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Catalytic asymmetric synthesis of α-(trifluoromethyl)benzylamine via cinchonidine derived base-catalyzed biomimetic 1,3-proton shift reaction

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Abstract

Here we describe catalytic asymmetric synthesis of α-(trifluoromethyl)benzylamine (**1**) via biomimetic transamination using chiral base. Imine **4** was isomerized to Schiff base **5** using 50 mol.% of cinchonidine derivatives as a catalyst in chloroform, methanol or acetonitrile. In the case of cinchonidine **6** as a catalyst, the reaction conducted in chloroform allowed for 79% conversion of the starting imine **4** in 52 days. The product imine **5** was obtained of (*R*) absolute configuration in 35% ee as individual compound without any byproducts. The catalyst **6** can be recovered (>95%) by adding *n*-hexane to the reaction mixture followed by a simple filtration.

Keywords: 1,3-Proton shift reaction; Fluorine and compounds; Imines; Operationally convenient conditions; Biomimetic reductive amination; Cinchonidine derived bases; Catalytic asymmetric synthesis

1. Introduction

In the recent years, the interest in the synthesis of fluoroorganic compounds has been continuously increasing because of unique effect that a fluorine atom or fluorine-containing substituents can impart on physical (materials) and biological (agrochemicals and pharmaceuticals) properties of organic compounds. In particular, trifluoromethyl-containing amines are important building blocks [1] in preparation of various fluorinated biologically active compounds [2]. Therefore, many research groups are focusing their interest on development of new methods for preparation of trifluoromethyl-containing amino compounds [3].

Over the recent decade, we have developed general methodology for practical preparation of fluorine-containing amino compounds via biomimetic transamination reaction (Scheme 1) [4,5]. In this approach, the benzylamine or its analogs acts as a source of nitrogen and the reducing reagent at the same time. The key transformation, 1,3-proton shift, can be efficiently catalyzed by organic bases such as triethylamine or DBU. Stoichiometric asymmetric version of this biomimetic transamination has been developed using enantiomers of α-(phenyl)ethylamine in place of the benzylamine. In particular, synthesis of α-(trifluoromethyl)benzylamine (**1**) via this biomimetic transamination has been reported by our group [3a]. On the other hand, the catalytic version of this practically useful reactions still remains virtually unexplored [6].

Here we describe an example of catalytic asymmetric biomimetic transformation of achiral imine derived from benzylamine and trifluoroacetophenone using some derivatives of cinchonidine as chiral base-catalysts, for the synthesis of α-(trifluoromethyl)benzylamine **1**.

2. Results and discussion

Cinchonidine derivatives **6–10** were synthesized from commercially available cinchonidine **6** (Fig. 1) using standard literature procedures [7]. The starting imine **4** was readily synthesized from α,α,α-trifluoroacetophenone **2** and benzylamine **3** in a pure form (>99.5%) after purification by short silica gel column chromatography and distillation (Scheme 2) [8]. The target imine **5** is known to be prone to racemization under a basic conditions due to the relatively high C–H acidity (configurationally unstable) of the proton directly attached to the stereogenic center. Therefore all reactions were conducted at room temperature to prevent any racemization. The

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Scheme 1.

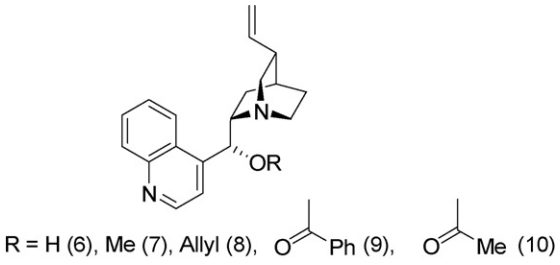


Fig. 1.

isomerization of imine **4** to Schiff base **5** were studied in chloroform using 50 mol.% of chiral bases (**6–10**). The results are summarized in Table 1.

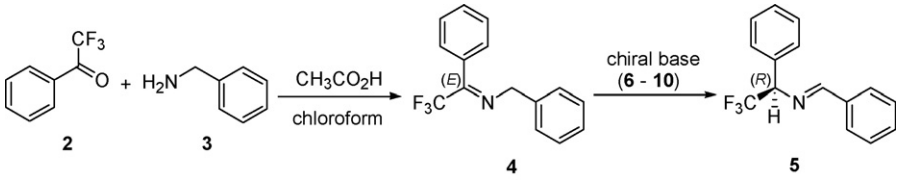
The most striking results we obtained are that the acylated derivatives **9** and **10** (entries 4 and 5) were virtually catalytically inactive while the unsubstituted cinchonidine **6** and its methyl **7** and allyl **8** derivatives showed a decent catalytic activity (entries 1, 2 and 3). These results can be rationalized considering the increased steric bulk around the nitrogen in the derivatives **9** and **10** as compared with **6–8**. Additionally, considering the electronic differences between **9**, **10** and **6–8**, one may suggest that the electron withdrawing ester functional group in **9** and **10** might lower the basicity of the amino group in these derivatives and therefore render them catalytically inactive.

In general the rates of the reactions catalyzed by the derivatives **6–8** were low. Thus, the unsubstituted cinchonidine **6** was found to be the most catalytically active followed by *O*-methyl **7** and *O*-allyl **8** derivatives. This order of catalytic activity strongly suggested that the steric bulk around the basic amino group in the cinchonidine derivatives may have a critical effect on their catalytic properties. On the other hand, determination of the enantioselectivity of these catalytic isomerizations revealed that in all three reactions catalyzed by the derivatives **6–8** the sense and degree of the asymmetric induction were virtually the same. Thus, the products **5** were obtained of (*R*) absolute configuration in 34–35% ee.

The effect of a solvent in these reactions was studied next. To this end the series of the derivatives **6–8**-catalyzed isomerizations of **4** to **5** were conducted in acetonitrile and methanol as a solvent instead of chloroform. The results of this study are collected in Table 2. In the case of the reactions conducted in methanol, approximately 85% of conversion was obtained after 55 days, which a slightly better conversion compared to the results obtained in chloroform. Unfortunately these reactions were less selective as about 16% of byproduct was observed, and obtained % ee was not improved (entries 1, 2 and 3). Using acetonitrile as a solvent, the reaction rate was significantly accelerated, and within 15 days the reactions were almost complete allowing the isolation of products **5** in virtually quantitative yield (entries 4 and 5). Unfortunately the % ee were lower as compared with the stereochemical outcome obtained for the reactions conducted in chloroform. On the other hand, the sense of the asymmetric induction was the same in all solvents studied as (*R*) configured **5** were obtained as major products. Taking into account all results obtained, one may suggest that the best conditions were using cinchonidine **6** as a catalyst in chloroform (Table 1, entry 1), because cinchonidine **6** was commercially available and relatively inexpensive. Moreover, since the catalyst **6** is not soluble in *n*-hexane, it was possible to recover (~95%) the catalyst **6** by adding *n*-hexane to the reaction mixture followed by filtration of the precipitated **6**. The recovery catalyst was used again to catalyze the isomerization conducted in chloroform and showed virtually the same catalytic activity (Table 2, entry 6).

The obtained imine **5** was hydrolyzed to give amine **1** in quantitative yield (Scheme 3). Further optical purification of the amine **1** of 35% ee to the enantiomerically pure form (>99.5% ee) was achieved using fractional crystallization of its salt with L-tartaric acid, as described in the literature [9].

To rationalize the stereochemical outcome of the reaction, the preference for the enantiomer of (*R*) absolute configuration, the following four transition states **A–D** can be considered (Fig. 2). Two transition state **A** and **C** would lead to the (*R*)-configured product **5** (major enantiomer) and **B** and **D** would give product with (*S*) absolute configuration (minor enantiomer). Taking into account that recent data strongly suggest that the stereochemically efficient bulk of a trifluoromethyl group is lager than that of a phenyl group [10], imine **4** is expected to be of (*E*) geometry. Considering steric bulk of the aromatic ring of cinchonidine **6** and imine **4**, TSs **C** and **D** can be ruled out as highly unlikely. On the other hand, in the TSs **A** and **B** there is steric interaction between the imine **4** and the substituents of the



Scheme 2.

Table 1
Isomerization of **4** to **5** using derivatives of cinchonidine **6–10** in chloroform

Entry	Cat.	Conversion (%)[a]					% ee
		8 day	31 day	38 day	45 day	52 day	
1	**6**	19	57	69	73	79	35
2	**7**	14	48	57	64	69	34
3	**8**	9	38	42	49	53	34
4	**9**	<1	2	2	4	4	–
5	**10**	<1	<1	<1	<1	<1	–

[a] The progress of the reactions was monitored by ^{19}F NMR.

Table 2
Isomerization of **4** to **5** using derivatives of cinchonidine **6–8**

Entry	Sovent	Cat.	Conversion (%)[a]					Sel.	% ee
			15 day	22 day	29 day	48 day	55 day		
1	MeOH	**6**	39	53	63	82	85	84	13
2	MeOH	**7**	33	45	56	74	78	84	37
3	MeOH	**8**	28	40	88	84	82	82	30
4	Acetonitrile	**7**	97	–	–	–	–	98	26
5	Acetonitrile	**8**	97	–	–	–	–	98	28
6	Chloroform	**6**[b]	34	47	58	76	–	–	–

[a] The progress of the reactions was monitored by ^{19}F NMR.
[b] Recovered catalyst.

amino group of cinchonidine **6**, which probably are responsible for the stereodifferentiation during the 1,3-proton transfer. Thus considering the steric interactions in the TS **A** and **B**, and taking into account that the stereochemically efficient bulk of a trifluoromethyl group is lager than that of a phenyl group, one might assume that the repulsive steric interaction in TS **A** between the phenyl group of imine **4** and the amino moiety of the catalyst **6**, can be more efficiently accommodated than the interaction between the trifluoromethyl group and the amine residue. However, considering modest level of asymmetric induction (35% ee), the difference in the stereochemical interactions in the TS **A** and **B** is not dramatic.

In summary, we have developed catalytic asymmetric synthesis of α-(trifluoromethyl)benzylamine **1** via biomimetic transamination using chiral external base as a catalyst. Imine **4** was isomerized to imine **5** using 50 mol.% of cinchonidine catalyst **6** in chloroform with about 35% ee. Optical pure amine **1** was obtained after hydrolysis of imine **5**, followed by recrystallization of its L-tartaric acid salt. The catalyst **6** can be efficiently recovered by adding *n*-hexane to the reaction mixture followed by filtration.

3. Experimental

3.1. General methods

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All the reactions were carried out under regular atmosphere without any special caution to exclude air. Yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H NMR spectrometry.

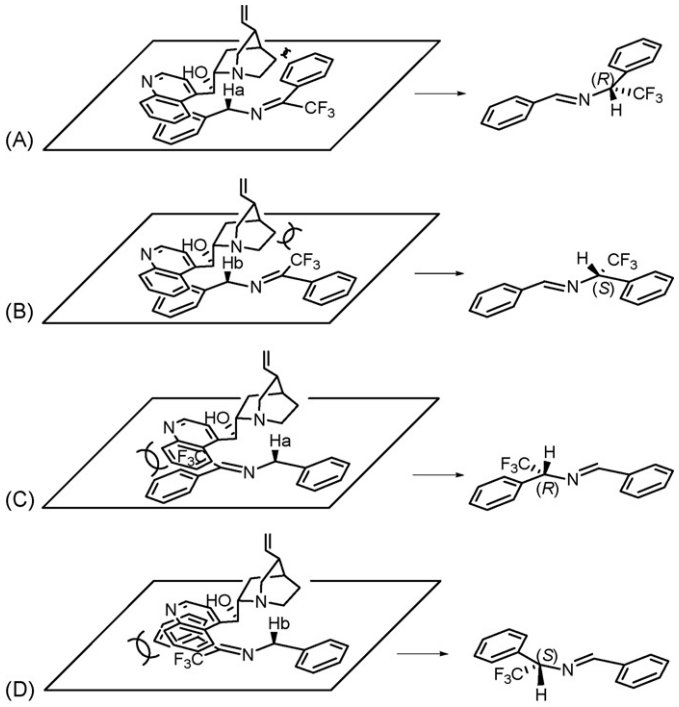
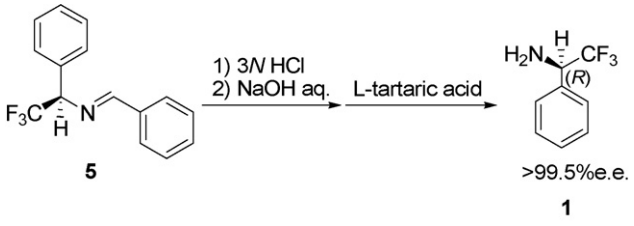


Fig. 2.

3.2. Synthesis of the α-(trifluoromethyl)benzylamine (*1*)

To the solution imine **4** (2.0 g, 7.60 mmol) in chloroform (24 mL), cinchonidine **6** (1.2 g, 50 mol.%,) was added at room temperature. The progress of the reactions was monitored by ^{19}F NMR. After the reaction, *n*-hexane (96 mL) was added, and the mixture stirred for 12 h at room temperature, and filtered. The precipitate could be used as a catalyst without any further purification. The solvent of the filtrate was removed under reduced pressure, and the residue was purified by column chromatography to remove a small amount of cinchonidine **6** to give imine **5** in quantitative yield. Imine **5** was stirred with 3N HCl (16 mL) and diethyl ether (10 mL) for 1 day at room temperature. After separation, 3N NaOH aq. was added to the aqueous layer until the solution became pH-14. After extraction with ethyl acetate, the solvent was removed under reduced pressure to give amine **1** (1.2 g, 6.74 mmol, 35.0% ee.). To the solution of imine **1** in 2-propanol (6.7 mL) and benzene (8.8 mL), L-tartaric acid (1.0 g, 6.74 mmol) was added at room



Scheme 3.

temperature. After dissolving the acid by heating the solution at 80 °C, the solution was cooled down to room temperature to precipitate the crystals. Five consecutive crystallizations gave the L-tartaric acid salt with amine **1** of at least 99.5% ee. (0.52 g, 1.59 mmol). The salt was decompoused with 3N NaOH, and amine **1** was extracted with ethyl acetate. The solvent was evaporated under reduced pressure to give amine **1** (0.26 g, 1.51 mmol, 99.5% ee.).

*3.3. Determination of the enantiomeric purity of the amine **1***

Imine **5** (0.13 g, 0.494 mmol) was stirred with 3N HCl (1.5 mL) and diethyl ether (1.0 mL) for 1 day at rt. After separation, 3N NaOH aq. was added to the aqueous layer until the solution became pH-14. After extraction with ethyl acetate, the ethyl acetate was removed under reduced pressure to give amine **1**. To the solution of triethylamine and amine **1** in dichloromethane, 3,5-dinitorobenzoyl chloride was added. The solution was stirred for 3 h at room temperature and the resulting mixture was washed with water. The organic layer was evaporated under reduced pressure. Thus, obtained product was used for determination of the enantiomeric purity. Since the compounds of this type, with trifluoromethyl group directly bonded to the stereogenic center, are prone to the enantiomer self-disproportionation effect [11], the corresponding 3,5-dinitorobenzoyl derivative [3a] of amine **1** was not isolated and the crude product was used for HPLC analyses.

Column: SUMICHIRAL OA-4500; eluent: *n*-hexane/dichloromethane/ethanol = 60/30/10; retention times: 14.7 min for (*S*) and 16.1 min for (*R*).

Acknowledgements

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References

[1] V.A. Soloshonok (Ed.), Fluorine-containing Synthons, ACS Symposium Series #911, Oxford University Press, 2005.
[2] V.A. Soloshonok, K. Mikami, T. Yamazaki, J.T. Welch, J. Honek (Eds.), Current Fluoroorganic Chemistry. New Synthetic Directions, Technologies, Materials and Biological Applications, ACS Symposium Series #949, Oxford University Press, 2006.
[3] (a) V.A. Soloshonok, T. Ono, J. Org. Chem. 62 (1997) 3030;
(b) B. Torok, G.K.S. Prakash, Adv. Synth. Catal. 345 (2003) 165;
(c) F. Gosselin, P.D. O'Shea, S. Roy, R.A. Reamer, C. Chen, R.P. Volante, Org. Lett. 7 (2005) 355;
(d) F. Huguenot, T. Brigaud, J. Org. Chem. 71 (2006) 7075;
(e) C. Lauzon, A.B. Charette, Org. Lett. 8 (2006) 2743;
(f) G.K.S. Prakash, R. Mogi, G.A. Olah, Org. Lett. 8 (2006) 3589.
[4] For full papers on biomimetic transamination of fluorinated carbonyl compounds, see:
(a) T. Ono, V.P. Kukhar, V.A. Soloshonok, J. Org. Chem. 61 (1996) 6563;
(b) V.A. Soloshonok, T. Ono, Tetrahedron 52 (1996) 14701;
(c) V.A. Soloshonok, V.P. Kukhar, Tetrahedron 52 (1996) 6953;
(d) V.A. Soloshonok, V.P. Kukhar, Tetrahedron 53 (1997) 8307;
(e) V.A. Soloshonok, I.V. Soloshonok, V.P. Kukhar, V.K. Svedas, J. Org. Chem. 63 (1998) 1878.
[5] For recent advances, see:
(a) V.A. Soloshonok, M. Yasumoto, J. Fluor. Chem. 127 (2006) 889;
(b) V.A. Soloshonok, H. Ohkura, M. Yasumoto, J. Fluor. Chem. 127 (2006) 924;
(c) V.A. Soloshonok, H. Ohkura, M. Yasumoto, J. Fluor. Chem. 127 (2006) 930;
(d) V.A. Soloshonok, H. Ohkura, K. Uneyama, Tetrahedron Lett. 43 (2002) 5449.
[6] V.A. Soloshonok, A.G. Kirilenko, S.V. Galushko, V.P. Kukhar, Tetrahedron Lett. 35 (1994) 5063.
[7] S. Diezi, A. Szabo, T. Mallat, A. Baiker, Tetahedron Asymmetry 14 (2003) 2573–2577.
[8] D.O. Berbasov, I.D. Ojemaye, V.A. Soloshonok, J. Fluor. Chem. 125 (2004) 603.
[9] Y. Wang, H.S. Mosher, Tetrahedron Lett. 32 (1991) 987–990.
[10] For our discussions on this subject see the following papers and references in them:
(a) V.A. Soloshonok, V.P. Kukhar, S.V. Galushko, N.Y. Svistunova, D.V. Avilov, N.A. Kuzmina, N.I. Raevski, Y.T. Struchkov, A.P. Pisarevsky, Y.N. Belokon, J. Chem. Soc. Perkin. Trans. 1 (1993) 3143–3155;
(b) V.A. Soloshonok, T. Hayashi, K. Ishikawa, N. Nagashima, Tetrahedron Lett. 35 (1994) 1055–1058;
(c) V.A. Soloshonok, D.V. Avilov, V.P. Kukhar, Tetrahedron 52 (1996) 12433–12442;
(d) V.A. Soloshonok, A.D. Kacharov, D.V. Avilov, T. Hayashi, Tetrahedron Lett. 37 (1996) 7845–7848;
(e) V.A. Soloshonok, A.D. Kacharov, D.V. Avilov, K. Ishikawa, N. Nagashima, T. Hayashi, J. Org. Chem. 62 (1997) 3470–3479;
(f) M. Kanai, M. Yasumoto, Y. Kuriyama, K. Inomiya, Y. Katsuhara, K. Higashiyama, A. Ishii, Org. Lett. 5 (2003) 1007–1010.
[11] (a) V.A. Soloshonok, Angew. Chem. In. Ed. Engl. 45 (2006) 766–769;
(b) V.A. Soloshonok, D.O. Berbasov, J. Fluor. Chem. 127 (2006) 597–603;
(c) V.A. Soloshonok, D.O. Berbasov, Chim. Oggi/Chem. Today 24 (2006) 44–47.