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Chiral Sterically Congested Phosphane-Amide Bifunctional Organocatalysts in Asymmetric Aza-Morita–Baylis–Hillman Reactions of *N*-Sulfonated Imines with Methyl and Ethyl Vinyl Ketones

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A series of chiral sterically congested phosphane-amide bifunctional Lewis bases **L1**–**L3** have been successfully synthesized and their application in asymmetric aza-Morita–Baylis–Hillman (aza-MBH) reactions of *N*-sulfonated imines with activated olefins such as methyl and ethyl vinyl ketone has been investigated under mild conditions. The corresponding aza-MBH adducts can be obtained in good-to-excellent yields (up to 98 %) and moderate-to-good enantioselectivities (up to 91 or 93 % *ee*) in dichloromethane at room temperature (20 °C) with these novel chiral bifunctional phosphane Lewis bases.

Introduction

The asymmetric Morita–Baylis–Hillman (MBH) and aza-Morita–Baylis–Hillman (aza-MBH) reactions are two of the most useful and interesting carbon–carbon bond-forming reactions, respectively giving enantiomerically enriched β-hydroxy or β-amino carbonyl compounds bearing an α-alkylidene group which have enormous potential synthetic utility under mild reaction conditions.[1] Over the last decade, great progress has been made in the development of catalytic asymmetric versions of these reactions and several excellent multifunctional organocatalysts for the aza-MBH reaction have been reported to achieve high enantioselectivities.[2] Among these successful chiral bifunctional organocatalysts, axially chiral 1,1′-binaphthalene-derived bifunctional phosphanes developed by us, Sasai and others have shown excellent chiral induction abilities for the aza-MBH reaction (Figure 1).[2b,2e,2h,2k,2m,2n,2p,2s] As the development of new and more efficient chiral bifunctional phosphanes is the main target in asymmetric MBH or aza-MBH

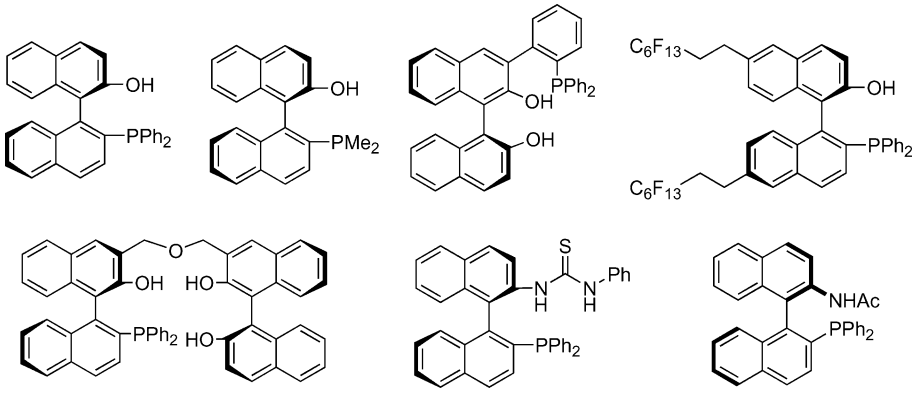

Figure 1. Some representative BINOL-derived bifunctional phosphanes for the aza-Morita–Baylis–Hillman reaction.

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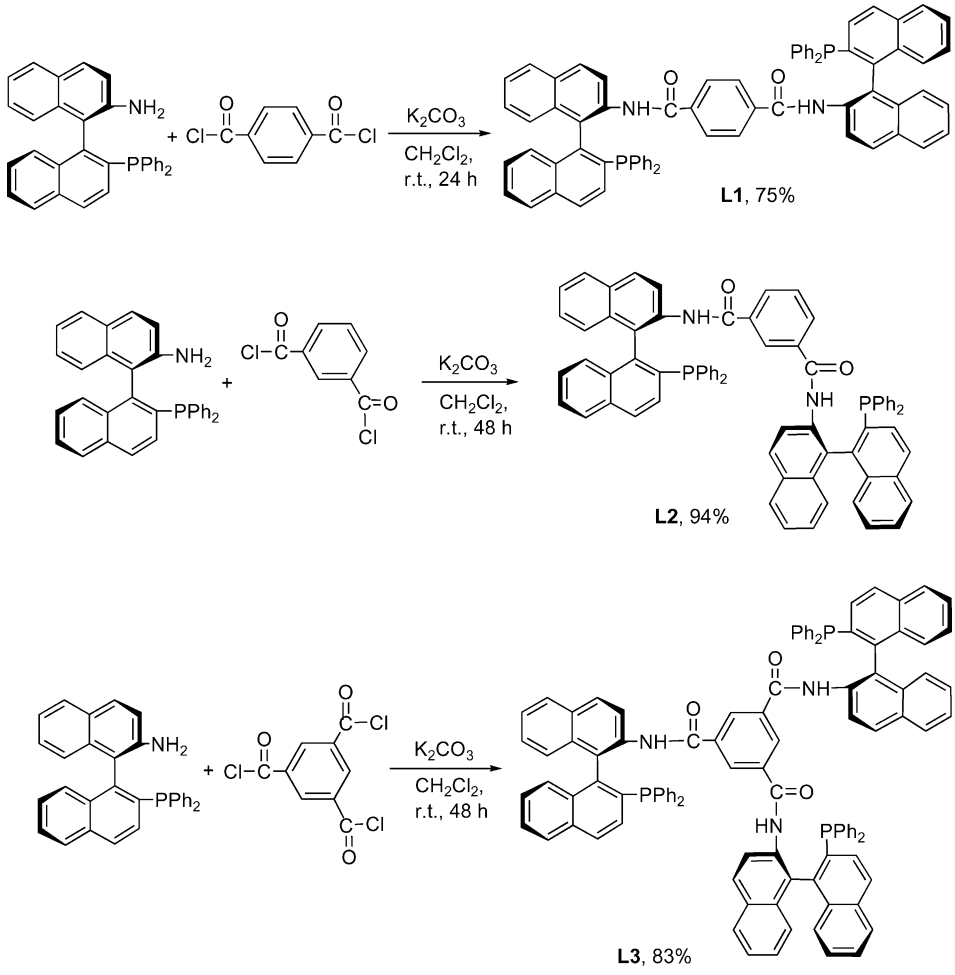
catalytic reactions, we have been continuing to develop such novel chiral bifunctional phosphanes for use in asymmetric MBH[3] and aza-MBH reactions. In this paper, we wish to report the synthesis of novel chiral sterically congested phosphane-amide bifunctional organocatalysts **L1**, **L2** and **L3** and their application in asymmetric aza-MBH reactions.

Results and Discussion

The synthetic route for the preparation of chiral sterically congested bifunctional phosphane-amide Lewis bases **L1**, **L2** and **L3** is straightforward and is clearly shown in Scheme 1. Treating (*R*)-2′-diphenylphosphanyl-1,1′-binaphthyl-2-ylamine[4] with terephthaloyl dichloride, isophthaloyl dichloride and 1,3,5-benzenetricarbonyl trichloride afforded the corresponding sterically congested chiral bifunctional phosphane-amide Lewis bases **L1**, **L2** and **L3** in good yields in dichloromethane at room temperature in the presence of potassium carbonate, respectively. The synthetic procedures are quite simple and detailed experimental procedures and the corresponding spectroscopic data are reported in the Supporting Information.[5]

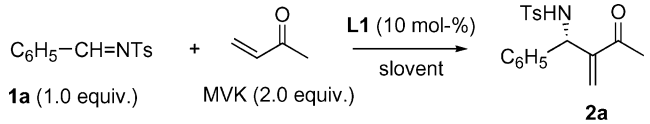
To investigate the catalytic activities of these novel chiral sterically congested phosphane-amide bifunctional Lewis bases in asymmetric aza-MBH reactions, an initial examination was carried out by using *N*-benzylidene-4-methylbenzenesulfonamide (**1a**) or *N*-(*p*-chlorobenzylidene)-4-methylbenzenesulfonamide (**1c**) and methyl vinyl ketone (MVK) as the substrates in the presence of 10 mol-% of chiral Lewis bases **L1**, **L2** or **L3** (6.7 mol-% similar P atom mol-% as **L1** and **L2**) in various solvents at room temperature (20 °C) or at a lower temperature. The results of these experiments are summarized in Tables 1, 2, and 3, respectively. As can be seen from Table 1, when the asymmetric aza-MBH reaction was carried out in dichloromethane (DCM), acetonitrile (MeCN), dimethyl sulfoxide (DMSO), toluene (PhMe) or tetrahydrofuran (THF) at room temperature (20 °C), the reactions proceeded smoothly to give the corresponding adduct **2a** in good yields and moderate enantiomeric excesses (up to 93% yield and 73% *ee*) in the presence of **L1** (10 mol-%), although no *ee* was observed in DMSO (Table 1, entries 1 and 3–6). Notably, the *ee* of **2a** could be further improved to 80% with 90% yield at 0 °C in DCM after 45 h under otherwise identical conditions (Table 1, entry 2). It also should be emphasized here that at –10 °C, the reaction became sluggish, giving **2a** in low yield. Thus, the best results are obtained under these reaction conditions at 0 °C when using **L1** as the chiral organocatalyst in this asymmetric aza-MBH reaction. With chiral sterically congested phosphane-amide bifunctional phosphane **L2**, examination of solvent effects and reaction temperatures revealed that the reaction should be carried out in DCM at room temperature (20 °C) for 24 h (Table 2, entries 3 and 4). Under these conditions, the corresponding adduct **2c** was obtained in 98% yield and 84% *ee*. At –10



Scheme 1. Synthesis of chiral bifunctional phosphane-amide Lewis bases **L1**–**L3**.

and 0 °C, **2c** was formed in yields of 72% and with 82 and 77% *ee* values in DCM, respectively (Table 2, entries 1 and 2). Other solvents were not as effective as DCM with **L2** as organocatalyst at room temperature (20 °C). With bifunctional phosphane-amide organocatalyst **L3** (6.7 mol-%), the reaction conditions were optimized in a similar way to that described above. The results of these experiments are summarized in Table 3. The aza-MBH reaction of **1c** with MVK afforded the corresponding adduct **2c** in 87% yield and 93% *ee* after 90 h at –10 °C as well as in 98% yield and 91% *ee* after 24 h at room temperature (20 °C) in DCM, which indicates that the more sterically congested phosphane-amide bifunctional Lewis base **L3** could also facilitate chiral induction in asymmetric aza-MBH reaction (Table 3, entries 1 and 2). Other solvents were not as effective as DCM with **L3** (6.7 mol-%) as organocatalyst under otherwise identical conditions (Table 3, entries 4–6). Therefore, if using **L3** (6.7 mol-%) as the chiral Lewis base in aza-MBH reactions in DCM, the reactions should be carried out at room temperature (20 °C) at the expense of around 2% *ee* because of the much reduced reaction time. It should be emphasized here that the corresponding aza-MBH adducts **2** are all obtained in the *S* configuration in all of the above cases.

Table 1. Screening of solvents and temperatures for the asymmetric aza-MBH reaction of *N*-benzylidene-4-methylbenzenesulfonamide (**1a**) (1.0 equiv.) with methyl vinyl ketone (MVK) (2.0 equiv.) catalysed by **L1** (10 mol-%).

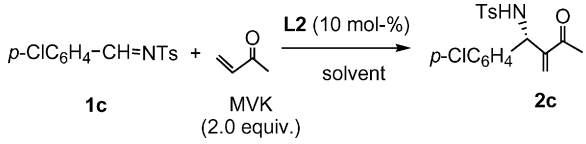


Entry	Solvent	Temp. [°C]	Time [h]	Yield[a] [%]	*ee*[b] [%]	Absolute configuration[c]
1	DCM	20	10	88	73	*S*
2	***DCM***	***0***	***45***	***90***	***80***	***S***
3	MeCN	20	52	66	65	*S*
4	DMSO	20	32	73	0	*S*
5	PhMe	20	45	93	65	*S*
6	THF	20	66	79	70	*S*

[a] Isolated yields. [b] Determined by HPLC with a chiral column. [c] Determined by the sign of the specific rotation.

The control experiments outlined in Scheme 1 indicated that the chiral sterically congested phosphane-amide bifunctional phosphanes **L2** and **L3** are indeed more effective than the original chiral bifunctional phosphane-amide **L4** [(*R*)-*N*-(2′-diphenylphosphanyl-1,1′-binaphthyl-2-yl)benzamide] (20 mol-%) because when **L4** (20 mol-%) was used as catalyst,[6] the corresponding adduct **2c** was formed in 84% yield and 78% *ee* under identical conditions (Scheme 2). Moreover, (2′-diphenylphosphanyl-1,1′-binaphthyl-2-yl)dimethylamine (**L5**, 20 mol-%) did not catalyse this reaction under the standard conditions,[6] which suggests that an active amide proton in the catalyst is crucial for this asymmetric catalytic process and chiral phosphanes **L1**–**L4** are LB (Lewis base) and BA (Brønsted acid) bifunctional phosphane Lewis bases (Scheme 1).[2b,2e]

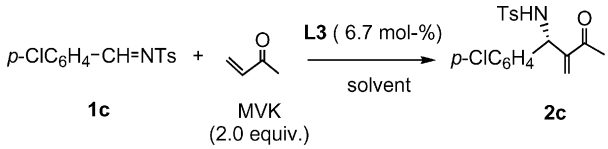
Table 2. Asymmetric aza-Morita–Baylis–Hillman reactions of *N*-(*p*-chlorobenzylidene)-4-methylbenzenesulfonamide (**1c**) (1.0 equiv.) with methyl vinyl ketone (MVK) (2.0 equiv.) in the presence of **L2** (10 mol-%).



Entry	Solvent	Temp. [°C]	Time [h]	Yield[a] [%]	*ee*[b] [%]	Absolute configuration[c]
1	DCM	–10	90	72	82	*S*
2	DCM	0	24	72	77	*S*
3	***DCM***	***r.t.***	***24***	***98***	***84***	***S***
4	DCM	r.t.	10	48	84	*S*
5	PhMe	r.t.	24	63	74	*S*
6	DCE	r.t.	24	61	84	*S*
7	MeCN	r.t.	24	37	50	*S*

[a] Isolated yields. [b] Determined by HPLC with a chiral column. [c] Determined by the sign of the specific rotation.

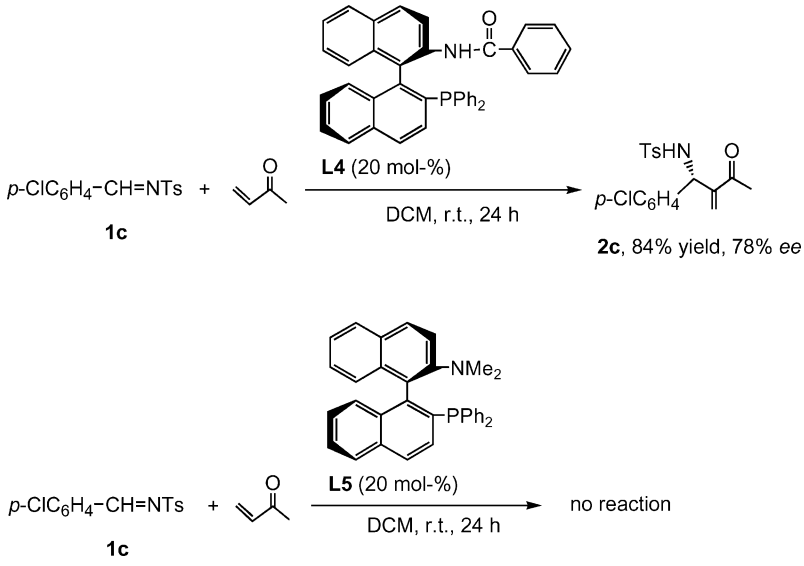
Table 3. Aza-Morita–Baylis–Hillman reactions of *N*-(*p*-chlorobenzylidene)-4-methylbenzenesulfonamide (**1c**) (1.0 equiv.) with methyl vinyl ketone (MVK) (2.0 equiv.) in the presence of **L3** (6.7 mol-%).



Entry	Solvent	Temp. [°C]	Time [h]	Yield[a] [%]	*ee*[b] [%]	Absolute configuration[c]
1	DCM	–10	90	87	93	*S*
2	DCM	r.t.	24	98	91	*S*
3	DCM	r.t.	10	66	90	*S*
4	PhMe	r.t.	24	55	80	*S*
5	DCE	r.t.	24	81	91	*S*
6	MeCN	r.t.	24	52	73	*S*

[a] Isolated yields. [b] Determined by HPLC with a chiral column. [c] Determined by the sign of the specific rotation.

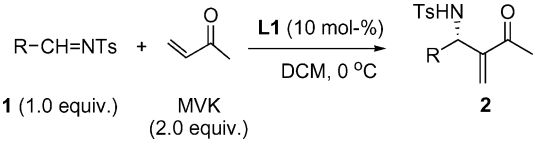
With the optimal reaction conditions identified, we next turned our attention to examining the scope of these catalytic, asymmetric aza-MBH reactions using a variety of *N*-sulfonated imines with MVK or ethyl vinyl ketone (EVK). We found that when **L1** was utilized as the catalyst, the corresponding aza-MBH reaction adducts **2b**–**2g** were obtained in moderate-to-good *ee* values (up to 87%) along with good-to-high yields at room temperature (20 °C), irrespective of whether the imines **1** have electron-withdrawing or -donating groups on the benzene substituent (Table 4, entries 1–6). In addition, the range of *N*-sulfonated imines that can be used with **L2** (10 mol-%) and **L3** (6.7 mol-%) as the organocatalyst in the aza-MBH reactions has also been examined and the results are shown in Table 5. The data show that **L3** is more effective than **L2** under optimal conditions, giving the corresponding adducts **2** in higher *ee* values [up to 91% *ee* for *N*-(*p*-nitrobenzylidene)-4-methylben-



Scheme 2. Control experiments in the aza-Morita–Baylis–Hillman reaction.

zenesulfonamide (**1h**)] and similar chemical yields (Table 5, entries 1–4). Therefore, we used **L3** (6.7 mol-%) as the organocatalyst to examine the reactions of other *N*-sulfonated imines with MVK and EVK. The results of these experiments are outlined in Table 6. The corresponding adducts **2d**,**f**,**g**, **2i**–**k** and **3a**,**b** were obtained in moderate-to-good yields and *ee* values (Table 6, entries 1–8). With the *ortho*-substituted *N*-sulfonated imines **1j** and **1k**, the corresponding adducts were formed in lower *ee* values, which suggests that these chiral sterically congested phosphane-amide bifunctional phosphanes are not suitable for use in asymmetric aza-MBH reactions with sterically hindered *N*-sulfonated imines (Table 6, entries 5 and 6).

Table 4. Asymmetric aza-MBH reactions of *N*-(arylmethylidene)arylsulfonamides (1.0 equiv.) with methyl vinyl ketone (MVK) (2.0 equiv.) catalysed by **L1** (10 mol-%).

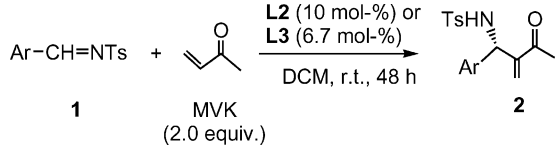


Entry	R	Time [h]	Yield[a] [%]	*ee*[b] [%]	Absolute configuration[c]
1	*p*-MeC_6H_4 (**1b**)	48	**2b**, 84	77	*S*
2	*p*-ClC_6H_4 (**1c**)	23	**2c**, 98	87	*S*
3	*p*-BrC_6H_4 (**1d**)	24	**2d**, 89	79	*S*
4	*m*-$NO_2C_6H_4$ (**1e**)	27	**2e**, 82	68	*S*
5	*m*-ClC_6H_4 (**1f**)	24	**2f**, 73	70	*S*
6	*m*-FC_6H_4 (**1g**)	24	**2g**, 72	70	*S*

[a] Isolated yields. [b] Determined by HPLC with a chiral column. [c] Determined by the sign of the specific rotation.

To compare our original chiral phosphane Lewis base (*R*)-2′-diphenylphosphanyl-1,1′-binaphthyl-2-ol [(*R*)-**L6**], aza-MBH reactions using (*R*)-**L6** as organocatalyst under similar conditions were carried out and the results are shown in Table 7.[2b,2e] As can be clearly seen, the chiral

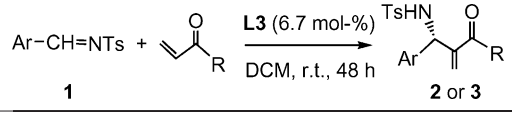
Table 5. Asymmetric aza-Morita–Baylis–Hillman reactions of *N*-(arylmethylidene)arylsulfonamides (1.0 equiv.) with methyl vinyl ketone (MVK) (2.0 equiv.) in the presence of **L2** (10 mol-%) or **L3** (6.7 mol-%).



Entry	Ar	Yield with **L2**/**L3**[a] [%]	*ee* with **L2**/**L3**[b] [%]	Absolute configuration[c]
1	C_6H_5 (**1a**)	**2a**, 83/73	64/79	*S*
2	*p*-MeC_6H_4 (**1b**)	**2b**, 82/79	80/81	*S*
3	*m*-$NO_2C_6H_4$ (**1e**)	**2e**, 60/64	79/85	*S*
4	*p*-$NO_2C_6H_4$ (**1h**)	**2h**, 79/81	82/91	*S*

[a] Isolated yields. [b] Determined by HPLC with a chiral column. [c] Determined by the sign of the specific rotation.

Table 6. Asymmetric aza-Morita–Baylis–Hillman reactions of *N*-(arylmethylidene)arylsulfonamides (1.0 equiv.) with methyl vinyl ketone (MVK) or ethyl vinyl ketone (EVK) (2.0 equiv.) in the presence of **L3** (6.7 mol-%).

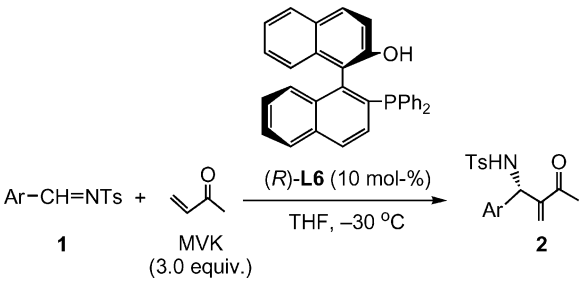


Entry	Ar	R	Yield[a] [%]	*ee*[b] [%]	Absolute configuration[c]
1	*p*-BrC_6H_4 (**1d**)	Me	**2d**, 83	87	*S*
2	*m*-ClC_6H_4 (**1f**)	Me	**2f**, 87	86	*S*
3	*m*-FC_6H_4 (**1g**)	Me	**2g**, 92	84	*S*
4	*p*-FC_6H_4 (**1i**)	Me	**2i**, 89	85	*S*
5	*o*-ClC_6H_4 (**1j**)	Me	**2j**, 77	50	*S*
6	*o*-BrC_6H_4 (**1k**)	Me	**2k**, 73	35	*S*
7	*p*-ClC_6H_4 (**1c**)	Et	**3a**, 80	85	*S*
8	*p*-BrC_6H_4 (**1d**)	Et	**3b**, 69	80	*S*

[a] Isolated yields. [b] Determined by HPLC with a chiral column. [c] Determined by the sign of the specific rotation.

sterically congested phosphane-amide bifunctional Lewis bases **L1**, **L2** and **L3** have similar chiral induction abilities at room temperature (20 °C) in DCM as our original chiral phosphane Lewis base (*R*)-**L6** at –30 °C in THF under the standard conditions. Therefore, we believe that these chiral phosphane-amide bifunctional Lewis bases may have practical use in asymmetric aza-MBH reactions as the reaction can be carried out at 0 °C or room temperature (20 °C) to give the products in good yields and *ee* values.

Table 7. Asymmetric aza-Morita–Baylis–Hillman reactions of *N*-(arylmethylidene)arylsulfonamide **1** (1.0 equiv.) with methyl vinyl ketone (3.0 equiv.) in the presence of chiral phosphane Lewis base (*R*)-**L6** (10 mol-%).



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

[a] Isolated yields. [b] Determined by HPLC with chiral column. [c] Determined by the sign of specific rotation.

In conclusion, we have synthesized a series of novel chiral sterically congested phosphane-amide bifunctional Lewis bases **L1**–**L3** and investigated their application in the asymmetric aza-Morita–Baylis–Hillman reactions of *N*-sulfonated imines with MVK and EVK under mild conditions. The corresponding aza-MBH adducts can be obtained in good-to-excellent yields (up to 98%) and moderate-to-good enantioselectivities (up to 91 or 93%) in DCM at room temperature (20 °C). Efforts are underway to examine the effect of these chiral bifunctional organocatalysts on other types of asymmetric MBH or aza-MBH reactions and to improve their chiral induction abilities in MBH or aza-MBH reactions.

Experimental Section

General Remarks: All solvents were purified by distillation. Unless otherwise stated, all reactions were carried out under argon. ^1H NMR spectra were recorded with a Bruker AM-300 spectrometer as solutions in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard; *J* values are given in Hz. Mass spectra were recorded with a HP-5989 instrument and HRMS were measured with a Finnigan MA+ mass spectrometer. Infrared spectra were measured with a Perkin–Elmer 983 spectrometer. Melting points were obtained with a Yanagimoto micromelting point apparatus and are uncorrected. *N*-Sulfonated imines **1** were prepared according to the literature. Commercial reagents were used without further purification. All reactions were monitored by TLC on Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out at increased pressure using 200–300 mesh silica gel. The optical purities of the aza-Morita–Baylis–Hillman adducts were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. Chiralcel AD, AS, TBB and OJ; eluent: hexane/2-propanol; flow rate, 0.7 mL min^{-1}; detection: 254 or 220 nm light) and the absolute configurations of the major enantiomers were assigned according to the sign of the specific rotation.

Typical Reaction Procedure for L3-Catalysed Aza-Morita–Baylis–Hillman Reaction of *N*-Sulfonated Imines with MVK: A 10 mL Schlenk tube containing *N*-(*p*-chlorobenzylidene)-4-methylbenzenesulfonamide (**1c**) (37 mg, 0.125 mmol) and **L3** (13 mg. 0.0086 mmol) was degassed and the reaction vessel was protected under argon. Then DCM (1.0 mL) and methyl vinyl ketone (MVK) (21 μL, 0.25 mmol) was added to the Schlenk tube. The reaction mixture was stirred at 20 °C for 24–48 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, eluent: EtOAc/petroleum ether, 1:4) to yield the corresponding aza-Morita–Baylis–Hillman adduct as a colorless solid, which was immediately subjected to chiral HPLC to analyse the enantiomeric excess.

Supporting Information (see also the footnote on the first page of this article): Experimental details, ^1H NMR spectroscopic and analytic data for dendritic chiral phosphane Lewis bases **L1**–**L5** and aza-Morita–Baylis–Hillman reaction products, and chiral HPLC traces of the compounds shown in Tables 1–6 and Scheme 1.

Acknowledgments

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[5] Detailed procedures for the preparation of **L1**, **L2** and **L3** are reported in the Supporting Information.

[6] The synthesis of **L4** and **L5** can be found in ref.[4a,2s] and their spectroscopic data are reported in the Supporting Information.

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