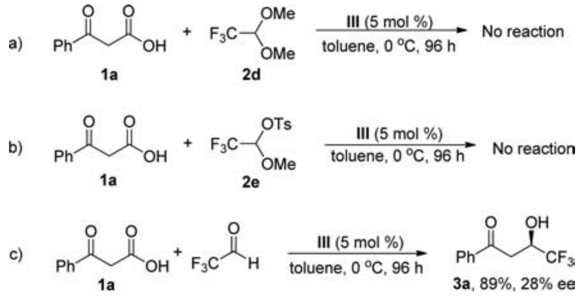


entry	catalyst (mol %)/ substrate 2	solvent/temp (°C)/ time (h)	yield (%)[b]	ee (%)[c]
1	**I** (10)/**2a**	CH_2Cl_2/0/48	89	26
2	**II** (10)/**2a**	CH_2Cl_2/0/48	90	11
3	**III** (10)/**2a**	CH_2Cl_2/0/48	91	88
4	**IV** (10)/**2a**	CH_2Cl_2/0/48	88	47
5	**V** (10)/**2a**	CH_2Cl_2/0/48	89	17
6	**VI** (10)/**2a**	CH_2Cl_2/0/48	86	10
7	**VII** (10)/**2a**	CH_2Cl_2/0/48	88	6
8	**VIII** (10)/**2a**	CH_2Cl_2/0/48	85	16
9	**IX** (10)/**2a**	CH_2Cl_2/0/48	90	10
10	**III** (10)/**2a**	THF/0/48	92	84
11	**III** (10)/**2a**	Et_2O/0/48	89	64
12	**III** (10)/**2a**	MeOH/0/48	0	0
13	**III** (10)/**2a**	hexane/0/48	72	78
14	**III** (10)/**2a**	toluene/0/48	92	95
15	**III** (10)/**2a**	toluene/0/96	98	95
16	**III** (5)/**2a**	toluene/0/96	98	95
17	**III** (1)/**2a**	toluene/0/120	90	90
18	**III** (5)/**2a**	toluene/10/96	88	90
19	**III** (5)/**2a**	toluene/25/96	80	83
20	**III** (5)/**2b**	toluene/0/96	95	90
21	**III** (5)/**2c**	toluene/0/96	95	93

[a] The reactions were carried out using **1a** (0.3 mmol, 49.2 mg), **2a**–**c** (0.2 mmol), and chiral bisoxazoline catalysts **I**–**IX** (1–10 mol %) in the solvent at the stated temperature for the stated time. [b] Isolated yields obtained as averages of two runs. [c] Determined by chiral-phase HPLC. The absolute configuration of **3a** is based on a comparison of the optical rotation with the literature value.[11,12]



Scheme 1. Several Control Reactions



In order to compare with trifluoroacetaldehyde hydrate and hemiacetals, we also carried out two control experiments using acetals **2d** and **2e** as the substrates. However, no desired product **3a** was observed under the otherwise identical reaction conditions (Scheme 1a,b). In addition, subjecting trifluoroacetaldehyde to the optimum reaction conditions delivered the aldol product **3a** in 89% yield, albeit with low enantioselectivity (28% ee) (Scheme 1c). These experimental results revealed that the hydroxyl group of the hydrate and hemiacetal substrates is critically important to both the activity and enantioselectivity of this aldol reaction, in which the hydrate and hemiacetals can be activated and oriented by hydrogen

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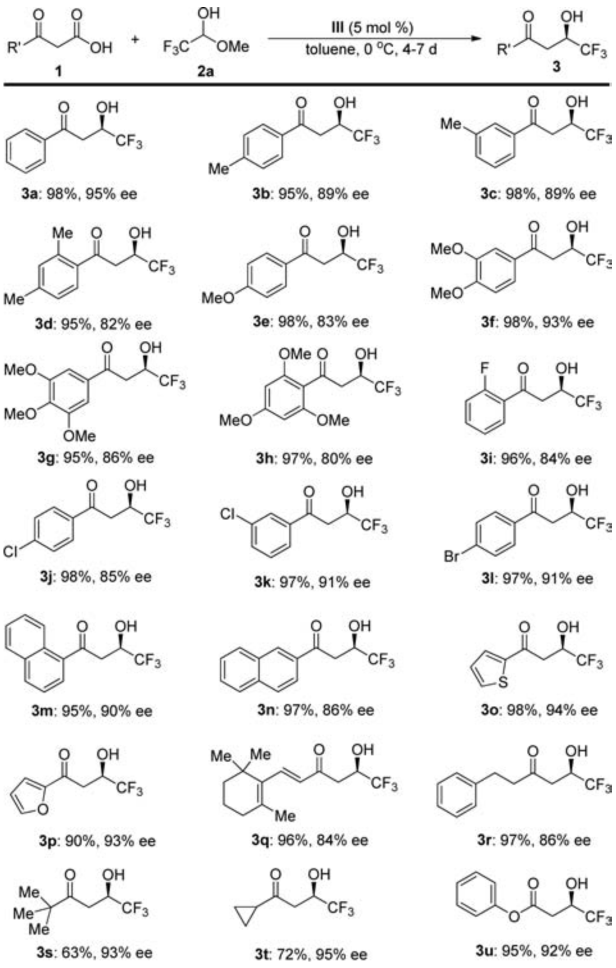
bonding with the bisoxazoline catalyst. To probe the interaction between substrates and catalyst, we conducted some NMR spectroscopic experiments (see SI-Figures 2−5). When bisoxazoline catalyst **III** was added to a solution of trifluoroacetaldehyde methyl hemiacetal **2a** in $[D_8]$-toluene, the broad singlet of the OH proton of **2a** at 2.48 ppm rapidly disappeared. In addition, as the loading amount of the bisoxazoline catalyst was increased from 0.1 to 1 equiv, the quartet signals of the CH proton and carbon of **2a** became a doublet of quartets at 4.34 and 93.40 ppm (^{1}H and ^{13}C NMR), respectively (SI-Figures 2 and 3), whereas the doublet for the CF_3 group was converted to a triplet signal at −82.38 ppm (^{19}F NMR) (SI-Figure 4). This indicates that two diastereomeric complexes stemmed from the interaction of the bisoxazoline and hemiacetal. Similar ^{1}H NMR experiments were carried out using a mixture of a β-keto acid and bisoxazoline catalyst **III** in $[D_8]$-toluene (SI-Figure 5). It was found that the sharp singlet of the CO_2H proton at 12.35 ppm became a broad singlet. Furthermore, upon addition of 1 equiv of catalyst **III** to a solution of the β-keto acid in $[D_8]$-toluene, two singlet signals (at 12.35 ppm for the acid proton and at 10.15 ppm for the enol proton) of the β-keto acid rapidly disappeared, and a new broad singlet at 8.42 ppm appeared, indicating the formation of a novel hydrogen-bonding complex.

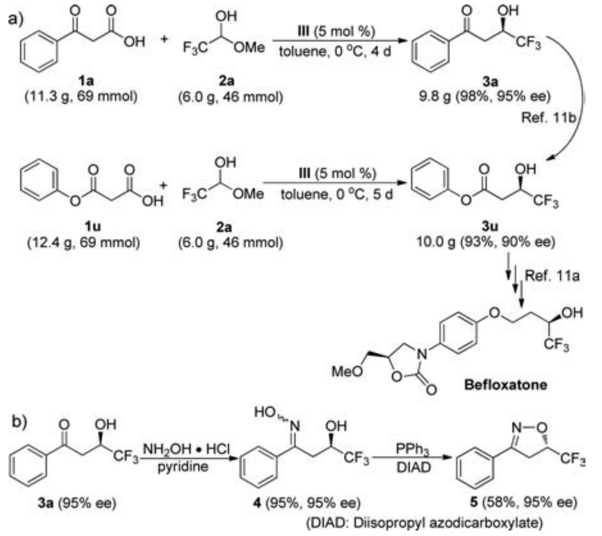
With the optimal conditions in hand, we turned our attention to an investigation of the substrate scope, and the results are summarized in Scheme 2. In the presence of 5 mol % bisoxazoline **III**, the reactions of *ortho*-, *meta*-, and *para*-substituted phenyl β-keto acids with trifluoroacetaldehyde methyl hemiacetal **2a** all proceeded smoothly, thus generating the aldol products **3a−l** in consistently excellent yields (95−98%) with good to high enantioselectivities (80−95% ee). 1-Naphthyl-, 2-naphthyl-, 2-thiophenyl-, and 2-furanyl-substituted β-keto acids were also found to be good substrates, delivering the desired products **3m−p** in high yields and enantioselectivities. Also, a β-ionone-derived β-keto acid was subjected to this aldol reaction under the same conditions, and the corresponding product **3q** was obtained in 96% yield with 86% ee. It is noteworthy that alkyl-substituted β-keto acids could also be used as the nucleophilic partner, and good results were obtained for the aldol adducts **3r−t**. To further define the scope of our methodology, the reaction of the less reactive malonic acid half oxyester with **2a** was tested. The decarboxylative aldol condensation of this substrate proceeded efficiently to give the product **3u** in 95% yield with 92% ee.

Scheme 2. Scope of This Electrophilic Reaction



With the success of the bisoxazoline-catalyzed aldol reaction as a means to provide chiral trifluoromethylated alcohols with the carbonyl functionality, we decided to explore the synthetic scalability and application of this asymmetric transformation (Scheme 3). As expected, almost the same results were obtained when the enantioselective aldol condensation of β-carbonyl acids **1a** and **1u** with trifluoroacetaldehyde methyl hemiacetal **2a** was run on a decagram scale. Notably, the chiral bisoxazoline catalyst was easily recovered by flash chromatography in excellent yield (94%). The recovered catalyst could be reused without any loss of reactivity and enantioselectivity. Both of the aldol products **3a** and **3u** are versatile synthetic intermediates and can be readily transformed to the antidepressant drug befloxatone following literature procedures (Scheme 3a).[11a,b] Moreover, the trifluoromethylated β-keto alcohols are also important intermediates for the synthesis of biologically active isoxazoles.[11c,d] For example, a hydroxylamination process using $NH_2OH{\cdot}HCl$ gave rise to the corresponding ketoxime **4**, which was then converted into trifluoromethylated isoxazoline **5** by means of a Mitsunobu cyclization.[14] In all of these processes, no loss of enantiomeric purity was observed (Scheme 3b).

Scheme 3. Scaled-Up Reaction and Further Transformation



In summary, we have proved that C_2-symmmetric chiral bisoxazolines can be employed as small-molecule hydrogen-bond-acceptor catalysts for enantioselective synthesis. The development of an organocatalytic asymmetric decarboxylative aldol reaction of β-carbonyl acids with trifluoroacetaldehyde hemiacetals is especially notable given the high enantioselectivity and the demonstrable applicability of this method to the facile synthesis of biologically active agents. This study should encourage further development of novel asymmetric transformations by directly using C_2-symmmetric chiral bisoxazolines as organocatalysts. We also anticipate that the hydrogen-bond-acceptor catalysis will open a new avenue for enantioselective synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03256.

Experimental details and NMR data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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