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Chiral Thiourea-Phosphine Organocatalysts in the Asymmetric Aza-Morita–Baylis–Hillman Reaction

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Abstract: A new kind of bifunctional (thio)urea-phosphine catalyst was synthesized and applied to the aza-Morita–Baylis–Hillman reaction of *N*-sulfonated imines with methyl vinyl ketone, phenyl vinyl ketone, ethyl vinyl ketone or acrolein. Moderate to excellent *ee* and yields of the products were obtained under mild reaction conditions.

Keywords: asymmetric catalysis; Morita–Baylis–Hillman reaction; NMR spectroscopy; organic catalysis; thiourea-phosphine organocatalysts

Introduction

The Morita–Baylis–Hillman reaction, one of the most important methods for converting simple starting materials to densely functionalized products in a catalytic and atom economic way, has undergone remarkable progress since the first report in a patent in 1972.[1] Due to the great potential of the products for further transformation also the superior mild reaction conditions, the development of a suitable asymmetric version of this reaction has attracted considerable interest in recent years. Various chiral catalysts and cocatalysts were developed and, very recently, a chiral medium for this reaction was also reported.[2] Among these successful chiral catalysts, the chiral BINOL-derived bifunctional phoshpines developed by us and Sasai et al. showed excellent asymmetric induction for the aza-Morita–Baylis–Hillman reaction (Figure 1).[2e,k,l,n,q,r]

The hydrogen bonding between the phenol group and the intermediate was thought to be essential to achieve good enantioselectivity. We further envisioned that replacing the phenol group with a (thio)-urea group might also give similar catalytic activity and good asymmetric induction ability. As is well known, the steric and electronic nature of the (thio)-urea group can be easily tuned by reacting the corresponding amine with different iso(thio)cyanates. Thus far, various (thio)urea derivatives have been successfully used for a variety of diastereo- and enantioselective reactions and the versatility of these (thio)urea derivatives as general acids has been demonstrated by several groups.[3] Recently, thioureas have also been applied to the asymmetric Morita–Baylis–Hillman reactions.[2m,o,t] However, the synthesis and application of bifunctional (thio)urea-phosphine organocatalyst has never been reported. Herein, we wish to report the synthesis and application of bifunctional chiral (thio)urea-phosphine organocatalysts in the asymmetric aza-Morita–Baylis–Hillman reaction.

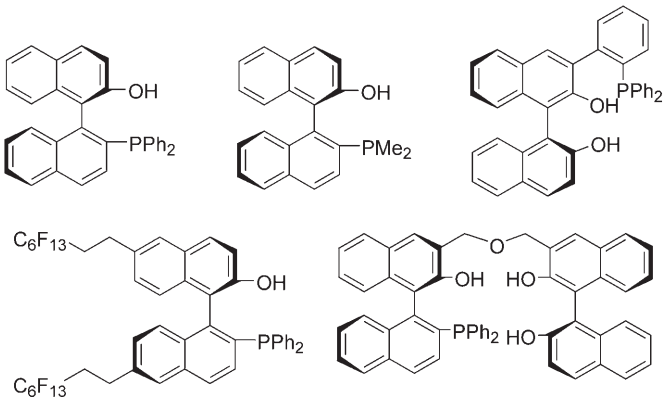
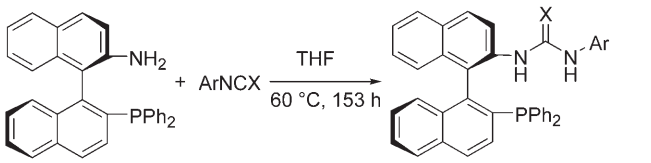


Figure 1. Some representative BINOL-derived bifunctional phosphines for the aza-Baylis–Hillman reaction.

Results and Discussion

As shown in Scheme 1, we first synthesized three catalysts by condensation of the chiral aminophosphine[4]

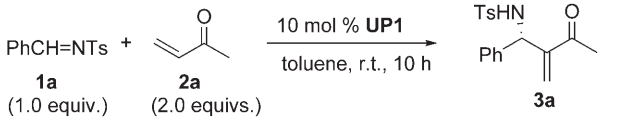


Ar = C_6H_5, X = S: **UP1** 70%
Ar = 3,5-$(CF_3)_2C_6H_3$, X = S: **UP2** 94%
Ar = C_6H_5, X = O: **UP3** 78%

Scheme 1. The synthesis of bifunctional (thio)urea-phosphines.

with iso(thio)cyanate in tetrahydrofuran (THF) at 60 °C.

Then the catalytic activity of **UP1** was tested using the reaction of *N*-benzylidene-4-methylbenzenesulfonamide (**1a**) and methyl vinyl ketone (**2a**) as a model. Initially, we used long-stored **1a** as the substrate and a moderate yield and *ee* of the corresponding aza-Morita-Baylis–Hillman adduct **3a** was obtained. However, when we used fresh-prepared **1a** to repeat the same reaction under the same conditions, product **3a** was formed in rather low yield and *ee* (Scheme 2).



long-stored **1a**: 78% yield, 70% *ee*
fresh-prepared **1a**: 12% yield, 16% *ee*

Scheme 2. The reactions of **1a** and **2a** catalyzed by **UP1**.

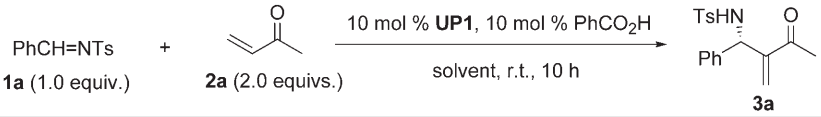
Therefore, we analyzed the long-stored **1a** by ^{1}H NMR spectroscopy and found that it contained a small amount of 4-methylbenzenesulfonamide and benzoic acid. Then we used the fresh-prepared **1a** as the starting material and added some 4-methylbenzenesulfonamide or benzoic acid to the reaction system and found that benzoic acid could accelerate the reaction rate and improve the *ee* of product **3a**. Using 10 mol% of benzoic acid as additive, various solvents were first examined for the reaction of fresh-prepared **1a** and **2a** catalyzed by **UP1**. The results are presented in Table 1 and dichloromethane was found to be the best solvent in terms of both yield and *ee* of **3a** (Table 1, entry 3).

Using dichloromethane as the solvent, the loading of benzoic acid was also examined from the range of 2.0 mol% to 50 mol% (Table 2). It was found that using 5.0 mol% of benzoic acid could give the highest *ee* (Table 2, entry 2).

Next, various additives with different steric hindrance and acidic strength were examined, and the results are shown in Table 3. It was found that the acidities of the additives could significantly affect the yield and the *ee* of the product. Additives with weaker acidity or stronger acidity all resulted in lower yields and *ee* (Table 3, entries 1–7). Only those additives with similar acidity to benzoic acid ($pK_a = 4.20$) could give satisfactory results (Table 3, entries 8–12).[5] Of the additive examined, benzoic acid could give the highest *ee* and yield.

Using 5 mol% benzoic acid as the additive, the catalytic activity of **UP2** and **UP3** was also examined. As can be seen from Scheme 3, **UP2** and **UP3** were both less effective than **UP1**. We further performed the reaction between **1a** and **2a** at 0 °C using **UP1** as the catalyst and 5 mol% benzoic acid as the additive. It

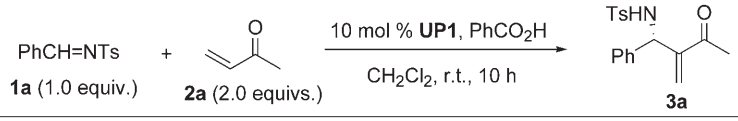
Table 1. Screening of the solvents for the reaction of **1a** and **2a** catalyzed by **UP1** and benzoic acid.



Entry	Solvent	Yield [%][a]	*ee* [%][b]	Absolute configuration
1	PhMe	97	77	*S*
2	THF	96	71	*S*
3	CH_2Cl_2	96	87	*S*
4	MeCN	74	82	*S*
5	*t*-amyl-OH	57	43	*S*
6	DMSO	58	0	*S*
7	CH_2ClCH_2Cl	92	87	*S*

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

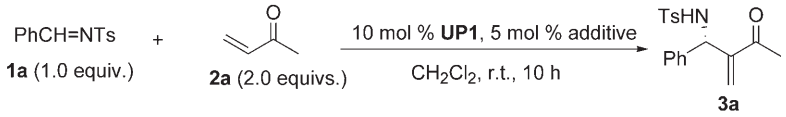
Table 2. Screening of benzoic acid loading for the reaction of **1a** and **2a** catalyzed by **UP1**.

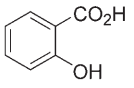
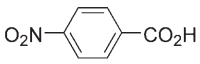
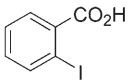
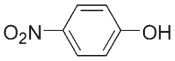
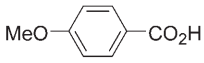
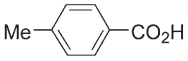
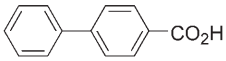
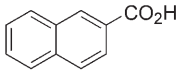


Entry	$PhCO_2H$ (mol %)	Yield [%][a]	*ee* [%][b]	Absolute configuration
1	2	81	87	*S*
2	5	97	91	*S*
3	20	56	72	*S*
4	50	11	74	*S*

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

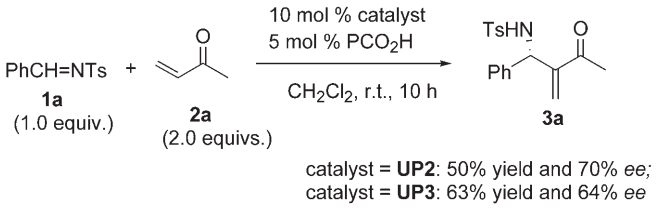
Table 3. Screening of the additives for the reaction of **1a** and **2a** catalyzed by **UP1**.



Entry	Additive	pK_a	Yield [%][a]	*ee* [%][b]	Absolute configuration
1	TsOH	-	16	37	*S*
2	HCO_2H	3.75	30	55	*S*
3	$PhOCH_2CO_2H$	3.17	23	61	*S*
4		2.98	18	32	*S*
5		3.44	38	79	*S*
6		2.86	41	76	*S*
7		7.15	32	17	*S*
8	$PhCH_2CO_2H$	4.31	94	86	*S*
9		4.49	96	90	*S*
10		4.36	96	88	*S*
11		-	94	87	*S*
12		4.16	95	88	*S*

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

was found that the reaction rate decreased significantly and the enantioselectivity did not change obviously. After 72 h, imine **1a** was consumed and product **3a** was obtained in 95% yield and 92% *ee*. Thus we established the optimized reaction conditions for this reaction: using 10 mol% **UP1** as the catalyst and 5



Scheme 3. The reaction of **1a** and **2a** catalyzed by **UP2** or **UP3**.

mol % benzoic acid as the additive to perform the reaction at room temperature.

Under the optimized reaction conditions, several other imines could also react with methyl vinyl ketone to give the products in high yields and moderate to excellent *ee* (Table 4). Various substituents at *o*-, *m*- or *p*-position in the aromatic rings of the imines were tolerated (Table 4, entries 1–8 and 10). Besides imines of aryl aldehydes, a cinnamoyl *N*-sulfonated imine was also a suitable electrophile for this reaction to give the corresponding aza-Morita–Baylis–Hillman product in moderate *ee* and yield (Table 4, entry 9). It should be noted here that the *ee* of the product was independent of the reaction time. For the reaction of **1a** with **2a** under the above optimized reaction conditions, the product of **3a** could be obtained in 45 % yield and 88 % *ee* within 1 hour. Thus, the racemization of the product or autocatalysis was not involved in this catalytic system.[6,7]

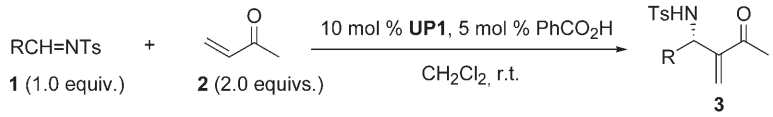
Acrolein, ethyl vinyl ketone and phenyl vinyl ketone could also react with **1a** to give the corresponding aza-Morita–Baylis–Hillman products in moderate yields and *ee* under the same reaction conditions (Table 4). The absolute configurations of all these products shown in Table 1, Table 2, Table 3, Table 4 and Table 5 were assigned by comparison of their signs of specific rotation and HPLC spectra with those reported ones.[2i,k]

In order to clarify if the thiourea group in **UP1** was essential to give good asymmetric induction. We prepared **CP1**, which has the same skeleton with **UP1** and lacks the thiourea group. The catalytic activity of **CP1** was examined under the same optimized reaction conditions. As can be seen from Scheme 4, the catalytic activity of **CP1** was significantly lower than that of **UP1**. Even after a prolonged reaction time, imine **1a** could not be consumed completely and the yield of **3a** was only 62 %. Furthermore, the asymmetric induction ability of **CP1** was even lower and just 13 % *ee* of **3a** was obtained. So introducing a thiourea group to the catalyst was pivotal to accelerate the reaction rate and improve the enantioselectivity of the product.

To gain more mechanistic insight into this reaction, a rational mechanism was proposed upon ^{31}P NMR spectroscopic investigations (see the Supporting Information).

According to the above observation and earlier reports,[2i,j,k,p,q,r] we proposed a detailed mechanism shown in Scheme 5 for this reaction. We believe that **UP1** acted as a bifunctional organocatalyst in this reaction. The phosphine served as a nucleophile to initiate the reaction and the thiourea group served as a

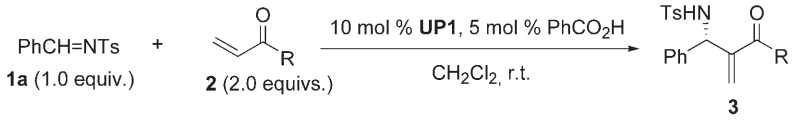
Table 4. The reaction of other *N*-tosylaldimines **1** with **2a** catalyzed by **UP1** and benzoic acid.



Entry	R	Time [h]	Yield [%][a]	*ee* [%][b]	Absolute configuration
1	*p*-MeC_6H_4	10	**3b**, 98	90	*S*
2	*p*-FC_6H_4	10	**3c**, 94	90	*S*
3	*p*-ClC_6H_4	10	**3d**, 98	90	*S*
4	*p*-BrC_6H_4	10	**3e**, 97	88	*S*
5	*p*-$MeOC_6H_4$	80	**3f**, 91	70	*S*
6	*m*-$NO_2C_6H_4$	5	**3g**, 95	88	*S*
7	*m*-FC_6H_4	10	**3h**, 96	91	*S*
8	*m*-ClC_6H_4	10	**3i**, 98	97	*S*
9	C_6H_5CH=CH	10	**3j**, 61	67	*S*
10	*o*-ClC_6H_4	19	**3k**, 90	70	*R*

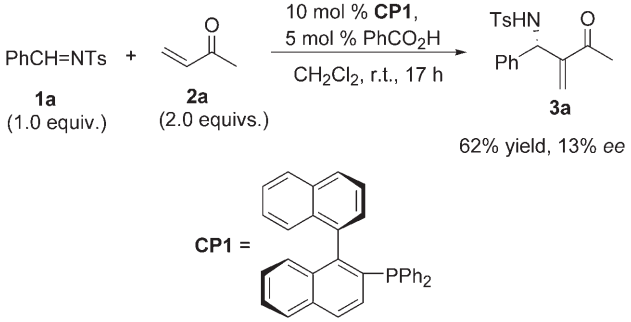
[a] Isolated yields.
[b] Determined by chiral HPLC.

Table 5. The reaction of **1a** with other activated alkenes **2** catalyzed by **UP1** and benzoic acid.



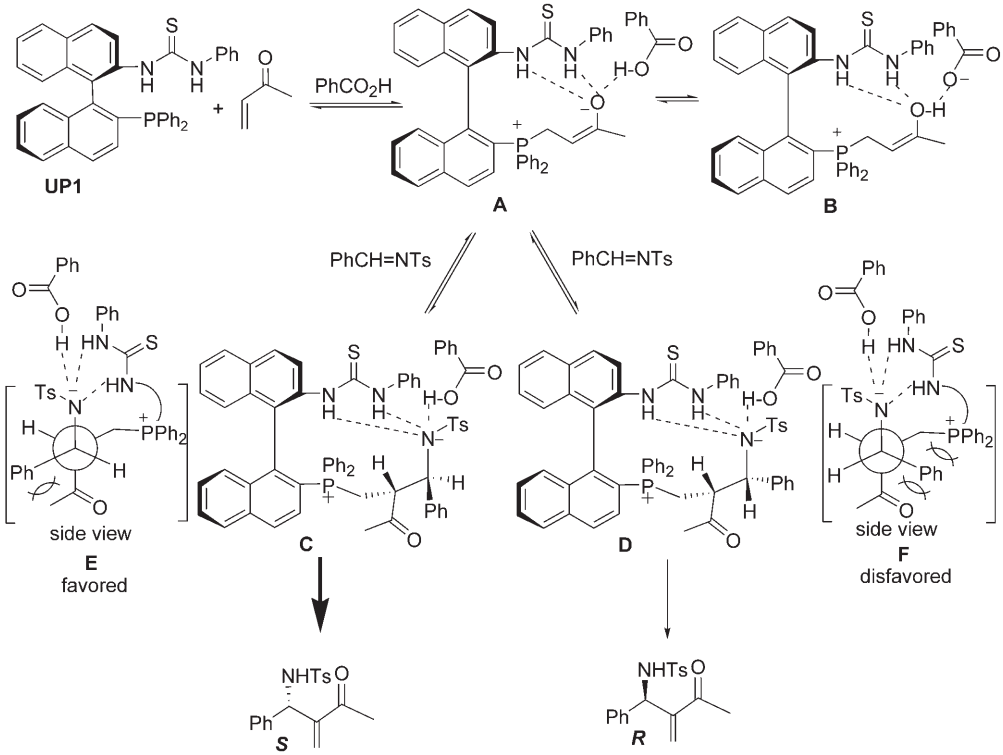
Entry	R	Time [h]	Yield [%][a]	*ee* [%][b]	Absolute configuration
1	H	3	**3l**, 81	67	*S*
2	Et	56	**3m**, 69	77	*S*
3	C_6H_5	5	**3n**, 80	73	*S*

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



Scheme 4. The reaction of **1a** with **2a** catalyzed by **CP1** and benzoic acid.

hydrogen-bonding donor to stabilize the *in situ* generated intermediate. First, Micheal addition of **UP1** to MVK afforded enolate intermediate **A**, which might be deprotonated by benzoic acid to form intermediate **B**. Then intermediate **A** underwent a Mannich reaction with imine **1a** to give the hydrogen-bonding stabilized intermediates **C** and **D**. However, as shown in the Newman projections **E** and **F**, the steric repulsion between the C(O)Me group with the phenyl group and the phenyl group with two phenyl groups in the phosphorus atom suggest that intermediate **C** is more stable than **D** in this relatively stabilized transition state. Subsequently intermediate **C** underwent proton



Scheme 5. A plausible reaction mechanism.

transfer and elimination to give the (*S*)-enriched aza-Morita–Baylis–Hillman product. Intermediate **B** might be in a very rapid equilibrium with intermediate **A**. The ^{31}P NMR signal at approximately 27 ppm might correspond to the average value of intermediate **B** and intermediate **A** (see the Supporting Information). Intermediate **A** and intermediate **B** were all stabilized by hydrogen bonding and they might be more stable under the reaction conditions. So it was inclined to form intermediate **A** and intermediate **B** in their equilibrium with free **UP1**, MVK and benzoic acid in the solution. As this can be seen from the ^{31}P NMR spectroscopic investigations in the Supporting Information, when 5 mol% benzoic acid (half amount to **UP1**) was added, the two signals were nearly in the same strength. When the amount of benzoic acid was increased to 20 mol% (double amount to **UP1**), the signal corresponding to free **UP1** could hardly be detected (see the Supporting Information). The dramatic effect of benzoic acid to accelerate the reaction rate and improve the *ee* of the product can be explained as follows. First, benzoic acid could provide a proton to form intermediate **B** and the anion could act as a hydrogen-bonding accepter to give further stabilization. Second, benzoic acid as the proton source could accelerate the proton transfer step for the formation of the product and suppress some reversible steps which might cause some loss of the enantioselectivity.[6,8] Too much benzoic acid or other stronger acid would disfavor the formation of intermediate **A** in its equilibrium with intermediate **B**. A weaker acid was not so efficient as a proton source to generate a similar enol intermediate and accelerate the reaction rate and thus poorer yield and enantioselectivity were observed.

Conclusions

In conclusion, we have synthesized a new kind of bifunctional (thio)urea-phosphine organocatalyst. In the aza-Morita–Baylis–Hillman reaction of *N*-sulfonated imines with MVK, PVK, EVK or acrolein under the catalysis of **UP1** and benzoic acid in dichoromethane at room temperature, 67–97% *ee* and 61–98% yields of the corresponding adducts were obtained. A rational mechanism was proposed based upon ^{31}P NMR spectroscopic investigations (see Supporting Information). Efforts are in progress to explore other applications of these new organocatalysts.

Experimental Section

General Remarks

Unless otherwise stated, all reactions were carried out under argon atmosphere. All solvents were purified by distillation. Other commercially available reagents were used without further purification. *N*-Tosylimines,[9] 2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ylamine[4] and **CP1**[10] were prepared according to the literature. All reactions were monitored by TLC. Flash column chromatography was carried out at increased pressure. Infrared spectra were measured on a Perkin-Elmer 983 spectrometer. ^{1}H NMR, ^{31}P NMR and ^{13}C NMR spectra were recorded on a Varian Mercury vx 300 NMR spectrometer in $CDCl_3$ using tetramethylsilane as the internal standard. Mass and HR-MS spectra were recorded with a Finnigan MA+ mass spectrometer or an Ion Spec 4.7 Tesla FTMS mass spectrometer. Melting points were obtained by means of a micro melting point apparatus and are uncorrected.

Typical Procedure for the Synthesis of Bifunctional Chiral Phospine-Thiourea UP1

To a solution of (*R*)-2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-ylamine (454 mg, 1.0 mmol) in THF (1.0 mL) was added phenyl isothiocyanate (144 μL, 1.2 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 153 h. After the reaction was completed, the solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (SiO_2, eluent: EtOAc/petroleum ether = 1/8) to afford *(*R*)-1-(′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-yl)-3-phenylthiourea* (**UP1**): as a white solid; yield: 412 mg (70%); mp 122–124 °C; $[\alpha]_D^{20}$: +193.2 (*c* 1.00, $CHCl_3$); IR (KBr): ν = 3339, 3164, 3053, 2924, 1594, 1533, 1497, 1433, 1329, 1309, 1265, 1238, 1187, 817, 743, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 6.58 (2H, d, *J* = 5.4 Hz), 6.70 (1H, d, *J* = 8.4 Hz), 6.89–7.39 (18H, m), 7.50–7.56 (1H, m), 7.83 (1H, d, *J* = 8.1 Hz), 7.93 (2H, d, *J* = 8.1 Hz), 8.00 (1H, d, *J* = 8.4 Hz), 8.18 (1H, d, *J* = 8.4 Hz): ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): δ = −13.0; MS (MALDI): *m/Z* = 589 (M^+ + 1); HR-MS (MALDI): *m/z* = 589.1880, calcd. for $C_{39}H_{30}N_2PS^+$: 589.1862.

(R)-1-(3,5-Bis-trifluoromethyl-phenyl)-3-(2′-diphenylphosphanyl-[1,1′]binaphthalenyl-2-yl)-urea (UP2): colorless solid; mp 90–92 °C; $[\alpha]_D^{20}$: +363.9 (*c* 1.00, $CHCl_3$); IR (KBr): ν = 3358, 3053, 1534, 1478, 1382, 1278, 1252, 1178, 1133, 742, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 6.74 (1H, d, *J* = 8.1 Hz), 6.97–7.30 (13H, m), 7.38 (1H, d, *J* = 3.9 Hz, NH), 7.39–7.56 (4H, m), 7.62 (2H, s), 7.67 (1H, d, *J* = 8.1 Hz), 7.90–7.95 (3H, m), 8.08 (1H, d, *J* = 8.4 Hz), 8.22 (1H, d, *J* = 3.9 Hz, NH); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): δ = −12.9; MS (ESI): *m/z* = 725 (M^+ + 1); HR-MS (ESI): *m/z* = 725.1617, calcd. for $C_{41}H_{28}N_2F_6PS^+$: 725.1609.

(R)-1-(2′-Diphenylphosphanyl-[1,1′]binaphthalenyl-2-yl)-3-phenylurea (UP3): white solid; mp 152–154 °C, $[\alpha]_D^{20}$: +89.7 (*c* 0.70, $CHCl_3$); IR (KBr): ν = 3382, 3338, 3051, 1662, 1596, 1549, 1524, 1497, 1433, 1311, 1284, 1244, 743, 695 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 5.96 (1H, s, NH), 6.01 (1H, s, NH), 6.68 (2H, d, *J* = 7.2 Hz), 6.76 (1H, d, *J* = 8.4 Hz), 6.94–7.54 (19H, m), 7.84–7.93 (3H, m), 8.00 (1H, d,

$J=9.3$ Hz), 8.32 (1H, d, $J=9.3$ Hz); ^{31}P NMR (121.45 MHz, $CDCl_3$, 85% H_3PO_4): $\delta=-13.7$; MS (ESI): $m/z=573$ (M^++ 1); HR-MS (ESI): $m/z=573.2085$, calcd. for $C_{39}H_{30}N_2PO^+$: 573.2090.

Typical Procedure for UP1 and Benzoic Acid-Catalyzed Aza-Morita-Baylis–Hillman Reaction of *N*-Sulfonated Imine 1a with MVK

To a solution of imine **1a** (65 mg, 0.25 mmol), **UP1** (15 mg, 0.025 mmol) and benzoic acid (0.15 mg, 0.0125 mmol) in dichloromethane (1.0 mL) was added methyl vinyl ketone (42 μL, 0.5 mmol) at room temperature. Then reaction mixture was stirred at room temperature for 10 h. After the reaction was completed, the solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (SiO_2, eluent: EtOAc/petroleum ether=1/5) to afford *4-methyl*-N-*(2-methylene-3-oxo-1-phenylbutyl)benzenesulfonamide* (**3a**) as a colorless solid; yield: 80 mg (97%); mp 138–142 °C; $[\alpha]_D^{20}$: +32.4 (*c* 1.00, $CHCl_3$), ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): $\delta=2.16$ (3H, s, Me), 2.41 (3H, s, Me), 5.26 (1H, d, $J=8.4$ Hz, CH), 5.64 (1H, d, $J=8.4$ Hz, NH), 6.10 (1H, s), 6.11 (1H, s), 7.01–7.11 (2H, m, Ar), 7.18–7.26 (5H, m, Ar), 7.66 (2H, d, $J=7.8$ Hz, Ar); HPLC (AD column; λ = 254 nm; eluent: hexane/2-propanol=80/20; flow rate: 0.7 mL min^{-1}): $t_{major}=11.46$ min, $t_{minor}=13.04$ min; *ee* % = 91%.

The ^{1}H NMR spectroscopic data are consistent with those reported in the literature[2k] and the absolute configuration of **3a** was assigned by comparison of the sign of specific rotation and HPLC spectra with the reported one.[2k]

Supporting Information

Aza-Morita–Baylis–Hillman reaction products, experimental details, ^{31}P NMR spectroscopic investigations in Figures S2–S11, and chiral HPLC traces of the compounds shown in Table 3, Table 4 and Table 5 as well as Scheme 2, Scheme 3 and and Scheme 4.

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