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Synthesis of Chiral Fluorinated Propargylamines via Chemoselective Biomimetic Hydrogenation

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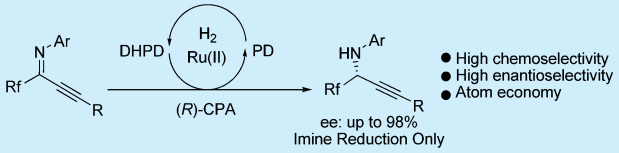
Supporting Information

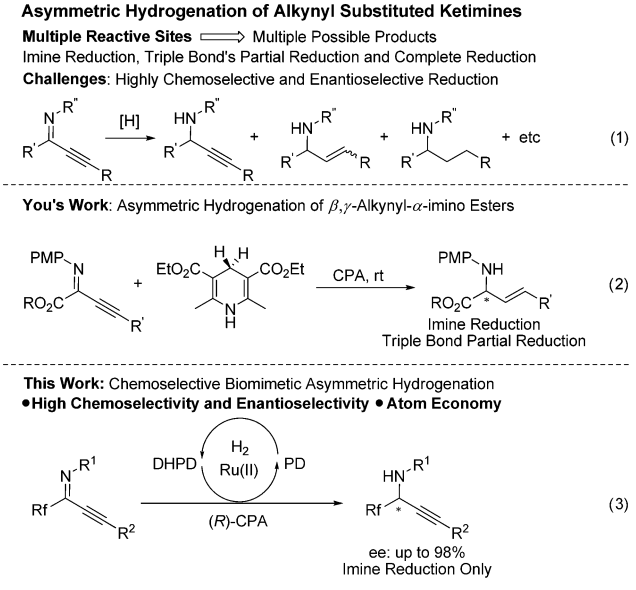
ABSTRACT: A highly enantioselective synthesis of chiral fluorinated propargylamines was developed through phosphoric acid and ruthenium-catalyzed chemoselective biomimetic hydrogenation of the carbon−nitrogen double bond of fluorinated alkynyl ketimines in the presence of a carbon−carbon triple bond. This reaction features high chemoselectivity and slow background reaction. In addition, selective transformations of the chiral fluorinated propargylamines were also reported.



Chiral propargylamines are valuable and important synthetic intermediates for the synthesis of biologically active compounds and natural products.[1] As a result, continuous efforts have been devoted to explore the facile and efficient methodologies for their construction.[2] Among these synthetically and biologically important compounds, fluorinated propargylamines occupy a particularly significant position and are expected to be a class of substantial building blocks for further derivatizations and pratical utilities, due to the fact that introduction of fluorine atoms into organic molecules can greatly modify their physical, chemical, and biological properties.[3] Despite their impressive significance, synthesis of fluorinated propargylamines is still under-explored to date, and existing strategies are typically concentrated in the asymmetric alkynylation of fluorinated imines. For instance, in 2004, the Zanda and Qing groups reported the synthesis of fluorinated propargylamines through an acetylide addition to trifluoromethyl-substituted ketimines using an *N*-sulfinyl moiety as the chiral auxiliary.[4] Later, the Zn-mediated[5a−e] and Rh-catalyzed[5f] enantioselective alkynylation of fluorinated imines were also developed. Therefore, a convenient and straightforward procedure for their preparation in optically pure form is highly demanded.

Asymmetric (transfer) hydrogenation of the alkynyl-substituted fluorinated ketimines is a potentially efficient method for the synthesis of chiral fluorinated propargylamines because of simple operation and high atom-economy. Although asymmetric hydrogenation,[6a−d] transfer hydrogenation,[6e−g] and hydrosilylation[6h] of simple fluorinated ketimines have been successfully achieved, hydrogenation of alkynyl-substituted fluorinated ketimines for the synthesis of chiral fluorinated propargylamines is still a great challenge. These difficulties can be attributed to the following factors. First, chemoselectivity for asymmetric hydrogenation of the alkynyl ketimines is difficult to control for the multiple possible reactive sites (C═N and C≡C bonds), including reduction of imine, partial reduction of the triple bond, and complete reduction of the triple bond (Scheme 1, eq 1). You's group reported an asymmetric transfer hydrogenation of

Scheme 1. Synthesis of Chiral Fluorinated Propargylamines through Chemoselective Reduction



β,γ-alkynyl-α-imino esters to afford *trans*-alkenyl-α-imino esters, which involved both C═N reduction and partial reduction of the C≡C bond (eq 2).[7a,b] Second, the C−F bond is easily cleaved in transition-metal-catalyzed systems.[7c] Herein, we report an enantioselective synthesis of fluorinated propargylamines by highly chemoselective biomimetic hydrogenation of the C═N

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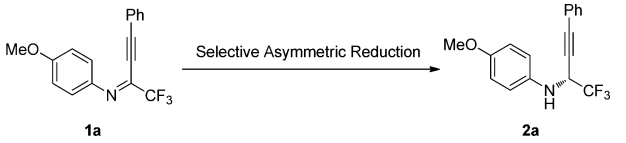
bond of fluorinated alkynyl ketimines in the presence of a C≡C bond with up to 98% ee (eq 3).

To probe the feasibility of selective asymmetric reduction synthesis of fluorinated propargylamines, 4-methoxy-*N*-(1,1,1-trifluoro-4-phenylbut-3-yn-2-ylidene)aniline (**1a**) was chosen as the model substrate (Table 1). First, we focused our attention on

Table 1. Selective Asymmetric Reduction



1a **2a**

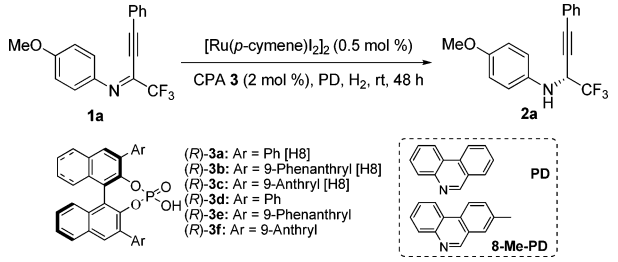
catalyst	hydrogen source	conv (%)	ee (%)
$Pd(OCOCF_3)/(R)$-BINAP	H_2	<5	
$[Ir(COD)Cl]_2/(R)$-BINAP	H_2		
CPA **3a**	HEH	<5	
CPA **3a**	benzothiazoline	6	31
CPA **3a**	DHPD	52	71

the most predominant approach for the hydrogenation of imine catalyzed by transition metal. Unfortunately, no desired product was observed with the combination of $Pd(OCOCF_3)_2/(R)$-BINAP. Meanwhile, in the presence of $[Ir(COD)Cl]_2/(R)$-BINAP, most of the starting material remained and a small amout of mixed reducted products was observed. Considering the excellent substrate tolerance and selectivity of chiral phosphoric acid catalyzed asymmetric transfer hydrogenation, we turned our attention to organocatalytic asymmetric transfer hydrogenation. Subsequently, a series of asymmetric transfer hydrogenation systems were tested. For instance, under a chiral phosphoric acid (CPA)/Hantzsch ester system originally developed by Rueping, List, and MacMillan,[8] no conversion was observed. Because the hydride transfer mode (1,4 and 1,2) and hydrogen transfer ability exerts a significant influence on the reactivity and enantioselectivity,[9] we turn to the 1,2-hydrogen sources, such as benzothiazolines, which were developed by Akiyama and serve as a versatile hydrogen source for organocatalytic transfer hydrogenation and have been widely used for asymmetric reduction of imines.[10] Moderate 31% ee of enantioselectivity was obtained using CPA/benzothiazoline for alkynyl ketimine reduction, albeit with low conversion (6%). Additionally, another simple and commercially available 1,2-hydride transfer hydrogen source was examined. Moderate reactivity (52% conversion) and enantioselectivity (71% ee) could be obtained using the CPA/dihydrophenanthridine (DHPD) system in which DHPD acts as a good biomimetic 1,2-hydrogen source.

Biomimetic hydrogenation was successfully used for the preparation of chiral compounds due to the mild conditions, a wide range of substrates, and high reactivity and enantioselectivities. Very recently, our group[9d,11] developed several models of in situ regeneration of nicotinamide adenine dinucleotide phosphate (NAD(P)H),[12] which was applied to the asymmetric biomimetic hydrogenation of a series of cyclic imines and heteroaromatics. Later, Beller and co-workers[13] developed an elegant iron-catalyzed hydrogenation of benzoxazinones with our NAD(P)H model/DHPD. The 1,2-hydride transfer hydrogen source of DHPD could be regenerated in situ under mild conditions with a unique performance.[11c] Therefore, we assumed that in situ regeneration of DHPD could be employed for the asymmetric synthesis of **2a** due to cost and availability, but this may cause a background reaction and the reduction of the C≡C bond in the presence of a transition metal catalyst.

With this consideration in mind, we further optimized the reaction conditions. Gratifyingly, **2a** was obtained with 59% conversion and 66% ee in the presence of (*R*)-CPA **3a**, $[Ru(p\text{-cymene})I_2]_2$, and PD (phenanthridine) under hydrogen gas at room temperature. Notably, **1a** was inactive without the addition of PD. Subsequently, different solvents were examined, and it was found that solvents played a crucial role in reactivity and enantioselectivity; 1,2-dichloroethane was the best choice (Table 2, entries 1–4). Then, some commercially available chiral

Table 2. Evaluation of Reaction Parameters[a]



1a **2a**

entry[a]	solvent	CPA	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	**3a**	59	66
2	THF	**3a**	4	77
3	toluene	**3a**	28	74
4	$ClCH_2CH_2Cl$	**3a**	80	79
5	$ClCH_2CH_2Cl$	**3b**	79	91
6	$ClCH_2CH_2Cl$	**3c**	79	93
7	$ClCH_2CH_2Cl$	**3d**	88	84
8	$ClCH_2CH_2Cl$	**3e**	83	93
9	$ClCH_2CH_2Cl$	**3f**	84	94
10[d]	$ClCH_2CH_2Cl$	**3f**	98	94
11[d,e]	$ClCH_2CH_2Cl$	**3f**	>95	95

[a]Conditions: **1a** (0.1 mmol), CPA **3** (2 mol %), solvent (2.0 mL), phenanthridine (10 mol %), $[Ru(p\text{-cymene})I_2]_2$ (0.5 mol %), H_2 (500 psi), rt, 48 h. [b]Conversion was determined by ^{1}HNMR. [c]Determined by chiral HPLC analysis. [d]H_2 (1000 psi). [e]8-Methylphenanthridine.

phosphoric acids were evaluated, and the best enantioselectivity was obtained with **3f** (entries 4–9). The conversion was further improved, and excellent enantioselectivity was retained with increased hydrogen pressure (entry 10). Fortunately, excellent conversion and enantioselectivity could be obtained when phenanthridine was replaced by 8-methylphenanthridine (entry 11). Thus, the optimized condition was established: $[Ru(p\text{-cymene})I_2]_2/(R)$-**3f**/$ClCH_2CH_2Cl/H_2$ (1000 psi)/8-methylphenanthridine/RT.

With the optimized conditions in hand, exploration of substrate scope was carried out (Scheme 2). Various substrates performed very well under the standard reaction conditions. It was noteworthy that the electronic properties and position of substituents on the aromatic ring (*R*) had a marginal effect on reactivity and enantioselectivity (**2a**–**e**). Subsequently, substrates with different alkyl and alkenyl at R were tested, and high yields (98%) and excellent enantioselectivities (94–95% ee) could be obtained (**2f**,**g**). Impressively, the diyne-substituted fluorinated ketimine gave 95% yield and 94% enantioselectivity (**2h**), which is a useful building block for the synthesis of agrochemicals and compounds with potential biological activity. Furthermore, various kinds of *N*-aryl-substituted substrates were also examined; both electron-donating and electron-withdrawing

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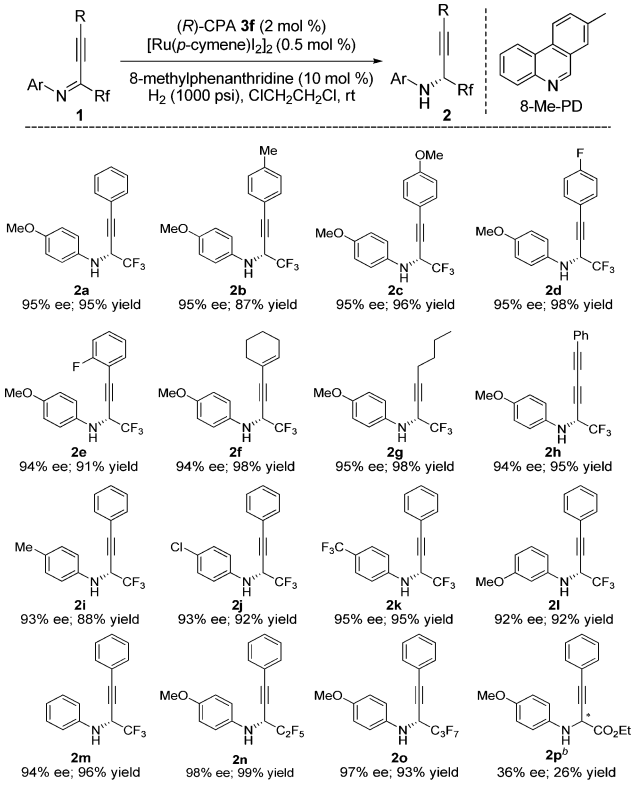
Scheme 2. Biomimetic Hydrogenation of Fluorinated Imines 1[a]



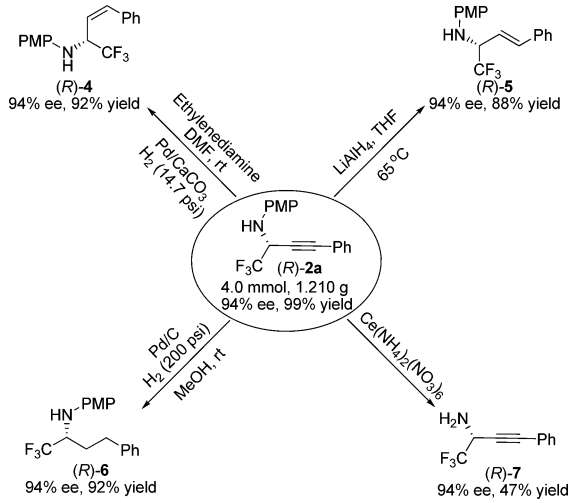
[a]Conditions: Alkynyl-substituted fluorinated ketimines **1a**−**o** (0.2 mmol), CPA **3f** (2 mol %), $ClCH_2CH_2Cl$ (2.0 mL), 8-methylphenanthridine (10 mol %), $[Ru(p\text{-cymene})I_2]_2$ (0.5 mol %), H_2 (1000 psi), rt, 48 h. Isolated yields. The ee values were determined by chiral HPLC analysis. [b]Toluene was used instead of $ClCH_2CH_2Cl$.

groups as well as *meta*-substituents did not inhibit the reactions, and the corresponding products were obtained in 88−96% yields and 92−95% ee. In addition, different perfluoroalkyl-substituted imines **1n** and **1o** were also tested, with 98 and 97% ee obtained, respectively. Meanwhile, phenylacetylenyl-substituted α-imino ester **1p** was tested for the reaction with moderate reactivity and enantioselectivity, but the carbon−carbon triple bond also remains, which is different from result reported by You's group.[7a]

After establishing the facile approach for the synthesis of fluorinated propargylamines by biomimetic asymmetric hydrogenation, we further evaluated the practical utility (Scheme 3). The biomimetic asymmetric hydrogenation of **1a** was carried out on gram scale, and the desired product was furnished with 94% ee and 99% yield. Meanwhile, the remaining C≡C bond is an attractive functional group for further modifications.[14] For example, reduction of **2a** in $Pd/CaCO_3/H_2$ and $LiAlH_4$ systems provided (*Z*)-alkene **4** and (*E*)-alkene **5** in 92 and 88% yield, respectively. Chiral amine **6** was obtained in 92% yield by complete reduction of **2a** with Pd/C. Significantly, optical purity of these reduction products still remained. The absolute configuration was determined as *R* by comparison with the sign of optical rotation of **6** reported in the literature.[6c] In addition, the *p*-methoxyphenyl group of hydrogenated products can be readily removed through oxidative cleavage of the hydrogenated product **2a**, giving the chiral primary amine (*R*)-**7**.

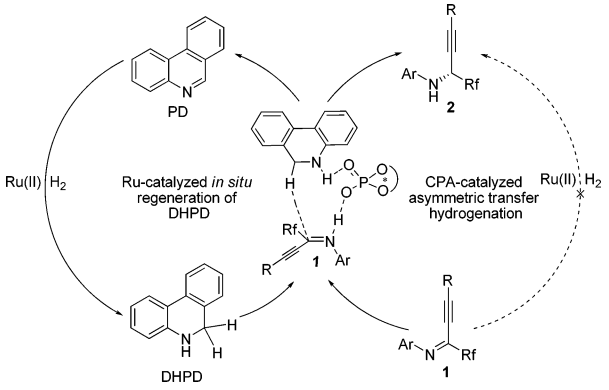
Concerning the mechanism, the chemoselective biomimetic asymmetric hydrogenation comprises two cascade redox cycles

Scheme 3. Gram Scale and Derivatization of (*R*)-2a



promoted by Ru(II)/CPA relay catalysis (Scheme 4). First, the DHPD is generated from PD by Ru-catalyzed hydrogenation.

Scheme 4. Proposed Mechanism of Biomimetic Asymmetric Hydrogenation Process



Second, the selective asymmetric transfer hydrogenation of **1** by DHPD gave the product in the presence of chiral Brønsted acid. The excellent enantioselectivity achieved in this biomimetic chemoselective asymmetric hydrogenation was attributed to the very slow background reaction and high chiral induction of organocatalyst **3**.

In summary, we have successfully developed a novel and efficient method for enantioselective synthesis of fluorinated propargylamines by chemoselective biomimetic hydrogenation with up to 98% ee. The DHPD can be generated from PD under mild conditions. Keys to success include the CPA/DHPD selective hydrogenation of the C=N bond in the presence of a C≡C bond and very slow background reactions. In addition, a series of transformations of the chiral fluorinated propargylamines have been developed. Further investigations on the applications of this method are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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