CHEMISTRY
A EUROPEAN JOURNAL

Catalytic, Asymmetric Aza-Baylis–Hillman Reaction of *N*-Sulfonated Imines with Activated Olefins by Quinidine-Derived Chiral Amines

Min Shi,* Yong-Mei Xu, and Yong-Ling Shi[a]

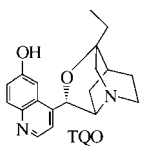
Abstract: The chiral nitrogen Lewis base, tricyclic cinchona alkaloid derivative TQO, is an effective promoter in the catalytic, asymmetric aza-Baylis–Hillman reaction of *N*-sulfonated imines Ar−CH=NR′ **1** (R′ = Ts, Ms, Ns, SES) with various activated olefins such as methyl vinyl ketone (MVK), ethyl vinyl ketone (EVK), acrolein, methyl acrylate, phenyl acrylate, or α-naphthyl acrylate to give the corresponding adducts in moderate to good yields with good to high *ee* (up to 99%) at −30 °C or 45 °C in various solvents, including DMF/MeCN (1:1, v/v). The first such reaction of **1** with the simplest Michael acceptor MVK and methyl acrylate has been achieved with excellent enantioselectivity. The adducts derived from MVK and EVK had the opposite absolute configuration to those from acrolein, methyl acrylate, phenyl acrylate, and α-naphthyl acrylate. A plausible mechanism has been proposed on the basis of previous reports and the authors' investigations. An effective bifunctional chiral nitrogen Lewis base–Brønsted acid system has been revealed in this type of aza-Baylis–Hillman reaction.

Keywords: betaines · Lewis bases · asymmetric catalysis · aza-Baylis–Hillman reaction · enantioselectivity

Introduction

Great progress has been made in development of the Baylis–Hillman (BH) reaction,[1] including several catalytic, asymmetric versions,[2] since Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of a strong Lewis base such as 1,4-diazabicyclo[2.2.2]octane (DABCO) in 1972.[3] However, the catalytic, asymmetric BH reaction is still not fruitful, because until now it has been limited to the specialized α,β-unsaturated ketones or acrylates such as ethyl vinyl ketone (EVK) (71% *ee*),[2a] 2-cyclohexen-1-one[2b] or 1,1,1,3,3,3-hexafluoroisopropyl acrylate (99% *ee*)[2c] and naphthyl acrylate (91% *ee*).[2d] For the simplest methyl vinyl ketone (MVK), 81% *ee* has been attained in the presence of a special nucleophile-loaded peptide and L-proline.[2e] High enantioselectivity (>90% *ee*) has not so far been reported in BH reactions involving simple Michael acceptors such as MVK or methyl acrylate with a Lewis base promoter.

During our investigations,[4] we have found that the reactions with MVK or methyl acrylate of arylaldehydes bearing electron-donating groups such as Et or MeO on the phenyl ring were either sluggish or did not occur at all under the traditional BH conditions. We therefore used *N*-tosylated imines (*N*-arylmethylidene-4-methylbenzenesulfonamides, ArCH=NTs) instead of arylaldehydes in the traditional BH reaction with MVK or methyl acrylate,[5] because we expected the tosylated imino group to have high reactivity toward nucleophilic attack, even when the phenyl ring bears electron-donating groups. Indeed, such reactions, promoted by a catalytic amount of a Lewis base such as DABCO or 4-(dimethylamino)pyridine (DMAP), give exclusively the normal aza-BH adducts in good yields for many *N*-arylmethylidene-4-methylbenzenesulfonamides.[5b,c] As a suitable chiral nitrogen Lewis base for a catalytic, asymmetric version of this reaction, we chose 4-(3-ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]dec-5-yl)quinolin-6-ol (TQO) (10 mol%)[2c,g,6], because it is easily prepared from (+)-quinidine[2c,g,6] and high enantiomeric excesses were achieved in the reactions of 1,1,1,3,3,3-hexafluoroisopropyl acrylate with arylaldehydes.[2c] We have previously reported an unprecedented catalytic, asymmetric aza-BH reaction of *N*-tosylated imines **1** with MVK and methyl acrylate uti-



[a] Prof. M. Shi, Dr. Y.-M. Xu, Y.-L. Shi
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (P. R. China)
Fax: (+86) 21-6416-6128
E-mail: mshi@pub.sioc.ac.cn

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

DOI: 10.1002/chem.200400872

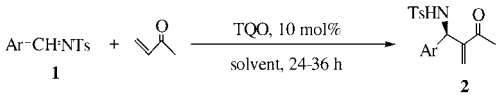
lizing TQO to achieve >90% *ee* in good yield under mild conditions.[5d] This was the first case in which a high *ee* (>90%) could be realized using the simplest Michael acceptor, MVK. The structure of TQO plays a very important role in achieving high *ee* in this reaction.[2c,5d] Exploration for a novel and highly efficient chiral Lewis base for catalytic, asymmetric BH reactions is a very attractive and competitive field. Here, we report in full detail such a reaction of *N*-sulfonated imines with various activated olefins, including ethyl vinyl ketone (EVK), acrolein, phenyl acrylate, and α-naphthyl acrylate. An interesting inversion of absolute configuration between the adducts derived from MVK and EVK and those from acrolein, methyl acrylate, phenyl acrylate and α-naphthyl acrylate has also been revealed.

Results and Discussion

Catalytic, asymmetric aza-Baylis–Hillman reaction of *N*-sulfonated imines

Reactions with MVK and EVK: The results with *N*-tosylated imines **1** such as *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide **1c** and *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** as substrates for the reaction with MVK in the presence of TQO are summarized in Table 1.

Table 1. Aza-Baylis–Hillman reactions of *N*-(4-ethylbenzylidene)-4-methylbenzenesulfonamide **1c** or *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** (1.0 equiv) with methyl vinyl ketone (2.0 equiv) in the presence of TQO (10 mol%).

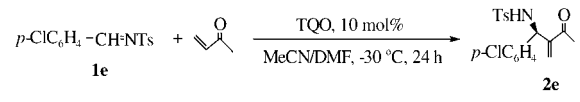


Entry	Ar	1	Solvent	Time [h]	Temp. [°C]	2	Yield [%][a]	*ee* [%]
1	*p*-EtC_6H_4	**1c**	THF	36	20	**2c**	30	62
2	*p*-EtC_6H_4	**1c**	THF	24	−25	**2c**	33	76
3	*p*-EtC_6H_4	**1c**	MeCN	24	0	**2c**	50	78
4	*p*-EtC_6H_4	**1c**	MeCN	24	−20	**2c**	64	86
5	*p*-EtC_6H_4	**1c**	DMF	24	−20	**2c**	55	93
6	*p*-EtC_6H_4	**1c**	DMF	24	−40	**2c**	50	96
7	*p*-ClC_6H_4	**1e**	THF	24	0	**2e**	71	42
8	*p*-ClC_6H_4	**1e**	THF	24	−20	**2e**	65	63
9	*p*-ClC_6H_4	**1e**	MeCN	24	−30	**2e**	80	81
10	*p*-ClC_6H_4	**1e**	DMF	24	−30	**2e**	51	95

[a] Yield of isolated product.

At 0°C~20°C (room temperature), moderate enantioselectivities (42–78% *ee*) for the corresponding adducts **2c** and **2e** were achieved in THF or MeCN (Table 1, entries 1, 3, and 7). Moreover, at lower temperatures (−20 to −30°C), the *ee* values of **2c** and **2e** could reach 86% and 81%, with 64% and 80% yield, respectively (Table 1, entries 4 and 9). The highest *ee* values (96% and 95%) for **2c** and **2e** were achieved in DMF at −30 to −40°C with 50% and 51% yield (Table 1, entries 6 and 10). Thus, the highest *ee* value was attained at −30°C in DMF, but the best chemical yield at −30°C in MeCN. To obtain the aza-BH adducts **2** with high *ee* values and yields, we next investigated the reaction of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** with MVK in MeCN/DMF at −30°C (Table 2). The best reaction conditions were obtained with MeCN/DMF = 1:1 (v/v) at −30°C, which gave **2e** in 71% yield with 93% *ee* (Table 2, entry 3). The absolute configuration of **2e** was determined by X-ray crystallography to be *R*-enriched (Figure 1).[7]

Table 2. Aza-Baylis–Hillman reactions of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** (1.0 equiv) with methyl vinyl ketone (2.0 equiv) in the presence of TQO (10 mol%).



Entry	MeCN/DMF (v/v)	Yield of **2e** [%][a]	*ee* [%]	Absolute configuration
1	5:1	76	78	*R*
2	4:1	78	90	*R*
3	1:1	71	93	*R*
4	1:2	66	93	*R*

[a] Yield of isolated product.

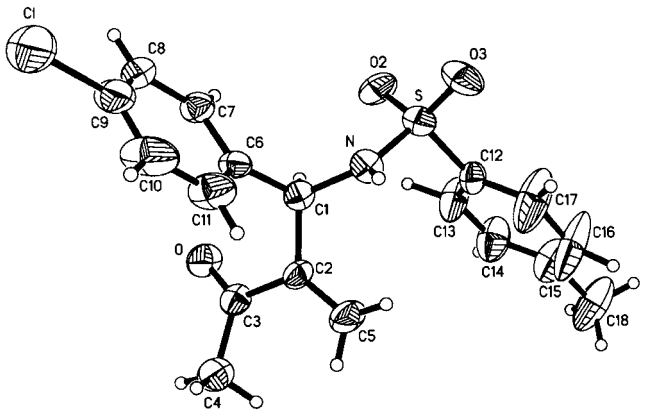
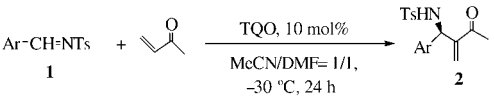


Figure 1. Crystal structure of **2e** (ORTEP drawing).

In the reaction of other *N*-tosylated imines **1** with MVK in the presence of TQO as a chiral nitrogen Lewis base, similar results were obtained under the optimized reaction conditions (Table 3). Aza-BH adducts of **1** were obtained with high *ee* values (90–99%) and moderate to good yields (58–80%; Table 3, entries 1–5). *N*-(*p*-Nitrobenzylidene)-4-methylbenzenesulfonamide (**1g**), *N*-furan-2-ylmethylene-4-methylbenzenesulfonamide (**1h**), and 4-methyl-*N*-(3-phenylallylidene)benzenesulfonamide (**1i**) with MVK under the same reaction conditions gave **2g**–**2i** with moderate *ee* values (Table 3, entries 6–8). No adduct **2g** was observed in DMF at −40°C, because *N*-(4-nitrobenzylidene)-4-methylbenzenesulfonamide decomposes rapidly in DMF under these conditions. The *ee* of **2** can reach over 99% after one recrystallization from CH_2Cl_2/hexane (1:6, v/v) in most cases.

Table 3. Aza-Baylis–Hillman reactions of *N*-tosylated imines **1** (1.0 equiv) with methyl vinyl ketone (2.0 equiv) in the presence of TQO (10 mol%) under the optimized reaction conditions.

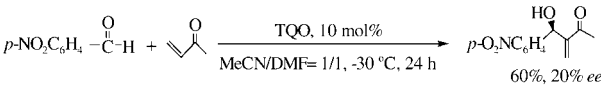


Entry	Ar	1	2	Yield [%][a]	*ee* [%]	Absolute configuration
1	C_6H_5	**1a**	**2a**	80	97[b]	*R*
2	*p*-MeC_6H_4	**1b**	**2b**	80	96	*R*
3	*p*-EtC_6H_4	**1c**	**2c**	74	96	*R*
4	*p*-$MeOC_6H_4$	**1d**	**2d**	67	99[c,e]	*R*
5	*p*-$NO_2C_6H_4$	**1f**	**2f**	58	90	*R*
6	*p*-EtC_6H_4	**1g**	**2g**	60	74[d]	*R*
7		**1h**	**2h**	61	73[e]	*R*
8	C_6H_5–CH=CH	**1i**	**2i**	54	46[e]	*R*

[a] Yield of isolated product. [b] In DMF, yield: 57%; 96% *ee*. [c] In DMF, yield: 59%; 99% *ee*. [d] In DMF, no imine BH adduct was formed because the imine decomposed quickly. [e] The reaction mixture was stirred for 36 h.

For other *N*-sulfonated imines such as *N*-mesylated imine **1j** (ArCH=N–Ms) and *N*-SES-protected imine **1l** (β-trimethylsilylethanesulfonamide: $Me_3SiCH_2CH_2SO_2N$=CHAr), this catalytic, asymmetric aza-BH reaction proceeded smoothly under the same conditions to give the corresponding adducts **3a** and **3c** in good yields with 89% and 80% *ee*, respectively (Table 4, entries 1 and 3). However, we found that *N*-4-nitrobenzenesulfonated imine **1k** (ArCH=N–Ns), which should be the most active electrophile in this aza–BH reaction, decomposed rapidly under the same reaction conditions and the corresponding aza-BH adduct **3b** was not formed (Table 4, entry 2).

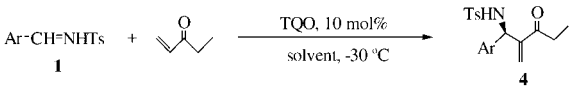
In the traditional BH reaction of *p*-nitrobenzaldehyde with MVK under the same conditions, the adduct was obtained in only 20% *ee* with 60% yield of isolated product (Scheme 1). Use of sulfone-protected imine as substrate is important for achieving high enantioselectivity in BH reactions with MVK as acceptor, although high enantiomeric excesses have been achieved in the reactions of 1,1,1,3,3,3-hexafluoroisopropyl acrylate with aldehydes.[2c]



Scheme 1. Baylis–Hillman reaction of *p*-nitrobenzaldehyde with MVK in the presence of TQO (10 mol%).

The results for optimized reaction conditions with *N*-tosylated imine **1a** and with EVK as the substrate at −30°C are summarized in Table 5. In MeCN or THF, the corresponding adduct **4a** was obtained in 42% and 49% yield with 86% and 55% *ee*, respectively, with an *R*-enriched configuration (Table 5, entries 1 and 2). In DMF, adduct **4a** was obtained in 44% yield with 90% *ee* (Table 5, entry 3). When this reaction was carried out in MeCN/DMF (1:1 (v/v) at −30°C, 94% *ee* could be achieved after 22 h in 54% yield (Table 5, entry 4). These should be the best conditions for this reaction. For several other *N*-tosylated imines (**1b**, **1e**, and **1m**), similar results were obtained (Table 5, entries 5–7). The recrystallization of **4** gave a higher *ee*. For example, after one recrystallization of **4b** from CH_2Cl_2/hexane (1:3, v/v), the *ee* of **4b** reached 99.9% (Table 5, entry 5). In general, this type of aza-BH reaction is more sluggish than that of MVK under the same conditions, although high enantioselectivity could still be achieved.

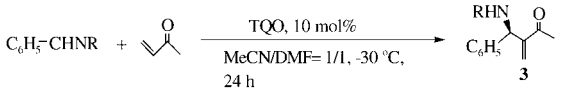
Table 5. Aza-Baylis–Hillman reactions of *N*-tosylated imines **1** (1.0 equiv) with ethyl vinyl ketone (2.0 equiv) in the presence of TQO (10 mol%).



Entry	Ar	1	Solvent	Time [h]	4	Yield [%][a]	*ee* [%]	Absolute configuration
1	C_6H_5	**1a**	MeCN	84	**4a**	42	86	*R*
2	C_6H_5	**1a**	THF	84	**4a**	49	55	*R*
3	C_6H_5	**1a**	DMF	48	**4a**	44	90	*R*
4	C_6H_5	**1a**	MeCN/DMF (1:1)	22	**4a**	54	94	*R*
5	*p*-MeC_6H_4	**1b**	MeCN/DMF (1:1)	41	**4b**	49	87[b]	*R*
6	*p*-FC_6H_4	**1e**	MeCN/DMF (1:1)	22	**4c**	54	84	*R*
7	*p*-ClC_{64}	**1m**	MeCN/DMF (1:1)	22	**4d**	46	82	*R*

[a] Yield of isolated product. [b] After one recrystallization from CH_2Cl_2/hexane, the *ee* can reach 99.9%.

Table 4. Aza-Baylis–Hillman reactions of other *N*-sulfonated imines **1** (1.0 equiv) with methyl vinyl ketone (2.0 equiv) in the presence of TQO (10 mol%).

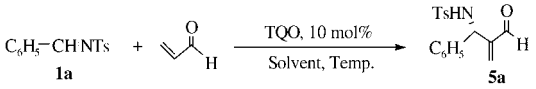


Entry	C_6H_5CH=NR	1	3	Yield [%][a]	*ee* [%]	Absolute configuration
1	C_6H_5CH=N–Ms	**1j**	**3a**	58	89[b]	–[c]
2	C_6H_5CH=N–Ns	**1k**	**3b**	0	–	–
3	4-MeC_6H_4CH=N–SES	**1l**	**3c**	71	80[b]	–[c]

[a] Yield of isolated product. [b] Determined by chiral HPLC. [c] The sign of specific rotation.

Reactions with acrolein, methyl acrylate, phenyl acrylate, α-naphthyl acrylate, and acrylonitrile: We found that the catalytic, asymmetric aza-BH reaction of *N*-tosylated imines **1** with acrolein proceeded smoothly in the presence of TQO. The solvent survey showed that THF was the best solvent for this reaction (Table 6). The *ee* achieved reached 85% in 58% yield at −25°C, and 72% in 71% yield at room tem-

Table 6. Aza-Baylis–Hillman reactions of *N*-(benzylidene)-4-methylbenzenesulfonamide **1a** (1.0 equiv) with acrolein (2.0 equiv) in the presence of TQO (10 mol%).

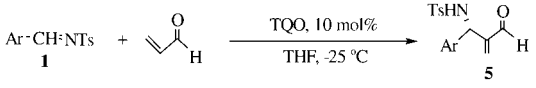


Entry	Solvent	Temp. [°C]	Time [h]	Yield of **5a**[%][a]	*ee* [%]	Absolute configuration
1	THF	−25	10	58	85	*S*
2[b]	THF	−25	24	57	85	*S*
3	CH_2Cl_2	−25	96	20	78	*S*
4	CH_3CN/DMF (1:1)	−25	4	24	71	*S*
5	THF	RT	4	71	72	*S*

[a] Yield of isolated product. [b] 0.25 mol% of TQO was employed.

perature (20°C), with an *S*-enriched configuration (Table 6, entries 1 and 5). In MeCN/DMF (1:1, v/v), the *ee* achieved was 71% at −25°C (Table 6, entry 4). This reaction is fairly effective in THF in the presence of TQO because a shorter reaction time is required than with MVK or EVK. Using 0.25 mol% TQO as a chiral nitrogen Lewis base, a similar result was obtained after 24 h (Table 6, entry 2). Under the optimized conditions, we next examined the aza–BH reaction of other *N*-tosylated imines **1** with acrolein (Table 7). The adducts **5b–f** were obtained in 83–89% *ee* with moderate to good yields (Table 7, entries 1–5.

Table 7. Asymmetric aza-Baylis–Hillman reaction of *N*-tosylated imines **1** with acrolein (2.0 equiv) in the presence of TQO (10 mol%).

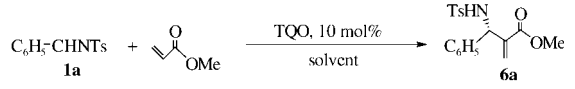


Entry	Ar	**1**	Time [h]	**5**	Yield [%][a]	*ee* [%]	Absolute configuration
1	*p*-MeC_6H_4	**1b**	20	**5b**	55	83	*S*
2	*p*-ClC_6H_4	**1e**	10	**5c**	62	87	*S*
3	*p*-FC_6H_4	**1m**	10	**5d**	61	88	*S*
4	*m*-ClC_6H_4	**1n**	4.5	**5e**	65	89	*S*
5	*p*-BrC_6H_4	**1o**	5	**5f**	72	89	*S*

[a] Yield of isolated product.

However, the reactions of *N*-tosylated imines **1** with methyl acrylate in MeCN/DMF (1:1, v/v) at −20°C, MeCN at room temperature, or DMF at 0°C were sluggish, and most *N*-tosylated imines decomposed during the reaction in DMF or MeCN (Table 8, entries 1–3). However, we had found previously that, with DABCO as a Lewis base in dichloromethane at 0°C, the reaction proceeded smoothly to give the adducts **6** in good yields.[5e] Moreover, in the presence of TQO, adduct **6a** was obtained with 67–83% *ee* in 60–65% yields with an *S*-enriched configuration in the reaction of **1a** with methyl acrylate in dichloromethane (Table 8, entries 4–7). At 0°C, the highest *ee* was achieved after 36 or 72 h. Similar enantioselectivity was obtained from this reaction at −20°C. For other *N*-tosylated imines **1** in the presence of TQO, products **6** were obtained in 58–87% yields

Table 8. Aza-Baylis–Hillman reactions of *N*-(benzylidene)-4-methylbenzenesulfonamide **1a** (1.0 equiv) with methyl acrylate (2.0 equiv) in the presence of TQO (10 mol%).

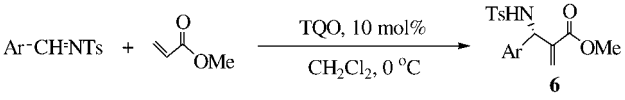


Entry	Solvent	Temp. [°C]	Time [h]	Yield of **6a** [%][a]	*ee* [%]	Absolute configuration
1	MeCN/DMF (1:1)	−20	24	NR[b]	–	–
2	MeCN	RT	72	33	52	*S*
3	DMF	0	36	–[c]	–	*S*
4	CH_2Cl_2	RT	55	60	67	*S*
5	CH_2Cl_2	0	72	62	83	*S*
6	CH_2Cl_2	0	36	60	83	*S*
7	CH_2Cl_2	−20	72	65	75	*S*

[a] Yield of isolated product. [b] No reaction. [c] Starting material imine **1a** decomposed.

with 70–83% *ee* (Table 9). *N*-Mesylated imine **1j** and *N*-nitrobenzenesulfonated imine **1k** produced the corresponding adducts **6j** and **6k** in the similar yields and *ee* (Table 9, entries 9 and 10). In general, this type of aza-BH reaction is relatively sluggish in comparison to that with MVK or acrolein.

Table 9. Aza-Baylis–Hillman reactions of *N*-sulfonated imines **1** (1.0 equiv) with methyl acrylate (2.0 equiv) in the presence of TQO (10 mol%).

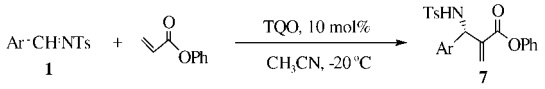


Entry	Ar	**1**	Time [h]	**6**	Yield [%][a]	*ee* [%]	Absolute configuration
1	C_6H_5	**1a**	72	**6a**	62	83	*S*
2	*p*-MeC_6H_4	**1b**	72	**6b**	67	80	*S*
3	*p*-EtC_6H_4	**1c**	72	**6c**	62	82	*S*
4	*p*-$MeOC_6H_4$	**1d**	72	**6d**	64	70	*S*
5	*p*-ClC_6H_4	**1e**	36	**6e**	60	77	*S*
6	*m*-FC_6H_4	**1f**	32	**6f**	87	83	*S*
7	*p*-$NO_2C_6H_4$	**1g**	35	**6g**	60	72	*S*
8	2,3-$Cl_2C_6H_3$	**1i**	38	**6i**	58	71	*S*
9	$C_6H_5CH{=}N{-}Ms$	**1j**	68	**6j**	72	77	*S*
10	$C_6H_5CH{=}N{-}Ns$	**1k**	72	**6k**	60	83	*S*

[a] Yield of isolated product.

Chen and co-workers reported previously that using phenyl acrylate, CH=CH−C(O)OPh, or α-naphthyl acrylate, CH=CH−C(O)O(α-Nap), as a Michael acceptor, the BH reaction with aldehydes can be significantly accelerated in the presence of DABCO (30 mol%).[8] Encouraged by this result, we exchanged methyl acrylate for the more reactive phenyl acrylate as a Michael acceptor (2.0 equiv) for the catalytic, asymmetric aza-BH reaction with *N*-sulfonated imines **1** (1.0 equiv). The solvent effects and reaction temperatures were first examined similarly to those described in Table 8. We found that the best conditions were reaction in acetonitrile at −20°C. The results with phenyl acrylate are summarized in Table 10. The adducts **7** were obtained with

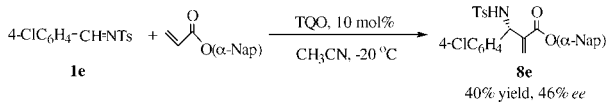
Table 10. Aza-Baylis–Hillman reactions of *N*-sulfonated imines **1** (1.0 equiv) with phenyl acrylate (2.0 equiv) in the presence of TQO (10 mol%).



Entry	Ar	1	Time [h]	7	Yield [%][a]	*ee* [%]	Absolute configuration
1	C_6H_5	**1a**	24	**7a**	67	74	*S*
2	*p*-MeC_6H_4	**1b**	72	**7b**	68	69	*S*
3	*m*-MeC_6H_4	**1c**	72	**7c**	84	74	*S*
4	*m*-FC_6H_4	**1f**	8	**7d**	83	82	*S*
5	*2,3*-$Cl_2C_6H_3$	**1i**	20	**7e**	81	67	*S*

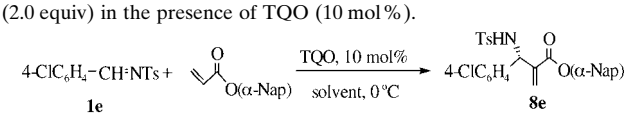
[a] Yield of isolated product.

67–82% *ee* in 67–84% yields (Table 10, entries 1–5). Using *N*-tosylated imine **1e** as substrate and α-naphthyl acrylate as a Michael acceptor under the same conditions, this reaction was sluggish and the corresponding adduct **8e** was obtained with 46% *ee* in 40% yield (Scheme 2). We examined this reaction at 0°C in various solvents; in MeCN for 12 h, 78% *ee* can be achieved in 67% yield (Table 11, entry 1). In DMF, the yield of **8e** reached 81% with 45% *ee* after 22 h (Table 11, entry 5). The mixed solvent did not improve the *ee* or yield (Table 11, entries 7 and 8). The best result was obtained in MeCN at 0°C. Under the optimized conditions, we also examined its general applicability to other *N*-sulfonated imines through the aza–BH reaction of **1a** with α-naphthyl acrylate (Scheme 3). Adduct **8a** was obtained in 85% yield with 80% *ee*. In general, similar results to that



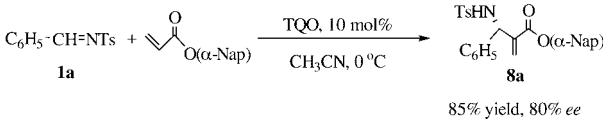
Scheme 2. Catalytic, asymmetric aza-Baylis–Hillman reaction of *N*-sulfonated imine **1e** (1.0 equiv) with α-naphthyl acrylate (2.0 equiv).

Table 11. Aza-Baylis–Hillman reactions of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** (1.0 equiv) with α-naphthyl acrylate (2.0 equiv) in the presence of TQO (10 mol%).



Entry	Solvent	Time [h]	Yield of **8e** [%][a]	*ee* [%]	Absolute configuration
1	MeCN	12	67	78	S
2	THF	17	65	72	*S*
3	CH_2Cl_2	22	46	73	*S*
4	dioxane	21	77	56	*S*
5	DMF	22	81	45	*S*
6	acetone	47	64	65	*S*
7	DMF/CH_2Cl_2 (1:1)	12	72	70	*S*
8	DMF/MeCN (1:1)	12	65	74	*S*

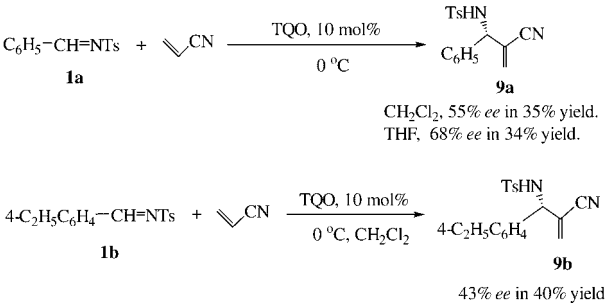
[a] Yield of isolated product.



Scheme 3. Catalytic, asymmetric aza-Baylis–Hillman reaction of *N*-sulfonated imine **1a** (1.0 equiv) with α-naphthyl acrylate (2.0 equiv).

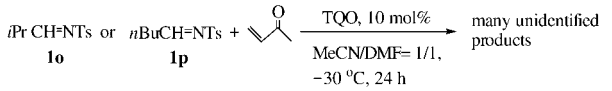
for phenyl acrylate were obtained in the reaction of *N*-sulfonated imines **1** with α-naphthyl acrylate.

In addition, aza-BH reaction of **1a** with acrylonitrile afforded adduct **9a** in 35% yield with 55% *ee* in CH_2Cl_2, and in 34% yield with 68% *ee* in THF, under the same conditions as for methyl acrylate. Another *N*-tosylated imine, **1b**, gave a similar result (Scheme 4).



Scheme 4. Aza-Baylis–Hillman reaction of *N*-(benzylidene)-4-methylbenzenesulfonamide **1a** (1.0 equiv) with acrylonitrile (2.0 equiv).

To extend the scope and explore the limitations of this novel reaction, we tried to synthesize aliphatic *N*-tosylated imines as starting materials. However, we found that many of these are very labile, even when stored below −20°C. We used literature procedures to prepare the aliphatic *N*-tosylated imines **1o** and **1p**,[9] which must be used immediately for the reaction. The attempted catalytic, asymmetric aza-BH reaction of **1o** and **1p** with MVK in the presence of TQO under the same conditions gave many unidentified products, and the aza-BH adduct was not formed (Scheme 5).



Scheme 5. Aza-Baylis–Hillman reaction of aliphatic imines with MVK in the presence of TQO (10 mol%).

In this systematic investigation of the aza-BH reaction of *N*-sulfonated imines **1** with the simplest Michael acceptors such as MVK, EVK, acrolein, methyl acrylate, and acrylonitrile, and with sterically large Michael acceptors such as phenyl acrylate and α-naphthyl acrylate, moderate to excellent enantioselectivities have been achieved, depending on the Michael acceptors employed. The reaction rate and the *ee* achieved are fairly sensitive to the solvents and reaction

temperatures employed. Careful examination of these conditions is required to achieve higher yields and *ee* values.

Determination of absolute configuration: The absolute configuration of adducts **2**, which have negative specific rotation, recrystallized from dichloromethane and hexane, was found by X-ray diffraction to be *R*-enriched (Supporting Information).[5d] The absolute configuration of adducts **3** and **4**, which also have negative specific rotation, can be assigned as *R*-enriched by comparison of their sign of specific rotation with those we reported previously.[5d,h] We found adducts **5** and **6** to have positive specific rotation and their absolute configurations can be assigned as *S*-enriched by comparison of their sign of specific rotation with those reported by Hatakeyama.[2g,5h] It is therefore necessary to determine their absolute configurations unambiguously. We attempted to determine the absolute configuration of **6** by X-ray diffraction similarly to the adduct **2e**. The single crystal of **6d** was indeed obtained by recrystallization from dichloromethane and hexane (1:4, v/v). However, the X-ray data indicated that the crystal structure of **6d** (Figure 2) is a racemate (see Supporting Information). Our careful examination revealed that recrystallization of adducts **6**, **7**, and **8** with a variety of solvents, such as toluene, ethyl acetate, dichloromethane, and acetonitrile, lead to a decrease in *ee* in the resulting crystals and an increase in *ee* in the mother liquors. Therefore, adducts **6**, **7**, and **8** could not be recrystallized to an enantiopure form, and it is impossible to determine their absolute configurations by X-ray diffraction. To clarify this interesting inversion of stereochemistry further, the absolute configurations of **5**–**7** were confirmed unambiguously to be *S*-enriched by the method reported by Li and Hatakeyama,[2g,10] namely, by transforming the products to the corresponding phenylglycine derivatives and comparing them to authentic samples prepared from (*R*)-phenylglycine (Scheme 6).[11] The absolute configurations of adducts **8** and **9** have been assigned as *S*-enriched by the same method (Scheme 6).

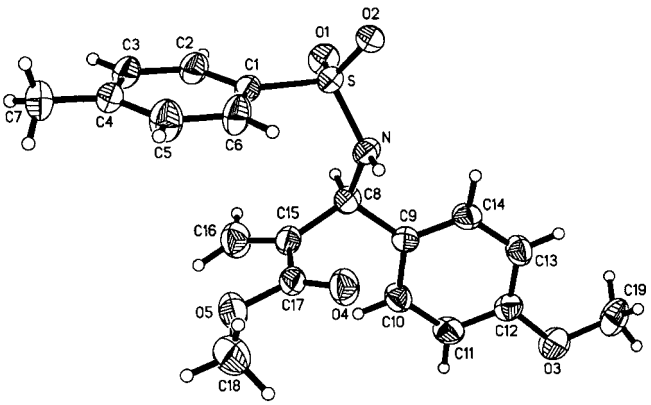
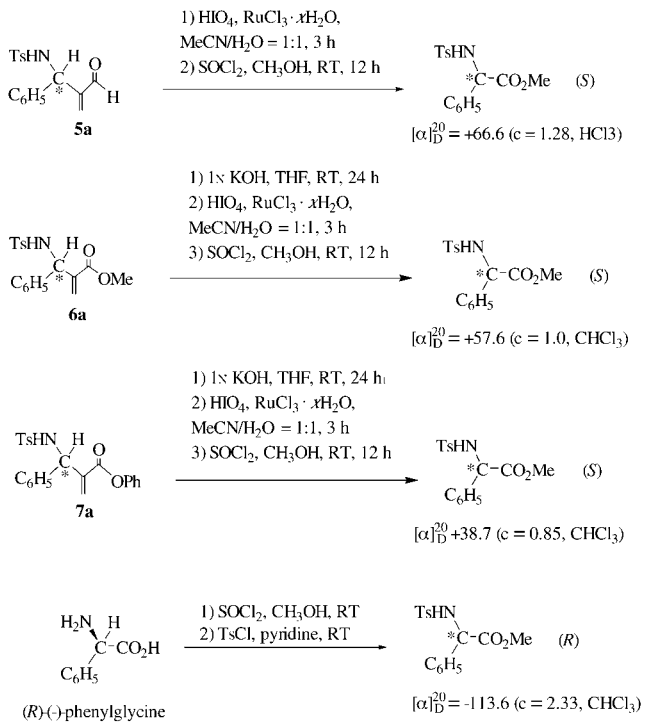
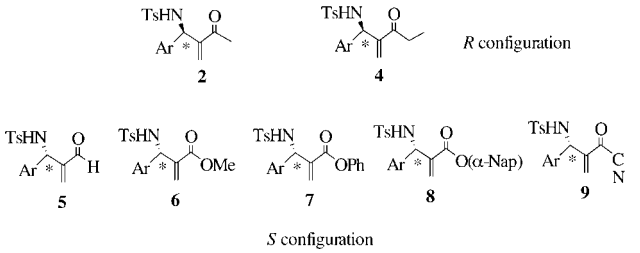


Figure 2. Crystal structure of **6d** (ORTEP drawing).



Scheme 6. Determination of absolute configuration of **5**–**8**.

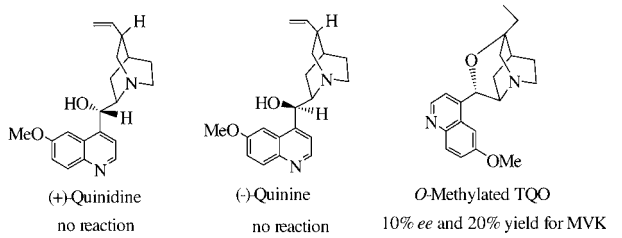


Scheme 7. The absolute configuration of adducts.

We have elucidated this inversion of absolute configuration; Scheme 7 shows that if the Michael acceptors have α-protons, the adducts are produced in *R*-enriched configuration, and otherwise the configuration is *S*-enriched. This result suggests that the steric bulkiness of activated olefins may play a key role in the resulting absolute stereochemistry of the adducts in this reaction.

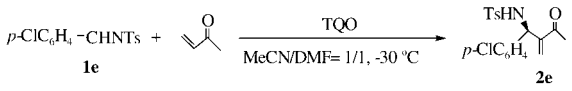
Mechanistic explanation: (+)-Quinidine or (−)-quinine showed no catalytic activity for this reaction. The hydroxyl group on the quinolyl ring is also crucial, because the reaction became sluggish and gave the product with only about 10% *ee* in very low yield when *O*-methylated TQO was used as the chiral Lewis base (Scheme 8). Thus, the structure of the Lewis base plays an important role in this reaction.

We further confirmed that when 10–30 mol% TQO was used in the aza-BH reaction of **1e** with MVK, the adducts **2e** were formed with similar *ee* values (Table 12). In the reaction of **1e** with methyl acrylate, similar results were obtained. This result suggests that this asymmetric aza–BH reaction catalyzed by chiral nitrogen Lewis base TQO is a unimolecular process.



Scheme 8. Catalytic activity in the aza-BH reaction.

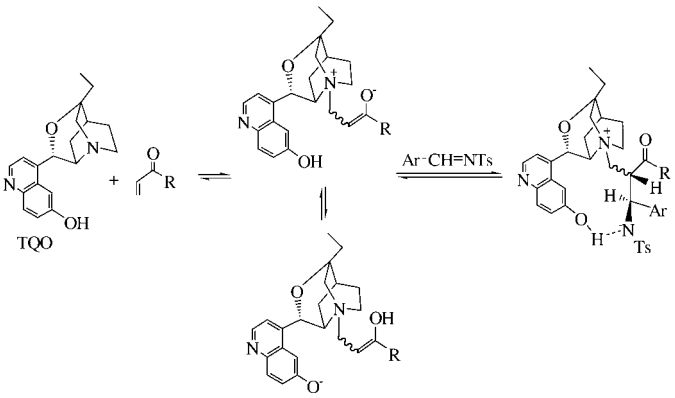
Table 12. Aza-Baylis–Hillman reactions of *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide **1e** (1.0 equiv) with methyl vinyl ketone in the presence of TQO (10–30 mol %).



Entry	TQO [mol %]	Yield of **2e** [%][a]	*ee* [%]	Absolute configuration
1	10	77	93	R
2	15	78	92	*R*
3	20	75	93	*R*
4	30	76	93	*R*

[a] Yield of isolated product.

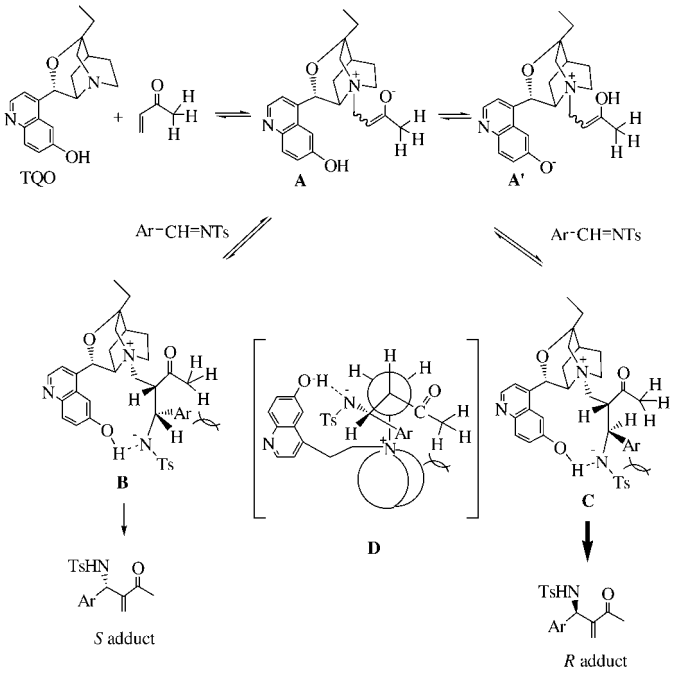
A key intermediate of the reaction (Scheme 9) is based on the mechanism proposed by Hatakeyama and on our own results reported above.[2c,g] We believe that the key



Scheme 9. Key intermediate for the catalytic, asymmetric aza-Baylis–Hillman reaction of *N*-sulfonated imines with activated olefins.

factor is the intramolecular hydrogen bonding between the phenolic OH group and the nitrogen-centered anion, stabilized by a sulfonyl group to give a relatively rigid transition state in this reaction.

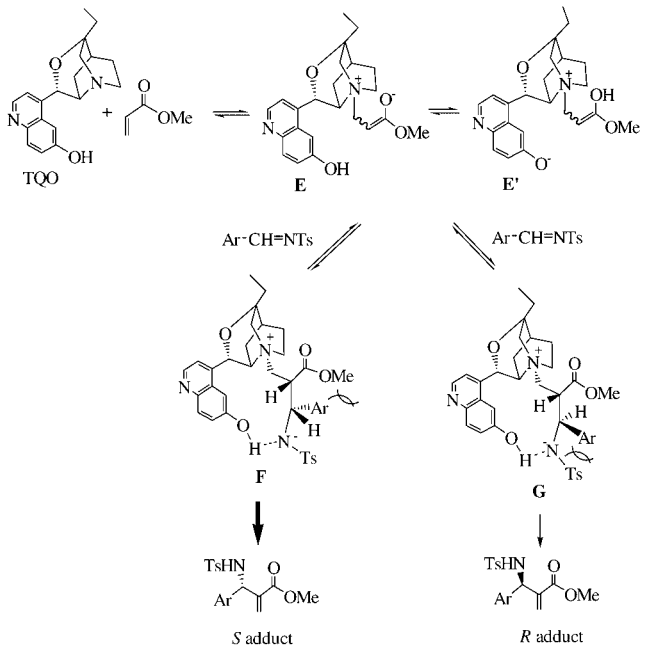
The following mechanistic explanation could rationalize the outcome of the absolute configuration of the adducts (Schemes 10 and 11). Michael addition of TQO to a α,β-unsaturated ketone or ester gives enolate **A** equilibrated with enol **A′**, or **E** equilibrated with enol **E′**, which in turn undergoes Mannich reaction with *N*-sulfonated imine to furnish an equilibrium mixture of several diastereomers. For Michael acceptors MVK and EVK, two betaine intermediates **B** and **C** are in an equilibrium which is stabilized by intramolecular hydrogen bonding between the amidate ion and the phenolic OH, and are nearly ideal for the subsequent E2 or E1cb elimination for stereoelectronic reasons,[2c,g] as indicated in Newman projection **D** (Scheme 10) according



Scheme 10. A plausible reaction mechanism for the catalytic, asymmetric aza-Baylis–Hillman reaction of imines with MVK.

to the generally accepted mechanism of the BH reaction,[1,3] which was strongly consolidated by Santos's findings based on an ESI/MS/MS spectroscopic investigation recently.[12] Since MVK and EVK have α-protons in their structures, they are sterically larger than methyl acrylate (OMe) and phenyl acrylate (OPh).[13] The intermediate **B** suffers from severe steric interactions between the Ar and the methyl group in the MVK and TQO moieties (Newman projection **D**). On the other hand, intermediate **C** has only the steric interaction between the aromatic group and the *N*-sulfonated group (Scheme 10). Conversely, the intermediate **C** suffers from fewer steric interactions. Therefore, intermediate **C** undergoes facile elimination to furnish *R*-enriched adducts and regenerates the nitrogen Lewis base.

For Michael acceptors acrolein, methyl acrylate, phenyl acrylate, α-naphthyl acrylate, and acrylonitrile, which do not have α-protons, the ammonium enolate **E** formed reacts with *N*-sulfonated imines to give two betaine intermediates **F** and **G** in a similar equilibrium through Mannich reaction; these are stabilized by intramolecular hydrogen bonding between the amidate ion and the phenolic OH group (Scheme 11). Since methyl acrylate and phenyl acrylate do not have α-protons in their structures, they are sterically smaller than MVK and EVK.[13] The steric interaction of the



Scheme 11. A plausible reaction mechanism for the catalytic, asymmetric aza-Baylis–Hillman reaction of N-sulfonated imines with methyl acrylate.

N-sulfonated group with the aromatic group in this stabilized transition state **G** is more severe than that of the ester moiety and aromatic group in intermediate **F**, and causes the formation of the aza–BH adduct with an *S* configuration.[2c,g]

Overall, we believe that TQO acts as a bifunctional chiral ligand promoter in this reaction.[14] The nitrogen atom in the quinuclidine moiety acts as a Lewis base (LB) to initiate the BH reaction and the phenolic OH group acts as a Lewis acid through hydrogen bonding (BA = Brønsted acid as a Lewis acid) to stabilize the key enolate intermediate and the reaction intermediate. Thus, this is an LBBA bifunctional chiral ligand catalytic system. The key factor is the intramolecular hydrogen bonding between the phenolic OH and the nitrogen anion stabilized by the sulfonyl group. Moreover, the use of *N*-sulfonated imines, instead of aldehydes, can drive the reaction forward and perhaps cut down on the reversibility shown in Schemes 9–11 which usually erodes the enantioselectivity in the BH reaction.

We have achieved the highest *ee* values so far for the aza–BH reaction involving MVK, EVK, acrolein, methyl acrylate, phenyl acrylate, or α-naphthyl acrylate as a Michael acceptor. Moreover, this is the first case of a highly enantioselective aza-Baylis–Hillman reaction of imines with α,β-unsaturated ketones or esters to be reported. An interesting inversion of stereochemistry between MVK or EVK and acrolein, methyl acrylate, phenyl acrylate, or α-naphthyl acrylate has been revealed. A plausible mechanism has been proposed on the basis of previous reports and our own results. Continuing efforts are under way to elucidate the mechanistic details of this reaction and to discover its scope and limitations.

Experimental Section

General: Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J* values are in Hz. Mass spectra were recorded with an HP-5989 instrument. *N*-Tosylimines were prepared according to the literature.[15] All the solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo-Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 200–300-mesh silica gel at increased pressure. The optical purities of the BH adducts were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. Chiralcel OD, AS and OJ; eluent, hexane/2-propanol (95:5, v/v); flow rate, 1.0 mL min^{-1}; detection, 254 nm light). The absolute configuration of the major enantiomer of **2e**, recrystallized from dichloromethane/hexane (1:4, v/v), was determined from its X-ray crystal structure and the others were subsequently assigned by comparing the sign of the specific rotation with that of an authentic sample.

Typical reaction procedure for TQO-catalyzed aza-Baylis–Hillman reaction of methyl vinyl ketone with *N*-(*p*-ethylbenzenesulfonyl)benzaldimine 1c: To a solution of **1c** (72 mg, 0.25 mmol) and TQO (8.0 mg, 0.025 mmol) in CH_3CN/DMF (1:1, v/v) (1.0 mL) was added methyl vinyl ketone (41 μL, 0.5 mmol) at −30 °C. The reaction mixture was stirred at −30 °C for 24 h. After the reaction was completed, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2; eluent, EtOAc/petroleum ether, 1:5, v/v) to yield **2c** (66 mg, 74 %) as a colorless solid.

***N*-[1-(4-Ethylphenyl)-2-methylene-3-oxobutyl]-4-methylbenzenesulfonamide (2c)**: Yield 66 mg (74 %); colorless solid (96 % *ee*), m.p. 114–115 °C; $[\alpha]_D^{25} = -46.9°$ (c = 1.00 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 1.23 (t, ^3J(H,H) = 7.6 Hz, 3H; Me), 2.15 (s, 3H; Me), 2.39 (s, 3H; Me), 2.54 (q, ^3J(H,H) = 7.6 Hz, 2H; CH_2), 5.20 (d, ^3J(H,H) = 8.4 Hz, 1H; NH), 5.51 (d, ^3J(H,H) = 8.4 Hz, 1H; CH), 6.09 (s, 2H), 6.97 (d, ^3J(H,H) = 6.1 Hz, 2H; Ar), 6.98 (d, ^3J(H,H) = 6.1 Hz, 2H; Ar), 7.21 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar), 7.63 (d, ^3J(H,H) = 8.4 Hz, 2H; Ar); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ = 15.51, 21.42, 26.25, 28.29, 58.29, 126.44, 127.22, 127.89, 129.08, 129.38, 136.09, 137.44, 143.16, 143.54, 146.66, 198.26; IR ($CHCl_3$): $\tilde{\nu}$ = 1674 cm^{-1} (C=O); MS (70 eV): *m/z* (%): 358 (0.5) [M^++1], 288 (5.6) [M^+−69], 202 (100) [M^+−155]; elemental analysis calcd (%) for $C_{20}H_{23}NO_3S$: C 67.20, H 6.49, N 3.92; found: C 67.04, H 6.42, N 3.74.

HPLC conditions: OD-H column, 25 °C, 2-propanol/*n*-hexane = 3:97 (v/v), 1.0 mL min^{-1}, major peak: 43.22 min; minor peak: 50.06 min.

Typical reaction procedure for TQO-catalyzed aza-Baylis–Hillman reaction of methyl acrylate with *N*-benzenesulfonyl benzaldimine 1a: To a solution of **1a** (130 mg, 0.5 mmol) and TQO (16 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added methyl acrylate (90 μL, 1 mmol) at 0 °C. The reaction was stirred at 0 °C for 36 h. After the reaction was completed, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2; eluent, EtOAc/petroleum ether, 1:5, v/v) to yield **6a** (107 mg, 62 %) as a colorless solid.

Methyl 2-[phenyl(toluene-4-sulfonylamino)methyl]acrylate (6a): Yield 107 mg, 62 %; colorless solid (83 % *ee*); m.p. 76–78 °C; $[\alpha]_D^{25} = +19.5°$ (c = 0.88 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ = 2.40 (s, 3H; Me), 3.60 (s, 3H; Me), 5.29 (d, ^3J(H,H) = 9.2 Hz, 1H; NH), 5.65 (d, ^3J(H,H) = 9.2 Hz, 1H; CH), 5.83 (s; 1H), 6.22 (s; 1H), 7.13–7.18 (m, 2H; Ar), 7.21–7.33 (m, 5H; Ar), 7.67 (d, ^3J(H,H) = 8.6 Hz, 2H; Ar); ^{13}C NMR ($CDCl_3$, TMS, 75.4 MHz): δ = 21.4, 51.8, 58.6, 126.4, 127.0, 127.5, 127.6, 128.4, 129.3, 137.4, 138.4, 138.5, 143.2, 165.6; IR ($CHCl_3$): $\tilde{\nu}$ = 1708 cm^{-1} (C=O), 1633 cm^{-1} (C=C); MS (70 eV): *m/z* (%): 314 (1.94) [M^+−31], 190 (100.00) [M^+−155], 155 (67.94) [$MeC_6H_4SO_2^+$]; HRMS: calcd for $C_{17}H_{16}NO_3S$: 314.0859 [M^+−OCH_3]; found: 314.0890; elemental analysis calcd (%) for $C_{18}H_{19}NO_4S$: C 62.59, H 5.54, N 4.06; found: C 62.57, H 5.68, N 3.92.

HPLC conditions: AS column, 25 °C, 2-propanol/*n*-hexane = 40:60 (v/v), 0.6 mL min^{-1}; major peak: 20.90 min; minor peak: 25.91 min.

Acknowledgements

We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology, and the National Natural Science Foundation of China for financial support (20025206, 203900502, and 20272069).

[1] For reviews, see: a) D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001–8062; b) S. E. Drewes, G. H. P. Roo, *Tetrahedron* **1988**, *44*, 4653–4670; c) E. Ciganek, *Org. React.* **1997**, *51*, 201–350; d) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–892.

[2] a) A. G. M. Barrett, A. S. Cook, A. Kamimura, *Chem. Commun.* **1998**, 2533–2534; b) N. T. McDougal, S. E. Schaus, *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095; c) Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220; d) K.-S. Yang, W.-D. Lee, J.-F. Pan, K.-M. Chen, *J. Org. Chem.* **2003**, *68*, 915–919; e) J. E. Imbriglio, M. M. Vasbinder, S. J. Miller, *Org. Lett.* **2003**, *5*, 3741–3743. Other references: f) P. Langer, *Angew. Chem.* **2000**, *112*, 3177–3180; *Angew. Chem. Int. Ed.* **2000**, *39*, 3049–3052; g) S. Kawahara, A. Nakano, T. Esumi, Y. Iwabuchi, S. Hatakeyama, *Org. Lett.* **2003**, *5*, 3103–3105 (in this paper, Hatakeyama has pointed out that *S*-enriched ester should have a plus sign on the specific rotation); h) P. R. Krishna, V. Kannan, P. V. N. Reddy, *Adv. Synth. Catal.* **2004**, *346*, 603–606; i) Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589–5594; j) K. S. Yang, K.-M. Chen, *Org. Lett.* **2000**, *2*, 729–732. Alternative approaches for asymmetric Baylis–Hillman reactions: k) L. J. Brzezinski, S. Refel, J. W. Leahy, *J. Am. Chem. Soc.* **1997**, *119*, 4317–4318; l) T. Hayase, T. Shibata, K. Soai, Y. Wakatsuki, *Chem. Commun.* **1998**, 1271–1272; m) Y. M. A. Yamada, S. Ikegami, *Tetrahedron Lett.* **2000**, *41*, 2165–2169.

[3] a) A. B. Baylis, M. E. D. Hillman, *Ger. Offen.* **1972**, *2*, 155113; *Chem. Abstr.* **1972**, *77*, 34174q; M. E. D. Hillman, A. B. Baylis, US 3743669, **1973** b) K. Morita, Z. Suzuki, H. Hirose, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815–2815.

[4] a) M. Shi, J.-K. Jiang, Y.-S. Feng, *Org. Lett.* **2000**, *2*, 2397–2400; b) M. Shi, Y.-S. Feng, *J. Org. Chem.* **2001**, *66*, 406–411; c) M. Shi, J.-K. Jiang, S.-C. Cui, Y.-S. Feng, *J. Chem. Soc. Perkin Trans. 1* **2001**, 390–393; d) M. Shi, J.-K. Jiang, *Tetrahedron* **2000**, *56*, 4793–4797; e) M. Shi, C.-Q. Li, J.-K. Jiang, *Chem. Commun.* **2001**, 833–834; f) M. Shi, L. H. Chen, *Chem. Commun.* **2003**, 1310–1311.

[5] a) M. Shi, Y.-M. Xu, *Chem. Commun.* **2001**, 1876–1877; b) M. Shi, Y.-M. Xu, *Eur. J. Org. Chem.* **2002**, 696–701; c) M. Shi, Y.-M. Xu, G.-L. Zhao, X.-F. Wu, *Eur. J. Org. Chem.* **2002**, 3666–3679; d) M. Shi, Y.-M. Xu, *Angew. Chem.* **2002**, *114*, 4689–4692; *Angew. Chem. Int. Ed.* **2002**, *41*, 4507–4510; e) Y.-M. Xu, M. Shi, *J. Org. Chem.* **2004**, *69*, 417–425; f) M. Shi, Y. M. Xu, *J. Org. Chem.* **2003**, *68*, 4784–4790; g) G. L. Zhao, J. W. Huang, M. Shi, *Org. Lett.* **2003**, *5*, 4737–4739; h) M. Shi, L. H. Chen, *Chem. Commun.* **2003**, 1310–1311; i) Baylis–Hillman reaction of methyl acrylate with imines: P. Perlmutter, C. C. Teo, *Tetrahedron Lett.* **1984**, *25*, 5951–5952; j) M. Takagi, K. Yamamoto, *Tetrahedron* **1991**, *47*, 8869–8882; k) Baylis–Hillman reaction of MVK with imine generated in situ: S. Bertenshaw, M. Kahn, *Tetrahedron Lett.* **1989**, *30*, 2731–2732; l) D. Balan, H. Adolfsson, *J. Org. Chem.* **2002**, *67*, 2329–2334, and references therein.

[6] The catalyst TQO was first prepared by Hoffmann and von Riesen. See: C. von Riesen, H. M. R. Hoffmann, *Chem. Eur. J.* **1996**, *2*, 680–684.

[7] Crystal data of **2e**: empirical formula: $C_{18}H_{18}ClNO_3S$; formula weight: 363.84; temperature: 293(2) K; crystal system: monoclinic; space group: $P2_1$; unit cell dimensions: a = 8.513(3), b = 12.076(4), c = 9.767(3) Å, β = 112.259(6)°, V = 929.3(5) Å^3; Z = 2; ρ_{calcd} = 1.300 mg m^{-3}; F_{000} = 380; final R indices [$I>2\sigma(I)$]: R_1 = 0.0475, R_2 = 0.0833. Crystal data of **6d**: empirical formula: $C_{19}H_{21}NO_5S$; formula weight: 375.43; temperature: 293(2) K; crystal system: triclinic; space group: $P\bar{1}$; unit cell dimensions: a = 9.0701(10), b = 10.2182(12), c = 11.4286(13) Å, α = 83.630(2)°, β = 70.883(2)°, γ = 68.598°, V = 931.74(18) Å^3; Z = 2; ρ_{calcd} = 1.338 mg m^{-3}; F_{000} = 396; final R indices [$I>2\sigma(I)$]: R_1 = 0.0489, R_2 = 0.0716. CCDC-167239 (**2e**) and CCDC-172329 (**6d**) 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.

[8] W. D. Lee, K. S. Yang, K.-M. Chen, *Chem. Commun.* **2001**, 1612–1613.

[9] F. Chemla, V. Hebbe, J. F. Normant, *Synthesis* **2000**, *1*, 75–77.

[10] a) G. Li, H. X. Wei, B. R. Whittlesey, N. N. Batrice, *J. Org. Chem.* **1999**, *64*, 1061–1065; b) K. L. Reddy, K. B. Sharpless, *J. Am. Chem. Soc.* **1998**, *120*, 1207–1217.

[11] K. Kobayashi, T. Okamoto, T. Oida, S. Tanimoto, *Chem. Lett.* **1986**, 2031–2032.

[12] L. S. Santos, C. H. Pavam, W. P. Almeida, F. Coelho, M. N. Eberlin, *Angew. Chem.* **2004**, *116*, 4430–4433; *Angew. Chem. Int. Ed.* **2004**, *43*, 4330–4333.

[13] This steric effect imposed by the larger Me substituent is consistent with the *A* value reported for OMe, OPh, and Me groups (0.75, 0.65, and 1.74, respectively). See: E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, **1994**, pp. 696–697.

[14] Bifunctional chiral ligands: a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942–1944; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871–1873; b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178; c) M. Takamura, Y. Hamanashi, H. Usuda, M. Kanai, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 1716–1718; *Angew. Chem. Int. Ed.* **2000**, *39*, 1650–1652.

[15] B. E. Love, P. S. Raje, T. C. Williams, *Synlett* **1994**, 493–494.

Received: August 25, 2004
Revised: November 28, 2004
Published online: January 25, 2005