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An efficient synthesis of optically active trifluoromethyl aldimines *via* asymmetric biomimetic transamination†

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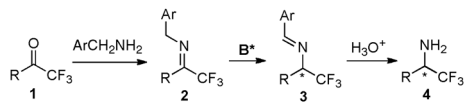
This communication describes a chiral base-catalyzed asymmetric [1,3]-proton shift of trifluoromethyl ketimines, giving a wide variety of trifluoromethyl aldimines containing various functional groups with up to 94% ee.

Optically active trifluoromethyl amines are very important functional moieties present in various biologically and medicinally significant compounds.[1,2] They are frequently prepared from imines by asymmetric reduction and nucleophilic addition.[3–7] Chiral base-catalyzed asymmetric [1,3]-proton shift of trifluoromethyl ketimines to aldimines provides another attractive approach to enantiomerically enriched trifluoromethyl amines and their derivatives.[8,9] An early example of asymmetric synthesis of trifluoromethyl-β-amino acids *via* such a process was reported by Soloshonok and co-workers in 1994.[8a] In later studies, Plaquevent and co-workers showed that as high as 71% ee was obtained.[8d] Recently, we reported an efficient chiral base-catalyzed biomimetic transamination of α-keto esters to α-amino esters with high ee's.[10] Along these lines, we have been exploring if trifluoromethyl amines can also be obtained from the corresponding ketones with high enantioselectivity *via* a similar transamination process (Scheme 1). During our studies, a related study with high ee's was reported by Deng and Wu.[11] Herein, we wish to report our own efforts on this subject.



Scheme 1

Several ketimines (**5**) derived from 1,1,1-trifluoro-4-phenylbutan-2-one and different benzylamines were initially examined for the asymmetric [1,3]-proton shift using catalyst **C1** (Fig. 1) (Table 1, entries 1–5). While little conversions were observed with $BnNH_2$ and 2-Cl(C_6H_4)CH_2NH_2 (Table 1, entries 1 and 2), high conversions (72–100%) were obtained with 4-NO_2(C_6H_4)-CH_2NH_2, 4-CN(C_6H_4)CH_2NH_2, and 2-Cl–4-CN(C_6H_3)CH_2NH_2, giving the corresponding aldimines with 21–28% ee (Table 1, entries 3–5) when the reactions were carried out at 55 °C in benzene. It appears that electron-withdrawing groups on benzylamines enhance the acidity of the benzylic hydrogen and facilitate the proton shift. To further improve the enantioselectivity, various quinine NH derivatives at the 6′ position were subsequently investigated with 2-Cl–4-CN(C_6H_3)CH_2NH_2 as an amine donor (Table 1, entries 6–14). Results show that the steric and electronic effects of the nitrogen substituent have a significant impact on the enantioselectivity. In general, catalysts with nitrogen substituents (**C2–C10**) gave higher ee's than those with the OH group (**C1**). A catalyst with benzenesulfonamide (**C6**), which was shown to be highly enantioselective for the transamination of α-keto ester,[10c] gave 76% ee in this case (Table 1, entry 10). Lower ee's were obtained for catalysts with

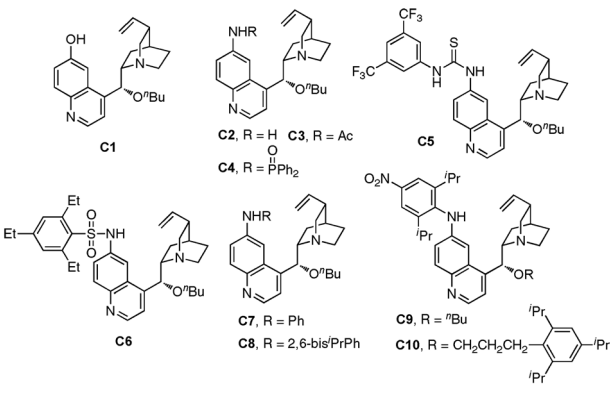


Fig. 1 Selected examples of catalysts examined.

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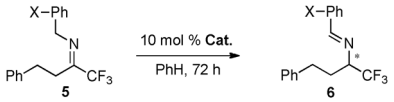
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, HPLC data for determination of enantiomeric excesses, X-ray structure of ketimine **7a** (CCDC 912043), and NMR spectra. See DOI: 10.1039/c2cc37423d

Table 1 Studies on benzylamines and catalysts[a]



Entry	X	Cat.	T (°C)	Conv.[b] (%)	ee[c] (%)
1	H	**C1**	55	Trace	—
2	2-Cl	**C1**	55	Trace	—
3	4-NO_2	**C1**	55	100	21
4	4-CN	**C1**	55	72	25
5	2-Cl–4-CN	**C1**	55	100	28
6	2-Cl–4-CN	**C2**	55	100	60
7	2-Cl–4-CN	**C3**	55	100	61
8	2-Cl–4-CN	**C4**	55	100	39
9	2-Cl–4-CN	**C5**	55	100	58
10	2-Cl–4-CN	**C6**	55	100	76
11	2-Cl–4-CN	**C7**	55	100	68
12	2-Cl–4-CN	**C8**	55	100	79
13	2-Cl–4-CN	**C9**	55	100	87
14	2-Cl–4-CN	**C10**	55	100	89
15	2-Cl–4-CN	**C10**	20	100	94

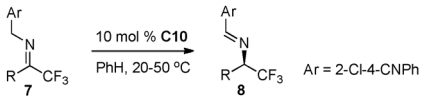
[a] All reactions were carried out with imines **5** (0.50 mmol) and catalyst (0.05 mmol) in benzene (0.50 mL) for 72 h. [b] The conversion was determined by ^{1}H NMR of the crude reaction mixture based on imines **5**. [c] The ee's were determined by chiral HPLC (Chiralcel OD-H for entry 3 and Chiralpak AD-H for entries 4–15).

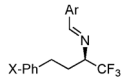
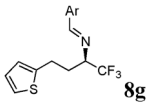
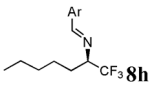
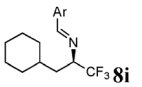
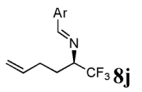
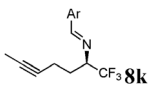
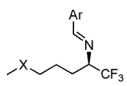
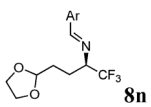
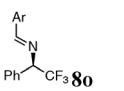
amine (**C2**), acetylamine (**C3**), diphenylphosphinic amide (**C4**), and thiourea (**C5**) (Table 1, entries 6–9). Catalysts with anilines were also synthesized and examined for the reaction. A catalyst with 4-NO_2–2,6-diisopropylaniline (**C10**) gave the highest ee (89%) (Table 1, entry 14). The ee was further increased to 94% when the reaction temperature was lowered to 20 °C (Table 1, entry 15). The 2,6-diisopropyl and NO_2 groups on the aniline are beneficial for the enantioselectivity (Table 1, entries 11–13).

As shown in Table 2, the asymmetric [1,3]-proton shift catalyzed by **C10** can be applied to a wide variety of trifluoromethyl ketimines generated from 2-Cl–4-CN(C_6H_3)CH_2NH_2 to give the corresponding aldimines in 92–99% yield and with up to 94% ee. Ketimines derived from various substituted 1,1,1-trifluoro-4-phenylbutan-2-ones gave similarly high ee (Table 2, entries 1–6), indicating that the substituent on the phenyl group of the substrate had little effect on the enantioselectivity. High yield and ee were also obtained for a substrate containing thiophene (Table 2, entry 7). Trifluoromethyl ketimines with non-aromatic groups were also found to be effective substrates, giving the aldimines in 93–99% yield and with 86–94% ee (Table 2, entries 8–14). The side chains can contain saturated (Table 2, entries 8 and 9) or unsaturated aliphatic groups (Table 2, entries 10 and 11) and heteroatoms like O and S (Table 2, entries 12–14). It is particularly worth mentioning that high yields were obtained in all these cases. However, lower ee was obtained with ketimine derived from 2,2,2-trifluoroacetophenone (Table 2, entry 15).

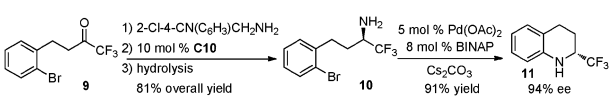
The resulting aldimines could be readily hydrolyzed to optically active trifluoromethyl amines. Such an example is shown in Scheme 2. Chiral trifluoromethyl amine **10** can be obtained from ketone **9** in 81% overall yield. The Pd-catalyzed cyclization[12] of **10** led to chiral 2-trifluoromethyl tetrahydroquinoline **11**

Table 2 Catalytic asymmetric [1,3]-proton shift of trifluoromethyl imines[a]



Entry	Imine (**8**)[b]	Yield[c] (%)	ee[d] (%)
			
1	**8a**, X = H	99	94
2	**8b**, X = *o*-Cl	99	94
3	**8c**, X = *o*-Br	98	94
4	**8d**, X = *p*-Me	99	94
5	**8e**, X = *p*-Cl	99	93
6	**8f**, X = *p*-OCH_3	98	94
7	 **8g**	92	91
8	 **8h**	95	94
9	 **8i**	96	94
10	 **8j**	93	91
11	 **8k**	95	90
			
12	**8l**, X = O	93	86
13	**8m**, X = S	99	90
14	 **8n**	94	86
15	 **8o**	99	67

[a] All reactions were carried out with imines **7** (0.50 mmol) and catalyst **C10** (0.05 mmol) in benzene (0.50 mL). For entries 1–6, 11 and 15, the reactions were carried out at 20 °C for 72 h. For entries 7, 8, 10, and 12–14, the reactions were carried out at 35 °C for 72 h. For entry 9, the reaction was carried out at 35 °C for 72 h and another 24 h at 50 °C. [b] For entries 1 and 15, the absolute configuration (*R*) was determined by comparing the optical rotation with the reported ones of the corresponding HCl salt after hydrolysis (ref. 7*a*). The absolute configurations of remaining imines were tentatively proposed by analogy. [c] The isolated yield based on imines 7. [d] The ee's were determined by chiral HPLC (Chiralpak AD-H column for entries 1, 4–6 and 15; Chiralcel OD-H column for entries 2, 3 and 13; and Chiralpak AS-H column for entries 7–12 and 14).



Scheme 2

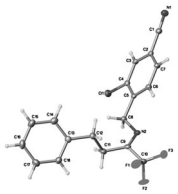


Fig. 2 The X-ray structure of ketimine **7a**.

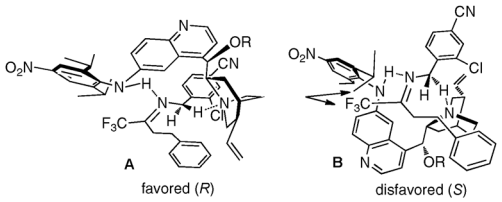


Fig. 3 The proposed transition model for transamination.

(a potentially useful structure moiety in drug design)[2a] in 91% yield and with 94% ee.

A precise understanding of the origin of the enantioselectivity awaits further study. Based on the X-ray structure of ketimine **7a** (Fig. 2), a plausible transition state model is proposed in Fig. 3. The NH group is likely to form a hydrogen bond with the imine of the substrate to facilitate the deprotonation. The 4-NO_2 group on the aniline may increase the acidity of the NH group and consequently enhance the hydrogen bonding. The (*S*)-trifluoromethyl aldimine is disfavored probably due to the unfavorable interaction between the isopropyl group of the catalyst and the trifluoromethyl group of the substrate in transition state B.

In summary, we have developed an efficient quinine-derived chiral base-catalyzed asymmetric [1,3]-proton shift process for trifluoromethyl ketimines to produce a wide variety of trifluoromethyl aldimines in 92–99% yield and with up to 94% ee. The resulting aldimine can be readily converted to optically active trifluoromethyl amine. The current process further demonstrates that organocatalytic biomimetic transamination provides a useful approach to synthesize optically active amine derivatives from carbonyl compounds. The development of more effective catalytic systems and the expansion of other carbonyl substrates are currently underway.

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