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Nickel-Catalyzed Chemoselective Asymmetric Hydrogenation of α,β-Unsaturated Ketoimines: An Efficient Approach to Chiral Allylic Amines

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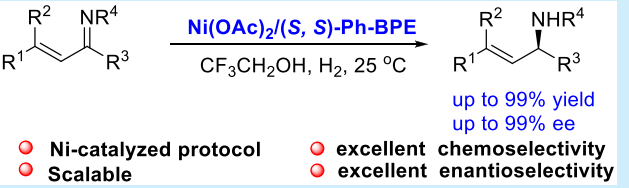
Supporting Information

ABSTRACT: An efficient synthetic route to chiral allylic amines has been developed by nickel/(*S,S*)-Ph-BPE complex catalyzed chemoselective asymmetric hydrogenation of α,β-unsaturated ketoimines. Varieties of α,β-unsaturated ketoimines have been well tolerated in this transformation to give chiral allylic amines with high yields and excellent ee values (up to 99% yield, up to 99% ee). A gram-scale reaction with 0.2 mol % catalyst loading has also been achieved.



Chiral allylic amines are valuable chiral building units for synthesis of natural products, pharmaceuticals, and bioactive molecules.[1] As a result, tremendous efforts have been focused on the synthesis of chiral allylic amines, and a great deal of methods have been well documented. The representative methods include transition metal catalyzed enantioselective allylic amination,[2] asymmetric addition of potassium alkenyltrifluoroborates to *N*-tosyl imines,[3] asymmetric reductive coupling of alkynes and imines,[4] asymmetric rearrangement of prochiral allylic imidates,[5] and asymmetric hydroamination of allenes or alkynes.[6] However, most of these approaches suffered from some drawbacks, such as poor substrate generality, high catalyst loading, and tedious operating procedures, which greatly impeded the applications of these methods in organic synthesis. Hence, the development of new synthetic methods for chiral allylic amines is highly desirable.

In past decades, transition metal catalyzed asymmetric hydrogenation has emerged as one of the most robust approaches to chiral molecules due to its high efficiency and perfect atom economy.[7] In this context, asymmetric hydrogenation of α,β-unsaturated ketoimines and α-vinyl enamines was regarded as a potential synthetic route to chiral allylic amines, and it has intrigued organic chemists for years. However, owing to the formidable difficulty in retaining the C−C double bonds during reduction, the successful examples on the preparation of chiral allylic amines by enantioselective hydrogenation are rare.[8] Furthermore, all these successful examples heavily rely on noble transition metal catalysts, which unavoidably suffered from some intrinsic shortcomings of noble metal catalyst, such as being expensive, poisonous, and environmentally deleterious. Accordingly, a cheap and efficient catalytic system for asymmetric hydrogenation is in urgent demand in green chemistry.

Recently, nickel-catalyzed asymmetric hydrogenation, because of its inherent advantages in cost and sustainability, has attracted great interest.[9] In this context, Hamada reported his pioneering work on nickel catalyzed asymmetric hydrogenation of ketones.[10] Subsquently, Zhou,[11] Chirik,[12] Zhang,[13] and our group[14] developed Ni-catalyzed enantioselective hydrogenation of imines and alkenes, which exhibited the great potential of nickel catalysts in asymmetric hydrogenation. However, to date, Ni-catalyzed chemoselective and enantioselective reduction of α,β-unsaturated ketoimines has not been reported. The possible reason lies in the fact that both ketoimines and conjugated alkenes can be well hydrogenated by nickel catalysts (Scheme 1a and 1b), which makes the chemoselective reduction of the imine group of α,β-unsaturated ketoimine extremely difficult. In addition, the reaction was further challenged by over-reduction. Inspired by our previous work on Rh-catalyzed chemoselective asymmetric hydrogenation of α-vinyl ketone/enamide[8b,c,14] and our recent work on nickel-catalyzed enantioselective hydrogenation of enamides,[15] we

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Scheme 1. Ni-Catalyzed Asymmetric Hydrogenation

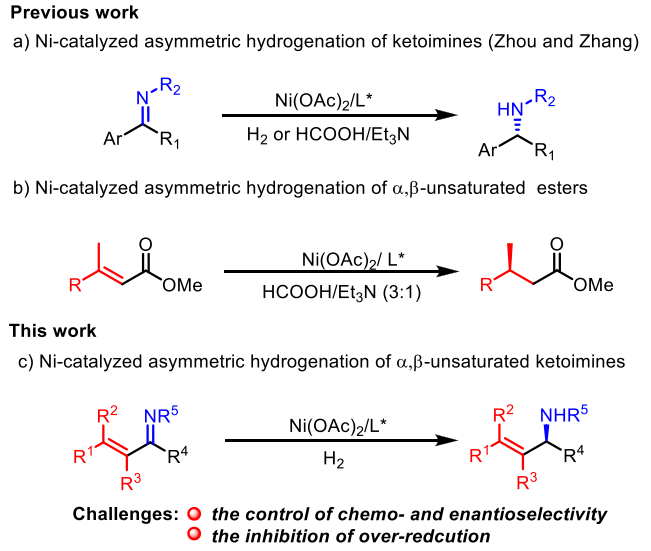
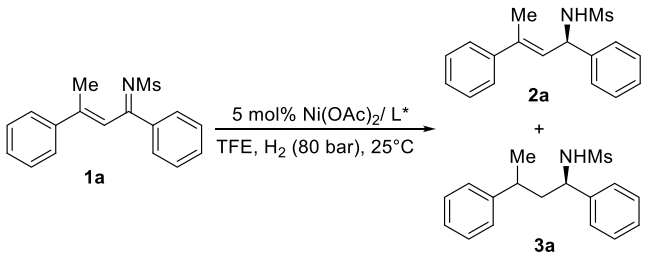


Table 1. Ligand Screening[a]



entry	ligand	conv (%)	2a/3a[b]	ee of 2a (%)[c]
1	L1	>99	62:38	90
2	L2	>99	50:50	95
3	L3	88	98:2	98
4	L4	>99	>98:2	99
5	L5	NR	NA	NA
6	L6	46	98:2	−87
7	L7	73	98:2	−79
8[d]	L4	NR	NA	NA

[a]Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), $Ni(OAc)_2$ (5 mol %), and ligand (5.5 mol %) in CF_3CH_2OH (1 mL) under H_2 (80 atm) at 25 °C for 24 h. [b]The ratio was determined by ^1H NMR analysis. [c]Determined by HPLC analysis using a chiral stationary phase. [d]No H_2 was used. NR = no reaction, NA = not available.

think ligands may play a critical role in nickel catalyzed asymmetric hydrogenation of *α,β*-unsaturated ketoimines, making it possible to achieve the modulation of chemoselectivity by choosing a proper ligand and suitable reaction conditions. Herein, we report an efficient synthetic approach to chiral allylic amines via chemo- and enantioselective hydrogenation of *α,β*-unsaturated ketoimines.

Initial investigations began with the optimization of conditions for the asymmetric hydrogenation of N-Ms protected (*E*)-1,3-diphenylbut-2-en-1-imine **1a** (Table 1). When the reaction was conducted with 5 mol % $Ni(OAc)_2$ in TFE under 80 bar of H_2 at room temperature, various chiral diphosphine ligands were screened (Figure 1). First, (*S*)-Binapine, the privileged ligand, which exhibits excellent performance in nickel-catalyzed asymmetric hydrogenation of

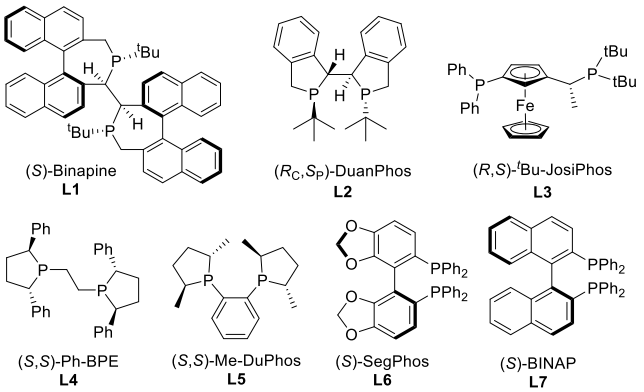
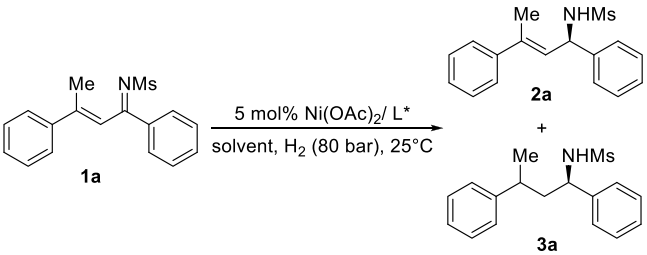


Figure 1. Structures of the phosphine ligands for asymmetric hydrogenation of **1a**.

Table 2. Solvent Screening[a]



entry	solvent	conv (%)	2a/3a[b]	ee[c](%)
1	TFE	>99	>98:2	99
2	HFIP	99	>98:2	96
3	MeOH	25	>98:2	>99
4	EtOH	8	>98:2	>99
5	IPA	3	NA	>99
6	DCM	NR	NA	NA
7	DCE	NR	NA	NA
8	1,4-dioxane	NR	NA	NA
9	THF	NR	NA	NA
10	EtOAc	NR	NA	NA
11	toluene	NR	NA	NA

[a]Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), $Ni(OAc)_2$ (5 mol %), and (*S,S*)-Ph-BPE (5.5 mol %) in solvent (1 mL) under H_2 (80 atm) at 25 °C for 24 h. [b]The ratio was determined by ^1H NMR analysis. [c]Determined by HPLC analysis using a chiral stationary phase. NR = no reaction, NA = not available.

ketoimines, was employed, and the reaction proceeded smoothly, although significant over-reduction product **3a** was detected (entry 1). Other Pchiral ligands, such as (R_C, S_P)-DuanPhos, also exhibited poor chemoselectivity in this transformation albeit with excellent catalytic activity and enantiocontrol (entry 2). To our delight, excellent chemo- and enantioselectivity were obtained when planar chiral phosphine ligand (*R,S*)-^{t}Bu-Josiphos was employed (entry 3). Further ligand screening disclosed that (*S,S*)-Ph-BPE is the best choice for this transformation, specifically affording chiral allylic amine **2a** in excellent yields with high ee values (entries 4−7). No target product was detected when the reaction was conducted without H_2, which ruled out the transfer hydrogenation pathways (entry 8).

Subsequently, the sovlent effects were evaluated and the results disclosed that the conversion of this reaction was extensively affected by the acidity of solvents. As shown in Table 2, when the acidic protic solvents, such as TFE and

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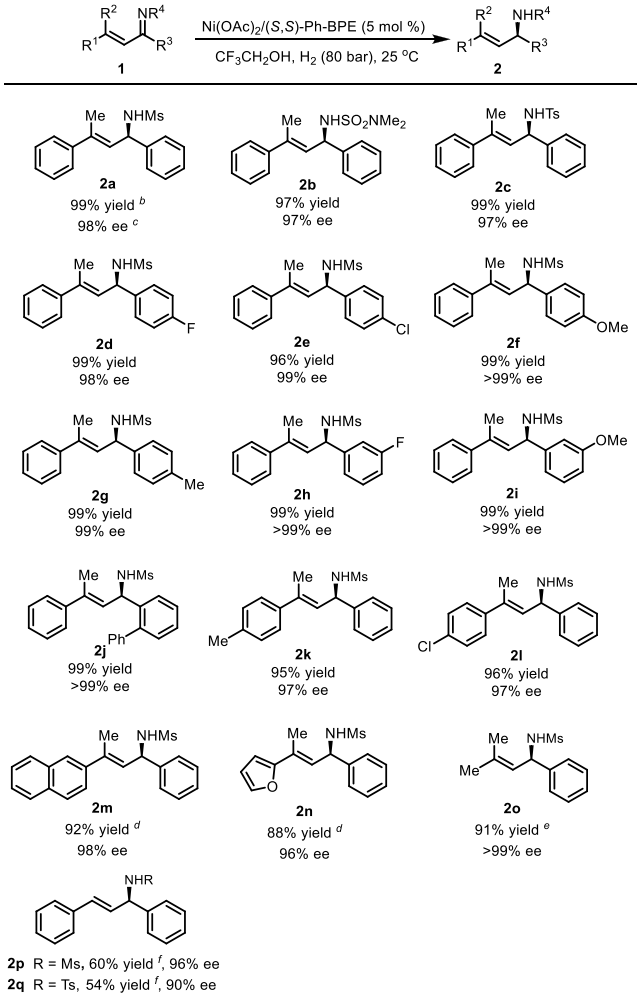
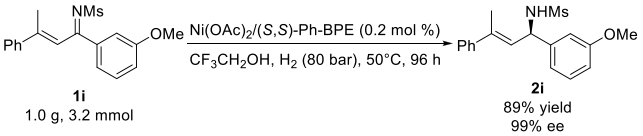
Scheme 2. Substrate Scope of Chemo- and Enantioselective Hydrogenation of α,β-Unsaturated Ketoimines[a]



[a]Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), $Ni(OAc)_2$ (5 mol %), and (*S*,*S*)-Ph-BPE (5.5 mol %) in CF_3CH_2OH (1 mL) under H_2 (80 atm) at 25 °C for 24 h. [b]Yield of the isolated product. [c]Determined by HPLC analysis using a chiral stationary phase. [d]At 50 °C. [e]Two h. [f]48 h.

Scheme 3. Gram-Scale Reaction



HFIP, were used, the reaction worked smoothly, specifically delivering the chiral allylic amine **2a** with excellent enantioselectivities (entries 1−2). Other protic solvents with less acidity, such as MeOH, EtOH, and *i*-PrOH, lead to a sharp decrease in yield, albeit with high enantioselecvity (entries 3−5). Aprotic solvents CH_2Cl_2, $ClCH_2CH_2Cl$, 1,4-dioxane, THF, EtOAc, and toluene also have detrimental effects to this transformation, causing the reaction to be completely inhibited (entries 6−11).

Under the optimized reaction conditions, we examined the substrate scope of Ni-catalyzed chemoselective asymmetric hydrogenation of α,β-unsaturated ketoimines (Scheme 2). Generally, the reaction exhibited good tolerance to various α,β-unsaturated ketoimines, furnishing a chiral allylic amine in high yields with excellent chemo- and enantioselectivities. When the protecting group of α,β-unsaturated ketoimines was changed from Ms to $-SO_2NMe_2$ or Ts, the reaction was not affected and proceeded very smoothly, affording target products in 97−99% yields with 97−98% ee (**2a**−**2c**). When R^1 and R^3 both are aryl groups, the substituents on the benzene ring have no effects on the reaction, all of them furnishing chiral allylic amines with high yields and excellent ee values. When R^1 was changed to a 2-naphthyl or 2-furanyl group, the reaction proceeded smoothly, albeit the yields decreased slightly (**2m**−**2n**). The reaction also worked very well when a methyl group replaced R^1 (**2o**). Notably, chalconeimines were also tolerated in this transformation to give target molecules (**2p**, **2q**) with moderate yields and excellent enantioselectivitities.[16,17]

To demonstrate the synthetic potential of this methodology, the gram-scale reaction was investigated with a low catalyst loading. To our delight, α, β-unsaturated ketoimine **1i** was hydrogenated with high chemoselectivity in the presence of 0.2 mol % catalyst loading, giving the corresponding product **2i** with 89% yield and 99% ee (Scheme 3).

In conclusion, we have developed nickel/(*S*,*S*)-Ph-BPE catalyzed highly chemo- and enantioselective hydrogenation of α,β-unsaturated ketoimines, giving corresponding chiral allylic amines in high yields and high ee's. Moreover, the reaction proceeded smoothly with 0.2 mol % catalyst loading at room temperature, which indicated that the method has potential applications in organic synthesis. Further studies on Ni-catalyzed enantioselective hydrogenation are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03365.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(16) Only trace over-reduction product was detected in this transformation, and the low isolated yield was attributed to low conversion. Full conversion can be obtained by increasing the temperature, but over-reduction product dramatically increased, which made purification very difficult.

(17) The absolute configuration of compound **2q** has been established by comparison with literature data (for *R*-**2q** in ref 2a: $([\alpha]_D^{25} = -31.4$ (c 1.0, $CHCl_3$), 95% ee for *R*; our experiment result of **2q**: $[\alpha]_D^{20} = -20.6$ (c = 1.0, $CHCl_3$) (90% ee)). All the other configurations are uncertain and based on the assumption that the configuration follows that of **2q**.

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