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Asymmetric sp^3 C–H functionalization via a chiral Brønsted acid-catalyzed redox reaction for the synthesis of cyclic aminals

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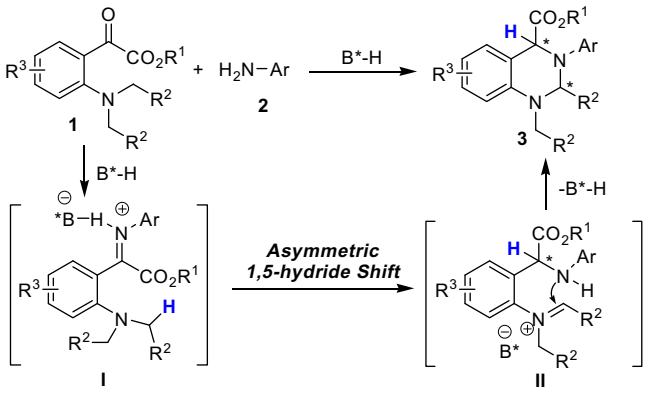
ABSTRACT

An organocatalytic asymmetric tandem 1,5-hydride transfer/ring closing reaction of *o*-aminobenzoketones with anilines to give cyclic aminals in fairly good diastereo- and enantioselectivities.

Direct functionalization of relatively inactive C–H bonds has been a research topic that has been receiving increasing interest in organic chemistry because it provides a strategically new opportunity for the creation of structurally complex and diverse organic molecules.[1] In this context, the intramolecular hydride transfer reaction (intramolecular redox process) proved to be a robust strategy describing various elegant reaction processes.[2] In particular, the *tert*-amino effect has attracted much attention triggering a number of transformations to facilely access synthetically interesting heterocycles under thermal conditions, which involve the functionalization of an α C–H bond to nitrogen.[3] However, enantioselective variants have not been available until Seidel and Kim established elegant asymmetric tandem 1,5-hydride transfer/ring closing reactions by using either chiral Lewis acid or organocatalyst, enabling the efficient synthesis of ring-fused tetrahydroquinolines in high enantiopurity.[4] More significantly, Akiyama established an elegant Brønsted acid-catalyzed 1,5-hydride transfer/ring closure to furnish tetrahydroquinolines in excellent levels of enantioselectivity.[5]

Previously, Akiyama and Seidel independently demonstrated that *o*-aminobenzaldehydes were able to be transformed into cyclic aminals under the catalysis of Brønsted acids, which proceeded via a 1,5-hydride shift process, whereas an enantioselective variant has not been described.[6] Herein, we will report an asymmetric synthesis of cyclic aminals via Brønsted acid-catalyzed redox reaction of *o*-aminobenzoketones **1** with anilines **2**. In principle, this reaction proceeds initially with the condensation of *o*-aminobenzoketone with aniline in the presence of a chiral Brønsted acid to generate an iminium species, which is presumably able to undergo an asymmetric 1,5-hydride shift process and a subsequent ring closing reaction to give a cyclic aminal (Scheme 1).

The validation of the hypothesis began with a reaction of ethyl 2-oxo-2-(2-(pyrrolidinyl)phenyl)acetate (**1a**) with 4-methoxyaniline (**2a**) conducted in toluene at 115 °C by using phosphoric acid **4a** as the catalyst. To our delight, the sequential condensation, [1,5] hydrogen shift, and 6-*endo* cyclization underwent smoothly to furnish an *endo*-diastereomer **3a** in 78% yield and a high diastereoselectivity, albeit with a low ee (Table 1, entry 1). Encouraged



Scheme 1. Proposed chiral Brønsted acid-catalyzed redox reaction for the synthesis of cyclic aminals.

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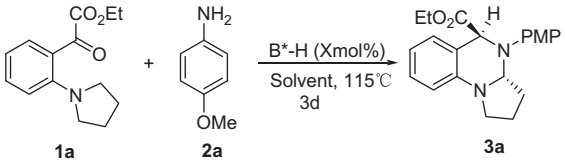
Table 1
Screening chiral phosphoric acids and optimizing reaction conditions[a]



1a 2a 3a

Entry	B*-H	X	Solvent	Yield[b] (%)	dr[c]	ee[d] (%)
1	**4a**	10	Toluene	78	12:1	−11[j]
2	**4b**	10	Toluene	60	12:1	−46[j]
3	**4c**	10	Toluene	66	7:1	−9[j]
4	**5a**	5	Toluene	80	14:1	85
5	**5b**	5	Toluene	87	12:1	27
6[e]	**5a**	5	Toluene	Trace	—	—
7[f]	**5a**	5	Toluene	51	10:1	90
8[g]	**5a**	5	Toluene	72	13:1	89
9	**5a**	5	PhCl	71	15:1	86
10	**5a**	5	*o*-Xylene	66	13:1	89
11	**5a**	5	*m*-Xylene	78	8:1	83
12	**5a**	5	*p*-Xylene	60	10:1	82
13[h]	**5a**	5	Toluene	86	14:1	80
14[i]	**5a**	5	Toluene	77	7:1	87
15	**5a**	10	Toluene	90	14:1	86

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in a solvent (1 mL), and the ratio of **1a**/**2a** is 1/1.25.
[b] Combined yield of both diastereomers.
[c] Diastereomeric ratio is determined by ^{1}H NMR spectroscopic analysis.
[d] Enantiomeric excess of major diastereomer is determined by chiral HPLC analysis.
[e] 3 Å MS was used.
[f] 4 Å MS was used.
[g] 5 Å MS was used.
[h] 0.5 mL toluene was used.
[i] 2 mL toluene was used.
[j] The opposite enantiomer was obtained to **3a**.

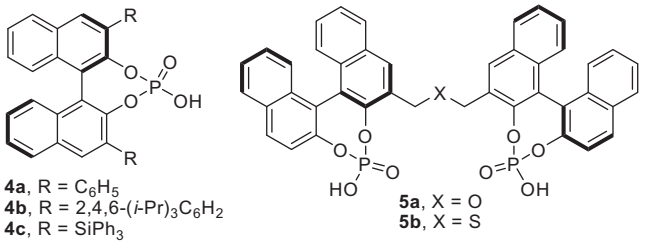
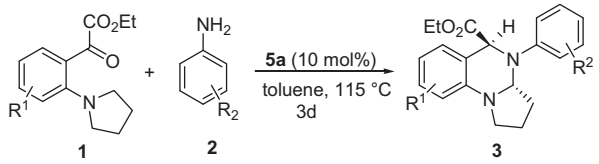


Figure 1. The catalysts evaluated in this study.

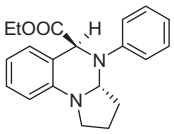
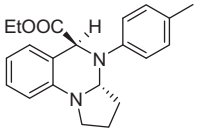
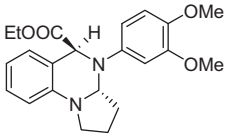
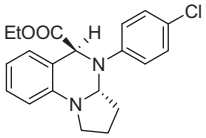
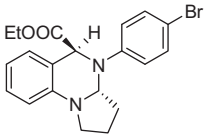
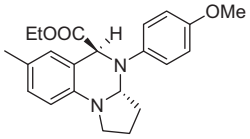
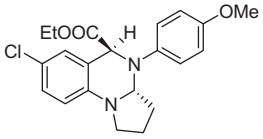
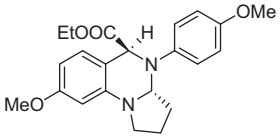
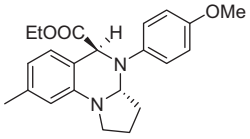
by this preliminary result, a number of chiral phosphoric acids derived from BINOL were evaluated (Fig. 1). It appeared that none of these catalysts provided satisfactory levels of enantioselectivity, although they showed good catalytic efficiency (Table 1, entries 1–3). Gratifyingly, the bisphosphoric acid **5a**,[7] was the most promising catalyst and provided an excellent yield and a high enantioselectivity of 85% ee (Table 1, entry 4). However, the bisphosphoric acid **5b** with a 3,3′-thiobis(methylene) linker offered a poor ee albeit in a high yield and diastereomeric ratio (Table 1, entry 5).

With the optimal catalyst **5a** in hand, further investigation was focused on the effect of reaction parameters including solvents, molecular sieves, and concentrations. The addition of molecular sieves led to a slight improvement in the enantioselectivity, but with a considerable erosion of the yield. For instance, the presence of 3 Å MS almost completely inhibited the reaction (Table 1, entry 6). The use of 4 Å and 5 Å MS as additives gave higher enantiomerical outcomes, but diminished yields were obtained (Table 1, entries 7 and 8 vs 4). Screening of solvents found that toluene was the best media for the reaction in terms of the conversion and stereoselectivity (Table 1, entries 4, and 9–12). Lowering the concentration eroded the enantioselectivity while elevating the

Table 2
Catalytic enantioselective tandem hydride transfer/ring closing reaction[a]



1 2 3

Entry	Product		Yield[b] (%)	*dr*[c]	*ee*[d] (%)
1		**3b**	81	10:1	74
2		**3c**	67	11:1	78
3		**3d**	76	10:1	79
4		**3e**	72	8:1	77
5		**3f**	57	10:1	80
6		**3g**	72	5:1	72
7		**3h**	44	7:1	74
8		**3i**	32	11:1	84
9		**3j**	55	5:1	84

[a] The reaction was carried out on a 0.1 mmol scale in toluene (1 mL), the ratio of **1**/**2** is 1/1.25.
[b] Combined yield of both diastereomers.
[c] Diastereomeric ratio is determined by ^{1}H NMR spectroscopic analysis.
[d] Enantiomeric excess of major diastereomer is determined by chiral HPLC analysis.

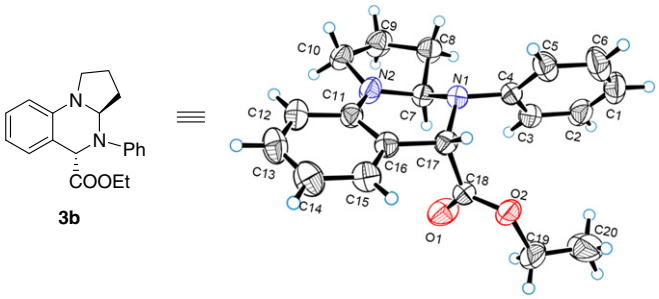


Figure 2. X-ray structure of compound **3b**.

concentration led to a diminished diastereoselectivity (Table 1, entries 13 and 14). The best result in terms of yield and stereoselectivity was obtained when the reaction was catalyzed by 10 mol % of **5a** (Table 1, entry 15, 90% yield, 86% ee).

The generality of the protocol for different substrates was next explored (Table 2). A number of anilines were first examined and it was found that either electronically donating or less withdrawing substituents on the benzene ring could be tolerated. In these cases, both diastereo- and enantioselectivities did not show great sensitivity to the substituents. Thus, a good yield and moderate enantioselectivity were obtained when aniline was used (74% ee, Table 2, entry 1) while either electronically rich anilines (methyl or methoxy) or electron-withdrawing anilines (bromo or chloro) were able to deliver **3** in good yield ranging from 57% to 76% and with high diastereomeric ratios ranging from 8/1 to 11/1 and fairly good enantioselectivities of up to 80% ee (Table 2, entries 2–5). In contrast, anilines bearing a strongly electron-withdrawing group provided a much lower yield and enantioselectivity.[8] A variety of ethyl 2-oxo-2-(2-(pyrrolidinyl)-phenyl)acetates **1** were finally examined. The introduction of electron-donating substituents at 4- or 5-position (Table 2, entries 6, 8, and 9) was well tolerable to give the desired compounds in high enantioselectivities, but the reaction conversion appeared to be highly dependent on the electronic feature. For example, a considerably lower yield was obtained in the reaction of 2-pyrrolidinyl phenyl keto esters bearing an electron-donating *para*-substituent (Table 2, entries 8 and 9), probably because the electron-donating group makes the corresponding imine functionality in situ formed less reactive toward the 1,5-hydride shift. Again, ethyl 2-(5-chloro-2-(pyrrolidin-1-yl) phenyl)-2-oxoacetate participated in the reaction in a good enantiomeric excess, but a moderate yield was offered (Table 2, entry 7). In this case, the *meta*-chloro substituent could be considered as an electron-donating group to make the keto ester electronically richer and hence a slower reaction was observed.

The absolute configuration of **3b** was determined by X-ray crystallographic analysis. After two recrystallizations, the crystalline **3b** was obtained in >99% ee. The X-ray structure revealed the absolute configuration of **3b** was assigned to be (3*R*, 5*S*) (Fig. 2).

In summary, we have disclosed an organocatalytic asymmetric tandem 1,5-hydride transfer/ring closing reaction of 2-pyrrolidinyl phenyl keto esters with anilines to give cyclic aminals in fairly good diastereo- and enantioselectivities. In this reaction, the intramolecular transfer hydrogenation (redox reaction) is the stereogenic step. This case represents the first example of organocatalytic asymmetric transfer hydrogenation of imines by exploiting inactive sp^3 C–H hydride donors in view of the fact that Hantzsch esters and other highly active hydride donors were exclusively used in the related reactions.[9,10] A further investigation on improving the stereoselectivity and on other related reactions is underway.

Acknowledgments

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Supplementary data

Supplementary data (experimental details and characterization data of new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.062.

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