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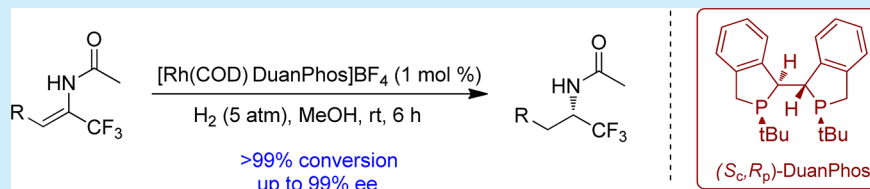
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Highly Efficient Synthesis of Chiral α -CF₃ Amines via Rh-Catalyzed Asymmetric Hydrogenation

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S Supporting Information



ABSTRACT: Highly enantioselective catalytic asymmetric hydrogenation of α -CF₃-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 -CF₃-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 ketimines,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 -CF₃-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 CF₃ 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.

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 biphenyl phosphine 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 hydrogenation.

Initially, α -trifluoromethylated enamides were easily prepared by condensation of ketone with acetamide according to reported procedure (Scheme 1),¹¹ and then α -CF₃-substituted

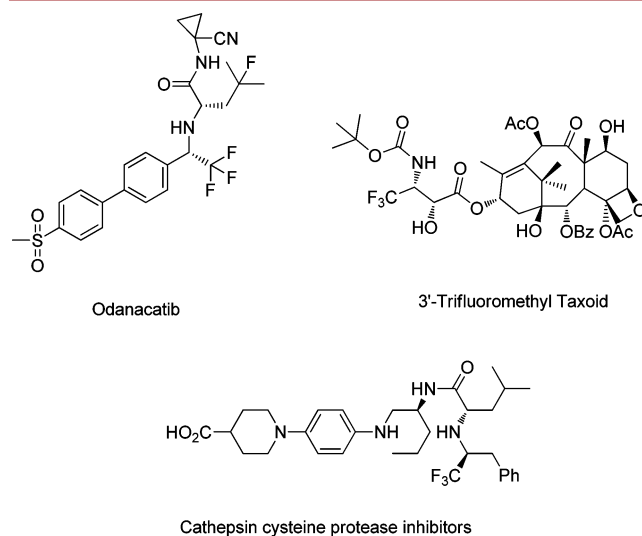
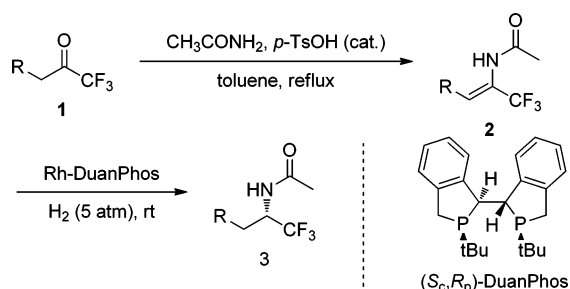


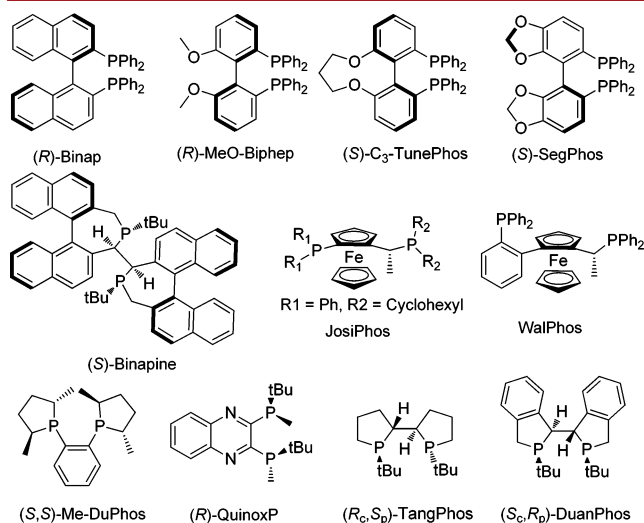
Figure 1. Examples of biologically active trifluoromethylated amino compounds.

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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 greatly 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 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 -CF₃-amines **3a–m** in

Table 1. Ligand Screening for Rh-Catalyzed Asymmetric Hydrogenation of **2a**^a

entry	ligand	conversion ^b (%)	ee ^c (%)
1	(<i>R</i>)-Binap	77	5
2	(<i>R</i>)-MeO-Biphep	87	29
3	(<i>S</i>)-C ₃ -TunePhos	82	48
4	(<i>S</i>)-SegPhos	81	55
5	(<i>S</i>)-Binapine	87	39
6	JosiPhos	>99	82
7	WalPhos	>99	8
8	(<i>S,S</i>)-Me-DuPhos	>99	93
9	(<i>R</i>)-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

^aAll reactions were carried out with a substrate/catalyst ratio of 100:1 at room temperature under 5 atm hydrogen pressure for 6 h. ^bDetermined by ¹H NMR spectroscopy. ^cThe ee value was determined by HPLC on a chiral phase. ^d0.1 mol % of catalysis, 30 atm, 24 h.

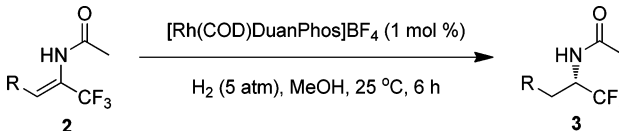
Table 2. Solvent Screening for Rh-Catalyzed Asymmetric Hydrogenation of **2a**^a

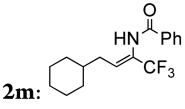
entry	solvent	conversion ^b (%)	ee ^c (%)
1	MeOH	>99	99
2	EtOH	>99	95
3	<i>i</i> -PrOH	>99	97
4	ethyl acetate	trace	
5	CH ₂ Cl ₂	>99	98
6	dioxane	>99	96

^aAll reactions were carried out with a substrate/Rh–DuanPhos catalyst ratio of 100:1 in MeOH for 6 h. ^bDetermined by ¹H NMR spectroscopy. ^cThe 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 -CF₃-amines **3m** in high yield with 97% ee (Table 3, entries 13). When the catalyst loading was decreased to 0.1 mol %, a higher H₂ 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

Table 3. Rh-Catalyzed Asymmetric Hydrogenation of α -CF₃-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-naphthyl	3k	95	99
12	2l : R = 2-thienyl	3l	94	99
13	2m : 	3m	96	97
14 ^d	2a : R = Ph	3a	97	99

^aUnless 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. ^bThe yield of the isolated product based on consumed starting material. ^cDetermined by chiral HPLC analysis. ^d0.1 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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