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Chiral phosphine Lewis base catalyzed asymmetric aza-Baylis–Hillman reaction of *N*-sulfonated imines with methyl vinyl ketone and phenyl acrylate†

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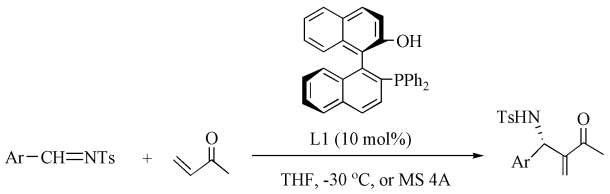
In the aza-Baylis–Hillman reaction of *N*-sulfonated imines with methyl vinyl ketone (MVK) promoted by chiral phosphine Lewis base: (*R*)-2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ol (10 mol%), the aza-Baylis–Hillman adducts 1 were obtained in good yields with high ee (70–94% ee) at −30 °C in THF. In CH_2Cl_2 upon heating at 40 °C, the aza-Baylis–Hillman reaction of *N*-sulfonated imines with phenyl acrylate gave the adducts 2 in high yields (60–97%) with moderate ee (52–77%).

Great progress has been made in the execution of the Baylis–Hillman reaction,[1] for which a catalytic asymmetric version has been published,[2] since Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of 1,4-diazabicyclo[2,2,2]octane (DABCO) in 1972.[3] 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 (71% ee) or 1,1,1,3,3,3-hexafluoroisopropyl acrylate (99% ee).[2a] High enantioselectivity has so far not been reported in Baylis–Hillman reactions involving simple Michael acceptors such as methyl vinyl ketone (MVK) or methyl acrylate.

During our own investigations on the aza-Baylis–Hillman reaction,[4] we disclosed that the aza-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-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.[4b] 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–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**[2a]] to achieve > 90% ee in good yields.[4d] 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. Nowadays, the exploration of a novel and highly efficient chiral Lewis base for catalytic, asymmetric Baylis–Hillman reaction is a very attractive and competitive field. Herein, we wish to report the catalytic, asymmetric aza-Baylis–Hillman reaction using a chiral phosphine Lewis base in which high enantioselectivities (> 90% ee) can also be realized.

Concerning the chiral phosphine Lewis bases, we selected (*R*)-2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ol (**L1**) as a chiral Lewis base for this reaction because it has a phenolic OH group like Lewis base **TQO**.[2a] We first used MVK as the Michael acceptor for the aza-Baylis–Hillman reaction with *N*-sulfonated imines (Scheme 1). In THF, at −30 °C (see ESI†), good to high enantioselectivities (76% ~ 91% ee) were achieved with *S* configuration[6] (Table 1). In general, for *N*-sulfonated imines having electron-donating groups on the phenyl ring, the reaction rate became slightly slow and the corresponding aza-Baylis–Hillman adducts **1** were obtained in lower yields (41 ~ 62%) with 76 ~ 83% ee under the same conditions (Table 1, entries 1–3). This is because the prolonged reaction time at low temperature caused the decomposition of *N*-sulfonated imines due to the ambient moisture. In order to improve the yields of **1**, we added molecular sieve 4A (100 mg for 0.5 mmol of substrate) into the reaction system to get rid of the moisture. As results, the yields of **1** were greatly improved with the addition of molecular sieve 4A (Table 1, entries 1–3, 5, 7–10) and did not significantly affect the ee of **1**. Only in some cases, the ee of **1** dropped ~ 2–6%. Values in parentheses are the results obtained in the presence of molecular sieve 4A in Table 1.



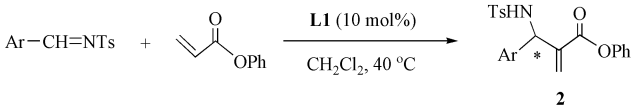
Scheme 1

We then carried out the aza-Baylis–Hillman reactions of various *N*-sulfonated imines with phenyl acrylate in the

Table 1 The aza-Baylis–Hillman reactions of *N*-sulfonated imines (1.0 eq) with methyl vinyl ketone in the presence of chiral Lewis base (10 mol%)

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

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



Scheme 2

† Electronic supplementary information (ESI) available: experimental section and chiral HPLC retention times. See http://www.rsc.org/suppdata/cc/b3/b301863f/

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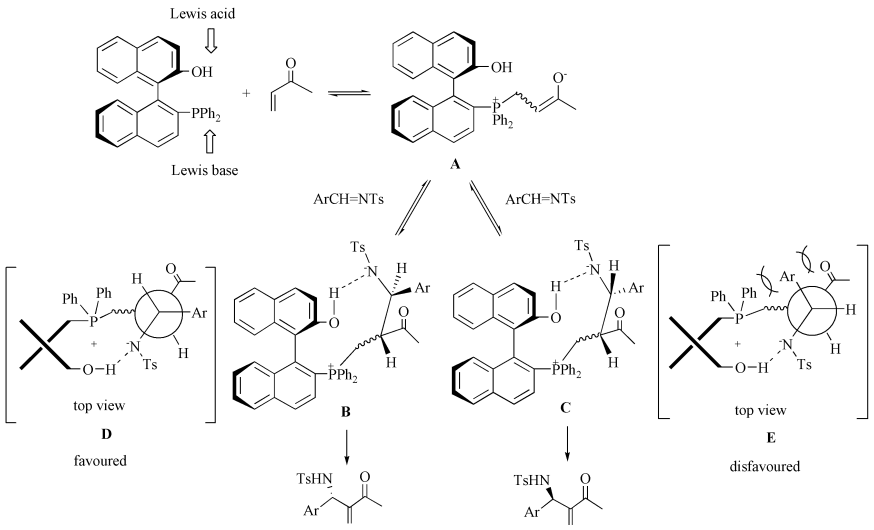

Scheme 3

Table 2 aza-Baylis–Hillman reactions of *N*-sulfonated imines (1.0 eq) with phenyl acrylate in the presence of chiral Lewis base **L1** (10 mol%) in dichloromethane at 40 °C.

Entry	Ar	Time/h	Yield/%[a]	ee/%[b]	Absolute configuration
			2a–i		
1	C_6H_5	12	84	61	ND
2	*p*-EtC_6H_4	12	60	53	(+)
3	*p*-FC_6H_4	12	80	69	(−)
4	*p*-ClC_6H_4	12	94	67	(+)
5	*p*-BrC_6H_4	12	85	77	(+)
6	*m*-FC_6H_4	12	89	63	(−)
7	*m*-ClC_6H_4	12	95	58	ND
8	*p*-$NO_2C_6H_4$	12	97	75	(−)
9	*m*-$NO_2C_6H_4$	12	89	52	(−)

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

presence of **L1** (Scheme 2). We found that in CH_2Cl_2 upon heating at 40 °C for 12 h, in most cases, the corresponding aza-Baylis–Hillman adducts **2** were formed in high yields (60–97%) with moderate ee (52–77%) (Table 2, entries 1–9). This is the best reaction condition for this version of aza-Baylis–Hillman reaction (see ESI†).

In Scheme 3, we briefly gave a mechanistic speculation on the chiral Lewis base **L1**.[2a] We believe that **L1** acted as a bifunctional chiral ligand in this reaction.[7] The phosphine atom acted as a Lewis base and the phenolic OH acted as a Lewis acid through hydrogen bonding. Michael addition of **L1** to MVK affords enolate **A**, which undergoes aldol reaction with *N*-sulfonated imines to give several diastereomeric intermediates according to the generally accepted reaction mechanism for Baylis–Hillman reaction. The key factor is the intramolecular hydrogen bonding between the phenolic OH and nitrogen anion stabilized by sulfonyl group to give relatively stable diastereomeric intermediates **B** and **C**. However, as shown in Newman projection **D** and **E** (top view), the steric repulsions between the C(O)Me group with the aromatic group and aromatic group with two phenyl groups on the phosphorus atom suggest that intermediate **B** is more stable than **C** in this stabilized transition state. Therefore, intermediate **B** undergoes facile elimination to produce the aza-Baylis–Hillman adduct with *S* configuration.

In order to get more mechanistic insight into this reaction, we carried out the ^{31}P NMR measurement of **L1** in the absence or presence MVK and imine. We found the ^{31}P NMR ($CDCl_3$, 85% H_3PO_4) spectroscopic data of **L1** showed a signal at −13.158 ppm, but the ^{31}P NMR ($CDCl_3$, 85% H_3PO_4) spectroscopic data of **L1**with MVK and imine (molar ratio = 1:5:5) elucidated a new signal at +25.297 ppm, which was believed to relate with **B**, along with peak of **L1** (see ESI†). Further investigation on this new signal is ongoing.

In conclusion, we found that in the aza-Baylis–Hillman reaction of various *N*-sulfonated imines with MVK using **L1** as a chiral phosphine Lewis base, 76–94% ee can be achieved at −30 °C in THF. In addition, good to excellent yields can be realized in the coexistence of molecular sieve 4A. In CH_2Cl_2 upon heating at 40 °C, the aza-Baylis–Hillman adducts **2** were formed in high yields (60–97%) with moderate ee (52–77%). At the present stage, this is the highest ee achieved for the Baylis–Hillman reaction using MVK as a Michael acceptor by a chiral phosphine Lewis base. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose its scope and limitations. Work along this line is currently in progress.

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