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Highly Efficient Synthesis of Chiral α-CF_3 Amines via Rh-Catalyzed Asymmetric Hydrogenation

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Supporting Information

ABSTRACT: Highly enantioselective catalytic asymmetric hydrogenation of α-CF_3-enamides has been achieved by employing rhodium−DuanPhos as the catalyst, which provides a readily accessible method for the synthesis of chiral trifluoromethylated amines. The reaction has a broad substrate scope; both aryl- and alkyl-substituted α-CF_3-enamides worked smoothly and afford the corresponding chiral amines in high yields and excellent enantioselectivities (up to 99% ee).

Fluorinated compounds have been widely used in pharmaceuticals, agrochemicals, materials, and fragrances because of their unique properties and proven physicochemical properties,[1,2] of which chiral α-substituted trifluoromethylamino compounds are especially important and have been developed as several well-known drugs (Figure 1).[3] Thus, the efficient synthesis of trifluoromethylated amine derivatives has attracted considerable attention, and many approaches have been developed. Examples of the representative methods to chiral α-trifluoromethylated amines include nucleophilic trifluoromethylation of *N*-*tert*-butylsulfinyl imines,[4] catalytic asymmetric reduction of trifluoromethyl ketoimines,[5] ring-opening reactions of active trifluoromethylated epoxide,[6] catalytic enantioselectivity isomerization or asymmetric proton shift of trifluoromethyl imines,[7] and kinetic resolution of racemic amines by using optically pure acids.[8] However, these process suffer from some drawbacks such as limited substrate scope and poor yields and enantioselectivities. On the other hand, asymmetric hydrogenation of α-CF_3-enamides, one of the most straightforward and environmentally benign approaches toward the synthesis of chiral trifluoromethylated amines, has not been achieved, probably because of the highly electron-withdrawing nature of the CF_3 group in the olefinic substrates. Therefore, developing a common methodology with broad substrates for asymmetric synthesis of α-trifluoromethylated amines by hydrogenation is highly desirable.

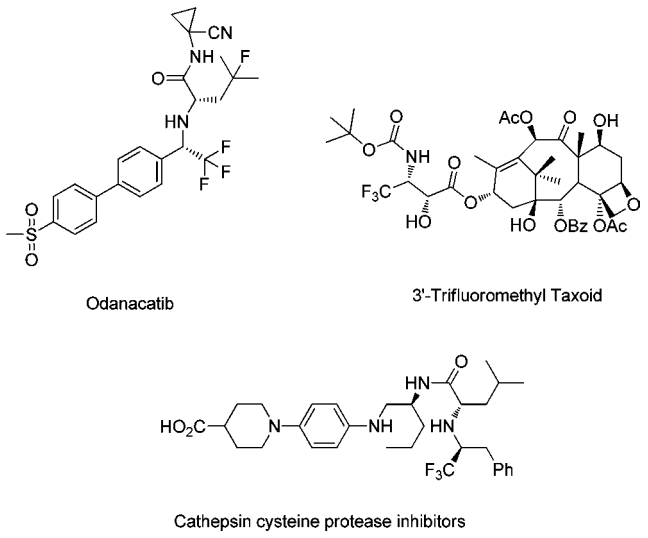

Figure 1. Examples of viologically active trifluoromethylated amino compounds.

In the past decades, asymmetric hydrogenation of enamides has become one of the most powerful strategies toward the synthesis of chiral amines and their derivatives.[9,10] In this context, our group developed a series of electron-rich and rigid P-chiral biphosphine ligands and achieved asymmetric hydrogenation of a series of multiply substituted enamides,[9a] including electron-deficient β-acylamino nitroolefins and β-acetylamino acrylosulfones,[10e,f] which heightened our interest in hydrogenation of electron-deficient enamides. Herein, we describe a highly efficient approach of synthesis of chiral trifluoromethylated amines by Rh-catalyzed asymmetric hydrogentaion.

Initially, α-trifluoromethylated enamides were easily prepared by condensation of ketone with acetamide according to reported procedure (Scheme 1),[11] and then α-CF_3-substituted

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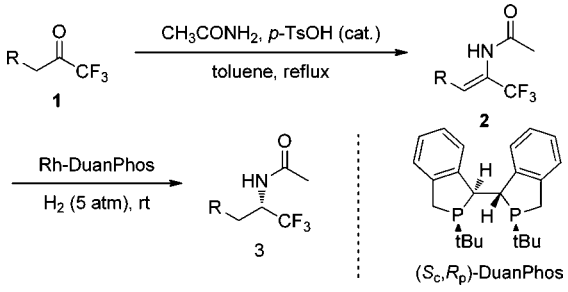
Scheme 1. Synthesis of Chiral α-Trifluoromethylated Amines through Hydrogenation of Enamides



enamide **2a** was chosen as a model substrate to optimize the reaction conditions. First, a variety of diphosphine ligands developed in our group and some commercial available chiral ligands were examined (Figure 2).

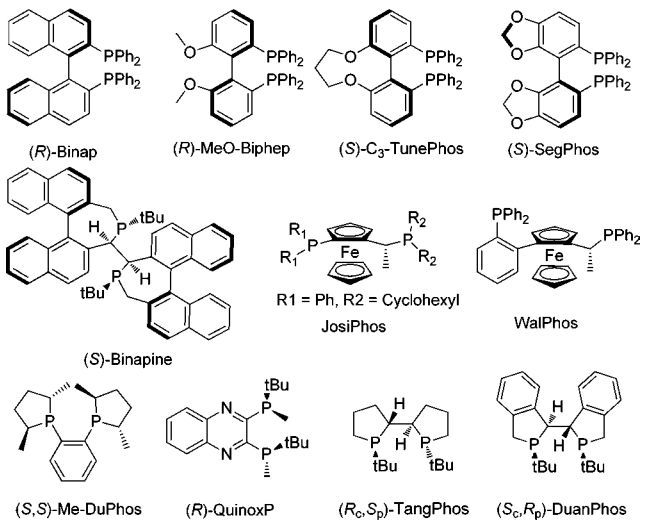


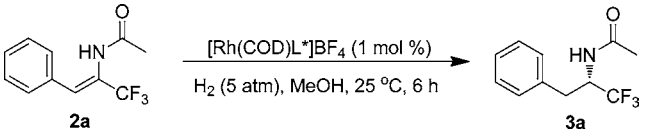
Figure 2. Structures of the phosphine ligands for hydrogenation of **2a**.

As shown in Table 1, the chiral biaryl bisphosphorus ligands exhibited good activities but only with poor to moderate enantioselectivities (Table 1, entries 1−5). When chiral ferrocenyl ligands and P-chiral diphosphine ligands were employed, the reaction worked very well and gave the desired product with complete conversion, but the enantioselectivity is great affected by the electronic effect (Table 1, entries 6−11). Generally, electron-donating P-chiral diphosphine ligands lead to excellent ee values, of which (R_c,S_p)-TangPhos and (S_c,R_p)-DuanPhos developed in our group gave the best results. When the the catalyst loading was decreased to 0.1 mol %, there was no effect on the conversion and enantioselectivities when (S_c,R_p)-DuanPhos was employed, but the ee value was slightly decreased when (R_c,S_p)-TangPhos was used as catalyst (Table 1, entries 12 and 13).

In order to further optimize the reaction conditions, a series of solvents were screened carefully. As shown in Table 2, all solvents examined here except for ethyl acetate were tolerated for this reaction, of which methanol is slightly better than other solvents in enantioselectivities (Table 2, entries 1−5).

Under the optimized conditions, ($Rh(COD)_2BF_4$/DuanPhos/MeOH/25 °C), the scope of α-trifluoromethylated enamides **2** was examined. As shown in Table 3, all reactions proceeded smoothly to give the desired α-CF_3-amines **3a−m** in

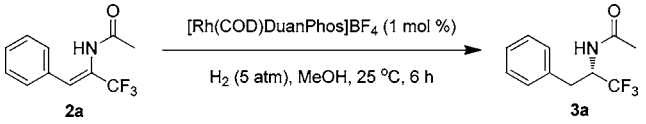
Table 1. Ligand Screening for Rh-Catalyzed Asymmetric Hydrogenation of 2a[a]



entry	ligand	conversion[b] (%)	ee[c] (%)
1	(*R*)-Binap	77	5
2	(*R*)-MeO-Biphep	87	29
3	(*S*)-C_3-TunePhos	82	48
4	(*S*)-SegPhos	81	55
5	(*S*)-Binapine	87	39
6	JosiPhos	>99	82
7	WalPhos	>99	8
8	(*S,S*)-Me-DuPhos	>99	93
9	(*R*)-QuinoxP	>99	98
10	(R_c,S_p)-TangPhos	>99	99
11	(S_c,R_p)-DuanPhos	>99	99
12[d]	(R_c,S_p)-TangPhos	>99	96
13[d]	(S_c,R_p)-DuanPhos	>99	99

[a]All reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature under 5 atm hydrogen pressure for 6 h. [b]Determined by ^{1}H NMR spectroscopy. [c]The ee value was determined by HPLC on a chiral phase. [d]0.1 mol % of catalysis, 30 atm, 24 h.

Table 2. Solvent Screening for Rh-Catalyzed Asymmetric Hydrogenation of 2a[a]



entry	solvent	conversion[b] (%)	ee[c] (%)
1	MeOH	>99	99
2	EtOH	>99	95
3	*i*-PrOH	>99	97
4	ethyl acetate	trace	
5	CH_2Cl_2	>99	98
6	dioxane	>99	96

[a]All reactions were carried out with a substrate/Rh−DuanPhos catalyst ratio of 100:1 in MeOH for 6 h. [b]Determined by ^{1}H NMR spectroscopy. [c]The ee value was determined by HPLC on a chiral phase.

94−97% and 97−99% ee. Aryl substrates with electron-rich and deficient substituents were suitable for this reaction (Table 3, entries 1−10). Replacing the aryl group with a fused aryl or heteroaryl group was well tolerated (Table 3, entries 11 and 12). Moreover, the hydrogenation of alkyl-substituted enamide **2m** furnished α-CF_3-amines **3m** in high yield with 97% ee (Table 3, entries 13). When the catalyst loading was decreased to 0.1 mol %, a higher H_2 pressure and a longer reaction time were needed to maintain the same conversion and enantioselectivity (Table 3, entries 14).The absolute configuration of product **3a** was confirmed to be *S*.[12]

In summary, we have developed an efficient approach toward the synthesis of chiral trifluoromethylated amines, enabled by the realization of an unprecedented highly enantioselective that is applicable to both aryl and alkyl trifluoromethyl enamides. The hydrogenation of substrates gave the desired products in excellent yields and enantioselectivities. It is believed that this

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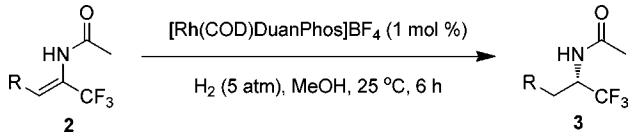
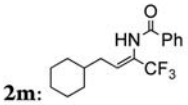
Table 3. Rh-Catalyzed Asymmetric Hydrogenation of α-CF_3-enamides[a]



entry	substrate	product	yield (%)[b]	ee (%)[c]
1	**2a**: R = Ph	**3a**	97	99
2	**2b**: R = 4-MePh	**3b**	96	99
3	**2c**: R = 3-MePh	**3c**	94	99
4	**2d**: R = 2-MePh	**3d**	93	97
5	**2e**: R = 4-ClPh	**3e**	97	99
6	**2f**: R = 3-ClPh	**3f**	94	99
7	**2g**: R = 2-ClPh	**3g**	93	99
8	**2h**: R = 4-FPh	**3h**	95	99
9	**2i**: R = 4-MeOPh	**3i**	96	98
10	**2j**: R = 4-^{t}BuPh	**3j**	96	99
11	**2k**: R = 2-napthyl	**3k**	95	99
12	**2l**: R = 2-thienyl	**3l**	94	99
13	 **2m**:	**3m**	96	97
14[d]	**2a**: R = Ph	**3a**	97	99

[a]Unless otherwise mentioned, all reactions were carried out with a substrate/catalyst ratio of 100:1 in MeOH at room temperature under 5 atm hydrogen pressure for 6 h. [b]The yield of the isolated product based on consumed starting material. [c]Determined by chiral HPLC analysis. [d]0.1 mol % of catalysis, 10 atm, 12 h.

strategy will provide a novel way for making chiral α-trifluoromethylated amines. Further investigations on asymmetric hydrogenation of functionalized enamides are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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