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Asymmetric Transfer Hydrogenation of Ketimines by Indoline as Recyclable Hydrogen Donor

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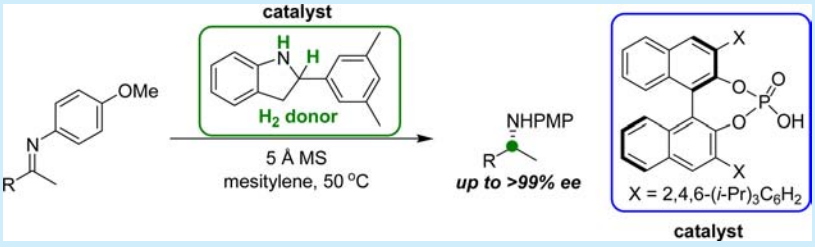
Supporting Information



ABSTRACT: The chiral phosphoric acid catalyzed enantioselective transfer hydrogenation of various ketimines was achieved by the use of 2-aryl indoline as the hydrogen donor. Corresponding chiral amines were obtained in good chemical yields with excellent enantioselectivities.

The demand for enantiomerically pure compounds has been steadily increasing in the fields of biochemistry and pharmaceutical chemistry in recent years. Chiral amines, in particular, are important building blocks in those fields, and it is thus imperative to develop synthetic methods for the construction of stereogenic centers bearing nitrogen. The asymmetric reduction of the C═N bond is one of the most straightforward approaches to afford the chiral amines.[1] Although a range of methods for the reduction of ketimines by means of chiral transition metal catalysts have been developed,[2] drawbacks persist, including the limited substrate scope and the danger of handling high-pressure hydrogen gas.

Inspired by the manner by which nature conducts reduction using NAD(P)H, an asymmetric transfer hydrogenation was developed, which employs hydrogen donors in the presence of chiral organocatalysts.[3,4] Whereas Hantzsch ester **1** is well-known and the most frequently used hydrogen donor,[5] we recently developed an asymmetric transfer hydrogenation that uses benzothiazoline **2** as the hydrogen donor and chiral phosphoric acid (Figure 1).[6] Benzothiazoline can be used for a range of reduction reactions to furnish chiral amines with high optical purity. Benzothiazoline has an *S*,*N*-acetal structure; thus, the hydrolysis of benzothiazoline proceeds in the presence of water. Although we have recently developed oxidative kinetic resolutions of indoline **3** derivatives involving hydrogen transfer to aromatic imines, the transfer hydrogenation of various imines was not fully examined.[7] As the sulfur atom of benzothiazoline is substituted by a carbon atom in the molecular structure of indoline, we can expect that indoline **3** would have higher stability than benzothiazoline and would be a more useful hydrogen donor.[8] However, another problem persisted: it was difficult to regenerate **2** by the reduction of benzothiazole due to the high stability of benzothiazole. We envisioned that the indole would be cleanly recovered after the hydrogenation reaction and be easily regenerated to the corresponding indoline by a simple reduction method.[9] We wish to report herein the phosphoric acid catalyzed transfer hydrogenation of aromatic ketimines and the reductive amination of aliphatic ketones using indoline as the hydrogen donor.

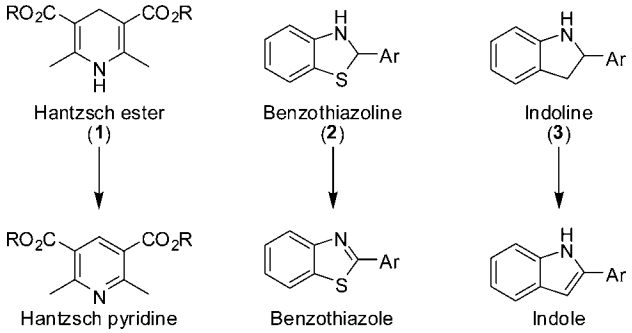


Figure 1. Molecular structures of hydrogen donors and their oxidized structures (Hantzsch ester, benzothiazoline, and indoline).

An initial attempt to perform the proposed transfer hydrogenation was carried out by using aromatic imine **5a** and an excess amount of racemic 2-phenylindoline **3a** in the presence of a catalytic amount of chiral phosphoric acid **4**[10] (10 mol %) and molecular sieves 5 Å (5 Å MS) at 50 °C (Scheme 1). When 1.4 equiv of *rac*-**3a** was employed for the transfer hydrogenation, target product **6a** was obtained in 71% yield with 85% ee and the remaining indoline **3a** was recovered in 62% yield with 91% ee. From this result, it was found that one enantiomer of indoline preferentially participated in the hydrogen transfer to imine **5a**.[7] The use of 2.0 equiv of *rac*-**3a**

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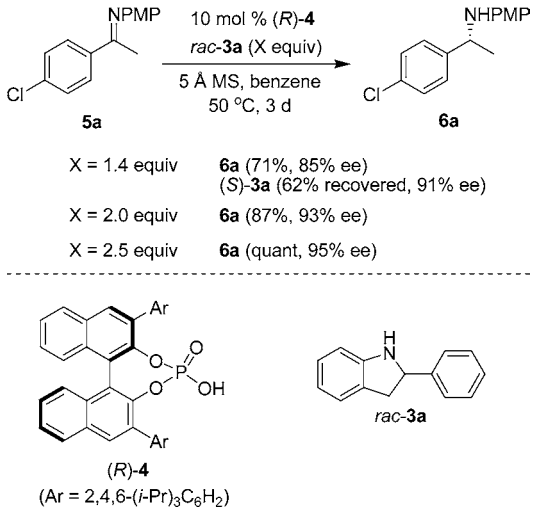
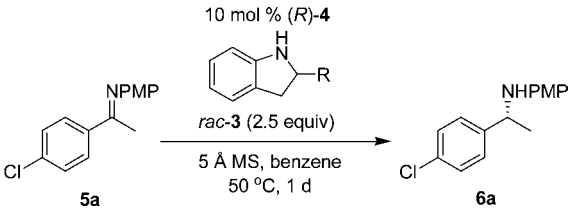
Scheme 1. Effect of Hydrogen Donor Loading



resulted in an 87% yield with 93% ee, and the hydrogen donor loading of 2.5 equiv produced the best result (quant, 95% ee).

Next, we examined the effect of a substituent of indoline. When indoline **3b** and alkyl-substituted indoline **3c** were used for the transfer hydrogenation, **6a** was obtained in 18% and 49% yields with 63% ee and 76% ee, respectively. The use of 2-aryl indolines **3d**–**3h** improved both chemical yields and enantioselectivities, and indoline **3h** bearing a 3,5-xylyl group at the 2-position was the best choice for this transfer hydrogenation. To our delight, changing the solvent from benzene to mesitylene further enhanced both yield and enantioselectivity (entry 8, Table 1). In addition, **6a** was obtained in a quantitative yield without loss of enantioselectivity despite the lower catalyst loading (entry 9, Table 1). Finally, the optimum reaction conditions were established as follows: 5 mol % (*R*)-**4**, imine **5** (1.0 equiv), and 2-(3,5-xylyl)indoline **3h** (2.5 equiv) in the presence of 5 Å MS in benzene at 50 °C.

Table 1. Effect of Substituent at 2-Position of Indoline[a]

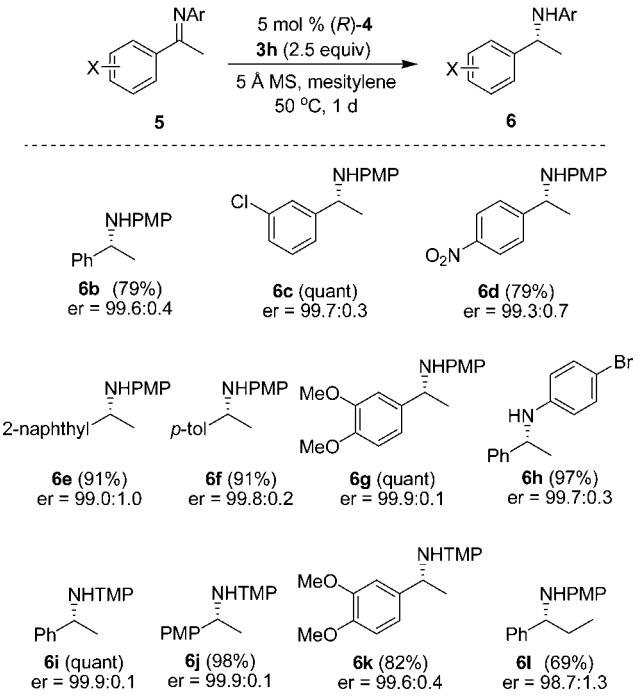


entry	R	yield (%)[b]	ee (% ee)[c]
1	H (**3b**)	18	63
2	Me (**3c**)	49	76
3	*p*-FC_6H_4 (**3d**)	92	94
4	*p*-$MeOC_6H_4$ (**3e**)	99	93
5	*m*-$MeOC_6H_4$ (**3f**)	92	98
6	2-naphthyl (**3g**)	81	98
7	3,5-xylyl (**3h**)	quant	99
8[d]	3,5-xylyl (**3h**)	quant	>99
9[d,e]	3,5-xylyl (**3h**)	quant	>99

[a]Conditions: Reactions were carried out on a 0.1 mmol scale with starting material **5a** (0.1 mmol), **3** (0.25 mmol), (*R*)-**4** (10 mol %), and 5 Å MS (50 mg) in benzene (0.1 M) at 50 °C for 3 days. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Mesitylene was used as solvent. [e](*R*)-**4** (5 mol %) was used.

With the optimum reaction conditions in hand, we examined the substrate scope of this asymmetric transfer hydrogenation of aromatic imines (Scheme 2). The reaction was found to tolerate

Scheme 2. Substrate Scope of Chiral Phosphoric Acid Catalyzed Asymmetric Transfer Hydrogenation Using Indoline[a,b,c]



[a]Conditions: Reactions were carried out on a 0.1 mmol scale with starting material **5** (0.1 mmol), **3h** (0.25 mmol), (*R*)-**4** (5 mol %), and 5 Å MS (50 mg) in mesitylene (0.1 M) at 50 °C for 3 days (details in Supporting Information). [b] Isolated yields. [c] Determined by chiral HPLC analysis. PMP = *p*-methoxyphenyl. TMP = 3,4,5-trimethoxyphenyl.

electron-withdrawing halo and nitro compounds, albeit with slightly lower yields in the latter. Ketimine **5e** having a sterically hindered 2-naphthyl group was also employed for this reaction, and **6e** was obtained in 91% yield with 98% ee. Corresponding amines **6f**–**6h** were also obtained in high to excellent yields with >99% ee's. Ketimines **5i**, **5j**, and **5k** bearing a 3,4,5-trimethoxyphenyl group on nitrogen[11] also proved to be suitable substrates (>99% ee). Ketimine **5l** could also be converted to the corresponding amine **6l** with 97% ee.

Next, we compared the reactivity of two hydrogen donors, benzothiazoline and indoline (Scheme 3).[12] Whereas the transfer hydrogenation that used benzothiazoline **2a** resulted in good yield with 97% ee, the chemical yield and enantioselectivity of **6a** were further improved to >99% with >99% ee when indoline **3h** was used. These results indicate that indoline **3h** is the effective reagent for the asymmetric transfer hydrogenation catalyzed by chiral phosphoric acid.

To further test the flexibility of this methodology, we performed the enantioselective reductive amination of aliphatic ketones.[6e] Using 5 mol % (*R*)-**4** and 2.5 equiv of **3h** in mesitylene (80 °C) gave desired product **7a** in a quantitative yield with 95% ee. It is worth noting that the use of benzothiazoline **2a** resulted in a much lower yield due to the low stability of **2a** under the reaction conditions employed (Scheme 4).

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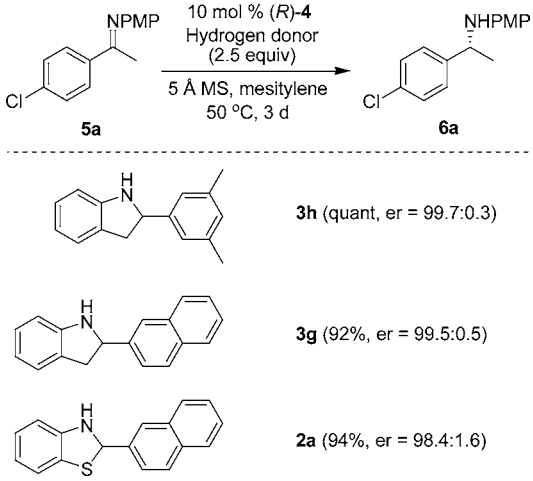
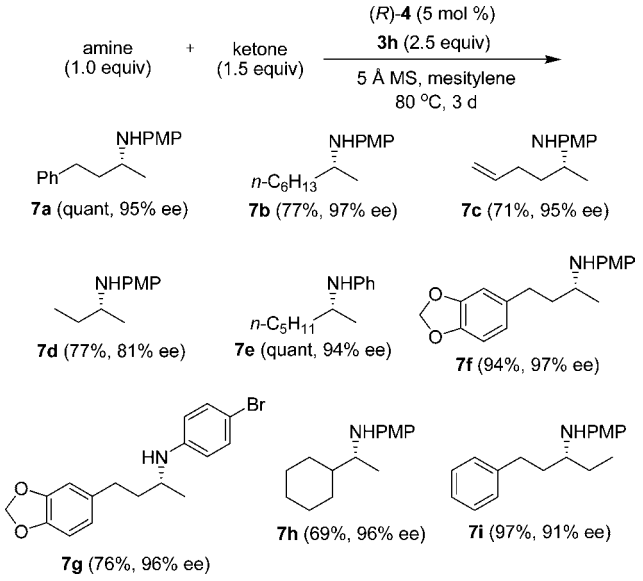
Scheme 3. Comparison of Reactivity and Selectivity between Indoline and Benzothiazoline[a,b,c]



[a]Conditions: Ractions were carried out on a 0.1 mmol scale with starting material **5** (0.1 mmol), **3** or **2a** (0.25 mmol), (*R*)-**4** (10 mol %), and 5 Å MS (50 mg) in mesitylene (0.1 M) at 50 °C for 3 days (details in Supporting Information). [b] Isolated yields. [c] Determined by chiral HPLC analysis.

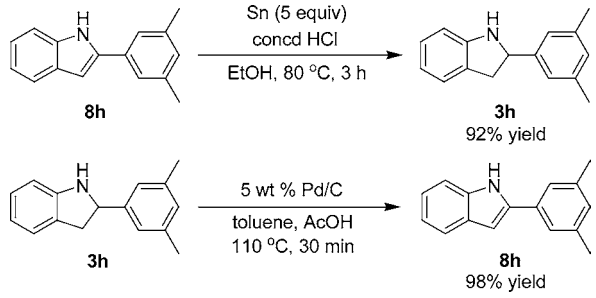
Scheme 4. Substrate Scope of Enantioselective Reductive Amination Using Indoline[a,b,c]



[a]Conditions: Reactions were carried out on a 0.1 mmol scale with amine (0.1 mmol), ketone (0.15 mmol), **3h** (0.25 mmol), (*R*)-**4** (5 mol %), and 5 Å MS (50 mg) in benzene (0.1 M) at 80 °C for 3 days (details in Supporting Information). [b] Isolated yields. [c] Determined by chiral HPLC analysis.

Then, we tried to regenerate indoline from the recovered indole (Scheme 5). When recovered indole **8h** was treated with tin powder and concentrated HCl in EtOH at 80 °C, indoline **3h** was obtained in 92% yield.[13] In addition, we discovered that the recovered indoline **3h** could also be converted to the indole **8h** in very high efficiency using a catalytic amount of Pd/C in toluene at 110 °C (98% yield).[14] Using the two-step reaction process, racemic indoline, which could be employed for the asymmetric transfer hydrogenation, could be fully recovered.

Scheme 5. Regeneration of Indoline and Indole



In conclusion, we have developed an asymmetric transfer hydrogenation of aromatic ketimines and a reductive amination of aliphatic ketones catalyzed by chiral phosphoric acid in the presence of indoline as the hydrogen donor. Various chiral amines were obtained in good yields with excellent enantioselectivities. Indoline proved to be an efficient hydrogen donor. The salient features are as follows: (1) Asymmetric transfer hydrogenation of aryl and aliphatic ketimines proceeded with high enantioselectivity. (2) 2-Aryl indoline could be regenerated by the reduction of 2-aryl indole after asymmetric transfer hydrogenation. (3) 2-Aryl indoline exhibited higher stability than benzothiazoline as a hydrogen donor in phosphoric acid catalyzed transfer hydrogenation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for all new compounds, NMR spectra for the products, HPLC charts. 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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