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Enantioselective hydrosilylation of ketimines with trichlorosilane promoted by chiral *N*-picolinoylaminoalcohols

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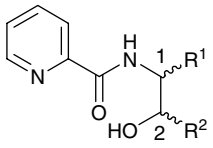
Abstract—Enantioselective hydrosilylation of *N*-aryl and *N*-benzyl ketimines with trichlorosilane catalyzed by readily accessible chiral *N*-picolinoylaminoalcohols proceeded smoothly furnishing chiral secondary amines in good yields (up to 93%) and moderate to excellent enantioselectivities (up to 95% ee).

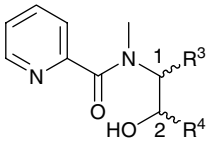
Chiral amines are versatile building blocks of natural products and common intermediates in the synthesis of pharmaceutical drugs and agrochemicals.[1] Enantioselective hydrogenation of ketimines represents one of the most convenient routes to optically active chiral amines. Traditional asymmetric high pressure hydrogenation of ketimines,[2] hydrosilylation of ketimines[3] and transfer hydrogenation of ketimines[4] catalyzed by chiral transition metal complexes suffer from the problem of metal leaching. Recently, synthesis of chiral secondary amines via metal-free asymmetric organocatalytic hydrogenation of ketimines received much attention due to the environmental benignancy of this method.[5,6] Biomimetic transfer hydrogenation of ketimines or reductive amination of ketones[5] with Hantzch esters catalyzed by chiral Brønsted acids proved to be powerful methods of the synthesis of chiral secondary amines. On the other hand, asymmetric hydrosilylation of imines employing trichlorosilane as a hydride source is also a promising alternative. Since the first asymmetric hydrosilylation of imines activated by *N*-formylpyrrolidine derivatives,[6a] analogous organo-catalysts[6b–i] and *S*-chiral sulfinamides[7] were developed to catalyze the reactions and showed good activities as well as high enantioselectivities. Besides, *N*-picolinoylpyrrolidine derivatives[8] and 2-pyridyloxazolines[9] which have no *N*-formyl unit were employed in the reactions too and afforded chiral amines with moderate to good yields and enantioselectivities. However, there have been only limited examples of enantioselective hydrosilylation of *N*-benzyl ketimines.[6a–c,e,8] Herein, we report our discovery of novel chiral *N*-picolinoylaminoalcohol derivatives **1**–**3** (Fig. 1), among which **2a** promoted hydrosilylation of a variety of *N*-aryl ketimines and *N*-benzyl ketimines with $HSiCl_3$ in good yields and moderate to excellent enantioselectivities.

First, catalysts **1a**–**e** derived from various aminoalcohols were evaluated in hydrosilylation of *N*-(1-phenylethylidene) benzenamine (**4a**). The structure of the catalyst has



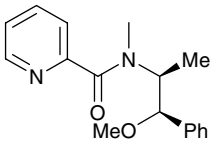
1

a, R^1 = Ph, R^2 = Ph, (1*S*, 2*R*)
b, R^1 = Ph, R^2 = Ph, (1*S*, 2*S*)
c, R^1 = Ph, R^2 = H, (1*R*)
d, R^1 = i-Pr, R^2 = H, (1*R*)
e, R^1 = H, R^2 = Ph, (2*R*)



2

a, R^3 = Me, R^4 = Ph, (1*S*, 2*R*)
b, R^3 = Me, R^4 = Ph, (1*S*, 2*S*)
c, R^3 = Ph, R^4 = Ph, (1*S*, 2*R*)
d, R^3 = Ph, R^4 = Ph, (1*S*, 2*S*)
e, R^3 = Ph, R^4 = H, (1*R*)



3

Figure 1. Catalysts evaluated in this study.

Keywords: Organocatalysis; Hydrosilylation; Imines; Chiral amines.
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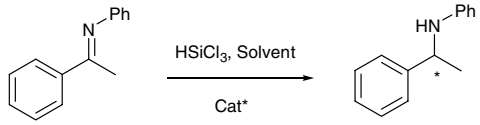
a remarkable influence on the results of the reaction. *(1R,2S)*-1,2-Diphenyl-2-aminoethanol derived catalyst **1a** gave the product with good yields but poor enantioselectivities (Table 1, entries 1 and 2). Its diastereomer **1b** provided the product with slightly higher ee values (Table 1, entries 3 and 4). **1c** which has only one chiral center bonded to amino group gave much better result (Table 1, entry 5) in dichloromethane. However, **1d** which has an isopropyl group on carbon 1 gave only racemic product (Table 1, entry 8). Catalyst **1e** which has only one chiral center bonded to hydroxy group gave almost racemic product (Table 1, entry 9). Therefore, it can be concluded that the chirality of the carbon bonded to amino group is determinant for the enantioselectivity of the reaction.

Then catalysts **2a** and **2b** derived from ephedrine and pseudoephedrine were employed in the reaction. Fortunately, we found that **2a** resulted in much higher enantioselectivities (Table 1, entries 11 and 14) in chloroform. Its diastereomer **2b** was obviously inferior to **2a** but superior to **1a**–**e** (Table 1, entries 15 and 16). We inferred that the methyl group on nitrogen might benefit to the enantioselectivity of the reaction. In search of more effective catalysts, we synthesized *N*-methyl derivatives **2c**, **2d**, and **2e**. As we expected, introduction of methyl group on nitrogen of catalysts **1a** and **1b** led to significant increase in enantioselectivity (Table 1, entries 1–4, vs 17–21). Meanwhile, it resulted in inversion of the configuration of the product. However, *N*-methyl derivative **2e** directed the reaction with almost racemic product (Table 1, entries 22 and 23). It appears that the effect of the structure of catalyst on the reaction is rather complicated. Moreover, methylation of the hydroxyl group of **2a** resulted in an obvious drop in enantioselectivity (Table 1, entry 24). It seems that the H-bonding between catalyst and substrate also makes an important contribution to enantioselectivity of the reaction.[6b]

Table 1. Survey of chiral catalysts for the hydrosilylation of ketimine **4a**



4a **5a**

Entry[a]	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	**1a**	CH_2Cl_2	90	5 (*S*)
2	**1a**	$CHCl_3$	88	20 (*S*)
3	**1b**	CH_2Cl_2	85	31 (*S*)
4	**1b**	$CHCl_3$	86	30 (*S*)
5	**1c**	CH_2Cl_2	84	65 (*S*)
6	**1c**	$CHCl_3$	91	18 (*S*)
7	**1c**	Toluene	80	0
8	**1d**	$CHCl_3$	90	0
9	**1e**	$CHCl_3$	76	6 (*S*)
10	**2a**	CH_2Cl_2	81	68 (*R*)
11	**2a**	$CHCl_3$	90	86 (*R*)
12	**2a**	Toluene	40	37 (*R*)
13	**2a**	THF	88	70 (*R*)
14	**2a**	$CHCl_3$	88	92[d] (*R*)
15	**2b**	CH_2Cl_2	82	46 (*R*)
16	**2b**	$CHCl_3$	90	73 (*R*)
17	**2c**	CH_2Cl_2	87	51 (*R*)
19	**2c**	$CHCl_3$	89	55 (*R*)
20	**2d**	CH_2Cl_2	88	34 (*R*)
21	**2d**	$CHCl_3$	87	55 (*R*)
22	**2e**	CH_2Cl_2	87	0
23	**2e**	$CHCl_3$	85	5 (*R*)
24	**3**	$CHCl_3$	89	70 (*R*)

[a] Unless specified otherwise, reactions were carried out with 10 mol % of catalyst and 2.0 equiv of $HSiCl_3$ on 0.2 mmol scale in 2.0 mL of organic solvent at 0 °C for 16 h.

[b] Isolated yield based on the imine.

[c] The ee values were determined by chiral HPLC. The configuration of the product was determined by comparison of the HPLC data with the literature data.[8]

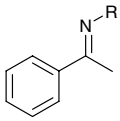
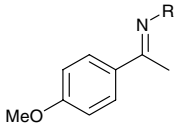
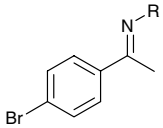
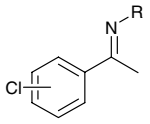
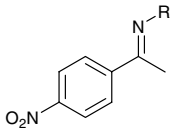
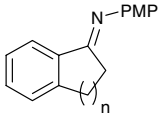
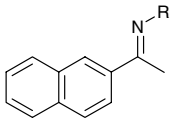
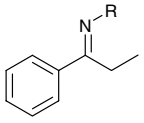
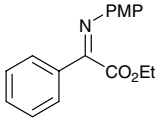
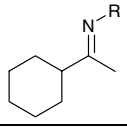
[d] 20 mol % catalyst was used and the reaction was carried out at −10 °C for 24 h.

The solvents also show dramatic effect on the reaction. Generally, chlorinated solvents are advantageous to the reaction. For most of the catalysts, chloroform is superior to dichloromethane except for **1c**, which resulted in much higher enantioselectivity in dichloromethane than in chloroform (Table 1, entries 5 and 6). When the reaction was carried out in toluene, both the reactivity and the enantioselectivity dropped greatly (Table 1, entries 7 and 12). We conjectured that the π–π interaction of catalyst with substrate was blocked in toluene, which led to low enantioselectivity. The use of non-protonic polar solvent THF also led to decrease in enantioselectivity (Table 1, entry 13). Perhaps it is due to the competitive coordination of THF with trichlorosilane.

Afterwards, under the optimal reaction conditions, a variety of ketimines **4a**–**y** were reduced with $HSiCl_3$ in $CHCl_3$ in the presence of 20 mol % **2a** at −10 °C (Table 2). Most of the aromatic ketimines were reduced smoothly to provide corresponding products in good yields and enantioselectivities. However, ketimine **4k**, which has a chloro substituent in the ortho position of the phenyl group of ketone moiety, was reduced in high yield but poor enantioselectivity (Table 2, entry 11). Tetralone derived ketimine **4o** was reduced in high ee value (Table 2, entry 15), while reduction of indanone-derived ketimine **4n** gave only moderate enantioselectivity (Table 2, entry 14). It seems that the conformation difference between six member ring and five member ring makes the transition structures of reactions of the two substrates much different. Meanwhile, α-ketimino ester **4t** was reduced to give protected α-phenylglycine in good yield and moderate enantioselectivity (Table 2, entry 20). Furthermore, moderate yields and enantioselectivities were afforded in reduction of aliphatic ketimines (Table 2, entries 24 and 25). In general, higher enantioselectivities were resulted with *N*-PMP ketimines than with *N*-Ph ketimines. It is noteworthy that *N*-benzyl ketimines (Table 2, entries 21–23) could also be reduced in good yields and enantioselectivities.

According to the literature,[10] *N*-PMP amines could undergo oxidative deprotection by CAN[10] or TCCA[6f] to give free amines. Furthermore, hydrogenolysis of the benzyl group of the addition product **5v** catalyzed by

Table 2. Reduction of ketimines **4** with trichlorosilane catalyzed by **2a**

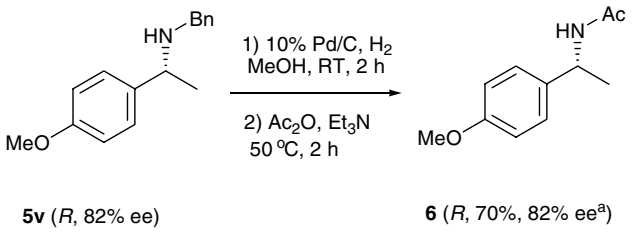
Entry[a]	Ketimines		Yield[b] (%)	ee[c] (%)
1		**4a** R = Ph	88	92
2		**4b** R = PMP[d]	90	93
3		**4c** R = Ph	91	89
4		**4d** R = PMP	82	92 (>99)
5		**4e** R = Ph	92	87
6		**4f** R = PMP	90	92
7		**4g** p-Cl R = Ph	90	90
8		**4h** p-Cl, R = PMP	84	91
9		**4i** m-Cl, R = Ph	88	85
10		**4j** m-Cl, R = PMP	90	88
11		**4k** o-Cl, R = PMP	91	43
12		**4l** R = Ph	85	76
13		**4m** R = PMP	80	88
14		**4n** $n = 1$	90	68
15		**4o** $n = 2$	85	95
16		**4p** R = Ph	93	90 (99)
17		**4q** R = PMP	86	90
18		**4r** R = Ph	91	76
19		**4s** R = PMP	88	84
20		**4t**	85	65
21		**4u** Ar = Ph	85	80
22		**4v** Ar = PMP	85	82
23		**4w** Ar = 2-naphthyl	80	82 (96)
24		**4x** R = Ph	70	67
25		**4y** R = PMP	71	61

[a] Unless specified otherwise, reactions were carried out with 20 mol % of catalyst and 2.0 equiv of $HSiCl_3$ on 0.2 mmol scale in 2.0 mL chloroform at −10 °C for 24 h.

[b] Isolated yield based on the ketimines.

[c] The ee values were determined by chiral HPLC, the data in parentheses were obtained after a single recrystallization.

[d] PMP = *p*-methoxyphenyl.



5v (*R*, 82% ee) **6** (*R*, 70%, 82% ee[a])

[a] Determined by GC using a chiral column (Chirasil-DEX CB).

Scheme 1. Hydrogenolysis of the benzyl group of **5v** and following protection with acetic group.

10% Pd/C gave the free amine smoothly without racemization (Scheme 1). Thus, the methodology is well established to synthesize optically active amines via organo-catalytic asymmetric hydrosilylation of *N*-PMP and *N*-benzyl ketimines.

In conclusion, we have developed a highly efficient metal-free catalyst, easily prepared from 2-picolinic acid and *(1R,2S)*-ephedrine, for the reduction of a variety of *N*-aryl ketimines and *N*-benzyl ketimines with trichlorosilane in high yields (<93%) and moderate to excellent ee values (<95%) under mild conditions.[11] However, at present, we cannot provide a reasonable mechanism to explain the effect of the structure of catalyst on the reaction, especially, the configuration of the product. The mechanistic aspects and the further application of the present catalyst to other reactions are under investigation, and will be reported in due course.

Acknowledgments

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11. Typical experimental procedure for the catalytic enantioselective hydrosilylation of ketimine **4** with catalyst **2a**: under an argon atmosphere, trichlorosilane (60 μL, 0.6 mmol) was introduced to a stirred solution of imine **4** (0.30 mmol) and catalyst **2a** (16.2 mg, 0.02 mmol) in anhydrous $CHCl_3$ (2 mL) at −10 °C. The mixture was allowed to stir at −10 °C for 24 h. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic extract was washed with brine and dried over anhydrous $MgSO_4$, filtered and evaporated. Purification by chromatography (silica gel, hexane/EtOAc) afforded pure amine **5**. The ee values were determined using established HPLC techniques with chiral stationary phases.