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Asymmetric Aza-Morita–Baylis–Hillman Reactions of Alkyl Vinyl Ketones with *N*-Protected Imines or In Situ Generated *N*-Protected Imines

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DABCO-catalyzed aza-MBH reactions of *N*-Boc imines with MVK and EVK have been thoroughly investigated in the paper. The asymmetric version of this aza-MBH reaction was also systematically investigated by using a chiral amine or a chiral phosphane catalyst. It was found that most of the *N*-protected imines are suitable substrates under the mild reaction conditions and are able to give the corresponding adducts in moderate yields with high *ee* values. The TQO- or LB1-catalyzed aza-MBH reactions of *N*-protected α-amidoalkyl phenyl sulfones or α-amidoalkyl *p*-tolyl sulfones with MVK could be well conducted, which provides a facile and direct route to obtain highly enantioselective aza-MBH adducts. The Boc protecting group of the aza-MBH product could be easily removed under acidic conditions to give the corresponding α-methylene-β-amino ketone or α-methylene-β-amino alcohol derivatives in good yields.

Introduction

The aza-Morita–Baylis–Hillman (aza-MBH) reaction is one of the most useful and interesting carbon–carbon bond-forming reactions to give enantiomerically enriched β,β-amino carbonyl compounds bearing an α-alkylidene group with enormous potential synthetic utility under mild reaction conditions.[1] Usually, the aza-MBH reaction occurs between activated imines and electron-deficient alkenes in the presence of a Lewis base, generally a tertiary amine or phosphane. Many kinds of activated imines have been involved in this reaction, such as tosylimines, nosylimines, SES-imines, and phosphinoylimines.[1j] Ts-Imines are the most commonly used electrophiles in aza-MBH reactions because of their easy preparation and high electrophilicity. However, removal of the Ts protecting group is difficult and limits further development of aza-MBH adducts. Thus far, some imines with easily removable protecting group have also been used in the aza-MBH reaction. For example, we have reported the aza-MBH reaction of *N*-arylmethylidenediphenylphosphinamides with activated olefins in the presence of various Lewis bases to afford the corresponding adducts in good yields.[2] Zhou et al. demonstrated that *N*-thiophosphoryl or *N*-thiophosphinoyl imines exhibited good reactivity with methyl vinyl ketone (MVK) or methyl acrylate in the aza-MBH reaction.[3] The *N*-thiophosphoryl moiety in the product can be readily deprotected through acidic methanolysis in excellent yields, which provides a convenient method for the synthesis of synthetically valuable α-methylene-β-amino ketone or acid derivatives. Aromatic *N*-carbamate-activated imines, especially Boc-protected ones, are seldom used in the aza-MBH reaction,[4] despite their high reactivity and the easy removal of the protecting group. Previously, Córdova[4b] reported that proline/DABCO-catalyzed aza-MBH reactions between aryl Boc imines and unmodified α,β-unsaturated aldehydes proceeded with high chemo- and enantioselectivity to furnish α-amino aldehydes with an α-alkylidene group. Recently, we reported the asymmetric aza-MBH reaction between tosylimines and MVK catalyzed by axially chiral 1,1′-binaphthalene-2,2′-diol (BINOL)-derived bifunctional phosphanes or 4-(3-ethyl-4-oxa-1-azatricyclo[4,4,0,$0^{3,8}$]dec-5-yl)-quinolin-6-ol (TQO, Scheme 1).[5] Inspired by our previous work and as a part of our continuing interest in nucleophilic phosphane and amine mediated or catalyzed reactions, we turned our attention to Lewis base catalyzed aza-MBH reactions between easily removable *N*-protected imines and alkyl vinyl ketones and its asymmetric version. Meanwhile, it is notable that the significantly simpler procedure involving the use of stable α-amido sulfones as imine precursors has been applied recently in phase-transfer-catalyzed aza-Henry-type reactions,[6] and cinchona alkaloid[7] or thourea-cinchona alkaloid[8] catalyzed Mannich reactions of malonates, DABCO-catalyzed aza-MBH reactions of electron-deficient alkenes,[9,10] and proline-catalyzed aza-MBH reactions of α,β-unsaturated aldehydes.[11] Thus, we envisioned to develop a facile and direct route to enantioselective aza-MBH adducts by the reaction of alkyl vinyl ketones with α-amido sulfones.

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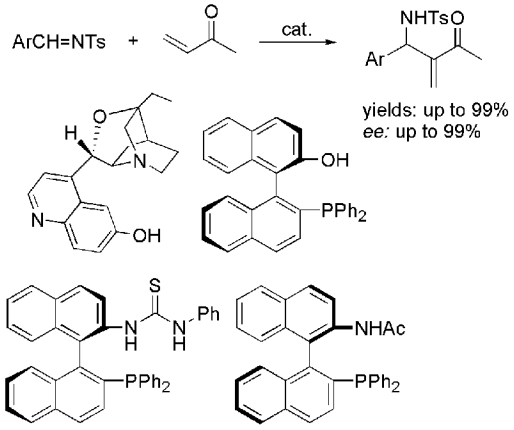


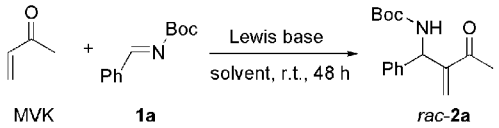
Scheme 1. Asymmetric aza-Morita–Baylis–Hillman reactions of *N*-sulfonated imines with MVK in our previous reports.

Results and Discussion

We initiated our investigations by seeking the best catalyst for the aza-MBH reaction between *N*-Boc imines **1** and MVK. Several phosphorus-containing or nitrogen-containing achiral Lewis bases were tested in the reaction of *N*-Boc imine **1a** with MVK in THF. 1,4-Diazabicyclic[2,2,2]octane (DABCO), which is one of the most popular catalysts used in MBH reactions, was the most effective catalyst, as it gave racemic aza-MBH product *rac*-**2a** in 75% yield. However, another nitrogen-containing Lewis base 4-(*N*,*N*-dimethyl)-aminopyridine (DMAP) could not catalyze this reaction (Table 1, Entries 1 and 4). PPh_3 is another commonly used catalyst in MBH reactions. In this reaction, it was less effective than DABCO and gave *rac*-**2a** in 55% yield under identical conditions. Moreover, increasing the nucleophilicities of the phosphanes compromised the yield of *rac*-**2a**. The stronger nucleophilic phosphane methyldiphenylphosphane (PPh_2Me) gave *rac*-**2a** in only 24% yield (Table 1, Entries 2 and 3). Decreasing the amount of DABCO from 20 to 10 mol-% led to a decrease in the yield of *rac*-**2a** from 75 to 44% (Table 1, Entries 1 and 5). Solvent effects were subsequently examined with the use of 10 mol-% of DABCO as the catalyst. The more polar solvents dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and 1,4-dioxane were suitable for this reaction and gave *rac*-**2a** in 45–55% yields (Table 1, Entries 6–8). Acetonitrile was the best solvent and gave *rac*-**2a** in 80% yield (Table 1, Entry 9). However, the moderately polar solvent toluene retarded the reaction and led to 24% yield of *rac*-**2a** (Table 1, Entry 10).

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of this reaction by using various *N*-Boc imines **1** with different substituents on the benzene rings, and the results are summarized in Table 2. Electron-withdrawing and electron-donating groups at the *ortho*, *meta*, or *para* position of the benzene ring of *N*-Boc imines **1** or furfural *N*-(*tert*-butoxycarbonyl)imine **1k** were employed; the reactions proceeded smoothly to give *rac*-**2** in moderate to good yields (Table 2, Entries 1–10). Unfortunately, this reaction was not suitable for alkyl *N*-Boc imines. Ethyl vinyl ketone (EVK) was also examined in this reaction to give the corresponding *rac*-**2l** in 35% yield (Table 2, Entry 11).

Table 1. Catalyst and solvent screening for the MBH reaction of MVK and *N*-Boc imine **1a**.

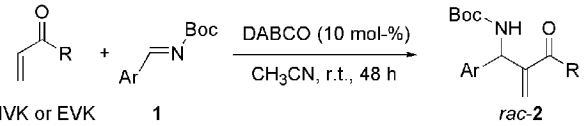


MVK **1a** *rac*-**2a**

Entry[a]	Lewis base	Solvent	Yield [%][b]
1	DABCO (20 mol-%)	THF	75
2	PPh_3 (20 mol-%)	THF	55
3	PPh_2Me (20 mol-%)	THF	24
4	DMAP (20 mol-%)	THF	trace
5	DABCO (10 mol-%)	THF	44
6	DABCO (10 mol-%)	DMSO	45
7	DABCO (10 mol-%)	DMF	55
8	DABCO (10 mol-%)	dioxane	45
9	DABCO (10 mol-%)	CH_3CN	80
10	DABCO (10 mol-%)	toluene	24

[a] All reactions were carried out with **1a** (0.2 mmol) and MVK (0.4 mmol) in the presence of Lewis base in solvent (1.0 mL) at room temperature. [b] Isolated yield.

Table 2. Aza-MBH reaction of other *N*-Boc imines with MVK or EVK catalyzed by DABCO.



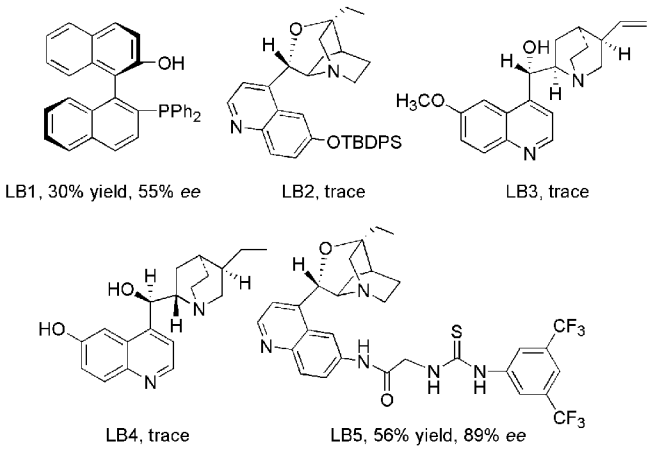
MVK or EVK **1** *rac*-**2**

Entry[a]	R	Ar	Yield [%][b]
1	Me	*p*-$CF_3C_6H_4$, **1b**	**2b**, 55
2	Me	*p*-FC_6H_4, **1c**	**2c**, 82
3	Me	*p*-BrC_6H_4, **1d**	**2d**, 77
4	Me	*p*-$MeOC_6H_4$, **1e**	**2e**, 66
5	Me	*p*-MeC_6H_4, **1f**	**2f**, 54
6	Me	*m*-MeC_6H_4, **1g**	**2g**, 71
7	Me	*m*-ClC_6H_4, **1h**	**2h**, 69
8	Me	*o*-$MeOC_6H_4$, **1i**	**2i**, 64
9	Me	*o*-ClC_6H_4, **1j**	**2j**, 71
10	Me	2-furyl, **1k**	**2k**, 68
11	Et	C_6H_5, **1a**	**2l**, 35

[a] All reactions were carried out with *N*-Boc imine **1** (0.2 mmol) and MVK or EVK (0.4 mmol) in the presence of DABCO in CH_3CN (1.0 mL) at room temperature. [b] Isolated yield.

In view of our results on aza-MBH reactions of *N*-Boc imines **1** with alkyl vinyl ketones catalyzed effectively by DABCO and PPh_3, the next logical step was to investigate the asymmetric version of this reaction by using some chiral catalysts that we reported before. First, (*R*)-2′-diphenylphosphanyl[1,1′]binaphthalenyl-2-ol (LB1) and TQO[12] were

tested in this reaction. With the use of LB1 (10 mol-%) as the catalyst, **2a** was obtained in 30% yield with 55%*ee* in dichloromethane (DCM); TQO was more effective and gave **2a** in 49% yield and 88%*ee* under the same reaction conditions. Some other cinchona alkaloid derivatives were also examined in this reaction (Scheme 2). Catalysts LB2, LB3, and LB4 could not catalyze this reaction, but LB5 gave **2a** in 56% yield and 89%*ee*.



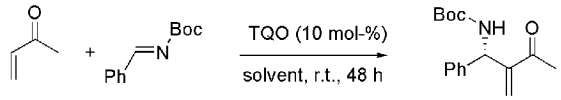
Scheme 2. Some chiral catalysts examined in the aza-MBH reaction of *N*-Boc imine **1a** and MVK.

Though LB5 could give slightly better results than TQO, the synthetically easier accessed TQO was chosen as the catalyst to proceed with the following investigations. By using TQO as the catalyst, solvents were optimized to improve the yield and enantioselectivity, and the results are summarized in Table 3. Higher *ee* values were attained at room temperature in THF and dioxane, 91 and 94%, respectively (Table 3, Entries 2 and 6). However, the yields were not so high. Addition of 4 Å MS and increasing the amount of TQO did not improve the yields (Table 3, Entries 3, 7, and 8). In acetonitrile, **2a** was obtained in the best yield of 96% with 87%*ee* at room temperature (20 °C; Table 3, Entry 4). At lower temperature (–30 °C), the *ee* value could not be improved and the yield fell to 60% (Table 3, Entry 8). Thus, the highest *ee* value was attained at room temperature in dioxane, but the best chemical yield was achieved at room temperature in acetonitrile. To obtain aza-MBH adduct **2a** in high *ee* and yield, we next investigated the reaction in acetonitrile/dioxane. The best conditions were acetonitrile/dioxane (1:2) to give **2a** in 82% yield with 91%*ee* (Table 3, Entry 15).

With these optimal reaction conditions, we next turned our attention to examine the scope of these catalytic, asymmetric aza-MBH reactions with respect to a variety of *N*-Boc imines. In the reaction of *p*-trifluoromethylbenzaldehyde *N*-Boc imine **1b** with MVK, similar yields were attained in acetonitrile (61%) or acetonitrile/dioxane (1:2, 60%). However, a higher *ee* value was obtained in acetonitrile/dioxane (1:2) than in acetonitrile (Table 4, Entries 1 and 2). Thus, examination of the reaction scope was only conducted in acetonitrile/dioxane (1:2). As shown in Table 4, electron-withdrawing and electron-donating groups at the *meta* or *para* position of the benzene ring of *N*-Boc imines **1** or furfural *N*-(*tert*-butoxycarbonyl)imine **1k** were employed, and the reactions proceeded smoothly to give **2** in moderate yields with high *ee* values (Table 4, Entries 3–8, 11, and 12). The absolute configuration of **2d** was determined by X-ray crystallography to be *S* (Figure 1). In the reaction of *N*-Boc imines **1** bearing a substituent at the *ortho* position of the benzene ring with MVK, *o*-methoxybenzaldehyde *N*-Boc imine **1i** gave aza-MBH adduct **2i** in 90%*ee*, but *o*-chlorobenzaldehyde *N*-Boc imine **1j** gave **2j** in only 60%*ee* (Table 4, Entries 9 and 10).

It is well documented that *N*-Boc-protected α-amidoalkyl *p*-tolyl sulfones or α-amidoalkyl phenyl sulfones can be considered as a stable, crystalline, and easy to handle equivalent of *N*-Boc imines. Recently, a number of papers have reported the nucleophilic addition to *N*-carbamate imines in situ generated from the aforementioned α-amido sulfones by base-induced elimination, which inspired us to envision the aza-MBH reaction of *N*-Boc α-amidoalkyl phenyl sulfone **3a** with MVK in the presence of cesium carbonate by using TQO as the catalyst. Aza-MBH adduct **2a** was obtained in 60% yield with rather low *ee* (2%*ee*; Scheme 3). The result showed that TQO had catalytic activity for this reaction; however, some loss of stereoselectivity was observed. It should be mentioned here that this reaction could not occur without TQO. Byproduct **9** was isolated from the reaction mixture, which implies that the intermediate generated from **3a** may directly react with MVK by a Michael-type addition during the formation of the *N*-Boc imine.

Table 3. Solvent screening for the asymmetric aza-MBH reaction of *N*-Boc imine **1a** with MVK.

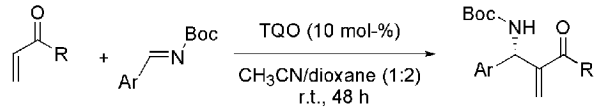


MVK **1a** **2a**

Entry[a]	Solvent	Yield [%][b]	*ee* [%][c]
1	DCM	49	88
2	THF	38	91
3[d]	THF	44	92
4	CH_3CN	96	87
5	DMF	82	88
6	dioxane	44	94
7[d]	dioxane	44	94
8[e]	dioxane	60	95
9	DMSO	76	86
10	toluene	49	90
11[f]	CH_3CN	60	86
12	CH_3CN/THF, 1:1	80	87
13	CH_3CN/dioxane, 1:1	73	90
14	CH_3CN/dioxane, 2:1	76	89
15	CH_3CN/dioxane, 1:2	82	91

[a] All reactions were carried out with *N*-Boc imine **1a** (0.2 mmol) and MVK (0.4 mmol) in the presence of TQO in solvent (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC. [d] 4 Å MS were added. [e] 20 mol-% of TQO was used. [f] At –30 °C.

Table 4. Aza-MBH reaction of *N*-Boc imines with MVK or EVK catalyzed by TQO.



MVK or EVK **1** **2**

Entry[a]	R	Ar	Yield [%][b]	*ee* [%][d]	Absolute configuration[e]
1	Me	*p*-$CF_3C_6H_4$, **1b**	**2b**, 60	93	*S*
2[c]	Me	*p*-$CF_3C_6H_4$, **1b**	**2b**, 61	87	*S*
3	Me	*p*-FC_6H_4, **1c**	**2c**, 82	93	*S*
4	Me	*p*-BrC_6H_4, **1d**	**2d**, 80	93	*S*
5	Me	*p*-$MeOC_6H_4$, **1e**	**2e**, 79	92	*S*
6	Me	*p*-MeC_6H_4, **1f**	**2f**, 57	90	*S*
7	Me	*m*-MeC_6H_4, **1g**	**2g**, 57	90	*S*
8	Me	*m*-ClC_6H_4, **1h**	**2h**, 87	94	*S*
9	Me	*o*-$MeOC_6H_4$, **1i**	**2i**, 56	90	*S*
10	Me	*o*-ClC_6H_4, **1j**	**2j**, 52	60	*S*
11	Me	2-furyl, **1k**	**2k**, 64	88	*S*
12	Et	C_6H_5, **1a**	**2l**, 52	92	*S*

[a] All reactions were carried out with *N*-Boc imine **1** (0.2 mmol) and MVK or EVK (0.4 mmol) in solvent (1.0 mL) at room temperature. [b] Isolated yield. [c] In CH_3CN. [d] Determined by chiral HPLC. [e] Determined by the sign of the specific rotation.

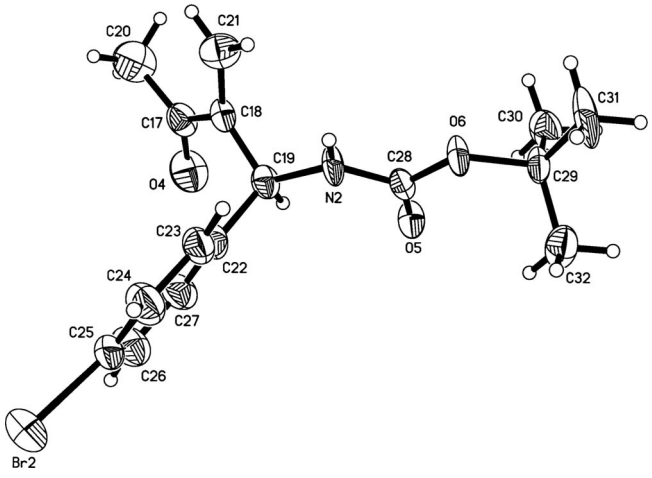
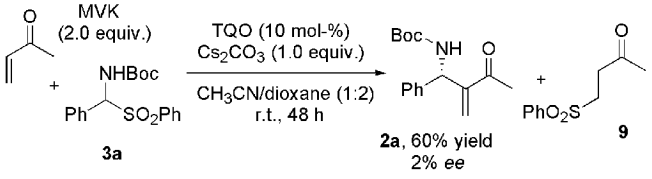


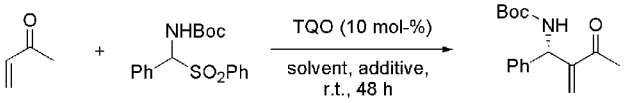
Figure 1. ORTEP drawing of compound **2d**.[13]



Scheme 3. The reaction of *N*-Boc α-amidoalkyl phenyl sulfone **3a** with MVK in the presence of cesium carbonate by using TQO as the catalyst.

Subsequently, solvent and additive effects were examined to improve the yield and enantioselectivity, and the results are summarized in Table 5. We hypothesized that chiral catalyst TQO may easily be protonated in the catalytic cycle, leading to poor enantioselectivity.[14] Thus, we added some auxiliary bases such as NEt_3 and iPr_2NH to avoid generation of a protonated chiral catalyst; however, the enantioselectivity did not improve (Table 5, Entries 1 and 2). Surprisingly, it was found that the enantioselectivity was improved with the use of water as an additive. By using toluene as the solvent and water (0.2 mL) as the additive, **2a** was obtained in 88%*ee*, though the yield was only 27% (Table 5, Entry 3). Acetonitrile and dioxane, which are suitable solvents for the aza-MBH reactions of *N*-Boc imines with MVK, gave poor results (Table 5, Entries 4 and 5). Without cesium carbonate and water, **2a** was obtained in 38% yield with 70%*ee*, which indicates the importance of water in this reaction. Decreasing the amount of water from 0.2 mL to 0.05 mL did not reduce the enantioselectivity, but a slightly higher yield was observed. Acetonitrile and dioxane were tested again under the same conditions, and the enantioselectivities were rather low, even though 5.0 equiv. of MVK was employed. Then, we examined the reaction temperature and other bases instead of cesium carbonate, which afforded unsatisfactory results (Table 5, Entries 13–16). The best enantioselectivity was obtained with 5.0 equiv. of MVK in toluene as the solvent and without any additives (Table 5, Entry 17); however, the yield was low under these conditions.

Table 5. The aza-MBH reaction of *N*-Boc-amidoalkyl phenyl sulfone **3a** with MVK by using TQO as the catalyst.



MVK **3a** **2a**

Entry[a]	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	CH_3CN	Cs_2CO_3 (1.0 equiv.), NEt_3 (0.2 mmol)	69	2
2	CH_3CN	Cs_2CO_3 (1.0 equiv.), iPr_2NH (0.2 mmol)	69	2
3[g]	toluene	Cs_2CO_3 (1.0 equiv.), H_2O (0.2 mL)	27	88
4[g]	CH_3CN	Cs_2CO_3 (1.0 equiv.), H_2O (0.2 mL)	22	38
5[g]	dioxane	Cs_2CO_3 (1.0 equiv.), H_2O (0.2 mL)	20	47
6	toluene	–	38	70
7	toluene	Cs_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	33	88
8[d]	CH_3CN	–	28	18
9[d]	CH_3CN	Cs_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	54	22
10[d]	dioxane	–	61	2
11[d]	dioxane	Cs_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	56	42
12[d]	DCM	Cs_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	51	78
13[d]	toluene	Cs_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	51	87
14[d,e]	toluene	Cs_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	31	65
15[d]	toluene	K_3PO_4 (1.0 equiv.), H_2O (0.05 mL)	38	54
16[d]	toluene	K_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	40	85
17[d]	toluene	–	51	90
18[f]	toluene	–	5	89

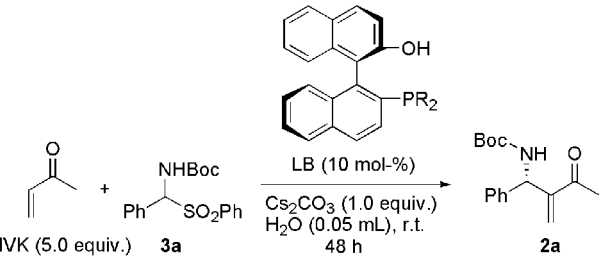
[a] The reactions were carried out with *N*-Boc-amidoalkyl phenyl sulfone **3a** (0.2 mmol) and MVK (0.4 mmol) in solvent (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC. [d] 5.0 equiv. of MVK was used. [e] At 50 °C. [f] At –20 °C. [g] 0.8 mL of solvent was used.

On the basis of the above experiments, we have identified a facile and direct route to obtain aza-MBH adducts by a one-pot approach, although we did not achieve it in high yield and excellent *ee* by using a chiral amine catalyst, which stimulated us to search other catalytically active and enantioselective catalysts. Then, we again turned our attention to chiral phosphane catalysts. LB1 was first examined in this reaction, leading to product **2a** in 87% yield with 26%*ee* (Table 6, Entry 1). Such a high yield encouraged us to examine other conditions to get higher enantioselectivity (Table 6). Without cesium carbonate, **2a** was obtained in a higher yield of 95% along with 23%*ee* (Table 6, Entry 2). Some other solvents, such as acetonitrile, dioxane, DCM, and THF, were further examined (Table 6, Entries 3–6). DCM gave the best reaction outcome: 98% yield and 50%*ee*. Using DCM as the solvent, catalysts LB6 and LB7 were examined, which led to higher enantioselectivities with relatively lower yields (Table 6, Entries 7 and 8). The enantioselectivity was found to be sensitive to the solvent, so we tried other chlorinated solvents using LB1 as the catalyst (Table 6, Entries 9–11). Chloroform gave **2a** in higher enantioselectivity: up to 65%*ee* (Table 6, Entry 9). In the presence of chloroform, by decreasing the temperature to –40 or –20 °C a similar enantioselectivity was achieved and the yield was quantitative at –20 °C. It is notable that the enantioselectivity dropped to 54%*ee* when water was not added to the reaction mixture (Table 6, Entry 14). Decreasing the amount of water from 0.05 to 0.0036 mL (1.0 equiv. of water), the enantioselectivity did not change (Table 6, Entries 13 and 15). The enantioselectivity increased slightly to 86%*ee* without cesium carbonate, which was the best result we obtained (Table 6, Entry 16). Catalysts LB7, LB8, and LB9 were also examined at –20 °C in chloroform, with 0.05 mL of water as the additive. Under these reaction conditions, LB7 and LB8 could not catalyze this reaction, and LB9 gave a slightly lower yield and enantioselectivity than LB1 (Table 6, Entries 17–19).

Subsequently, we used *N*-Boc-amidoalkyl *p*-tolyl sulfone **4a** as the substrate to examine the effect of the phenylsulfinate (Table 7). Under the same reaction conditions, the reactions of **4a** with MVK proceeded smoothly, leading to similar results in terms of yields and enantioselectivities (Table 7, Entries 1–3).

With these optimal reaction conditions, the scope of the aza-MBH reaction was further investigated with respect to a series of *N*-Boc α-amidoalkyl phenyl sulfones **3** by using LB1 as the catalyst (Table 8). Compared with the results in Table 4, LB1 gave product **2** in much higher yields, especially for those substrates possessing substituent at the *meta* or *para* position of the benzene ring, irrespective of their electronic nature, though the enantioselectivity was slightly lower (Table 8, Entries 1–3). In the reaction of *N*-Boc α-amidoalkyl phenyl sulfones **3** bearing substitutes at the *ortho* position of the benzene ring with MVK, **3i** gave aza-MBH adduct **2i** in 82%*ee*, but **3j** gave **2j** in only 60%*ee* (Table 8, Entries 4 and 5). These differences in enantioselectivity were similar to the results in the TQO-catalyzed aza-MBH reaction between *N*-Boc imines **1** and MVK (Table 4, Entries 9 and 10). It should be noted that **2b** and **2h** could be obtained in 97 and >99%*ee*, respectively, after being recrystallized once from petroleum ether and DCM.

Table 6. The aza-MBH reaction of *N*-Boc α-amidoalkyl phenyl sulfone **3a** with MVK by using LB1 as the catalyst.

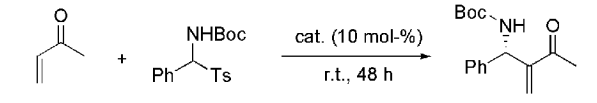


MVK (5.0 equiv.) **3a** **2a**

Entry[a]	Solvent	Yield [%][b]	*ee* [%][c]
1	DCM	87	26
2[d]	toluene	95	23
3	CH_3CN	73	2
4	dioxane	85	2
5	DCM	98	50
6	THF	82	3
7[e]	DCM	42	42
8[f]	DCM	43	64
9	chloroform	71	65
10	CCl_4	80	37
11	DCE	85	38
12[i]	chloroform	82	83
13[j]	chloroform	99	82
14[j,k]	chloroform	91	54
15[j,l]	chloroform	99	82
16[d,j]	chloroform	99	86
17[d,g,j]	chloroform	–	–
18[d,h],j]	chloroform	95	80
19[d,f,j]	chloroform	–	–

[a] All reactions were carried out with *N*-Boc α-amidoalkyl phenyl sulfone **3a** (0.2 mmol) and MVK (1.0 mmol). LB1, R = Ph; LB6, R = Bu; LB7, R = Cy; LB8, R = 3,5-bis(trifluoromethyl)phenyl; LB9, R = 3,5-dimethylphenyl. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Without Cs_2CO_3. [e] LB6 was used as the catalyst. [f] LB7 was used as the catalyst. [g] LB8 was used as the catalyst. [h] LB9 was used as the catalyst. [i] At –40 °C. [j] At –20 °C. [k] Without water. [l] 0.0036 mL of water was used.

Table 7. The aza-MBH reaction of *N*-Boc α-amidoalkyl *p*-tolyl sulfone **4a** with MVK using by LB1 or TQO as the catalyst.

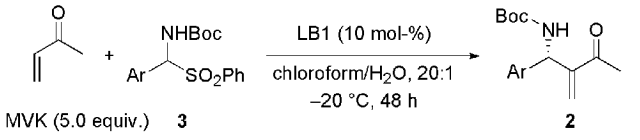


MVK (5.0 equiv.) **4a** **2a**

Entry[a]	Cat.	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	LB1	chloroform	Cs_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	84	68
2[d]	LB1	chloroform	H_2O (0.05 mL)	80	84
3	TQO	toluene	–	55	90

[a] All reactions were carried out with *N*-Boc α-amidoalkyl *p*-tolyl sulfone **4a** (0.2 mmol) and MVK (1.0 mmol) in solvent (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC. [d] At –20 °C.

Table 8. The aza-MBH reaction of *N*-Boc α-amidoalkyl phenyl sulfones **3** with MVK by using LB1 as the catalyst.

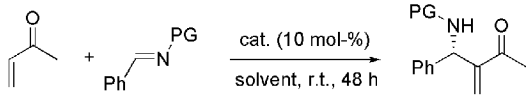


Entry[a]	Ar	Yield [%][b]	*ee* [%][c]	Absolute configuration[d]
1	*p*-$CF_3C_6H_4$, **3b**	**2b**, 89	87	*S*
2	*m*-MeC_6H_4, **3g**	**2g**, 98	83	*S*
3	*m*-ClC_6H_4, **3h**	**2h**, 97	90	*S*
4	*o*-$MeOC_6H_4$, **3i**	**2i**, 56	82	*S*
5	*o*-ClC_6H_4, **3j**	**2j**, 71	60	*S*
6	2-furyl, **3k**	**2k**, 94	82	*S*

[a] All reactions were carried out with *N*-Boc α-amidoalkyl phenyl sulfones **3** (0.2 mmol) and MVK (1.0 mmol) in chloroform (1.0 mL) and water (0.05 mL). [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by the sign of the specific rotation.

N-Bz or *N*-CO_2Et imines **5** were tested in the aza-MBH reaction with MVK (Table 9) to further investigate the scope and limitations of this reaction. For *N*-Bz imine **5a**, dioxane was a better solvent than acetonitrile in both yield and enantioselectivity to give the corresponding adduct **6a** in 75% yield with 86% *ee* (Table 9, Entry 3). Product **6b** was obtained in higher enantioselectivity than **6a** (93% *ee*; Table 9, Entry 6). According to these results, we conclude that *N*-carbamate imines, such as *N*-Boc or *N*-CO_2Et imines, are superior in providing higher levels of enantioselectivity than *N*-Bz imines in the aza-MBH reaction with MVK.

Table 9. Catalyst and solvent screening for the aza-MBH reaction of imines **5** with MVK.

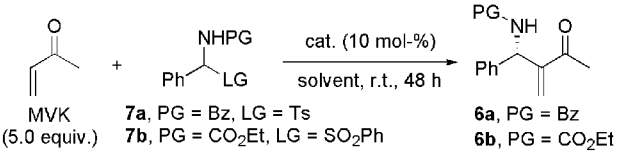


Entry[a]	PG	Solvent	Cat.	Yield [%][b]	*ee* [%][c]
1	Bz	CH_3CN	DABCO	**6a**, 54	–
2	Bz	CH_3CN	TQO	**6a**, 52	57
3	Bz	dioxane	TQO	**6a**, 75	86
4	CO_2Et	CH_3CN	DABCO	**6b**, 71	–
5	CO_2Et	CH_3CN	TQO	**6b**, 59	76
6	CO_2Et	dioxane	TQO	**6b**, 51	93

[a] All reactions were carried out with imines **5** (0.2 mmol) and MVK (0.4 mmol) in solvent (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC.

α-Amidoalkyl phenyl sulfones **7**, precursors of *N*-Bz or *N*-CO_2Et imines **5** went smoothly in their aza-MBH reactions with MVK (Table 10). Chiral phosphane catalyst LB1 exhibited its good catalytic activity and selectivity, affording corresponding adducts **6a** or **6b** in higher yields and enantioselectivities.

Table 10. The aza-MBH reaction of α-amidoalkyl phenyl sulfones **7** with MVK.



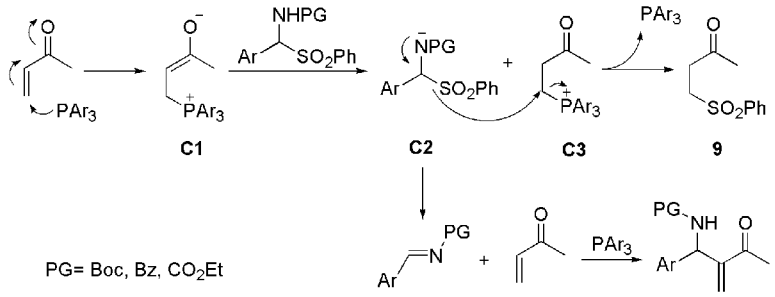
Entry[a]	Solvent	Cat.	Additive	Yield [%][b]	*ee* [%][c]
1	toluene	TQO	Cs_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	**6a**, –	–
2	toluene	TQO	Cs_2CO_3 (1.0 equiv.), H_2O (0.05 mL)	**6b**, 16	47
3[d]	chloroform	LB1	H_2O (0.05 mL)	**6a**, 99	89
4[d]	chloroform	LB1	H_2O (0.05 mL)	**6b**, 97	80

[a] All reactions were carried out with α-amidoalkyl phenyl sulfones **7** (0.2 mmol) and MVK (1.0 mmol) in solvent (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC. [d] At –20 °C.

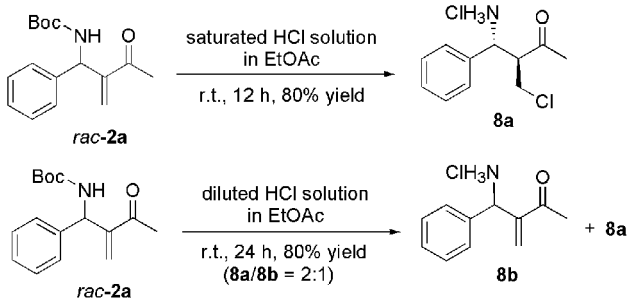
In our LB1-catalyzed aza-MBH reactions of *N*-protected α-amidoalkyl phenyl sulfones with MVK, the in situ formation of imines may be rationalized by the mechanism shown in Scheme 4. Catalyst LB1 as a nucleophile reacts with MVK to produce zwitterionic intermediate **C1**, which subsequently deprotonates the *N*-protected α-amidoalkyl phenyl sulfones to generate **C2** and **C3**. Anion **C2** releases phenylsulfinate to form the imine, and the phenylsulfinate undergoes nucleophilic substitution of **C3** to furnish product **9** and regenerate the catalyst.

Generally, the Boc group could be easily removed by using HCl in the presence of EtOAc. After **2a** was stirred in the EtOAc solution of HCl (a saturated solution with HCl gas, ca. 4.0 M) at room temperature for 12 h, a white solid was acquired (Scheme 5). Surprisingly, obtained product **8a** was an adduct of HCl with the normal product α-methylene-β-amino ketone **8b**, and the structure of product **8a** was assigned on the basis of spectroscopic analysis and subsequently confirmed unequivocally by single-crystal X-ray analysis (Figure 2). The Boc protecting group could also be successfully removed by using a dilute HCl solution of EtOAc (ca. 0.2 M) at room temperature, but a mixture of **8a** and the corresponding aza-MBH product **8b** was obtained in 80% yield (Scheme 5).

Reduction of the carbonyl group of *rac*-**2a** with $NaBH_4$ and $CeCl_3$ produced α-methylene-β-amino alcohol *rac*-**9b** as a pair of diastereoisomers (1:1) in good yield, and the Boc protecting group could also be easily removed with a EtOAc solution of HCl (a saturated solution with HCl gas) at room temperature for 12 h, affording product **10** in 90% yield (Scheme 6). Another more efficient method is to use easily available solid *p*-toluenesulfonic acid (TsOH) to remove the Boc protecting group.[16] After a solution of *rac*-**2a** and TsOH (4.0 equiv.) in DCM/THF (1:1) was stirred at room temperature for 48 h, the TsOH salt of the corresponding aza-MBH product α-methylene-β-amino ketone **11** was obtained in 80% yield in pure form (Scheme 6).



Scheme 4. Plausible mechanism for the in situ formation of imines in the LB1-catalyzed aza-MBH reaction of α-amidoalkyl phenyl sulfones with MVK.



Scheme 5. Removal of the Boc protecting group from adduct *rac*-**2a**.

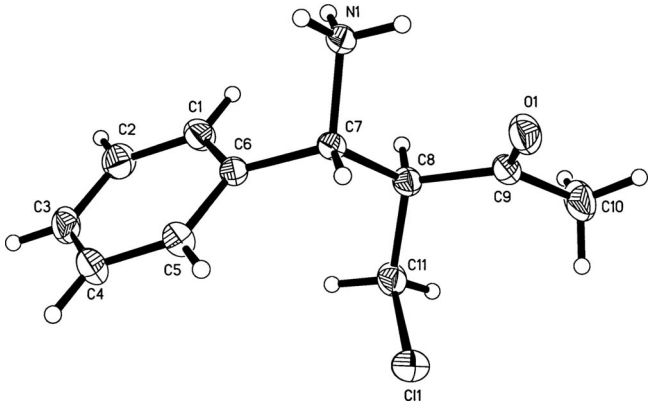
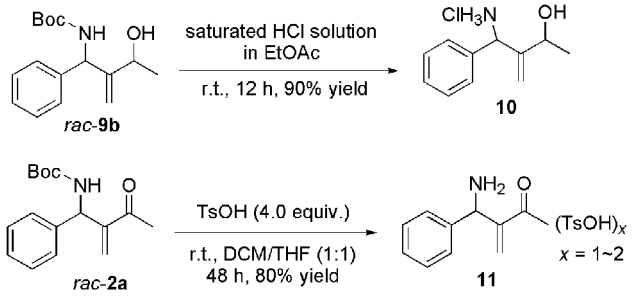


Figure 2. ORTEP drawing of compound **8a**.[15]



Scheme 6. Removal of the Boc group from adduct *rac*-**2a** or **9b**.

Conclusions

We have developed DABCO-catalyzed aza-MBH reactions of *N*-Boc imines with MVK and EVK. The asymmetric version of this aza-MBH reaction of *N*-protected imines was systematically investigated by using chiral amine and chiral phosphane catalysts. The reaction was found to be general with respect to various *N*-protected imines under mild reaction conditions, furnishing the corresponding adduct in moderate yield with high *ee* value. Gratifyingly, we have identified a facile and direct route to obtain highly enantioselective aza-MBH adducts from *N*-protected α-amidoalkyl phenyl sulfones with alkyl vinyl ketones catalyzed by chiral phosphane catalyst LB1. This one-pot approach avoids handling of preformed imines, which are usually unstable. Interestingly, an adduct of HCl with the corresponding aza-MBH product could be obtained during the removal of the Boc group of **2a** by using HCl in EtOAc, and the normal aza-MBH product could be also produced as a salt by treating **2a** with TsOH under mild conditions. Efforts are in progress to elucidate further mechanistic details of these reactions and to understand their scope and limitations.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Low- and high-resolution mass spectra were recorded by ESI method. The used organic solvents were dried by standard methods if it was necessary. Satisfactory CHN microanalyses were obtained with an analyzer. Commercially obtained reagents were used without further purification. All these reactions were monitored by TLC with silica-gel-coated plates. Flash column chromatography was carried out by using silica gel at increased pressure.

General Procedure for the DABCO- or TQO-Catalyzed Aza-MBH Reactions of *N*-Boc Imine 1 with MVK: *N*-Boc imine **1** (0.2 mmol), MVK (0.4 mmol), DABCO or TQO (0.02 mmol), and acetonitrile (1.0 mL) were added into a Schlenk tube. The reaction mixture was stirred at room temperature for 48 h, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography.

***rac*-2a:** White solid (44 mg, 80%), m.p. 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 1.44 (s, 9 H, CH_3), 2.30 (s, 3 H, CH_3), 5.53 (br. s, 1 H, NH), 5.65 (d, J = 8.4 Hz, 1 H, CH), 6.11 (s, 1 H, =CH), 6.22 (s, 1 H, =CH), 7.21–7.31 (m, 5 H, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 26.5, 28.3, 56.0, 79.6, 126.4, 126.7, 127.3, 128.4, 140.1, 147.8, 154.9, 198.8 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3443, 3350, 3088, 3062, 3030, 2980, 2931, 1723, 1494, 1454, 1367, 1283, 1248, 1174, 1046, 1023, 975, 885, 754, 700 cm^{-1}.

MS (ESI): *m/z* (%) = 298.1 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{16}H_{21}N_1Na_1O_3$ $[M + Na]^+$ 298.14136; found 298.14189.

General Procedure for the Removal of the Boc Group: Compound *rac*-**2a** (125 mg, 0.45 mmol) was stirred in an EtOAc (4.0 mL) solution of HCl (a saturated solution with HCl gas) at room temperature for 12 h, a white solid was formed, and the solvent was removed under reduced pressure. The residue was washed with Et_2O, and pure product **8a** (90 mg, 80% yield) was obtained as a white solid.

CCDC-739399 (for **2d**) and -743651 (for **8a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Spectroscopic data of all new compounds, detailed descriptions of the experimental procedures, X-ray data for compounds **2d** and **8a**.

Acknowledgments

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[13] Crystal data of **2d**: Empirical formula: $C_{16}H_{20}BrNO_3$; formula weight: 354.24; crystal size: $0.369 \times 0.317 \times 0.112$; crystal color, habit: colorless, prismatic; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 5.2878(8) Å, b = 20.966(3) Å, c = 15.487(2) Å, α = 90°, β = 97.8883(3)°, γ = 90°, V = 1700.8(4) Å^3; space group: $P2_1$; Z = 4; $D_{calcd.}$ = 1.383 g cm^{-3}; $F(000)$ = 728; R_1 = 0.0544, wR_2 = 0.1148. Diffractometer: Rigaku AFC7R.

[14] Aiken et al. demonstrated that protonated cinchona alkaloids could be catalytically active for asymmetric anhydride opening but the enantioselectivities were rather low; a) R. A. Aitken, J. Gopal, *Tetrahedron: Asymmetry* **1990**, *1*, 517; b) R. A. Aitken, J. Gopal, J. A. Hirst, *J. Chem. Soc., Chem. Commun.* **1988**, 632–634.

[15] Crystal data of **8a**: Empirical formula: $C_{11}H_{16}Cl_2NO_{1.50}$; formula weight: 257.15; crystal size: $0.453 \times 0.330 \times 0.297$; crystal color, habit: colorless, prismatic; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 27.807(3) Å, b = 5.8683(6) Å, c = 15.8859(16) Å, α = 90°, β = 103.310(2)°, γ = 90°, V = 2522.6(4) Å^3; space group: $C2/c$; Z = 8; $D_{calcd.}$ = 1.354 g cm^{-3}; $F(000)$ = 1080; R_1 = 0.0401, wR_2 = 0.1055. Diffractometer: Rigaku AFC7R.

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