Pure Appl. Chem., Vol. 77, No. 12, pp. 2105–2110, 2005.
DOI: 10.1351/pac200577122105

Chiral phosphine Lewis bases in catalytic, asymmetric aza-Morita–Baylis–Hillman reaction*

Min Shi‡ and Lian-Hui Chen

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Abstract: In the aza-Morita–Baylis–Hillman reaction of *N*-sulfonated imines with methyl vinyl ketone (MVK) promoted by chiral phosphine Lewis base: (*R*)-2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-ol (**LB1**) (10 mol %), the aza-Morita–Baylis–Hillman adducts were obtained in good yields with high ee (70–94 % ee) at –30 °C in THF. The scope and limitations of this reaction have been disclosed.

Keywords: aza-Baylis–Hillman; *N*-sulfonated imines; chiral phosphine Lewis bases; Baylis–Hillman reaction; methyl vinyl ketone.

INTRODUCTION

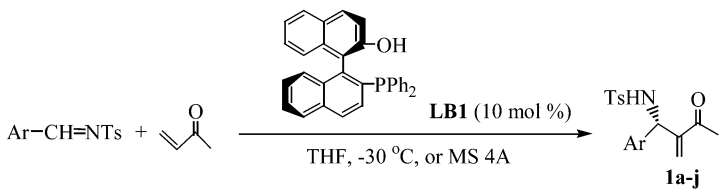
Great progress has been made in the execution of the Morita–Baylis–Hillman reaction [1] since the seminal report in 1972 [2] described the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of 1,4-diazabicyclo[2,2,2]octane (DABCO). Recent advances include a catalytic asymmetric version of the reaction [3], but limited to specialized α,β-unsaturated ketones or acrylates such as ethyl vinyl ketone (71 % ee) [3a], 2-cyclohexen-1-one (96 % ee) [3b], or 1,1,1,3,3,3-hexafluoroisopropyl acrylate (99 % ee) [3c]. Morita–Baylis–Hillman reactions involving simple Michael acceptors such as methyl vinyl ketone (MVK) or methyl acrylate have hitherto been characterized by poor enantioselectivity, thus offering a challenging and potentially fruitful area of investigation to broaden the scope of this general class of reactions. During our ongoing investigations of the aza-Morita–Baylis–Hillman reaction [4], we disclosed that the aza-Morita–Baylis–Hillman reactions of *N*-sulfonated imines (ArCH=NTs) [5] with MVK were promoted in the presence of catalytic amounts of Lewis bases such as triphenylphosphine (PPh_3) or DABCO to exclusively give the normal aza-Morita–Baylis–Hillman adducts in good yields for many *N*-sulfonated imines under mild conditions because the *N*-sulfonated imino group has high reactivity toward nucleophilic attack, even when the phenyl ring bears electron-donating groups [4a]. We then sought a suitable chiral Lewis base for a catalytic, asymmetric version of this reaction. Previously, we reported an unprecedented catalytic, asymmetric aza-Morita–Baylis–Hillman reaction of *N*-sulfonated imines with MVK utilizing a nitrogen Lewis base {4-(3-ethyl-4-oxa-1-azatricyclo[4,4,0,$0^{3,8}$]dec-5-yl)-quinolin-6-ol: **TQO** [3c]} to achieve >90 % ee in good yields [4b]. This is the first case in which high ee can be realized using the simple Michael acceptor MVK. The structure of this nitrogen Lewis base plays a very important role in this reaction for achieving high ee. Currently, the exploration of a novel and highly efficient chiral Lewis base

*Paper based on a presentation at the 7th IUPAC International Conference on Heteroatom Chemistry (ICHAC-7), Shanghai, China, 21–25 August 2004. Other presentations are published in this issue, pp. 1985–2132.
‡Corresponding author: E-mail: mshi@pub.sioc.ac.cn; Fax: 86-21-64166128

for catalytic, asymmetric Morita–Baylis–Hillman reaction is a very attractive and competitive field. Herein, we wish to report the catalytic, asymmetric aza-Morita–Baylis–Hillman reaction using a chiral phosphine Lewis base in which high enantioselectivities (>90 % ee) can also be realized.

RESULTS AND DISCUSSION

We selected (*R*)-2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-ol (**LB1**) as a chiral Lewis base for this reaction because it has a phenolic OH group like Lewis base **TQO** [3c]. We first used MVK as the Michael acceptor for the aza-Morita–Baylis–Hillman reaction with *N*-sulfonated imines (Scheme 1). In THF, at –30 °C, good to high enantioselectivities (76~91 % ee) were achieved with *S* configuration [4b] (Table 1). In general, for *N*-sulfonated imines having electron-donating groups on the phenyl ring, the reaction rate was slightly retarded and the corresponding aza-Morita–Baylis–Hillman adducts **1** were obtained in lower yields (41~62 %) with 76~83 % ee under the same conditions (Table 1, entries 1–3). It was suspected that moisture-induced decomposition of *N*-sulfonated imine may have intervened during prolonged reaction times at low temperature. This was verified, and yields of **1** were correspondingly improved by adding 4 Å molecular sieve (100 mg for 0.5 mmol of substrate) to the reaction medium. Reactions thus conducted under strictly anhydrous conditions showed marked improvement in yields of **1** (Table 1, entries 1–3, 5, 7–10), with little or no adverse effect on ee results. Only in some cases, the ee of **1** dropped ~2–7 %. Values in parentheses are the results obtained in the presence of 4 Å molecular sieve in Table 1.



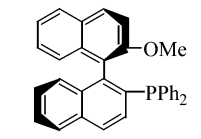
Scheme 1

Table 1 The aza-Baylis–Hillmann reactions of *N*-sulfonated imines (1.0 equiv) with MVK in the presence of chiral Lewis base (10 mol %).

Entry	Ar	Time/h	Yield/%[a] **1a–j**	ee/%[b]	Absolute configuration
1	C_6H_5	24 (36)[c]	**1a**, 49 (83)[c]	83 (83)[c]	*S*
2	*p*-MeC_6H_4	24 (36)	**1b**, 53 (82)	80 (81)	*S*
3	*p*-EtC_6H_4	36 (36)	**1c**, 62 (84)	76 (79)	*S*
4	*p*-FC_6H_4	18	**1d**, 84	81	*S*
5	*p*-ClC_6H_4	24 (24)	**1e**, 72 (90)	94 (87)	*S*
6	*p*-BrC_6H_4	18	**1f**, 85	83	*S*
7	*m*-FC_6H_4	36 (24)	**1g**, 26 (96)	91 (85)	*S*
8	*m*-ClC_6H_4	18 (24)	**1h**, 62 (88)	88 (88)	*S*
9	*p*-$NO_2C_6H_4$	12 (24)	**1i**, 60 (86)	94 (92)	*S*
10	*m*-$NO_2C_6H_4$	12 (24)	**1j**, 54 (91)	90 (88)	*S*

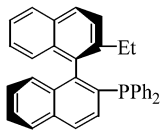
[a]Isolated yield.
[b]Determined by chiral HPLC.
[c]Values in parentheses are the results in the presence of MS 4 Å (100 mg).

It should be emphasized here that the phenolic hydroxy group (Ar–OH) on the naphthyl ring is crucial for this reaction because this reaction becomes sluggish and gives the product **1e** in 13 % yield with only 20 % ee (*R* configuration) using *O*-methylated ligand (MOP) **LB2** as a chiral Lewis base [6a] and in 22 % yield with 17 % ee (*R* configuration) using (2'-ethyl-[1,1']binaphthalenyl-2-yl)diphenylphosphane **LB3** as a chiral Lewis base [6a] under the same conditions (Scheme 2). The BINAP **LB4** shows no catalytic activity for this reaction. The (*R*)-2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-thiol **LB5** having a thiophenolic group on the naphthyl ring [6b,c] and the [2,3-bis-(2-diphenylphosphanyl-phenyl)-4-hydroxymethyl-cyclobutyl]methanol **LB6** [6d] having two aliphatic hydroxy groups show low catalytic activities under the same conditions. These results suggest that the acidity of the hydroxy group plays a very important role for chiral Lewis base **LB1** to be effective in the aza-Morita–Baylis–Hillman reaction. Other chiral ferrocene phosphine ligands **LB7** and **LB8** [6e,f] also have low catalytic activities for this reaction under the same conditions. Thus, the structure of phosphine Lewis base plays a significant role in this reaction (Scheme 2). Only (*R*)-2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-ol **LB1** having a phenolic hydroxy group can effectively catalyze this asymmetric aza-Morita–Baylis–Hillman reaction to give the products in good yields and ee.



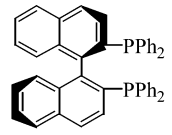
LB2

Yield: 13 %, ee: 20 %, *R*



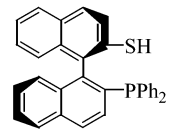
LB3

Yield: 17 %, ee: 22 %, *R*



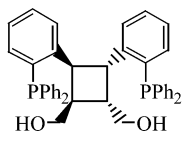
LB4

no reaction



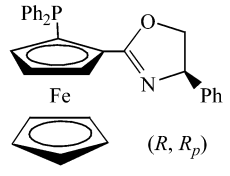
LB5

Yield: 35 %, ee: 39 %, *R*



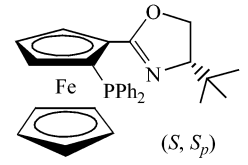
LB6

Yield: 78 %, ee: 18 %, *S*



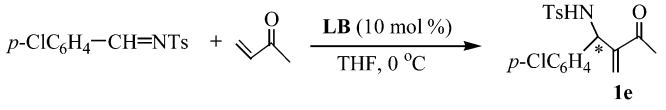
LB7

Yield: 45 %, ee: 65 %, *S*



LB8

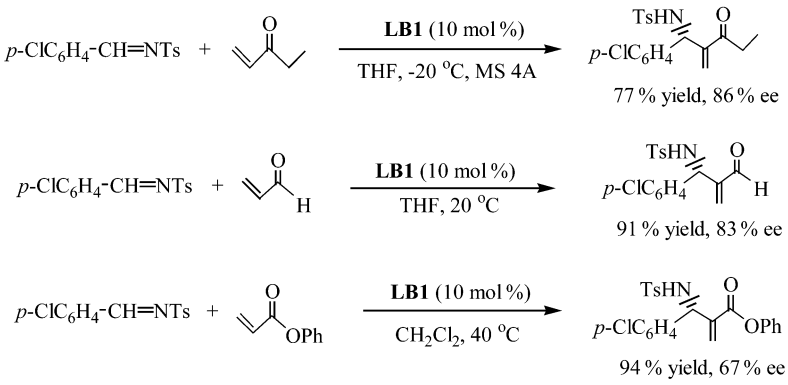
Yield: 44 %, ee: 38 %, *R*



1e

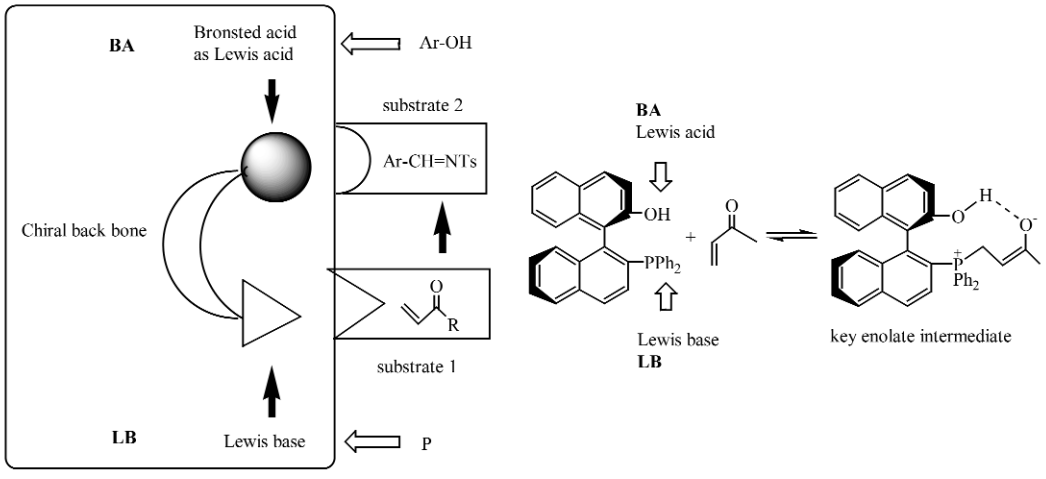
Scheme 2

The scope and limitations of this catalytic, asymmetric reaction for a variety of Michael acceptors such as ethyl vinyl ketone, acrolein, and phenyl acrylate with *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide under the corresponding optimized conditions have been shown in Scheme 3.



Scheme 3

In Fig. 1, we briefly gave a mechanistic speculation on the chiral Lewis base **LB1** [4a]. We believe that **LB1** acted as a bifunctional chiral catalyst in this reaction [7]. The phosphine atom acted as a Lewis base (**LB**) to initiate the Morita–Baylis–Hillman reaction and the phenolic OH group (Brønsted acid: **BA**) acted as a Lewis acid through hydrogen bonding to stabilize the reaction intermediate (Fig. 1). Thus, this is a **LBBA** (Lewis base and Brønsted acid) bifunctional catalyst system. The transition state of this reaction for the outcome of stereochemistry has been shown in previous literature [4a].

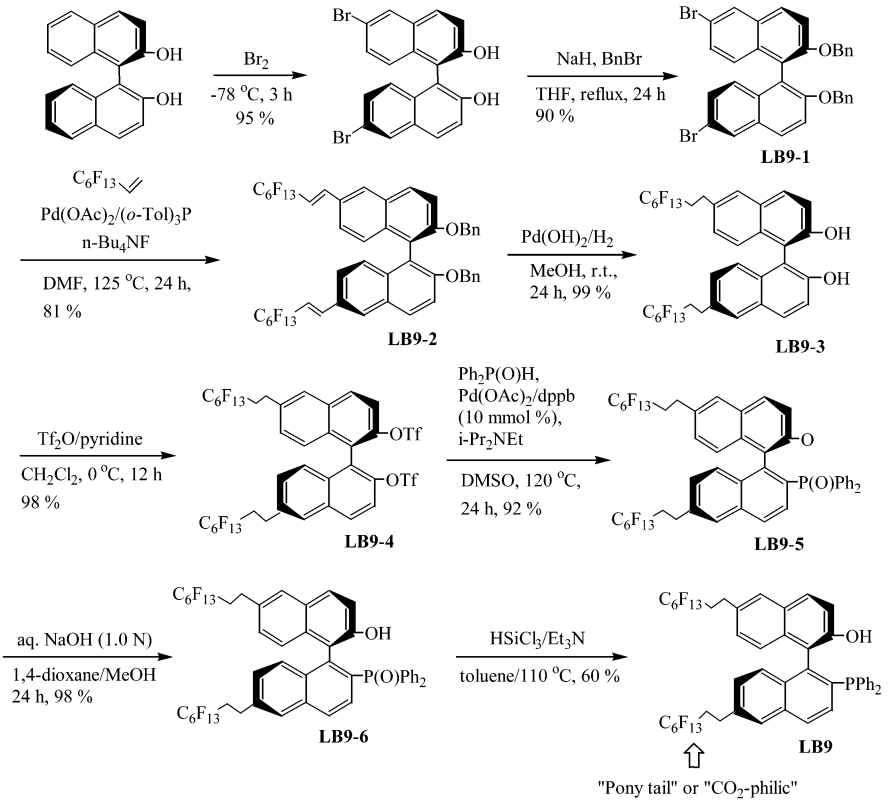


chiral phosphine Lewis base catalyst: **LBBA** bifunctional catalytic system.

Fig. 1 The plausible reaction mechanism.

The significant advantage in this chiral phosphine Lewis base system is that it is "structure-tunable". In Scheme 3, we presented the synthesis of a chiral Lewis base **LB9** with two perfluoroalkane long chains ("pony tail") on the 6,6'-position because the previous results on asymmetric catalysis have indicated that such a "pony tail" in chiral ligand can indeed improve the enantioselectivities under identical conditions [8]. Bromination and protection by benzyl group gave product **LB9-1**, which was subjected to the Heck-type coupling reaction with 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-1-octene in the presence of $Pd(OAc)_2$ and $(o\text{-Tol})_3P$ ligand in dimethylformamide (DMF) at 125 °C to furnish product **LB9-2** in good yield. Catalytic hydrogenation over $Pd(OH)_2/C$ in methanol gave product **LB9-3** in high yield [9]. The reaction of **LB9-3** with Tf_2O in the presence of pyridine produced the product **LB9-4**. The coupling

reaction of **LB9-4** with diphenylphosphite and hydrolysis with aqueous sodium hydroxide solution in 1,4-dioxane/MeOH mixed solvent produced the compound **LB9-6** in good yield. The reduction of phosphate **LB9-6** by $HSiCl_3$ and Et_3N in toluene at 120 °C afforded the chiral phosphine Lewis base **LB9** having so-called "pony tail" was obtained in good yield (Scheme 4). The preliminary examination in THF has been performed, and the results are summarized in Table 2. For various *N*-sulfonated imines, the corresponding adducts **1** were obtained in good yields and high ee at –20 °C (Table 2). This finding opens a way for the design and synthesis of special chiral phosphine Lewis bases which can be used in fluorous phase and $scCO_2$ in the future because a long perfluorinated alkyl chain, so-called "pony tail", could indeed help the catalyst in the fluorous phase and $scCO_2$ to become more effective [10].



Scheme 4

Table 2 aza-Baylis–Hillmann reactions of *N*-sulfonated imines (1.0 equiv) with MVK (3.0 equiv) in the presence of chiral Lewis base **LB9** (10 mol %).

Entry	Ar	Time/h	Yield/%[a] **1**	ee/%[b]	Absolute configuration
1	C_6H_5	48	**1a**, 91	71	*S*
2	*p*-ClC_6H_4	12	**1e**, 60	94	*S*
3	*p*-BrC_6H_4	24	**1f**, 83	93	*S*
4	*p*-FC_6H_4	24	**1g**, 69	92	*S*
5	*p*-$NO_2C_6H_4$	12	**1i**, 83	86	*S*
6	*m*-$NO_2C_6H_4$	24	**1j**, 84	95	*S*

[a]Isolated yield.
[b]Determined by chiral HPLC.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China for financial support (20025206, 203900502, and 20272069).

REFERENCES

1. (a) E. Ciganek. *Org. React*. **51**, 201 (1997); (b) D. Basavaiah, P. D. Rao, R. S. Hyma. *Tetrahedron* **52**, 8001 (1996).
2. (a) A. B. Baylis and M. E. D. Hillman. *Ger. Offen*. **2**, 155,113 (1972); *Chem. Abstr*. **77**, 34174q (1972); M. E. D. Hillman and A. B. Baylis. U.S. Patent 3,743,669 (1973); (b) K. Morita, Z. Suzuki, H. Hirose. *Bull. Chem. Soc. Jpn*. **41**, 2815 (1968).
3. (a) A. G. M. Barrett, A. S. Cook, A. Kamimura. *Chem. Commun*. 2533 (1998); (b) N. T. McDougal and S. E. Schaus. *J. Am. Chem. Soc*. **125**, 12094 (2003); (c) Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama. *J. Am. Chem. Soc*. **121**, 10219 (1999).
4. (a) M. Shi and Y.-M. Xu. *Chem. Commun*. 1876 (2001); (b) M. Shi and Y.-M. Xu. *Angew. Chem., Int. Ed. Engl.* **41**, 4503 (2002).
5. B. E. Love, P. S. Raje, T. C. Williams. *Synlett* 493 (1994).
6. (a) Y. Uozumi, A. Tanahashi, S.-Y. Lee. Lee, T. Hayashi. *J. Org. Chem*. **58**, 1945 (1993); (b) J. Kang, S. H. Yu, J. I. Kim, H. G. Cho. *Bull. Korean Chem. Soc*. **16**, 439 (1995); (c) S. Gladiali, S. Medici, G. Pirri, S. Pulacchini, D. Fabbri. *Can. J. Chem*. **79**, 670 (2001); (d) D. Zhao and K.-L. Ding. *Org. Lett.* **5**, 1349 (2003); (e) S.-L. You, X.-L. Hou, L.-X. Dai, B.-X. Cao, J. Sun. *Chem. Commun.* 1933 (2000); (f) W.-P. Deng, X.-L. Hou, L.-X. Dai, X.-W. Dong. *Chem. Commun.* 1483 (2000).
7. Bifunctional chiral ligands: see: Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki. *Angew. Chem., Int. Ed. Engl*. **36**, 1871 (1997).
8. (a) J.-W. Han and T. Hayashi. *Tetrahedron: Asymmetry* **13**, 325 (2002); (b) Y. Tian, Q.-C. Yang, T. C. W. Mak, K.-S. Chan. *Tetrahedron* **58**, 3951 (2002).
9. W.-P. Chen, L.-J. Xu, J.-L. Xiao. *Tetrahedron Lett.* **42**, 4275 (2002).
10. I. T. Horvath and J. Rabai. *Science* **266**, 72 (1994); (b) I. T. Horvath. *Acc. Chem. Res.* **31**, 641 (1998); (c) D. P. Curran. *Angew. Chem., Int. Ed. Engl.* **37**, 1175 (1998).