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Chiral Bifunctional Organocatalysts in Asymmetric Aza-Morita−Baylis−Hillman Reactions of Ethyl (Arylimino)acetates with Methyl Vinyl Ketone and Ethyl Vinyl Ketone

Min Shi,*,† Guang-Ning Ma,‡ and Jun Gao†

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China, and School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 MeiLong Road, Shanghai 200237, China

mshi@mail.sioc.ac.cn

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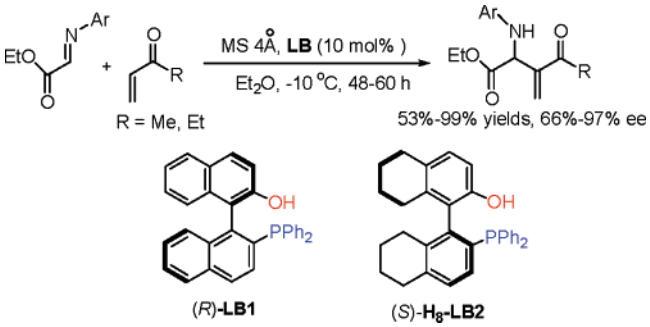

The bifunctional chiral phosphine Lewis base (*R*)-2′-diphenylphosphino-[1,1′-binaphthalene]-2-ol is an effective organocatalyst in the asymmetric aza-MBH reaction of ethyl (arylimino)acetates **1** with MVK and EVK to give the corresponding adducts in moderate to good yields and good to high enantiomeric excesses under mild conditions.

Morita−Baylis−Hillman reactions involving simple Michael acceptors such as methyl vinyl ketone (MVK) or methyl acrylate have hitherto been characterized by poor enantioselectivity, thus offering a challenging and potentially fruitful area of investigation to broaden the scope of this general class of reactions.[1] Recently, aza-Morita−Baylis−Hillman (aza-MBH) reactions of *N*-sulfonated imines (ArCH = NTs) or *N*-phosphorated imines [ArCH = NP(O)R_2] (Figure 1) with various Michael acceptors, such as MVK and ethyl vinyl ketone (EVK), have received much attention, and several excellent reaction systems using chiral nitrogen and phosphine Lewis bases to achieve moderate to high enantioselectivities have been reported.[2,3] These findings suggest an alternative strategy to improve enantioselectivity in asymmetric aza-MBH reactions, such as using more synthetically useful imines as substrates. We have reported some preliminary results regarding the use of ethyl (arylimino)acetates **1** (Figure 1) as the reactive imine electrophiles,[4] with MVK and EVK to produce the corresponding highly functionalized adducts ethyl 3-acetyl-2-arylaminobut-3-enoates and ethyl 2-arylamino-3-propionylbut-3-enoates **2** in good yields, using triphenylphosphine as a Lewis base promoter.[5] Since this class of adducts can be transformed to various nitrogen-containing compounds by simple reactions, we investigated the corresponding asymmetric aza-MBH reaction of ethyl (arylimino)acetates **1** with MVK and EVK in the presence of bifunctional chiral phosphine Lewis bases (*R*)-**LB1**, (*S*)-**LB1**, and (*S*)-**H_8-LB2**, and monofunctional organocatalyst (*R*)-**MOP** (Figure 2).

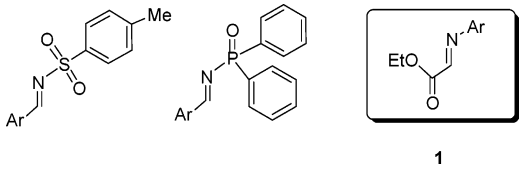

FIGURE 1. Structures of imines.

For optimization studies, the aza-MBH reaction of imine **1a** with MVK catalyzed by **LB1** (10 mol %) was selected as the model reaction. We initiated our investigation by screening a

* Address correspondence to this author. Fax: 86-21-64166128.
† Chinese Academy of Sciences.
‡ East China University of Science and Technology.

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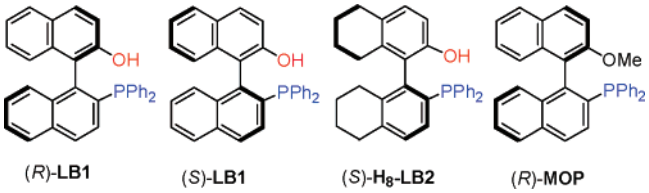
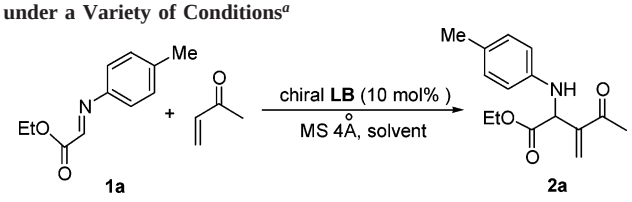


FIGURE 2. Bifunctional organocatalysts (*R*)-**LB1**, (*S*)-**LB1**, and (*S*)-H_8-**LB2** and the monofunctional organocatalyst (*R*)-**MOP**.

TABLE 1. Asymmetric Aza-MBH Reaction of 1a with MVK under a Variety of Conditions[a]



entry	solvent	chiral **LB**	temp (°C)	time (h)	yeild[b] (%)	ee[c] (%)
1	MeCN	(*R*)-**LB1**	25	48	58	68
2	THF	(*R*)-**LB1**	25	48	trace	n.d.[d]
3	DMSO	(*R*)-**LB1**	25	48	complex	n.d.[d]
4	DMF	(*R*)-**LB1**	25	48	complex	n.d.[d]
5	toluene	(*R*)-**LB1**	25	48	80	84
6	Et_2O	(*R*)-**LB1**	25	48	83	84
7	CH_2Cl_2	(*R*)-**LB1**	25	48	79	83
8	Et_2O	(*R*)-**MOP**	25	48	n.r.[d]	n.d.[d]
9	Et_2O	(*R*)-**LB1**	0	48	81	88
10	toluene	(*R*)-**LB1**	−10	48	98	89
11	Et_2O	(*R*)-**LB1**	−10	48	98	92
12	Et_2O	(*R*)-**LB1**	−20	60	90	91
13	Et_2O	(*R*)-**LB1**	−30	72	90	90
14	Et_2O	(*S*)-H_8-**LB2**	−10	48	81	−92
15	Et_2O	(*S*)-**LB1**	−10	48	80	−93

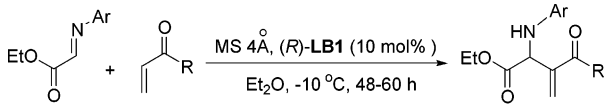
[a] Ethyl (*p*-methylphenylimino)acetate (0.5 mmol), MVK (0.75 mmol), **LB1** (0.05 mmol, 22.5 mg) or **H8-LB2** (0.05 mmol, 23.2 mg), molecular sieves (100 mg), and 1.5 mL of solvent were used. [b] Isolated yields. [c] Determined by chiral HPLC, using Chiralpak OD-H column. [d] n.d. = not determined; n.r. = no reaction.

series of solvents and temperatures in the presence of 4 Å molecular sieves.[6] The results are summarized in Table 1.

As can be seen from Table 1, we found that the solvent employed significantly affected the reaction. For example, the corresponding adduct **2a** was obtained in 58% yield and 68% ee at room temperature (25 °C) in acetonitrile, and only a trace of **2a** or complex product mixtures were obtained in THF, DMSO, or DMF under otherwise identical conditions (Table 1, entries 1−4). To our delight, we found that **2a** could be obtained in 80% yield and 84% ee, and 83% yield and 84% ee in toluene and ether, respectively (Table 1, entries 5 and 6). In dichloromethane, **2a** also could be obtained in 79% yield and 83% ee (Table 1, entry 7). With **MOP** (10 mol %) as the catalyst in the same reaction under the standard conditions, no reaction occurred (Table 1, entry 8). This result suggests that the phenol group of **LB1** is crucial in this asymmetric aza-MBH reaction.[2b,f] Lowering the reaction temperature improved the ee of **2a**. At 0 °C in ether, **2a** was obtained in 81% yield and 88% ee (Table 1, entry 9). At −10 °C, **2a** was formed in 98% yield and 89% ee and 98% yield and 92% ee in toluene and ether, respectively (Table 1, entries 10 and 11). Carrying out the reaction at −20 or −30 °C in ether did not improve the ee of **2a** (Table 1, entries 12 and 13). With use of (*S*)-H_8-**LB2** and (*S*)-**LB1** as the catalysts in ether at −10 °C, **2a** was obtained in 92% ee and 93% ee with the opposite enantioselectivity and 81% and 80% yield, respectively (Table 1, entries 14 and 15).

(6) Ethyl (arylimino)acetates **1** are more moisture sensitive than *N*-sulfonated imines and *N*-phosphorated imines. It is necessary to remove any moisture by using molecular sieves 4Å.

TABLE 2. Asymmetric Aza-MBH Reaction of 1 with MVK or EVK under the Optimized Conditions[a]



entry	Ar	R	product	time (h)	yield[b] (%)	ee[c] (%)
1	*p*-$CH_3C_6H_4$ (**1a**)	Et	**2b**	48	99	94[e]
2	*m*-$CH_3C_6H_4$ (**1b**)	Me	**2c**	48	82	92[e]
3		Et	**2d**	48	86	90[e]
4	*p*-BrC_6H_4 (**1c**)	Me	**2e**	60	65	90[e]
5		Et	**2f**	60	69	94[e]
6	*p*-ClC_6H_4 (**1d**)	Me	**2g**	60	76	90[e]
7		Et	**2h**	60	60	88[e]
8	C_6H_5 (**1e**)	Me	**2i**	48	92	91[e]
9		Et	**2j**	48	89	92[d]
10	*p*-Cl, *o*-$CH_3C_6H_3$ (**1f**)	Me	**2k**	60	81	66[e]
11		Et	**2l**	60	66	92[d]
12	*p*-$CH_3OC_6H_4$ (**1g**)	Me	**2m**	60	80	93[f]
13		Et	**2n**	60	85	86[e]
14	*m*-$CF_3C_6H_4$ (**1h**)	Me	**2o**	60	75	89[e]
15		Et	**2p**	60	67	90[e]
16	*p*-FC_6H_4 (**1i**)	Me	**2r**	48	53	93[e]
17		Et	**2s**	48	66	97[e]

[a] Ethyl (arylimino)acetate (0.5 mmol), MVK or EVK (0.75 mmol), **LB1** (0.05 mmol, 22.5 mg), molecular sieves (100 mg), and 1.5 mL of ether were used at −10 °C under argon atmosphere. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Using Chiralpak AS-H column. [e] Using Chiralpak OD-H column. [f] Using Chiralpak AD-H column.

With the optimal reaction conditions identified, we next investigated the substrate scope of this interesting asymmetric aza-MBH reaction of **1** with Michael acceptors MVK and EVK. The results are summarized in Table 2. Substrate generality for this catalytic asymmetric reaction is satisfactory and the reaction can tolerate various substituents on the aromatic ring, whether they are electron donating or withdrawing. All reactions proceeded smoothly to give the corresponding adducts **2** in moderate to high yields (53−99%) and good to high ee (66−97%) under the optimal conditions (Table 2). For the reaction of a sterically hindered imine with MVK, the corresponding adduct **2k** was obtained in moderate enantiomeric excess (66% ee) (Table 2, entry 10).

In conclusion, we have devised an effective bifunctional chiral phosphine Lewis base-catalyzed asymmetric aza-MBH reaction of ethyl (arylimino)acetates **1** with MVK or EVK under mild conditions to give the corresponding adducts in moderate to high yields as well as good to high enantioselectivities. The further transformation of these adducts is being investigated and efforts are in progress to elucidate additional mechanistic details of these reactions and to understand their scope and limitations.

Experimental Section

Typical Reaction Procedure. To a mixture of corresponding ethyl (arylimino)acetate (0.5 mmol), methyl vinyl ketone (63.0 μL, 0.75 mmol), organocatalyst **LB1** (22.5 mg, 0.05 mmol), and 4Å molecular sieves (100 mg) was added anhydrous ether (1.5 mL) and the reaction solution was stirred under argon atmosphere at

−10 °C for the required time indicated in the tables. After the reaction solution was filtered and concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/18) to afford the corresponding pure product.

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Supporting Information Available: Analytical and spectroscopic data, including ^{1}H and ^{13}C NMR spectra, for the compounds shown in Tables 1 and 2, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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