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Chiral Phosphine Lewis Bases Catalyzed Asymmetric aza-Baylis−Hillman Reaction of N-Sulfonated Imines with Activated Olefins

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Abstract: In the aza-Baylis−Hillman reaction of N-sulfonated imines (*N*-arylmethylidene-4-methylbenzenesulfonamides and others) with methyl vinyl ketone, ethyl vinyl ketone, and acrolein, we found that, in the presence of a catalytic amount of chiral phosphine Lewis base such as (*R*)-2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ol **LB1** (10 mol %) and molecular sieve 4A, the corresponding aza-Baylis−Hillman adducts could be obtained in good yields with good to high ee (70−95% ee) at low temperature (∼−30 to −20 °C) or at room temperature in THF, respectively. In CH_2Cl_2 upon heating at 40 °C, the aza-Baylis−Hillman reaction of N-sulfonated imines with phenyl acrylate or naphthyl acrylate gave the adducts in good to high yields (60−97%) with moderate ee (52−77%). The mechanistic insight has been investigated by ^{31}P and ^{1}H NMR spectroscopic measurements. The key enolate intermediate, which has been stabilized by intramolecular hydrogen bonding, has been observed by ^{31}P and ^{1}H NMR spectroscopy. An effective bifunctional Lewis base and Brønsted acid phosphine Lewis base system has been disclosed in this catalytic, asymmetric aza-Baylis−Hillman reaction.

Introduction

Great progress has been made in the execution of the Baylis−Hillman reaction,[1] for which several catalytic, asymmetric versions have been published[2,3] since Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of strong Lewis base (LB) such as 1,4-diazabicyclo[2,2,2]octane (DABCO) in 1972.[4] However, the catalytic, asymmetric Baylis−Hillman reaction is still not fruitful, because it is limited to the specialized α,β-unsaturated ketones or acrylates such as ethyl vinyl ketone (EVK) (71% ee),[2a] 2-cyclohexen-1-one (96% ee),[2b] or 1,1,1,3,3,3-hexafluoroisopropyl acrylate (99% ee)[2c] and naphthyl acrylate (91% ee).[2d] For the simplest methyl vinyl ketone (MVK), 81% ee has been attained in the presence of a special nucleophile-loaded peptide and L-proline.[2e] No high enantioselectivity (>90% ee) has thus far been reported in Baylis−Hillman reactions involving simple Michael acceptors such as MVK or methyl acrylate by a chiral Lewis base promoter.

During our ongoing investigation on the Baylis−Hillman reaction,[5] we disclosed that the aza-Baylis−Hillman reactions of N-sulfonated imines **1** such as *N*-arylmethylidene-4-methylbenzenesulfonamides (ArCH═NTs)[6] with MVK were promoted in the presence of catalytic amounts of Lewis bases such as DABCO or triphenylphosphine (PPh_3) to exclusively give the normal aza-Baylis−Hillman adducts in good yields for many N-sulfonated imines **1** under mild conditions because the N-sulfonated imino group has high reactivity toward nucleophilic attack, even when the phenyl ring bears electron-donating groups.[4,6b] We then sought a suitable chiral Lewis base for a catalytic, asymmetric version of this reaction. Previously, we reported an unprecedented catalytic, asymmetric aza-Baylis−

(1) For reviews, see: (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062. (b) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (d) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−892. (e) Iwabuchi, Y.; Hatakeyama, S. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 2−14. (f) Cai, J.-X.; Zhou, Z.-H.; Tang, C.-C. *Huaxue Yanjiu* **2001**, *12*, 54−64.

(2) (a) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun*. **1998**, 2533−2534. (b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc*. **2003**, *125*, 12094−12095. (c) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc*. **1999**, *121*, 10219−10220. (d) Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K.-M. *J. Org. Chem.* **2003**, *68*, 915−919. (e) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741−3743 and Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601−610. For others, see: (f) Langer, P. *Angew. Chem., Int. Ed*. **2000**, *39*, 3049−3051. (g) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103−3105. (h) Krishna, P. R.; Kannan, V.; Reddy, P. V. N. *Adv. Synth. Catal.* **2004**, *346*, 603−606. (i) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589−5592. (j) Yang, K. S.; Chen, K. M. *Org. Lett.* **2000**, *2*, 729−731. For alternative approaches for asymmetric Baylis−Hillman reactions, see: (k) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc*. **1997**, *119*, 4317−4318. (l) Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun*. **1998**, 1271−1272. (m) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165−2169. (n) Krishna, P. R.; Kannan, V.; Reddy, P. V. N. *Adv. Synth. Catal.* **2004**, *346*, 603−606. (o) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521−2524. (p) Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun*. **1998**, 1271−1272. (q) Shi, M.; Xu, Y. M. *Tetrahedron: Asymmetry* **2002**, *13*, 1196−1200. (r) Mocquet, C. M.; Warriner, S. L. *Synlett* **2004**, 356−357. (s) Hayashi, Y.; Tamura, T.; Shoji, M. *Adv. Synth. Catal*. **2004**, *346*, 1106−1110. (t) Pan, J.-F.; Chen, K.-M. *Tetrahedron Lett*. **2004**, *45*, 2541−2543. (u) Langer, P. *Organic Synthesis Highlights V*; Schmalz, H.-G., Wirth, T., Eds.; Wiley-VCH: Weinheim, Germany, 2003; pp 165−177. (v) Krishna, P. R.; Kannan, V.; Sharma, G. V. M.; Rao, M. H. V. *Synlett* **2003**, 888−890. (w) Wei, H.-X.; Chen, D.; Xu, X.; Li, G.-G.; Pare, P. W. *Tetrahedron: Asymmetry* **2003**, *14*, 971−974 and references therein. (x) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577−1581. (y) Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867−7871. (z) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S.; Reddy, R. M. *Tetrahedron* **2001**, *57*, 8167−8172.

10.1021/ja0447255 CCC: $30.25

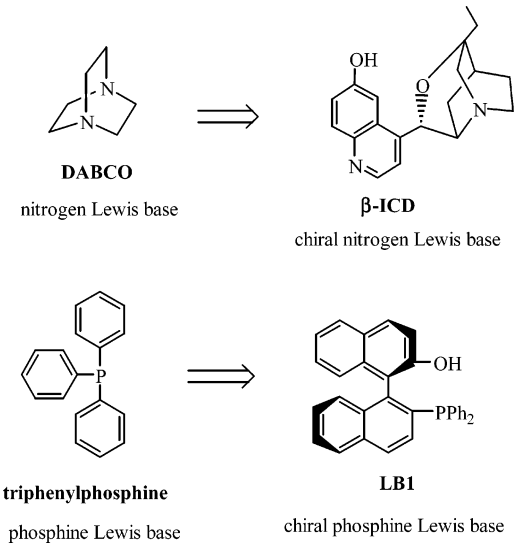
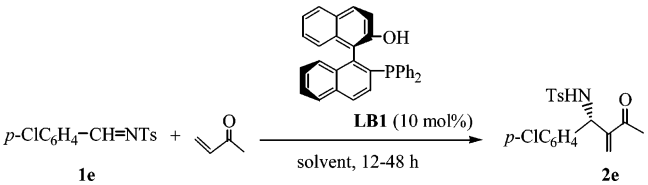


Figure 1. Structures of chiral Lewis bases.

Hillman reaction of N-sulfonated imines **1** with MVK utilizing a chiral nitrogen Lewis base [4-(3-ethyl-4-oxa-1-azatricyclo-[4,4,0,$0^{3,8}$]dec-5-yl)-quinolin-6-ol: β-**ICD**[2a,7]] (Figure 1) to achieve >90% ee in good yield.[6d] This is the first case in which high ee (>90%) can be realized using the simple Michael acceptor MVK. The structure of this nitrogen Lewis base such as the phenolic hydroxy group plays a significant role in this reaction for achieving high ee.[2c,6d] Currently, the exploration of a novel and highly efficient chiral Lewis base for catalytic, asymmetric Baylis–Hillman reaction is a very attractive and competitive field. Therefore, we attempted to seek out a chiral phosphine Lewis base for this reaction since a phosphine Lewis base such as PPh_3 is also an effective promoter for this reaction.[6b] After screening several chiral phosphine Lewis base catalysts, we found that (*R*)-2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ol **LB1**, having a phenolic hydroxy group, is also an effective chiral phosphine Lewis base for the catalytic, asymmetric aza-Baylis–Hillman reaction in which high enantioselectivities (94% ee) can also be realized (Figure 1). The preliminary result has already been communicated.[8] Herein, the full details on the scope and limitations and the mechanistic insight of this catalytic, asymmetric aza-Baylis–Hillman reaction are described. On the basis of these results, exploration of a chiral phosphine Lewis base for α,β-unsaturated cyclic ketone is also reported.

Table 1. aza-Baylis–Hillman Reactions of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** (1.0 equiv) with Methyl Vinyl Ketone (3.0 equiv) in the Presence of Chiral Lewis Base **LB1** (10 mol %)



1e **2e**

entry	solvent	temp/°C	time/h	yield/%[a]/**2e**	ee/%	absolute configuration
1	THF	20	12	86	84	*S*
2	THF	10	12	76	88	*S*
3	THF	0	48	84	90	*S*
4	THF	−30	48	72	94	*S*
5	CH_2Cl_2	10	12	38	82	*S*
6	toluene	10	24	17	67	*S*
7	MeCN	10	24	38	70	*S*
8	Et_2O	10	12	76	80	*S*
9	DMF	10	12	63	74	*S*
10	MeOH	10	24	20[b]	–	–

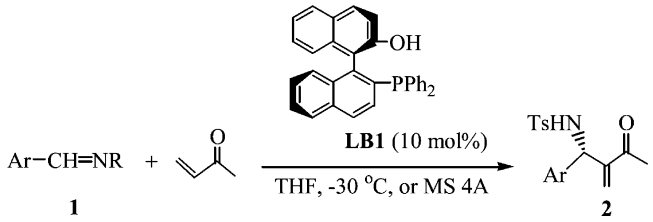
[a] Isolated yields. [b] Michael addition product derived from methanol to **2e** was obtained at the same time (Supporting Information).

Results and Discussion

1. The aza-Baylis–Hillman Reaction of N-Sulfonated Imines 1 with MVK Catalyzed by a Chiral Phosphine Lewis Base LB1. Concerning the chiral phosphine Lewis bases, we selected **LB1** as a chiral Lewis base for this reaction because it has a phenolic OH group similar to the chiral nitrogen Lewis base β-**ICD** (Figure 1).[2a] We first used MVK as the Michael acceptor for the aza-Baylis–Hillman reaction with *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** to develop the optimal reaction conditions. The results are summarized in Table 1. We were delighted to find that in this aza-Baylis–Hillman reaction, high enantiomeric excess (~80–90% ee) of the corresponding aza-Baylis–Hillman adduct **2e** with *S* configuration[8] can be achieved in good yields in tetrahydrofuran (THF), ether (Et_2O), or dichloromethane (CH_2Cl_2) at ~0–20 °C (room temperature) (Table 1, entries 1, 2, 3, 5, and 8). The coexistence of Lewis acid [$Ti(OPr^i)_4$] (10 mol %) did not improve the chemical yield and the ee of **2e** (see Supporting Information). At lower temperature (−30 °C), the ee of **2e** can reach 94% in 72% yield (Table 1, entry 4). When the reactions were carried out in toluene, acetonitrile (MeCN), or *N*,*N*-dimethylformamide (DMF), the corresponding aza-Baylis–Hillman adduct **2e** was obtained in lower ee and lower yields

(3) Other references related to asymmetric Baylis–Hillman reaction: (a) Li, G.-G.; Hook, J. D.; Wei, H.-X. *Org. Bioorg. Chem.* **2001**, 49–61. (b) Fox, D. J.; Medlock, J. A.; Vosser, R.; Warren, S. *J. Chem. Soc., Perkin Trans 1* **2001**, 2240–2249. (c) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030–2031. (d) Bauer, T.; Tarasiuk, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1741–1745. (e) Radha, K. P.; Kannan, V.; Ilangovan, A.; Sharma, G. V. M. *Tetrahedron: Asymmetry* **2001**, *12*, 829–837. (f) Li, G.-G.; Wei, H.-X.; Phelps, B. S.; Purkiss, D. W.; Kim, S. H. *Org. Lett.* **2001**, *3*, 823–826. (g) Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612–1620. (h) Jauch, J. *J. Org. Chem.* **2001**, *66*, 609–611. (i) Suzuki, D.; Urabe, H.; Sato, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3290–3292. (j) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Tetrahedron Lett.* **1999**, *40*, 7537–7540. (k) Evans, M. D.; Kaye, P. T. *Synth. Commun.* **1999**, *29*, 2137–2146. (l) Kataoka, T.; Iwama, T.; Tsujiyama, S.-i.; Kanematsu, K.; Iwamura, T.; Watanabe, S.-i. *Chem. Lett.* **1999**, 257–258. (m) Bocknack, B. M.; Wang, L.-C.; Krische, M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5421–5424 and references therein. (n) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664–4668. (o) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758–7759. (p) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110–1111.
(4) (a) Baylis, A. B.; Hillman, M. E. D. *Ger. Offen.* **1972**, 2,155,113; *Chem. Abstr.* **1972**, *77*, 34174q; Hillman, M. E. D.; Baylis, A. B. U.S. Patent **1973**, 3,743,669. (b) Morita, K.-I.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815–2819.
(5) (a) Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* **2000**, *2*, 2397–2400. (b) Shi, M.; Feng, Y.-S. *J. Org. Chem.* **2001**, *66*, 406–411. (c) Shi, M.; Li, C.-Q.; Jiang, J.-K. *Chem. Commun.* **2001**, 833–834.
(6) (a) Shi, M.; Xu, Y.-M. *Chem. Commun.* **2001**, 1876–1877. (b) Shi, M.; Xu, Y.-M. *Eur. J. Org. Chem.* **2002**, 696–701. (c) Shi, M.; Xu, Y.-M.; Zhao, G.-L.; Wu, X.-F. *Eur. J. Org. Chem.* **2002**, 3666–3679. (d) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507–4510. (e) Xu, Y.-M.; Shi, M. *J. Org. Chem.* **2004**, *69*, 417–425. (f) Shi, M.; Xu, Y. M. *J. Org. Chem.* **2003**, *68*, 4784–4790. (g) Zhao, G.-L.; Huang, J.-W.; Shi, M. *Org. Lett.* **2003**, *5*, 4737–4739. For reports related to the aza-Baylis–Hillman reaction of methyl acrylate with N-sulfonated imines, please see: (h) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett.* **1984**, *25*, 5951–5952. (i) Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869–8882. For reports related to the aza-Baylis–Hillman reaction of MVK with N-sulfonated imine generated in situ, please see: (j) Bertenshow, S.; Kahn, M. *Tetrahedron Lett.* **1989**, *30*, 2731–2732. (k) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2002**, *67*, 2329–2334 and references therein.
(7) The catalyst β-**ICD** was first prepared by Prof. Hoffman: von Riesen, C.; Jones, P. G.; Hoffmann, H. M. R. *Chem.–Eur. J.* **1996**, *2*, 673–679.
(8) Shi, M.; Chen, L. H. *Chem. Commun.* **2003**, 1310–1311.

Table 2. aza-Baylis−Hillman Reactions of *N*-(Arylmethylidene)arylsulfonamide **1** (1.0 equiv) with Methyl Vinyl Ketone (3.0 equiv) in the Presence of Chiral Lewis Base **LB1** (10 mol %) and MS 4A



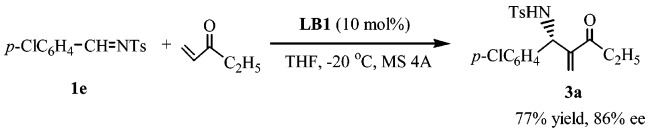
entry	Ar	R	No.	time/h	yield/%[a]/**2**	ee/%[b]	absolute configuration
1	C_6H_5	Ts	**1a**	24 (36)[c]	**2a**, 49 (83)[c]	83 (83)[c]	*S*
2	*p*-MeC_6H_4	Ts	**1b**	24 (36)	**2b**, 53 (82)	80 (81)	*S*
3	*p*-EtC_6H_4	Ts	**1c**	36 (36)	**2c**, 62 (84)	76 (79)	*S*
4	*p*-FC_6H_4	Ts	**1d**	18	**2d**, 84	81	*S*
5	*p*-ClC_6H_4	Ts	**1e**	24 (24)	**2e**, 72 (90)	94 (87)	*S*
6	*p*-BrC_6H_4	Ts	**1f**	18	**2f**, 85	83	*S*
7	*m*-FC_6H_4	Ts	**1g**	36 (24)	**2g**, 26 (96)	91 (85)	*S*
8	*m*-ClC_6H_4	Ts	**1h**	18 (24)	**2h**, 62 (88)	88 (88)	*S*
9	*p*-$NO_2C_6H_4$	Ts	**1i**	12 (24)	**2i**, 60 (86)	94 (92)	*S*
10	*m*-$NO_2C_6H_4$	Ts	**1j**	12 (24)	**2j**, 54 (91)	90 (88)	*S*
11[d]	*o*-ClC_6H_4	Ts	**1k**	24	**2k**, 85	61	*S*
12[d]	*o*-$NO_2C_6H_4$	Ts	**1l**	24	**2l**, 88	84	*S*
13[d]	*trans*-C_6H_5−CH=CH	Ts	**1m**	24	**2m**, 94	95	*S*
14[d]	*p*-ClC_6H_4	Ms	**1n**	24	**2n**, 94	82	*S*
15[d]	*p*-ClC_6H_4	*p*-$ClC_6H_4SO_2$	**1o**	24	**2o**, 94	89	*S*
16[d]	*p*-ClC_6H_4	Ns	**1p**	24	**2p**, −[e]	−[e]	*S*
17[d]	*p*-ClC_6H_4	SES	**1q**	72	**2q**, 53	89	*S*

[a] Isolated yields. [b] Determined by chiral HPLC. [c] Values in parentheses are the results in the presence of MS 4A (100 mg). [d] The reaction was carried out at −20 °C in the presence of MS 4A (100 mg). [e] The corresponding aza-Baylis−Hillmn adduct was not formed because this N-sulfonated imine decomposed quickly under reaction conditions.

(Table 1, entries 6, 7, and 9). In methanol, **2e** was obtained in 20% yield along with a Michael addition product derived from methanol to **2e** (Table 1, entry 10; see Supporting Information).[9] Thus, these optimized reaction conditions for this reaction are to carry out this reaction in THF at −30 °C in the presence of **LB1** (10 mol %).

In the reaction of other *N*-(arylmethylidene)-4-methylbenzenesulfonamides **1** with MVK using **LB1** as a chiral Lewis base under the optimized conditions, good to high enantioselectivities (∼76−91% ee) were achieved with *S* configuration (Table 2).[8] In general, for N-sulfonated imines **1** having electron-donating groups on the phenyl ring, the reaction rate was slightly slower and the corresponding aza-Baylis−Hillman adducts **2** were obtained in lower yields (∼41−62%) with ∼76−83% ee under the same conditions (Table 2, entries 1−3). This is because the prolonged reaction time at low temperature caused the decomposition of N-sulfonated imines **1** because of the ambient moisture. To improve the yields of **2**, we added molecular sieve 4A (100 mg for 0.5 mmol of substrate) into the reaction system to get rid of the ambient moisture. As a result, the isolated yields of **2** were greatly improved with the addition of molecular sieve 4A (Table 2, entries 1−3, 5, 7−10) and the ee of **2** was not significantly affected. Only in some cases, the ee of **2** dropped ∼2−6%. Values in parentheses are the results obtained in the presence of molecular sieve 4A in Table 2. For ortho-substituted N-sulfonated imines **1k** and **1l**, the corresponding adducts **2k** and **2l** were obtained in 85 and 88% yields with 61 and 84% ee, respectively, at −20 °C in the presence of molecular sieve 4A (Table 2, entries 11 and 12). For cinnamoyl N-sulfonated imine **1m**, the achieved ee of the corresponding adduct **2m** reached 95% in 94% yield (Table 2, entry 13).

Scheme 1



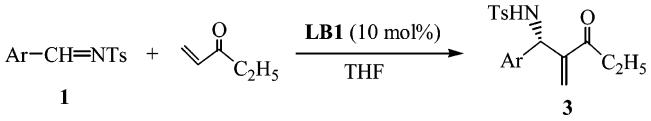
77% yield, 86% ee

Moreover, for other N-sulfonated imines such as *N*-mesylated imine **1n** (ArCH=N−Ms), *N*-*p*-chlorobenzenesulfonated imine **1o** (ArCH=N−$SO_2C_6H_4Cl$-*p*), and *N*-SES protected imine **1q** (*β*-trimethylsilylethanesulfonamide: $Me_3SiCH_2CH_2SO_2N$=CHAr), this catalytic, asymmetric aza-Baylis−Hillman reaction also proceeded smoothly at −20 °C in the presence of chiral phosphine promoter **LB1** and molecular sieve 4A in THF to give the corresponding adducts **3n**, **3o**, and **3q** in good to high yields with 89, 82, and 89% ee, respectively (Table 2, entries 14, 15, and 17). However, for *N*-4-nitrobenzenesulfonated imine **1p** (ArCH=N−Ns), which should be the most active electrophile in this aza-Baylis−Hillman reaction, we found that it decomposed rapidly under the reaction conditions, and the corresponding aza-Baylis−Hillman adduct **3p** was not formed (Table 2, entry 16).

2. Michael Acceptor Generality in This Reaction. Using EVK as a Michael acceptor, we also examined this aza-Baylis−Hillman reaction with N-sulfonated imines **1** using **LB1** as a chiral phosphine Lewis base under various reaction conditions. The results are shown in Supporting Information. The best reaction conditions to carry out this reaction are in THF at −20 °C in the presence of MS 4A to give **3a** in 77% yield with 86% ee as *S* configuration (Scheme 1). In general, the aza-Baylis−Hillman reaction rate of N-sulfonated imines **1** with

(9) The reaction mechanism for the Michael addition of methanol to α,*β*-unsaturated ketones has been disclosed recently: Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696−8697.

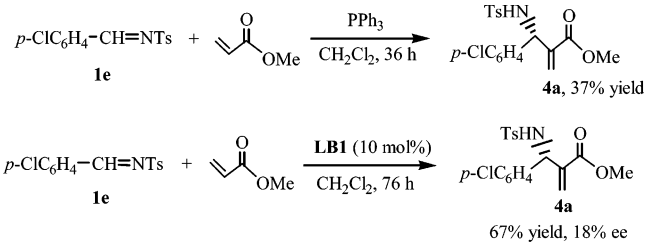
Table 3. aza-Baylis–Hillman Reactions of N-Sulfonated Imines **1** (1.0 equiv) with EVK (2.0 equiv) in the Presence of Chiral Lewis Base **LB1** (10 mol %) and MS 4A



entry	Ar	No.	reaction conditions	time/h	yield/%[a]/**3**	ee/%[b]	absolute configuration
1	C_6H_5	**1a**	−20 °C, MS 4A	96	**3b**, 52	80	*S*
2	*p*-FC_6H_4	**1d**	−20 °C	24	**3c**, 50	78	*S*
3	*p*-FC_6H_4	**1d**	−20 °C, MS 4A	84	**3c**, 56	86	*S*
4	*p*-BrC_6H_4	**1f**	−20 °C	48	**3d**, 66	86	*S*
5	*p*-BrC_6H_4	**1f**	−20 °C, MS 4A	84	**3d**, 78	85	*S*
6	*m*-FC_6H_4	**1g**	−20 °C, MS 4A	48	**3e**, 61	89	*S*
7	*m*-ClC_6H_4	**1h**	−20 °C, MS 4A	48	**3f**, 61	92	*S*
8	*p*-$NO_2C_6H_4$	**1i**	−20 °C, MS 4A	96	**3g**, 85	88	*S*
9	*p*-FC_6H_4	**1d**	−30 °C, MS 4A	7 d	**3c**, 17	88	*S*
10	*p*-BrC_6H_4	**1f**	−30 °C, MS 4A	7 d	**3d**, 40	88	*S*

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

Scheme 2



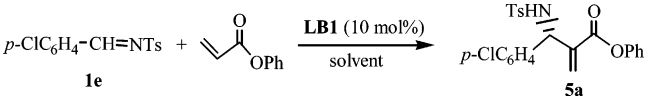
EVK is slower than that of N-sulfonated imines **1** with MVK under identical conditions. In addition, this reaction is sluggish at −30 °C in the presence of chiral phosphine Lewis base **LB1** (Supporting Information).

Under these optimized reaction conditions (−20 °C in THF with MS 4A), we next examined the aza-Baylis–Hillman reaction of other N-sulfonated imines **1** with EVK. The results are summarized in Table 3. The corresponding aza-Baylis–Hillman adducts **3** were obtained in ∼78−92% ee in moderate to good yields (Table 3, entries 1−8). The yields of **3** were indeed improved in the presence of MS 4A for other N-sulfonated imines **1** as well (Table 3, entries 2−5). Moreover, we further confirmed that at −30 °C in the presence of MS 4A, the aza-Baylis–Hillman reactions of N-sulfonated imines **1d** and **1f** having electron-withdrawing groups on the benzene ring with EVK are also sluggish and the adducts **3** were produced in low yields even after 7 days (Table 3, entries 9 and 10).

It should be noted that the ee of **2** and **3** can reach >99% after one recrystallization from CH_2Cl_2/hexane (1/6).

To extend the scope and limitations of this novel catalytic, asymmetric aza-Baylis–Hillman reaction catalyzed by chiral phosphine Lewis base, we examined the reaction of N-sulfonated imines **1** with methyl acrylate and phenyl acrylate using **LB1** as a promoter. As a result, we found that the aza-Baylis–Hillman reaction of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** with methyl acrylate is sluggish in the presence of tertiary phosphine Lewis base in many solvents. Using PPh_3 as a Lewis base in CH_2Cl_2, we obtained the corresponding aza-Baylis–Hillman adduct **4a** in 37% after 36 h at room temperature (Scheme 2). By means of chiral phosphine Lewis base **LB1** under the same conditions, **4a** was produced in 67% yield with 18% ee (Scheme 2). On the other hand, the aza-Baylis–Hillman reaction of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** with phenyl acrylate proceeded fairly smoothly in various solvents under mild conditions in the presence of PPh_3. Using **LB1** as a chiral Lewis base promoter in aza-Baylis–Hillman reaction of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** with phenyl acrylate, we obtained the corresponding adduct **5a** in moderate ee in various solvents (Table 4, entries 1−5). In THF, the achieved ee can reach 70%, but the yield is 40% after 72 h and 17% after 12 h (Table 4, entry 1). When the reaction was carried out in DMF, MeCN, toluene, and $^{i}PrO^{i}Pr$, the achieved ee is ∼40−63% (Table 4, entries 2−4, and 11). In dichloromethane at room temperature, the achieved ee is 71% in 70% yield (Table 4, entry 5). Thus, it seems to us that dichloromethane is the best solvent for this type of catalytic, asymmetric aza-Baylis–Hillman reaction. The reaction temperature significantly affected the reaction rate and the achieved ee in dichloromethane as well. At −40 °C, no reaction occurred, and at −20 °C, the yield is 25% with 60% ee. We eventually found that, upon heating in CH_2Cl_2 at 40 °C for 12 h, the aza-Baylis–Hillman adduct **5a** was obtained in 94% yield with 67% ee (Table 4, entry 10). This is the best reaction condition for this type of aza-Baylis–Hillman reaction. The addition of Lewis acid $Ti(OPr^{i})_4$ did not

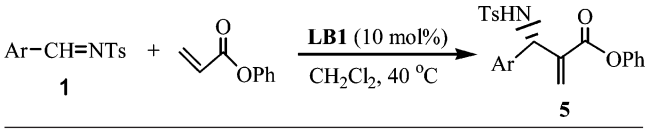
Table 4. aza-Baylis–Hillman Reactions of N-Sulfonated Imine **1e** (1.0 equiv) with Phenyl Acrylate (1.5 equiv) in the Presence of Chiral Lewis Base **LB1** (10 mol %) in Various Solvents



entry	temp (°C)	solvent	time/h	yield/%[a]/**5a**	ee/%[b]	absolute configuration
1	10	THF	72	40[c]	70	*S*
2	10	DMF	20	27	40	*S*
3	10	CH_3CN	20	70	58	*S*
4	10	Toluene	12	54	50	*S*
5	10	CH_2Cl_2	12	70	71	*S*
6	10	CH_3OH	15	NR	−	
7	−40	CH_2Cl_2	24	NR	−	
8	−20	CH_2Cl_2	24	25	60	*S*
9	0	CH_2Cl_2	20	59	67	*S*
10	40	CH_2Cl_2	12	94	67	*S*
11	40	$^{i}PrOPr^{i}$	12	36	63	*S*

[a] Isolated yield. [b] Determined by chiral HPLC. [c] In THF after 12 h, **5a** was obtained in 17 with 70% ee.

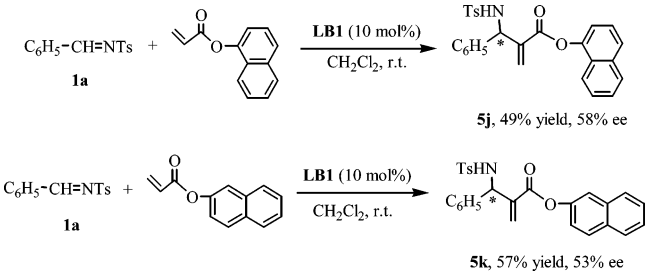
Table 5. aza-Baylis−Hillman Reactions of N-Sulfonated Imines **1** (1.0 equiv) with Phenyl Acrylate (1.5 equiv) in the Presence of Chiral Lewis Base **LB1** (10 mol %) in Dichloromethane at 40 °C



entry	Ar	No.	time/h	yield/%[a]/**5**	ee/%[b]	absolute configuration
1	C_6H_5	**1a**	12	**5b**, 84	61	*S*
2	*p*-EtC_6H_4	**1c**	12	**5c**, 60	53	*S*
3	*p*-FC_6H_4	**1d**	12	**5d**, 80	69	*S*
4	*p*-BrC_6H_4	**1f**	12	**5e**, 85	77	*S*
5	*m*-FC_6H_4	**1g**	12	**5f**, 89	63	*S*
6	*m*-ClC_6H_4	**1h**	12	**5g**, 95	58	*S*
7	*p*-$NO_2C_6H_4$	**1i**	12	**5h**, 97	75	*S*
8	*m*-$NO_2C_6H_4$	**1j**	12	**5i**, 89	52	*S*

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

Scheme 3



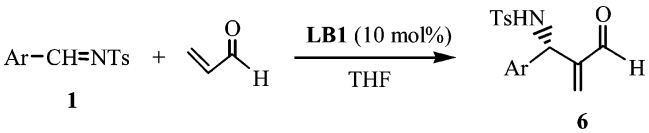
significantly improve the result under the same conditions (see Supporting Information).

Under these optimized reaction conditions, we next carried out the aza-Baylis−Hillman reactions of various N-sulfonated imines **1** with phenyl acrylate. The results are shown in Table 5. In most cases, the corresponding aza-Baylis−Hillman adducts **5** were formed in good to high yields (60−97%) with moderate to good ee (52−77%) (Table 5, entries 1−8).

Using α- or *β*-naphthyl acrylate as Michael acceptor under these reaction conditions, we obtained similar results for the corresponding adducts **5j** and **5k** (Scheme 3). This result suggests that the ee is not affected by the steric bulkiness in the ester moiety of acrylate in this reaction.

In addition to α,*β*-unsaturated ketones and esters, we also examined the aza-Baylis−Hillman reaction of N-sulfonated imines **1** with acrolein in the presence of chiral phosphine Lewis base **LB1**. In this type of aza-Baylis−Hillman reaction, THF is the best solvent on the basis of examination of the solvent effects in the way similar to that described above. The results are summarized in Table 6. Using *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** as the substrate at room temperature (20 °C) and 40 °C in THF, we obtained the corresponding aza-Baylis−Hillman adduct **6a** in high yields (91 and 94%) with good ee (83 and 81% ee) for ∼2−4 h, respectively (Table 6, entries 1 and 2). At lower reaction temperatures (∼−30 to 0 °C), this reaction became sluggish and the achieved ee decreased dramatically (Table 6, entries 3−5). We believe that in this case, the equilibrium of the Baylis−Hillman reaction leans toward the reaction product at higher temperature, whereas at lower temperature, the equilibrium leans toward the reversed way. This reversibility always impairs the enantioselectivity of Baylis−Hillman reaction. Thus, we carried out this aza-Baylis−Hillman

Table 6. aza-Baylis−Hillman Reactions of N-Sulfonated Imines **1** (1.0 equiv) with Acrolein (2.0 equiv)) in the Presence of Chiral Lewis Base **LB1** (10 mol %) in THF at Room Temperature



entry	Ar	No.	temp. °C	time h	yield %[a]/**6**	ee %[b]	absolute configuration
1	*p*-ClC_6H_4	**1e**	40	2	**6a**, 94	81	*S*
2	*p*-ClC_6H_4	**1e**	rt	4	**6a**, 91	83[c]	*S*
3	*p*-ClC_6H_4	**1e**	0	12	**6a**, 76	78	*S*
4	*p*-ClC_6H_4	**1e**	−20	12	**6a**, 63	68	*S*
5	*p*-ClC_6H_4	**1e**	−30	12	**6a**, 78	49	*S*
6	C_6H_5	**1a**	rt	4	**6b**, 88	86[c]	*S*
7	*p*-MeC_6H_4	**1b**	rt	12	**6c**, 97	76[c]	*S*
8	*p*-$MeOC_6H_4$	**1r**	rt	12	**6d**, 99	78[c]	*S*
9	*p*-FC_6H_4	**1g**	rt	4	**6c**, 86	84[c]	*S*
10	*p*-BrC_6H_4	**1f**	rt	4	**6f**, 96	79[c]	*S*
11	*m*-ClC_6H_4	**1h**	rt	4	**6g**, 74	82[c]	*S*

[a] Isolated yield. [b] Determined by chiral HPLC. [c] After one recrystallization from CH_2Cl_2/hexane (1/5), the achieved ee can reach 99.9%.

reaction of other N-sulfonated imine substrates **1** with acrolein at room temperature (20 °C). As a result, we found that the corresponding aza-Baylis−Hillman adducts **6** were formed in high yields with good ee for most of N-sulfonated imines **1** with *S* configuration (Table 6, entries 6−11). After one recrystallization from CH_2Cl_2/hexane (1/6), the ee of **6** can reach 99.9% (Table 6, entries 7−9).

We also tried to utilize the aliphatic N-sulfonated imines **1** (Me_2CH═NTs and BuCH═NTs) for this reaction under the same conditions as those described above.[10] However, the reaction was unsuccessful, and the corresponding aza-Baylis−Hillman adduct was not formed.

3. The Additives on This Catalytic, Asymmetric aza-Baylis−Hillman Reaction. It is well-known that some additives such as $LiClO_4$ and $Yb(OTf)_3$ can improve the reaction rate and enantioselectivity in Baylis−Hillman reaction.[2d,i,j,11] Therefore, in addition to $Ti(O^iPr)_4$ we examined other additives in the presence of chiral phosphine Lewis base **LB1** in THF in this catalytic, asymmetric reaction. The results are shown in Supporting Information. Additive $B(O^iPr)_3$ did not affect the ee and reaction rate. In the presence of Lewis acid $Yb(OTf)_3$ (4 mol %), this reaction became sluggish (42% yield and 74% ee for 72 h). No reaction occurred in the presence of $Yb(OTf)_3$ (10 mol %). These results suggest that the coexistence of Lewis acid impairs this reaction because of the coordination to the Lewis base active site. Using $LiClO_4$ as an additive, we observed a similar result (42% yield and 54% ee for 72 h; see Supporting Information). At any rate, these additives did not improve the enantioselectivities in this reaction.

4. The Structure of Chiral Phosphine Lewis Base on This Reaction. 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 **2e** in 13% yield with only 20% ee (*R* configuration)

(10) For the synthesis of aliphatic imines, see: Chemla, F.; Hebbe, V.; Normant, J. F. *Synthesis* **2000**, *1*, 75−77.
(11) (a) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett*. **1999**, *40*, 1539−1542. (b) Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett*. **2002**, *43*, 127−130. (c) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941−1947.

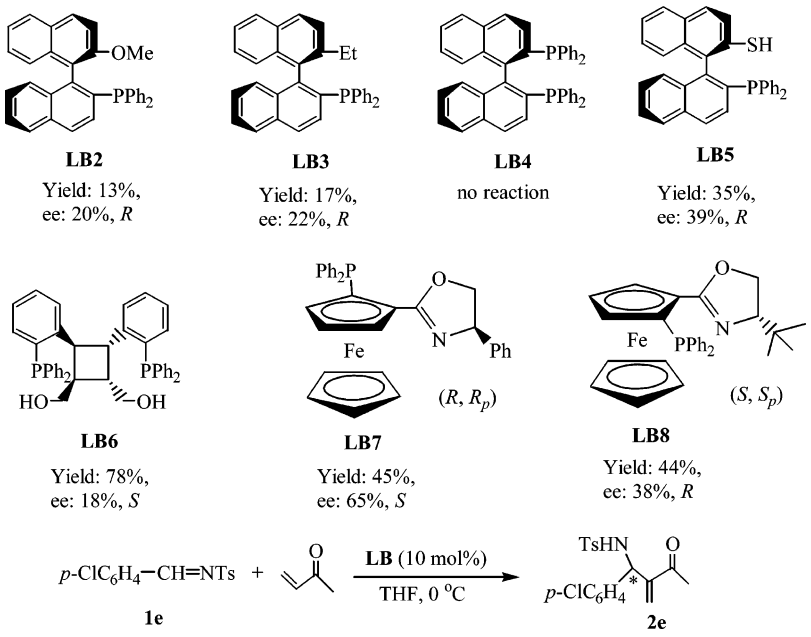


Figure 2.

using O-methylated ligand (MOP) **LB2** as a chiral Lewis base[12a] and in 17% yield with 22% ee (*R* configuration) using (2′-ethyl-[1,1′]binaphthalenyl-2-yl)diphenylphosphane **LB3** as a chiral Lewis base[12a] under the same conditions (Figure 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[12b,c] and the [2,3-bis-(2-diphenylphosphanylphenyl)-4-hydroxymethylcyclobutyl]methanol **LB6**[12d] 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-Baylis−Hillman reaction. Other chiral ferrocene phosphine ligands **LB7** and **LB8**[12e,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 (Figure 2). Only (*R*)-2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ol **LB1** having a phenolic hydroxy group can effectively catalyze this catalytic, asymmetric aza-Baylis−Hillman reaction to give the products in good yields and higher ee.

We described here an unprecedented catalytic, asymmetric aza-Baylis−Hillman reaction of N-sulfonated imines **1** with various activated olefins by a chiral phosphine Lewis base **LB1**. A catalytic, asymmetric aza-Baylis−Hillman reaction version using a variety of Michael acceptors was disclosed. Moreover, since chiral Lewis base **LB1** is a known compound that can be easily prepared according to the literature (Experimental Section in Supporting Information), we can carry out the above reaction in gram scale; for example, **1e** (2 g) with **LB1** (310 mg) under the same conditions as those shown in entry 5 of Table 2. It was confirmed that a similar result could be obtained (70% yield and 93% ee).

Moreover, to further explore the effective chiral phoshine Lewis bases for this reaction, we attempted to modify the structure of chiral phosphine Lewis base **LB1** to achieve higher ee and isolated yields under milder conditions.

5. The Modification of the Structure of Chiral Lewis Base LB1. We first decided to synthesize the 6-substituted and 6,6′-disubstituted chiral phosphine Lewis bases **LB9** and **LB10** because, on the basis of the previous reports related with (*R*)-binol in asymmetric catalysis, it is well-known that the introduction of substituents in the 6,6′-position of binol can improve the enantioselectivity to some extent.[13] As shown in Scheme SI-1, chiral phosphine Lewis base **LB9** was readily prepared by the bromination of the precursor of **LB1** to furnish **LB9-1** in 80% yield, which was reduced with $HSiCl_3$ and Et_3N in toluene at 120 °C to give **LB9** in 70% yield.[14] Chiral phosphine Lewis base **LB10** was prepared according to the Scheme SI-2 shown in Supporting Information. Dibromination of (*R*)-binol at −78 °C gave **LB10-1** in 92% yield in dichloromethane. Two phenolic hydroxy groups were protected by MOMCl in THF at 0 °C to afford **LB10-1** in quantitative yield. Kumada cross-coupling reaction with PhMgBr and deprotection of MOM group with aqueous HCl solution produced **LB10-3** in 90% yield.[15] The compound **LB10-4** was obtained by the reaction of **LB10-3** with Tf_2O in the presence of pyridine. The coupling reaction of **LB10-4** with diphenyl phosphite and hydrolysis with aqueous sodium hydroxide solution in MeOH/dioxane mixing solvent produced the compound **LB10-6** in good yield. The reduction of phosphate **LB10-6** by $HSiCl_3$ and Et_3N in toluene at 120 °C

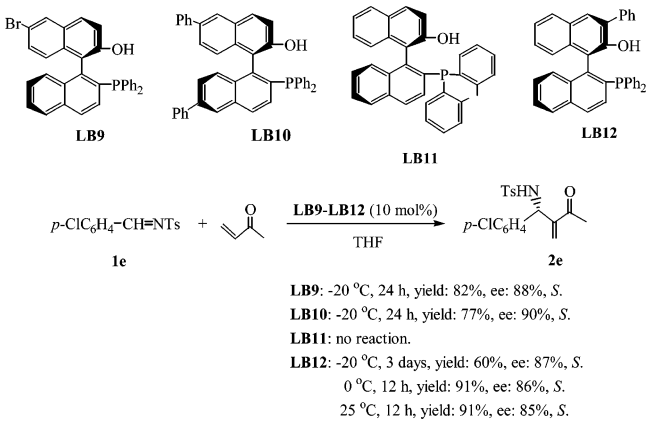
(12) (a) Uozumi, Y.; Tanahashi, A.; Lee. S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945−1948. (b) Kang, J.; Yu, S. H.; Kim, J. I.; Cho, H. G. *Bull. Korean Chem. Soc.* **1995**, *16*, 439−443. (c) Gladiali, S.; Medici, S.; Pirri, G.; Pulacchini, S.; Fabbri, D. *Can. J. Chem.* **2001**, *79*, 670−678. (d) Zhao, D. B.; Ding, K.-L. *Org. Lett.* **2003**, *5*, 1349−1351. (e) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933−1934. (f) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-W. *Chem. Commun.* **2000**, 1483−1484.

(13) (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 2001. Also see: (c) Han, J.-W.; Hayashi, T. *Tetrahedron: Asymmetry* **2002**, *13*, 325. (d) Tian, Y.; Yang, Q.-C.; Mak, T. C. W.; Chan, K.-S. *Tetrahedron* **2002**, *58*, 3951. (e) Han, J.-W.; Hayashi, T. *Chem. Lett.* **2001**, 976. (f) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun.* **1999**, 2185. (g) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem.−Eur. J.* **2001**, *7*, 4465.

(14) Nozaki, K.; Shibahara, F.; Itoi, Y.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1911−1918.

(15) (a) Chen, R.-F.; Qian, C.-T.; de Vries, J. G. *Tetrahedron Lett.* **2001**, *42*, 6919−6921. (b) Qian, C.-T.; Huang, T.-S.; Zhu, C.-J.; Sun, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2097−2103.

Scheme 4



afforded **LB10** in good yield (see Scheme SI-2 in Supporting Information).

By means of similar reaction procedures, we prepared another chiral phosphine Lewis base **LB11**, which has two methyl groups adjacent to the phosphine atom (see Scheme SI-3 in Supporting Information). On the other hand, chiral phosphine Lewis base **LB12**, having a phenyl group on the 3-position adjacent to the phenolic hydroxy group, was prepared according to Scheme SI-4 shown in Supporting Information. MOM-protected (*R*)-binol was treated by ^{t}BuLi in THF at −78 °C, and then the resulted solution was treated with $BrCF_2CF_2Br$ to give compound **LB12-1** in 75% yield.[16a] The Suzuki-type cross-coupling reaction of **LB12-1** with $PhB(OH)_2$ in the presence of Pd(0) catalyst produced compound **LB12-2** in 99% yield. The MOM-protecting group in **LB12-2** was removed to give the corresponding modified binol **LB12-3**, which was treated with Tf_2O to produce **LB12-4**.[16b] Upon transformations similar to those described above, chiral phosphine Lewis base **LB12** was obtained in good yield (see Scheme SI-4 in Supporting Information).

These chiral phosphine Lewis bases **LB9**−**LB12** were employed in the same catalytic, asymmetric aza-Baylis−Hillman reaction of N-sulfonated imines **1** with MVK or phenyl acrylate. The results are summarized in Tables SI-1−SI-5 in Supporting Information, respectively. The summarized results have been indicated in Scheme 4. The outcomes for comparison of chiral phosphine Lewis bases **LB1**, **LB9**, and **LB10** in the aza-Baylis−Hillman reaction of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** with MVK disclosed that **LB9** and **LB10** are similarly as effective as **LB1** in the aza-Baylis−Hillman reaction using MVK as a Michael acceptor. In addition, they have similar enantioselective induction abilities in this reaction. Moreover, we found that **LB11** has no catalytic ability for this reaction. These results suggest that Br and phenyl substituents on the 6,6′-position of binaphthalene framework do not significantly affect the reaction rate and enantioselectivity in this catalytic, asymmetric reaction, but the steric bulkiness around the phosphine atom plays a key role to initiate the reaction. It should be pointed out that by using **LB1**, **LB9**, and **LB10** as chiral Lewis base promoters in this reaction, we found that they are gradually oxidized into the corresponding phosphine oxides during the reaction. Chiral phosphine Lewis base **LB12**, having a phenyl substituent on the 3-position adjacent to the phenolic hydroxy group in the aza-Baylis−Hillman reaction of N-sulfonated imines **1** with MVK, is slightly less effective than **LB1** because at −20 °C, **2e** was obtained in 60% yield with 87% ee after 3 days in THF (Scheme 4). However, at 0 °C or 25 °C, **2e** was obtained in 91% yield with 86 and 85% ee, respectively, after 12 h (Scheme 4). At relatively higher temperature, this reaction proceeded smoothly to give the adduct in good enantioselectivity. Therefore, no MS 4A is required in this catalytic system. Overall, we found that chiral Lewis base **LB12** having a phenyl substituent adjacent to the phenolic hydroxy group produced the adducts in relatively higher ee under slightly milder conditions (0 and 25 °C) in the aza-Baylis−Hillman reaction using MVK as a Michael acceptor. We also confirmed that this Lewis base promoter is difficult to be oxidized to the corresponding phosphine oxide during the reaction under identical conditions as those of **LB1**, **LB9**, and **LB10**. It is still active and can be reused again for this reaction after recovery by silica gel column chromatography (Table SI-4, entry 4 in Supporting Information).

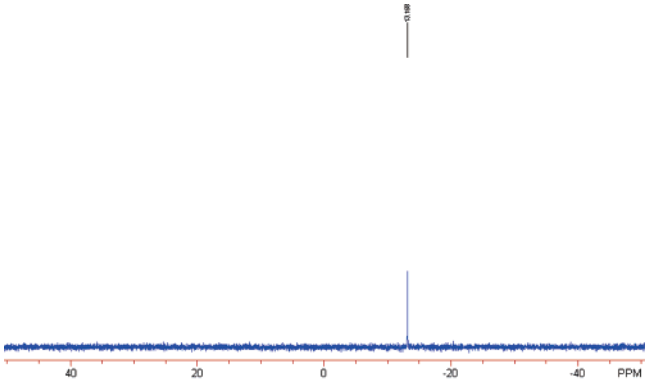


Figure 3. ^{31}P NMR spectrum of **LB1** in $CDCl_3$.

6. Mechanistic Survey. The absolute configuration of adduct **2** was determined to be (*S*)-enriched by comparison of the sign of specific rotation with its antipode.[17] For adducts **5** and **6**, their absolute configurations were unambiguously confirmed to be (*S*)-enriched by the method reported by Li and Hatakeyama, namely, transforming the products to the corresponding phenylglycine derivatives and comparing their signs of specific rotation to those of authentic samples prepared from (*R*)-phenylglycine as shown in Scheme SI-5 in Supporting Information.[2g,18,19] To get more mechanistic insight into this reaction, we carried out the ^{31}P NMR and ^{1}H NMR spectroscopic measurements of phosphine Lewis base in the absence or presence of MVK or N-sulfonated imines **1**. We found that the ^{31}P NMR ($CDCl_3$, 85% H_3PO_4) spectroscopic data of **LB1** showed a signal at −13.16 ppm (Figure 3), but the ^{31}P NMR ($CDCl_3$, 85% H_3PO_4) spectroscopic data of **LB1** with MVK (molar ratio = 1:5) elucidated a new signal at +25.30 ppm, which was believed to correspond to the phosphonium enolate,

(16) (a) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253−2256. (b) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920−6930.

(17) The absolute configuration of **2e** with *R* configuration was determined by X-ray analysis in our previous article, which has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 167239. The absolute configuration of the major enantiomer of **2** reported in this article was assigned according to the sign of their specific rotations by comparison of the $[\alpha]_D$.

(18) (a) Li, G.-G.; Wei, H.-X.; Whittlesey, B. R.; Batrice, N. N. *J. Org. Chem.* **1999**, *64*, 1061−1064. (b) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207−1217.

(19) Kobayashi, K.; Okamoto, T.; Oida, T.; Tanimoto, S. *Chem. Lett.* **1986**, 2031−3034.

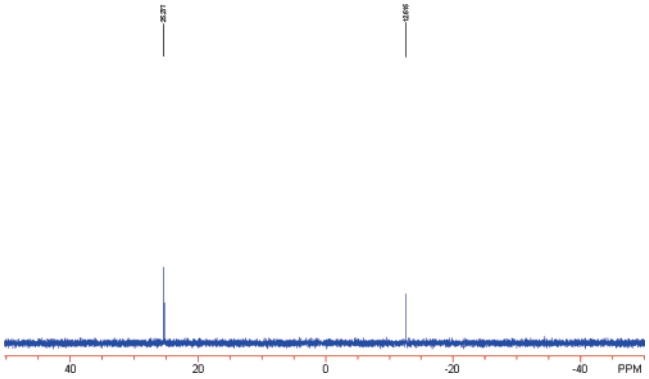


Figure 4. ^{31}P NMR spectrum of **LB1** with MVK in $CDCl_3$.

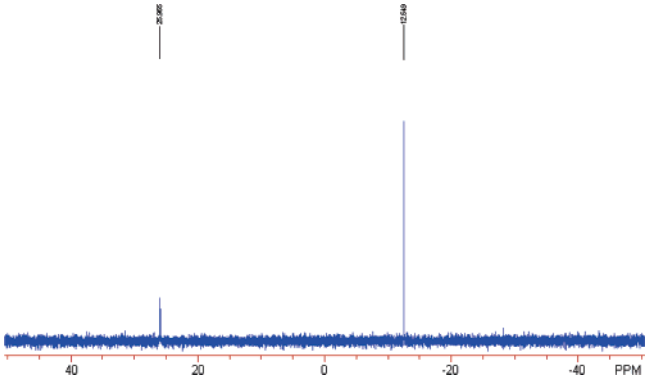


Figure 5. ^{31}P NMR spectrum of **LB1** with MVK and imine in $CDCl_3$.

along with the signal of **LB1** (Figure 4).[20] The ^{31}P NMR spectroscopic data of **LB1** with MVK and N-sulfonated imines did not change again (Figure 5). However, for the ^{31}P NMR spectroscopic data of phosphine Lewis base **LB2** (MOP) under the same conditions, no such alteration could be observed in the presence of MVK or N-sulfonated imines (see Figures SI-1−SI-3 in Supporting Information). The ^{1}H NMR spectroscopic data of **LB1** and **LB1** with MVK clearly indicated that the phenolic hydroxy group at 4.62 ppm in **LB1** shifted to another place with the addition of MVK (see Figures SI-4 and SI-5 in Supporting Information), suggesting the existence of a hydrogen-bonding interaction (O−H···O$^-$). In the ^{31}P NMR spectrum of **LB1**, the new signal that appeared at plus field with the addition of MVK along with the signal at minus field (free phosphine ligand) also indicated that the positively charged phosphine atom (P^+) species was formed and it was in equilibrium with free **LB1**. The interaction of the phenolic hydroxy group with the oxygen atom of MVK (hydrogen bonding) does indeed exist which stabilizes the in situ formed phosphonium enolate and leans the equilibrium to the formation enolate intermediate.[20] This is why a similar phenomenon was not observed in the ^{31}P NMR spectrum of **LB2** with the addition of MVK. In the case of **LB1** with phenyl acrylate, a similar phenomenon was observed (Figure 6).

The ^{31}P NMR spectrum of an authentic phosphonium iodide salt **A** derived from **LB1** with 4-iodobutan-2-one[21] was measured under the same conditions (Scheme 5). A signal at +26.07 ppm was recognized (Figure 7). Meanwhile, similar ^{1}H and ^{31}P

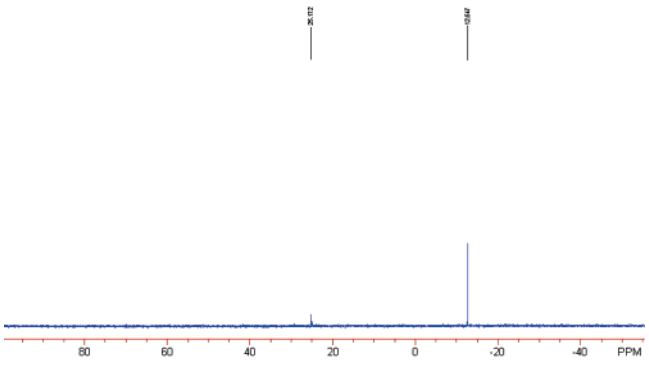


Figure 6. ^{31}P NMR spectrum of **LB1** with phenyl acrylate in $CDCl_3$.

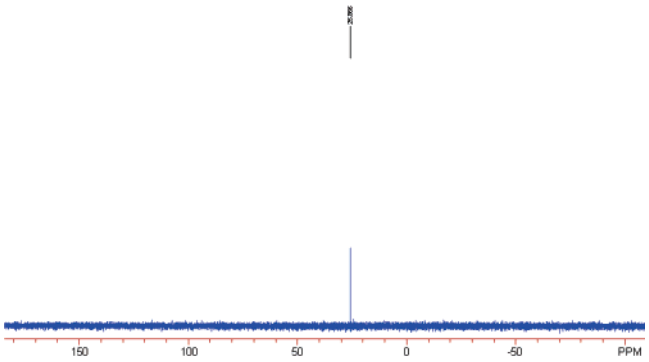
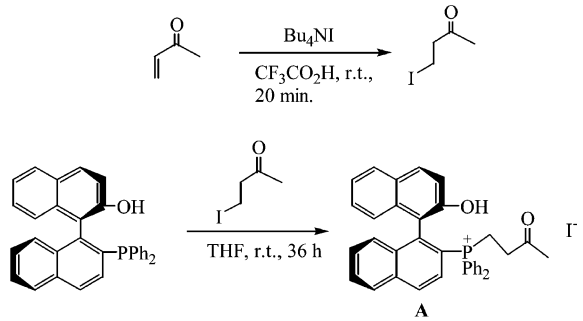


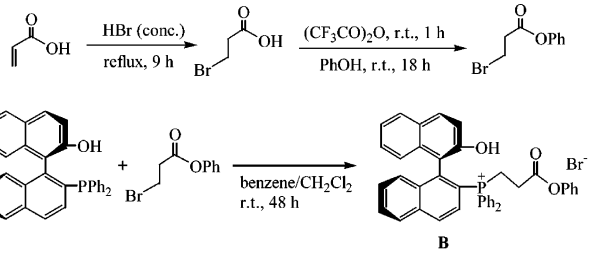
Figure 7. ^{31}P NMR spectrum of phosphonium iodide salt **A** in $CDCl_3$.

Scheme 5



^{31}P NMR ($CDCl_3$, 85% H_3PO_4) δ +26.07

Scheme 6



^{31}P NMR ($CDCl_3$, 85% H_3PO_4) δ +25.44

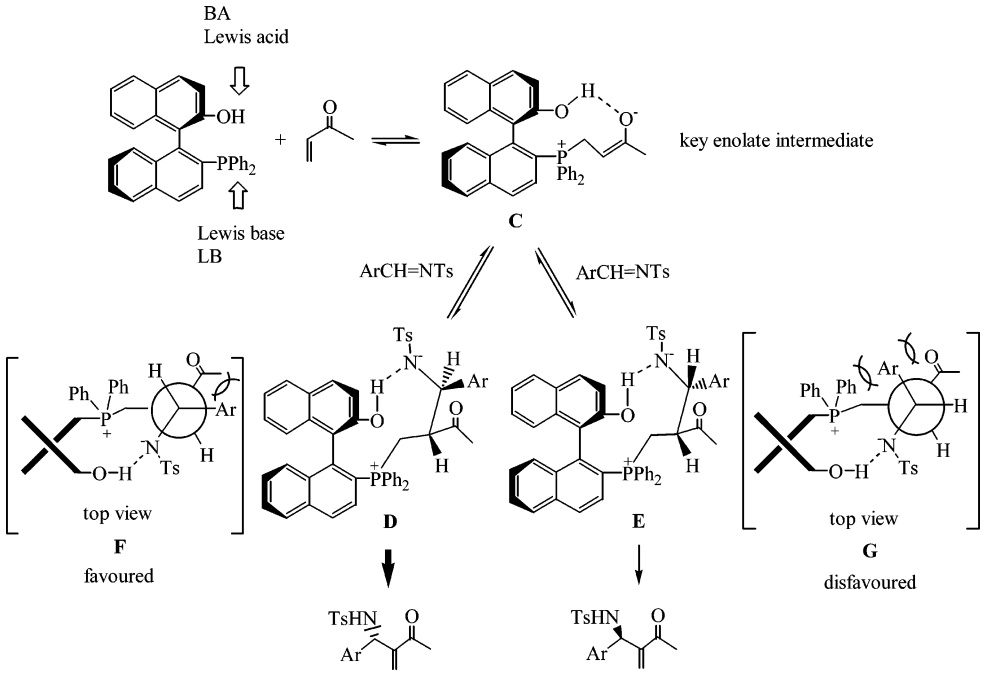
NMR measurements were carried out for the phosphonium bromide salt **B** derived from the reaction of **LB1** with 3-bromopropionic acid phenyl ester[22] as shown in Scheme 6. A signal at +25.44 ppm was recognized in the ^{31}P NMR spectrum under the same conditions (Figure 8), a result similar to that of phosphonium iodide salt **A**. These chemical shifts of phospho-

(20) The ^{31}P NMR signal of phosphine oxide of **L1** is at +31.38 ppm. The ^{31}P NMR signal of the positively charged phosphine (P^+) is in the range of ∼+10 to +30 ppm (please see: Kayser, M. M.; Hatt, K. L.; Hopper, D. L. *Can. J. Chem.* **1991**, *69*, 1929−1939).

(21) Marx, J. M. *Tetrahedron* **1983**, *39*, 1529−1532.

(22) (a) Eussen, von D. K. *Justus Liebigs Ann. Chem.* **1905**, *342*, 128−137. (b) Bruice, T. C.; Hegarty, A. F.; Felton, S. M.; Donzel, A.; Kundu, N. G. *J. Am. Chem. Soc.* **1970**, *92*, 1370−1378.

Scheme 7



nium salts **A** and **B** are similar to those observed in Figures 4 and 6, suggesting that the signals at plus field in Figures 4 and 6 should be structurally similar to those of phosphonium enolates. In Figure 9, we indicated the ^{1}H NMR spectrum of phosphonium iodide salt **B** in which the signal of phenolic hydroxy group dramatically shifted to the low field at 9.78 ppm along with some small amount of ethyl acetate as compared with that of phenolic hydroxy group at 4.60 ppm in the ^{1}H NMR spectrum of **LB1** (Figure 10). These results further strongly suggest that the reaction of **LB1** with α,β-unsaturated ketone or ester indeed produces a phosphonium enolate immediately and there is an intramolecular hydrogen bonding between the phenolic hydroxy group and oxygen atom of carbonyl group to stabilize the in situ formed phosphonium enolate and leans the equilibrium to the formation of enolate intermediate.

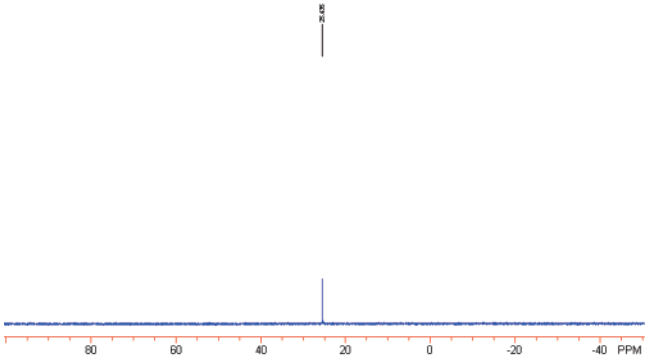


Figure 8. ^{31}P NMR spectrum of phosphonium iodide salt **B** in $CDCl_3$.

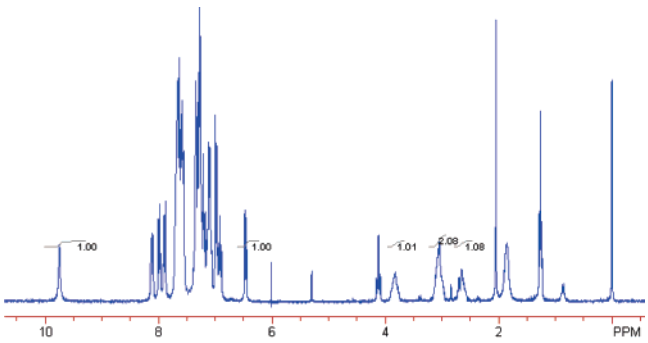


Figure 9. ^{1}H NMR spectrum of phosphonium iodide salt **B** with MVK in $CDCl_3$.

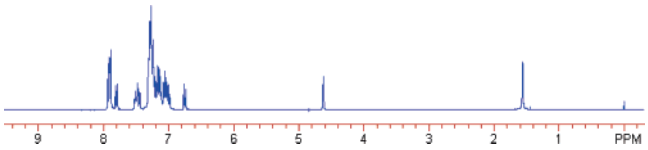
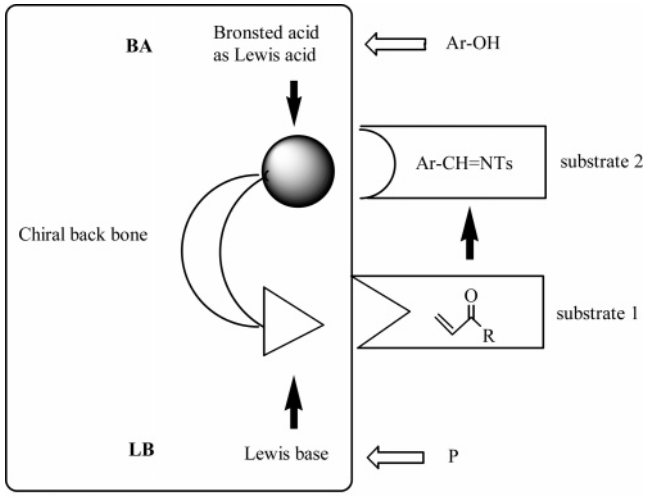


Figure 10. ^{1}H NMR spectrum of **LB1** in $CDCl_3$.

We believe that this kind of interaction is the driving force for the aza-Baylis−Hillman reaction catalyzed by **LB1** to be more effective than **LB2** (MOP). This unusual phenomenon also corresponds to the high chiral induction in this aza-Baylis−Hillman reaction catalyzed by **LB1**.

In Scheme 7, we give a detailed mechanistic explanation and rationalize the outcome of absolute stereochemistry of adducts on the catalysis of chiral phosphine Lewis base **LB1**.[8] We believe that **LB1** acts as a bifunctional chiral ligand in this reaction.[23] The phosphine atom acts as a Lewis base, and the phenolic OH group acts as a Lewis acid through hydrogen bonding (BA: Brønsted acid as a Lewis acid). LB is used to initiate the Baylis−Hillman reaction, and BA is utilized to stabilize the in situ formed key enolate intermediate and the reaction intermediate through hydrogen bonding. Thus, this is

(23) Bifunctional chiral ligands: Please see: (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. (c) Takamura, M.; Hamanashi, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650−1652. (d) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187−2209. (e) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660−2661.



chiral phosphine Lewis base catalyst: LBBA bifunctional catalytic system.

Figure 11.

a Lewis base and Brønsted acid (LBBA) bifunctional chiral ligand system (Figure 11). Michael addition of **LB1** to MVK affords the key enolate intermediate **C**, which undergoes aldol reaction with N-sulfonated imines **1** to give several diastereomeric intermediates according to the generally accepted reaction mechanism for the Baylis−Hillman reaction. The key factor is the intramolecular hydrogen bonding between the phenolic OH and the oxygen atom of carbonyl group for intermediate **C**. In addition, the intramolecular hydrogen bonding between the phenolic O−H and the nitrogen anion stabilized by sulfonyl group can produce relatively stable diastereomeric intermediates **D** and **E**. However, as shown in Newman projection **F** and **G** (top view), the steric repulsions between the C(O)Me group with the aromatic group and the aromatic group with two phenyl groups in the phosphorus atom suggest that intermediate **D** is more stable than **E** in this relatively stabilized transition state. Moreover, the use of N-sulfonated imines, instead of aldehydes, can drive the reaction forward and perhaps cut down on reversibility shown in Scheme 7, which usually erodes the enantioselectivity in Baylis−Hillman reaction. Therefore, intermediate **D** undergoes facile elimination to produce the aza-Baylis−Hillman adduct with (*S*)-enriched configuration.

7. The aza-Baylis−Hillman Reaction of N-Sulfonated Imines 1 with *β*-Substituted Michael Acceptor. The aza-Baylis−Hillman reaction of N-sulfonated imines **1** with *β*-substituted Michael acceptor is a more difficult task for organic chemists since the aza-Baylis−Hillman reaction using these substrates with DABCO or PPh_3 as a Lewis base leads to no reaction under normal conditions. Previously, we reported that when using a more nucleophilic phosphine Lewis base such as PBu_3 or $PPhMe_2$ to promote the aza-Baylis−Hillman reaction of N-sulfonated imines **1** with 2-cyclopenten-1-one, the corresponding aza-Baylis−Hillman adducts can be obtained in high yields within 5 h.[6a] On the basis of this result, we attempted the catalytic, asymmetric aza-Baylis−Hillman reaction of N-sulfonated imines **1** with 2-cyclopenten-1-one in the presence of chiral phosphine Lewis base. A more nucleophilic chiral phosphine Lewis base is required for this reaction because **LB1** showed no catalytic activity for this reaction. Therefore, we wish to report in this section an unprecedented catalytic, asymmetric aza-Baylis−Hillman reaction of N-sulfonated imines **1** with

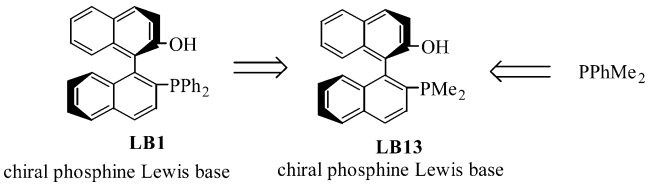
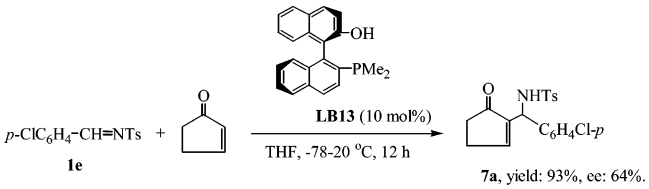


Figure 12. Structures of chiral Lewis bases.

Scheme 8



2-cyclopenten-1-one in the presence of a more nucleophilic chiral phosphine Lewis base under mild reaction conditions. The selection of chiral phosphine compounds is a key point for success in this reaction. On the basis of the above results, we decided to synthesize (*R*)-2′-dimethylphosphanyl-[1,1′]binaphthalenyl-2-ol **LB13** and utilized it as a chiral phosphine Lewis base in this reaction because it has a structure similar to that of chiral Lewis base **LB1** (a phenolic hydroxy group and a phoshine atom as a nucleophilic source) and Lewis base $PPhMe_2$ (a NaphthylPMe$_2$ group) (Figure 12). The synthesis of chiral phosphine Lewis base **LB13** has been indicated in Supporting Information (Scheme SI-6).[12a,24]

The reaction conditions for the catalytic, asymmetric version of N-sulfonated imines **1** with 2-cyclopenten-1-one were systematically examined using *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** as substrate. The results are briefly summarized in Scheme 8. When the reaction temperature was kept at low temperature such as −78 °C for 1 h and then raised to room temperature naturally, the ee of **7a** could reach 64% in 93% yield (Scheme 8). Further exploration of chiral phosphine Lewis base for this reaction is required. The detailed results will be reported in due course.

Moreover, it should be pointed out that when 4-(3-ethyl-4-oxa-1-azatricyclo[4,4,0,$0^{3,8}$]dec-5-yl)-quinolin-6-ol *β*-**ICD**[6d] was used as a chiral nitrogen Lewis base for the above catalytic, asymmetric aza-Baylis−Hillman reaction, no reaction occurred. On the basis of these results, it is very clear that the catalytic, asymmetric aza-Baylis−Hillman reaction of imines with *β*-substituted Michael acceptor is more difficult and is highly dependent on the structure of chiral Lewis base.

In conclusion, we found that in the aza-Baylis−Hillman reaction of N-sulfonated imines **1** with MVK using **LB1** as a chiral phosphine Lewis base, 76−95% ee can be achieved at −30 or −20 °C in THF. In addition, good to excellent yields can be realized in the coexistence of molecular sieve 4A. For Michael acceptors such as EVK and acrolein, similar results are obtained to give the corresponding adducts **3** and **6** in high ee. In CH_2Cl_2 upon heating at 40 °C, the aza-Baylis−Hillman adducts **5** derived from N-sulfonated imines **1** with phenyl acrylate were formed in high yields (60−97%) with moderate ee (52−77%). The substituent effects of this chiral phosphine Lewis base promoter system have been examined as well. In

(24) Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789−2798.

general, the substituents on the 6- or 6,6-positions of binaphthalene framework did not significantly affect the efficiency of this enantioselective catalytic system. The introduction of phenyl substituent on the position adjacent to the phenolic hydroxy group led this kind of phosphine Lewis base to be more stable and more efficient under milder conditions. A divergent structure of chiral phosphine Lewis bases can be designed and synthesized on the basis of the structure of **LB1**. We also found a simple and more nucleophilic chiral phosphine Lewis base (*R*)-2′-dimethylphosphanyl-[1,1′]binaphthalenyl-2-ol **LB13** to achieve the catalytic enantioselective aza-Baylis−Hillman reaction using cyclopent-2-en-1-one as a Michael acceptor. This is the first example of a catalytic, asymmetric aza-Baylis−Hillman reaction using α,*β*-unsaturated cyclic ketones as Michael acceptors, although the achieved ee is not very high. We believe that the chiral Lewis base of **LB1** acted as a bifunctional chiral ligand in this reaction (LBBA). The phosphine atom acted as a Lewis base, and the phenolic OH acted as a Lewis acid (BA) through hydrogen bonding. The key factor is the intramolecular hydrogen bonding between the phenolic OH and the oxygen atom of carbonyl group to stabilize the in situ formed key enolate intermediate on the basis of NMR spectroscopic investigation. In addition, the intramolecular hydrogen bonding between the phenolic OH and the nitrogen anion stabilized by the sulfonyl group can give a relatively stable or rigid transition state for achieving high enantioselectivity in the aza-Baylis−Hillman reaction. Efforts are underway to elucidate the mechanistic details of this reaction and the key factors of chiral Lewis bases in the Baylis−Hillman reaction and to disclose the scope and limitations of this reaction. Work along this line is currently in progress.

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Supporting Information Available: ^{13}C and ^{1}H NMR spectroscopic and analytic data for chiral phosphine Lewis bases **LB1**−**LB13**, the aza-Baylis−Hillman reaction products, experimental details, and chiral HPLC traces of the compounds shown in Tables 1−6 and Schemes 1−4 and 8. This material is available free of charge via the Internet at http://pubs.acs.org.

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