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Enantioselective Aza-Morita–Baylis–Hillman Reaction Using Aliphatic α-Amidosulfones as Imine Surrogates

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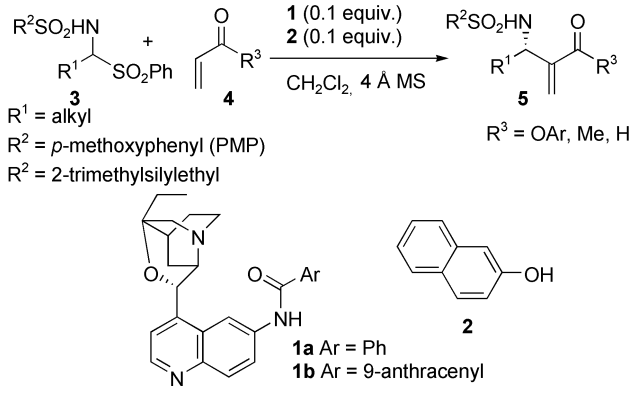
Abstract: The bifunctional catalyst 6′-deoxy-6′-acylamino-β-isocupreidine (**1**) served both as a base to trigger the in situ generation of *N*-sulfonylimine from readily available α-amidosulfones and as a chiral nucleophile to initiate the enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction. α-Methylene-β-amino-β-alkyl carbonyl compounds, difficultly accessible previously, can now be synthesized in excellent yields and enantioselectivities.

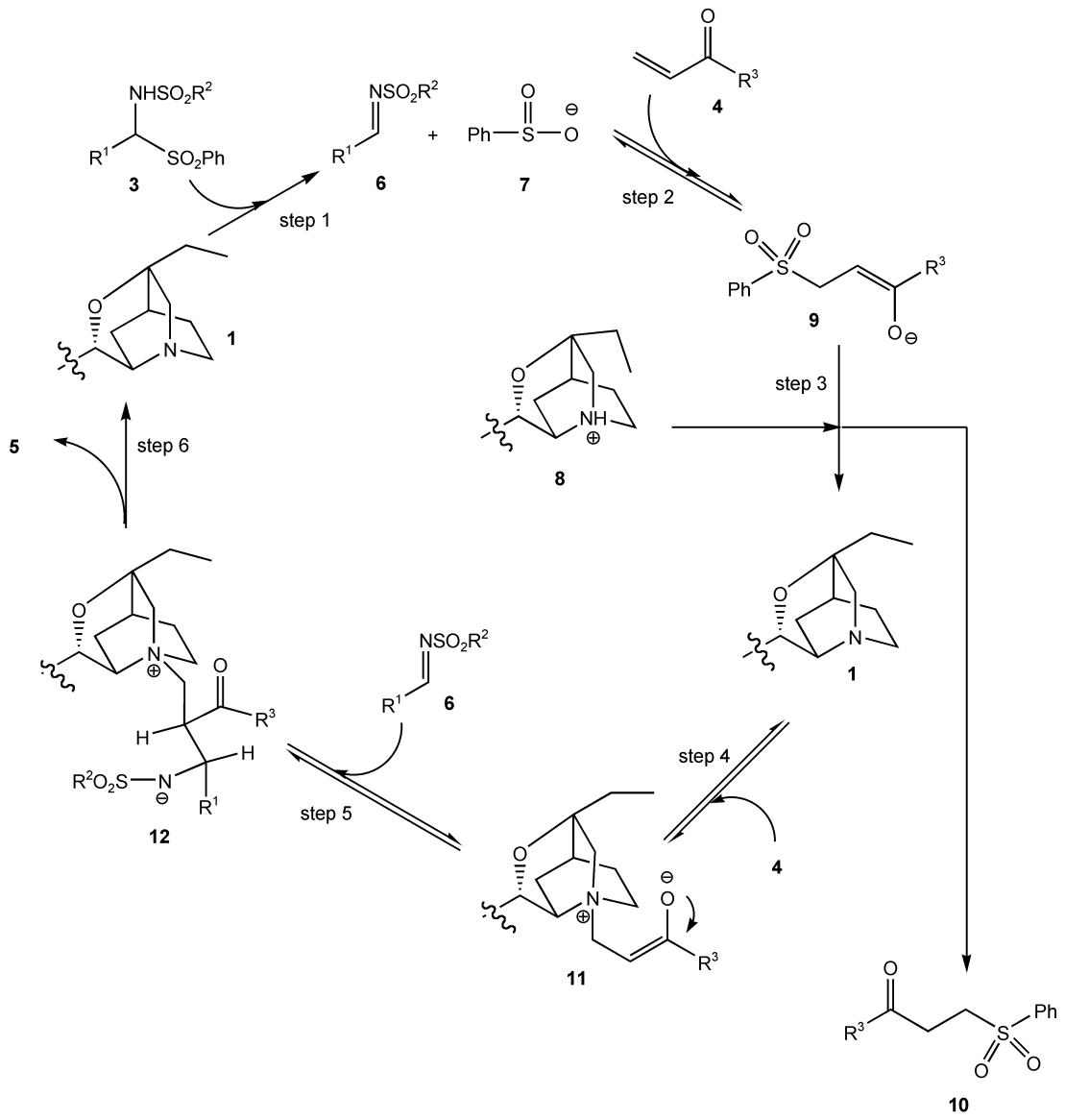
Keywords: α-amidosulfones; asymmetric synthesis; aza-Morita–Baylis–Hillman reaction; bifunctional organocatalysis; β-isocupreidine; organocatalysis

The aza-Morita–Baylis–Hillman (aza-MBH) reaction is a powerful tool for the preparation of synthetically useful α-methylene-β-amino carbonyl compounds.[1] Although significant progress has been made in this field,[2–6] the development of a catalytic asymmetric aza-MBH reaction with aliphatic imines has proven to be challenging. One of the main problems associated with the use of enolizable imines is their instability under aza-MBH conditions due to imine-enamine tautomerization and their subsequent side reactions. Indeed, degradation of aliphatic imines was observed under most of the reported catalytic conditions.[3b,d,k,4d,6] We recently described a dual catalyst system involving 6′-deoxy-6′-acylamino-β-isocupreidine (**1**) and the β-naphthol (**2**) that was able to convert aliphatic imines to the corresponding aza-MBH adducts (Scheme 1).[7] Although the enantioselectivity was excellent, the yield remained moderate at best. As a continuation of this research program, we assumed that generating the imine *in situ* under conditions conducive to the aza-MBH reaction could be a solution to the problem. Herein, we report the development of a catalytic asymmetric aza-MBH reaction between aliphatic *N*-sulfonyl-α-amidosulfones **3** and various Michael acceptors (MA, **4**) in the presence of a catalytic amount of **1** and **2** to afford the aza-MBH adducts (**5**) in excellent yields and enantioselectivities (Scheme 1). In this catalytic process, catalyst **1** served both as a base to trigger the formation of *N*-sulfonylimine and then as a nucleophile to catalyze the aza-MBH reaction.

The α-amidosulfones are known to be valuable precursors of imines.[8–9] Recently, the combination of proline catalysis with an excess of inorganic base has been exploited for the development of enantioselective aza-MBH reactions using aromatic α-amidosulfones as imine surrogates.[10] Since the β-isocupreidine derivative **1** having a tertiary amine could be considered as a base in addition to its nucleophilicity, we thought that it might be possible to develop a catalytic aza-MBH reaction using α-amidosulfones as substrates. The underlying principle is depicted in Scheme 2. Thus, catalyst **1** would act first as a base to convert **3** into *N*-sulfonylimine **6** and benzenesulfinate **7**. Michael addition of **7** to MA **4** would furnish the enolate **9**, which could in turn abstract a proton from



Scheme 1. Enantioselective aza-MBH reaction of α-amidosulfones.

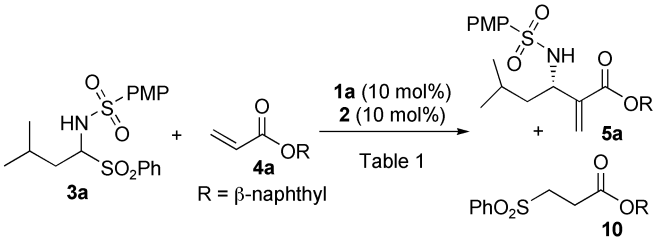


Scheme 2. α-Amidosulfones **6** as latent sulfonylimines in β-ICD-amide-catalyzed aza-MBH reaction: a postulated catalytic cycle.

the protonated catalyst **8** to afford the Michael adduct **10** with concurrent regeneration of catalyst **1**. The *in situ* generated imine and remaining MA would then enter into the aza-MBH reaction manifold in the presence of bifunctional catalyst **1** to provide the adduct **5** *via* intermediates **11** and **12**.[10] It is conceivable that **1** may undergo Michael addition to **4** (step 4), before it acted as a base, to generate **11** that could undergo a Rauhut–Currier-type reaction in the absence of electrophilic imine species.[11] However, we assumed that the reversibility of step 4 and the irreversible nature of step 1 would guarantee the successful generation of imine **6**, hence the overall domino process.[12] In addition, the fact that imine **6** is generated gradually *in situ* could potentially avoid side reactions associated with the instability of imine **6**, increasing consequently the yield of aza-MBH adduct **5**. The inclusion of achiral β-naphthol **2** was thought to increase the enantioselectivity of the aza-MBH reaction in accord with our earlier observations.[7]

To validate this hypothesis, we carried out the aza-MBH reaction of *N*-*p*-methoxybenzenesulfonyl-α-amidosulfone **3a** with β-naphthyl acrylate **4a** in the presence of a catalytic amount of 6′-deoxy-6′-benzamido-β-isocupreidine **1a** (Ar = Ph) and β-naphthol **2** (Table 1). At room temperature, the reaction of **3a** with two equivalents of **4a** provided indeed the desired product **5a** in 44% yield with 88% *ee*, along with ethyl 3-phenylsulfonylpropionate (**10**) in quantitative yield based on **3a** (*cf.* Supporting Information). By increasing the amount of Michael acceptor **4a** to 3 equivalents, the yield of **5a** increased significantly

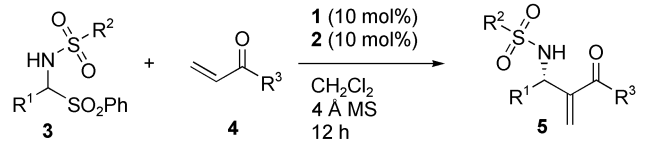
Table 1. Optimization of reaction conditions.



Entry[a]	**4a** [equiv.]	*T* [°C]	Additive	Yield [%][b]	*ee* [%]
1	2	r.t.	–	44[a]	88[a]
2	3	r.t.	–	71[a]	89[a]
3	3	r.t.	$NaHCO_3$	53[a]	88[a]
4	3	r.t.	4 Å MS	86[a]	90[a]
5	3	10	4 Å MS	>99 (57)[e]	92(87)[e]
6	3	10	4 Å MS	41[f]	77[f]

[a] *Reaction conditions:* **3a/1a/2** = 1/0.1/0.1 in CH_2Cl_2 (*c* 0.35).
[b] Isolated yield after column chromatography.
[c] Determined by chiral HPLC analysis.
[d] The absolute configuration of **4a** was determined to be (*S*)-enriched. For details see Supporting Information.
[e] Starting from imine.
[f] In the absence of β-naphthol (**2**).

Table 2. Enantioselective aza-MBH reaction with representative aliphatic *N*-sulfonyl-α-amidosulfones.



R^2 = *p*-methoxyphenyl
R^2 = 2-trimethylsilylethyl

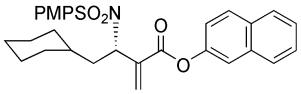
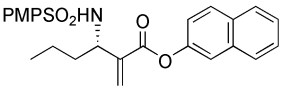
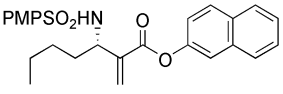
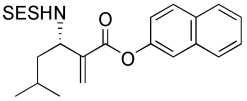
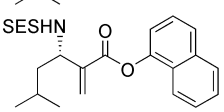
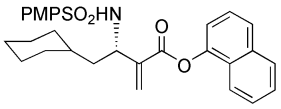
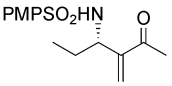
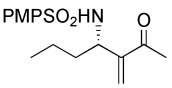
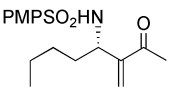
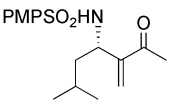
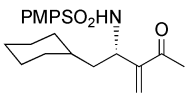
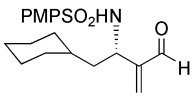
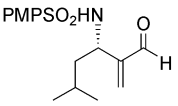
Entry[a]	Product **5**		Yield [%][d]	*ee* [%][e]
1[b]		**5b**	95	91
2[b]		**5c**	70	92
3[b]		**5d**	67	92
4[b]		**5e**	>99	91
5[b]		**5f**	88	94

Table 2. (Continued)

Entry[a]	Product **5**		Yield [%][d]	*ee* [%][e]
6[b]		**5g**	75	93
7[c]		**5h**	63	91
8[c])		**5i**	91	91
9[c]		**5j**	78	92
10[c]		**5k**	93 (47)[f]	93 (−18)[f]
11[c]		**5l**	86	90
12[b]		**5m**	54	86
13[b]		**5n**	56	87

[a] *Reaction conditions:* **3/4/1/2** = 1/3/0.1/0.1 in CH_2Cl_2 (*c* 0.35) in the presence of 4 Å MS at 10 °C, 12 h.
[b] Using **1a** as catalyst.
[c] Using **1b** as catalyst.
[d] Isolated yield after column chromatography.
[e] Determined by chiral HPLC analysis.
[f] In the absence of β-naphthol (**2**).

(71% yield, entry 2). The addition of inorganic base ($NaHCO_3$, entry 3) decreased the yield of **5a** probably due to the increased rate of imine generation. By lowering the temperature to 10 °C and adding MS 4 Å as an additive, the aza-MBH adduct **5a** was obtained in nearly quantitative yield with an enantiomeric excess of 92% (entry 3). Interestingly, in the absence of **2**, not only the *ee*, but also the yield of adduct was reduced (entry 6). A parallel experiment showed that use of alkyl α-amidosulfones resulted in a considerable improvement of both yield (99% *vs.* 57%) and enantioselectivity (92% *vs.* 87%) relative to reaction using preformed imines (entry 5).

Having established the optimal reaction conditions, we then probed the generality of this catalytic asymmetric aza-MBH reaction with a variety of Michael acceptors and aliphatic α-amidosulfones. As shown in Table 2, the *N*-sulfonyl-α-amidosulfones worked well with both α- or β-naphthyl acrylates to afford the cor-

responding (*S*)-aza-MBH adducts **5** in high yields (67–95%) with high enantioselectivities (up to 91% *ee*, entries 1–6). The reaction of linear aliphatic amidosulfones with methyl vinyl ketone (MVK) provided also the (*S*)-adduct in excellent yields and *ees* when **1b** (Ar = 9-anthracenyl) in combination with β-naphthol **2** was used as catalysis (entries 7–9). The reaction between α-amidosulfones derived from β-branched aldehydes with MVK under the same conditions afforded a low yield of adducts. However, when the reaction was carried out at 0 °C under otherwise identical conditions, the expected (*S*)-aza-MBH adducts were isolated in good yields and excellent enantioselectivities (entry 10). On the other hand, the amidosulfones derived from α-branched aldehydes were poor substrates leading to the aza-MBH adducts in low yields and low enantioselectivities. In the case of MVK, the presence of achiral additive **2** was of the utmost importance. In its absence, the aza-MBH reaction of **3a** with MVK gave the corresponding adduct with the opposite enantioselectivity in moderate yield and lower *ee*.[13] The achiral additive-induced reversal of enantioselectivity of the aza-MBH with MVK as Michael acceptor has recently been reported by us.[7b] Acrolein proved to be a suitable Michael acceptor for the reaction (entries 12 and 13). The α-*N*-trimethylsilylethanesulfonyl (SES)[14] alkyl sulfones was also accepted as a substrate to afforded the adduct in excellent yield (> 99%) and *ee* (91%, entry 4).[3c,4a]

The absolute configuration of adducts **5** was determined to be (*S*) by comparison of the specific optical rotation with known values (*cf.* Supporting Information). Addition of enolate to the *Re* face of the *in situ* generated *N*-sulfonylimines and the irreversibility of the Mannich reaction could be evoked to explain the observed enantioselectivity.[15]

In conclusion, we have demonstrated that α-amidosulfones are suitable substrates in the β-ICD-amide **1** and **2**-co-catalyzed aza-MBH reaction. In this domino process, catalyst **1** served both as a base to trigger the formation of *N*-sulfonylimine and then as a nucleophile to initiate the aza-MBH reaction. Acrylates, MVK and acrolein participated in the reaction with *in situ* generated alkylimines to afford uniformly the (*S*)-adducts in high yields and excellent enantioselectivities. Besides mild reaction conditions and operational simplicity, the present method allowed an easy access to α-methylene-β-amino-β-alkyl carbonyl compounds, expanding therefore significantly the generality of the enantioselective aza-MBH reaction.

Experimental Section

General Procedure

To a solution of α-amidosulfone (**3**, 0.073 mmol) and 50 mg of molecular sieves in dried dichloromethane at 0 °C or 10 °C were added catalyst (**1**, 0.0073 mmol, 0.1 equiv.), β-naphthol (**2**, 0.0073 mmol, 0.1 equiv.) and Michael acceptor (**4**, 0.22 mmol, 3.0 equiv.). The reaction mixture was stirred under argon atmosphere for 12 h. The reaction was stopped by passing the mixture through a short pad of silica gel using ethyl acetate as eluent. Solvents were removed under reduced pressure and the resulting crude product was purified by preparative TLC (*n*-heptane/EtOAc, 70/30) to afford the corresponding aza-MBH product.

Acknowledgements

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