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Highly enantioselective hydrosilylation of *N*-(1,2-diarylethylidene)arylamines†

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By employing a chiral Lewis base as the catalyst, enantioselective hydrosilylation of *N*-(1,2-diarylethylidene)arylamines was realized. The reactions proceeded smoothly to afford various chiral 1,2-diarylethanamines with good yields (up to 99%) in good enantioselectivities (up to 98%). Furthermore, one of the products was employed in the synthesis of a pharmaceutical substance.

Introduction

1,2-Diarylethanamines and their derivatives are important pharmaceutically or biologically active substances.[1] They have exhibited a wide range of biological activities, including neuroprotective properties,[1] analgesic activity,[2] anticonvulsant activity,[3] protein kinase B inhibition,[4] human β_3 adrenergic receptor agonistic activity,[5] estrogen receptor modulation[6] and other activities.[7] 1,2-Diarylethanamines were also employed in construction of various natural products and other physiologically active molecules.[8] Therefore, synthesis of 1,2-diarylethanamines is of great significance. Up to now, synthesis of racemic 1,2-diarylethanamines and their derivatives has been well developed.[9] However, preparation of enantioenriched 1,2-diarylethanamines has predominantly focused on diastereoselective synthesis and resolution.[7b,10] As far as we know, catalytic asymmetric synthesis of enantioenriched 1,2-diarylethanamines has seldom been systematically studied. Zhou and co-workers employed a Rh(I) complex of the chiral spiro phosphonite ligand to catalyze enantioselective hydrogenation of 1-(1,2-diarylvinyl)pyrrolidines to provide 1-(1,2-diarylethyl)-pyrrolidines with excellent ee values.[11]

Recently, chiral Lewis base[12] promoted asymmetric hydrosilylation of C=N double bonds has been studied extensively.[13,14] A wide variety of valuable chiral nitrogen-containing compounds were prepared *via* this transformation. As part of our ongoing effort directed toward the development of Lewis base catalyzed asymmetric hydrosilylation of C=N double bond compounds,[14o–t] we have been trying to apply this methodology in the preparation of various intermediates of pharmaceutical compounds. Herein we present the highly enantioselective hydrosilylation of *N*-(1,2-diarylethylidene)-arylamines promoted by chiral Lewis bases. The reactions proceeded smoothly to provide pharmaceutically important 1,2-diarylethanamines in good yields (up to 99%) and good enantioselectivities (up to 98% ee). Subsequently, one of the products was employed in the synthesis of a protein kinase B inhibitor.

Results and discussion

First, chiral Lewis base catalysts **1a–h** (Fig. 1) were evaluated for their ability to promote the hydrosilylation of *N*-(1,2-diphenylethylidene)-4-methoxybenzenamine (**2a**) in dichloromethane at −10 °C for 24 hours. The results are summarized in Table 1.

As can be seen in Table 1, all of the catalysts **1a–h** (Fig. 1) catalyzed the hydrosilylation of **2a** to provide the product **3a** in good yields. Ephedrine-derived catalyst **1a**[14o,r] gave only moderate enantioselectivity (Table 1, entry 1). Proline-derived catalyst **1b**[14k,p] displayed better enantioselection (Table 1, entry 2). When catalysts **1c–e**[14q,t] bearing bulky substituents at the C4 position of the pyrrolidine ring were tested, remarkable increases in ee values were observed (Table 1, entries 3–5). Afterwards, several catalysts **1f**,[14q,t] **1g**[14q] and **1h** bearing larger aryl groups were also screened (Table 1, entries 6–8), in which **1h** delivered the highest ee value of 98% (Table 1, entry 8).

Therefore, **1h** was determined as the optimal catalyst and was employed in further investigations. Subsequently, various solvents were evaluated. Reactions in several chlorinated solvents resulted in similar yields and ee values (Table 1, entries 8–10). Good yields and slightly inferior enantioselectivities were obtained in toluene and THF (Table 1,

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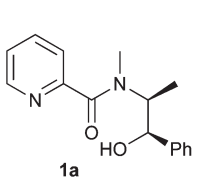
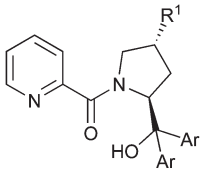


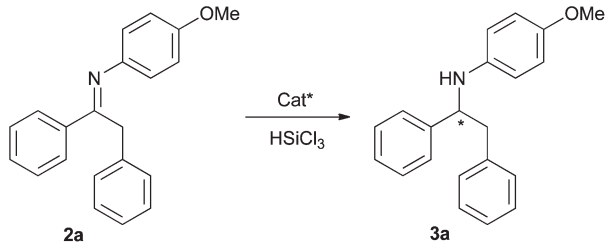
1a



1b: R^1=H, Ar=Ph
1c: R^1=OPiv, Ar=Ph
1d: R^1=OP(O)(OPh)$_2$, Ar=Ph
1e: R^1=O-isovaleryl, Ar=Ph
1f: R^1=OPiv, Ar=*p*-MeC_6H_4
1g: R^1=OPiv, Ar=*p*-MeOC_6H_4
1h: R^1=OPiv, Ar=*p*-PhC_6H_4

Fig. 1 Chiral Lewis base organocatalysts evaluated in this study.

Table 1 Enantioselective hydrosilylation of *N*-(1,2-diphenylethylidene)-4-methoxybenzenamine **2a** promoted by chiral Lewis base catalysts **1a–h**[a]

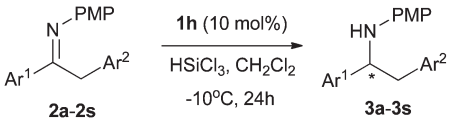


2a **3a**

Entry	Cat*	Solvent	*T* (°C)	Yield[b] (%)	ee[c] (%)
1	**1a**	CH_2Cl_2	−10	97	71
2	**1b**	CH_2Cl_2	−10	94	82
3	**1c**	CH_2Cl_2	−10	99	97
4	**1d**	CH_2Cl_2	−10	97	92
5	**1e**	CH_2Cl_2	−10	98	97
6	**1f**	CH_2Cl_2	−10	90	95
7	**1g**	CH_2Cl_2	−10	95	96
8	**1h**	CH_2Cl_2	−10	99	98
9	**1h**	$ClCH_2CH_2Cl$	−10	98	97
10	**1h**	Cl_3CCH_3	−10	97	96
11	**1h**	Toluene	−10	96	95
12	**1h**	THF	−10	97	95
13	**1h**	CH_2Cl_2	0	66	94
14[d]	**1h**	CH_2Cl_2	−20	99	95
15[e]	**1h**	CH_2Cl_2	−10	93	98
16[f]	**1h**	CH_2Cl_2	−10	85	97

[a] Unless specified otherwise, reactions were carried out with the catalyst (10 mol%) and $HSiCl_3$ (2.0 equiv.) on a 0.2 mmol scale in the appropriate solvent (3.0 mL) for 24 hours. [b] Isolated yield based on **2a**. [c] The ee values were determined by using chiral HPLC. [d] The reaction was carried out for 36 hours. [e] 5 mol% of **1h** was used. [f] 2.5 mol% of **1h** was used.

Table 2 Enantioselective hydrosilylation of *N*-(1,2-diarylethylidene)arylamines **2a–s** promoted by chiral Lewis base catalyst **1h**[a]



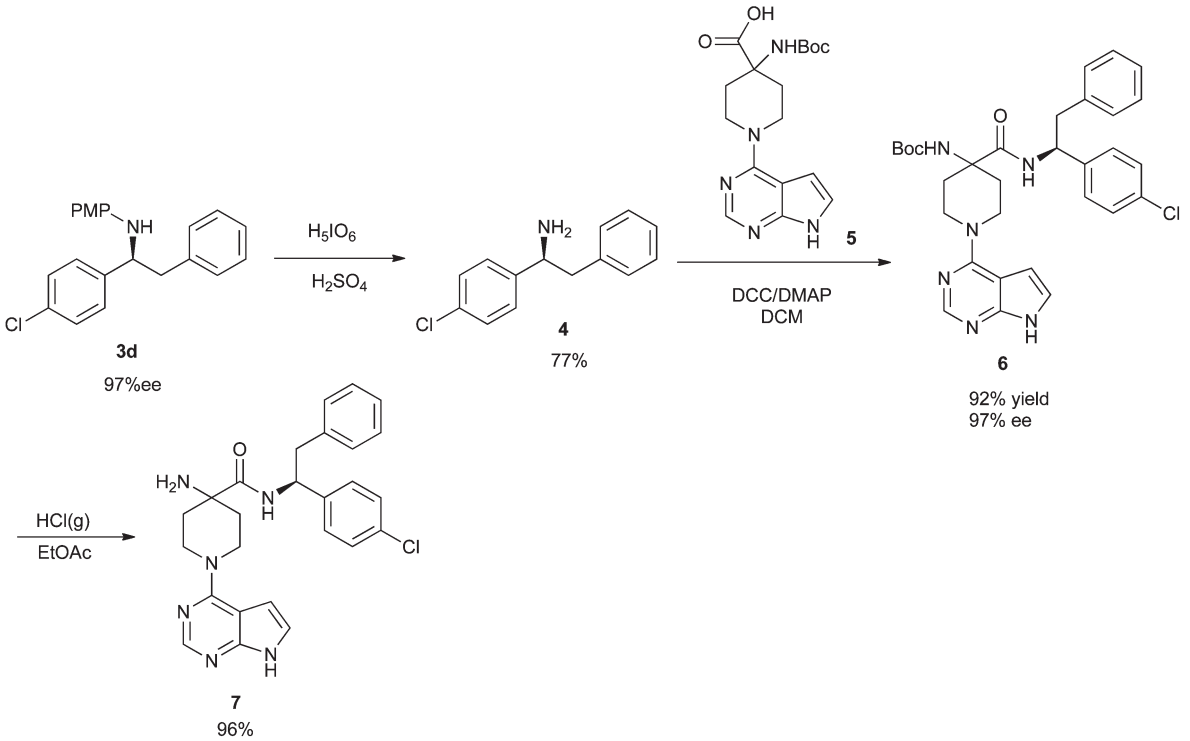
2a-2s **3a-3s**

Entry	2 (Ar^1, Ar^2)	Yield[b] (%)	ee[c] (%)	Conf.
1	**2a** (Ph, Ph)	99	98	(+)
2	**2b** (4-MeOC_6H_4, Ph)	97	97	(+)
3	**2c** (4-MeC_6H_4, Ph)	99	96	(+)
4	**2d** (4-ClC_6H_4, Ph)	99	97	*S* (+)[d]
5	**2e** (4-BrC_6H_4, Ph)	97	96	(+)
6	**2f** (3,4-$Me_2C_6H_3$, Ph)	99	97	(+)
7	**2g** (3,4,5-$Me_3C_6H_2$, Ph)	99	96	(+)
8[e]	**2h** (2-thienyl, Ph)	97	93	(+)
9[e]	**2i** (2-furanyl, Ph)	97	69	(−)
10[f]	**2i** (2-furanyl, Ph)	17	—	—
11	**2j** (Ph, 4-PhC_6H_4)	95	98	(+)
12	**2k** (Ph, 4-FC_6H_4)	95	98	(+)
13	**2l** (Ph, 2-ClC_6H_4)	98	95	(+)
14	**2m** (4-MeC_6H_4, 2,4,5-$F_3C_6H_2$)	87	98	(+)
15	**2n** (4-MeC_6H_4, 2-naphthyl)	92	97	(+)
16	**2o** (4-MeC_6H_4, 4-BrC_6H_4)	99	97	(+)
17	**2p** (4-MeC_6H_4, 4-MeOC_6H_4)	98	96	(+)
18	**2q** (4-BrC_6H_4, 4-ClC_6H_4)	99	97	(+)
19	**2r** (4-BrC_6H_4, 4-BrC_6H_4)	95	93	(+)
20	**2s** (4-MeC_6H_4, 4-ClC_6H_4)	97	97	(+)

[a] Unless specified otherwise, reactions were carried out with the catalyst **1h** (10 mol%) and $HSiCl_3$ (2.0 equiv.) on a 0.2 mmol scale in CH_2Cl_2 (3.0 mL) at −10 °C for 24 hours. [b] Isolated yield based on **2**. [c] The ee values were determined by using chiral HPLC. [d] The absolute configuration of **3d** was determined by comparison of the optical rotation value with the literature datum after being converted into a known compound.[10a] [e] The reactions proceeded for 18 hours. [f] The reaction was performed in the absence of the catalyst for 24 hours.

entries 11 and 12). Thus dichloromethane was selected as the most favourable solvent for the reaction. When the reaction was conducted at 0 °C, only 66% of the desired product was achieved because a lot of the substrate decomposed (Table 1, entry 13). Lowering the temperature to −20 °C did not benefit the enantioselection (Table 1, entry 14). When 5 mol% or 2.5 mol% of the catalyst was employed, the ee value kept the same level, however, the yield dropped evidently and decomposition of the substrate was observed (Table 1, entries 14 and 15). Therefore, 10 mol% of the catalyst was employed in the following study.

Having established the optimal conditions, the enantioselective hydrosilylation was expanded to a wide variety of *N*-(1,2-diarylethylidene)arylamines. The results are summarized in Table 2. Generally, when Ar^2 was phenyl, for Ar^1, phenyl groups bearing substituents in the *para* or *meta* position gave high yields as well as high ee values (Table 2, entries 1–7). The electronic nature of the substituents had little influence on the results. When Ar^1 was 1-thienyl, the reaction also provided good yield and good enantioselectivity (Table 2, entry 8). However, when Ar^1 was 1-furanyl, the reaction exhibited rather low enantioselection (Table 2, entry 9). When the reaction of 1-furanyl substrate **2i** was conducted in the absence of the catalyst, 17% of the product was obtained (Table 2, entry 10). Thus the lower ee value of **2i** could be ascribed to the background reaction. On the Ar^2 side, almost all of the substrates with Ar^2 bearing substituents in the *para*, *meta* or *ortho* position afforded high yields as well as high ee values (Table 2,



Scheme 1 Synthesis of protein kinase B inhibitor **7**.

entries 11–13, 15–20), except **2m** which gave the product with obviously lower yield perhaps due to the instability of the trifluoro substituted phenyl group (Table 2, entry 14).

To further illustrate the synthetic utility of this methodology, the product **3d** was employed in synthesis of a protein kinase B inhibitor 7[4] (Scheme 1). First, **3d** was treated with periodic acid to remove the PMP group to generate free amine **4**. The absolute configuration of **4** was determined as *S* by comparison of the optical rotation value with the literature datum.[10a] Then amine **4** was subjected to condensation with acid **5** to afford amide **6**. Finally, deprotection of **6** with hydrochloric acid accomplished the preparation of **7** in good yield.

Conclusions

In conclusion, we have demonstrated an efficient enantioselective hydrosilylation of *N*-(1,2-diarylethylidene)arylamines promoted by chiral Lewis bases. The reactions proceeded smoothly to provide the corresponding 1,2-diarylethanamines in good yields (up to 99%) and good enantioselectivities (up to 98% ee). In addition, product **3d** was deprotected to give free amine **4** which is a known compound. Thus the absolute configuration of **3d** was determined as *S* by comparison of the optical rotation value of **4** with the literature datum. Subsequently, **4** was converted to a protein kinase B inhibitor **7** successfully.

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