

Invertible Enantioselectivity in 6'-Deoxy-6'-acylamino- β -isocupreidine-Catalyzed Asymmetric Aza-Morita–Baylis–Hillman Reaction: Key Role of Achiral Additive

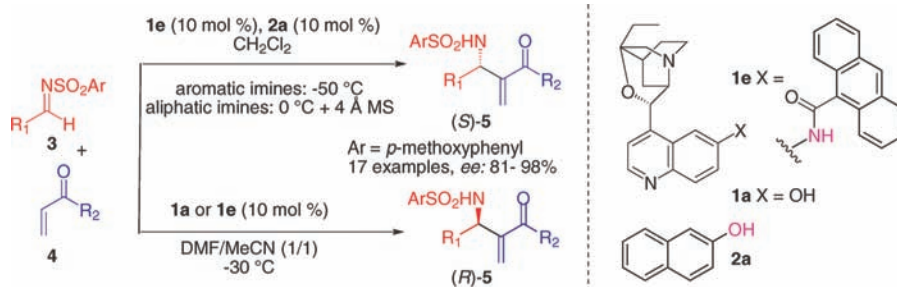
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ABSTRACT



The β -ICD (**1a**) or β -ICD-amide (**1e**)-catalyzed aza-Morita–Baylis–Hillman reaction between *N*-sulfonylimines **3** and alkyl vinyl ketones **4** produced the (*R*)-enriched adducts **5**. By adding a catalytic amount of β -naphthol (**2a**), the enantioselectivity of the same reaction was inverted leading to (*S*)-**5** in excellent yields and enantioselectivities. Both aromatic and aliphatic imines are accepted as substrates for this reaction.

The aza–Morita–Baylis–Hillman reaction (aza-MBH) produces α -methylene- β -aminocarbonyl derivatives from simple imines and electron-deficient alkenes in an atom-economic fashion.¹ During the past decade, this reaction has been extensively investigated especially in its catalytic asymmetric version² due to the high synthetic value of its adduct. The β -isocupreidine (β -ICD **1a**), originally synthesized by Hoffmann³ and developed by Hatakeyama for enantioselective MBH reaction,⁴ has later been demonstrated to be one of the most efficient catalysts for the aza-MBH reaction thanks to the work of Shi,⁵ Hatakeyama,⁶ and Adolfsson.⁷ Not-

withstanding the catalytic efficiency and the broad applicability of β -ICD, one serious drawback is that the enantiomer or pseudoenantiomer of **1a** is not easily avail-

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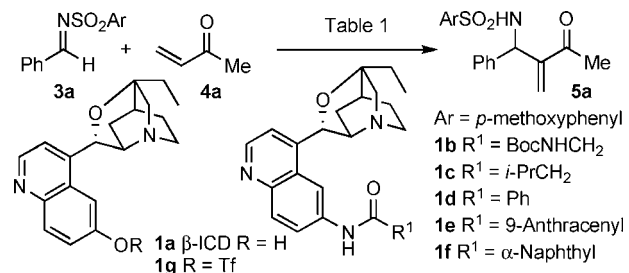
able,⁸ making the access to both enantiomers of aza-MBH adducts difficult.⁹ Intriguingly, it was noticed that the sense of asymmetric induction in the β -ICD-catalyzed aza-MBH reactions depended on the structure of electron-poor alkenes. Indeed, the aza-MBH reaction of methyl or ethyl vinyl ketone (MVK or EVK) with *N*-tosylimine afforded the (*R*)-enriched allylamine, whereas the (*S*)-enriched allylamine was obtained when acrylates, acrylonitrile, and acrolein were used as Michael acceptors.^{5,6}

We recently reported that 6'-deoxy-6'-acylamino- β -ICD (β -ICD-amide, **1b**, Table 1) was capable of catalyzing the

We also surmised that in the presence of this dual catalyst the enantioselectivity of the aza-MBH reflected directly that of the Mannich reaction. On the basis of this mechanistic assumption, we assumed that this dual catalytic system (**1** and **2**) should favor the (*S*)-aza-MBH product regardless of the nature of Michael acceptor used and set out to investigate the reaction between *N*-tosylimine **3** and MVK **4** which is known to provide the (*R*)-aza-MBH adduct. We report herein that the presence of an achiral additive (**2**) can indeed switch the enantioselectivity from *R* to *S* for the aza-MBH reaction between **3** and **4**. We also identified a new β -ICD-amide **1e**, which in combination with **2** was highly efficient for the access of (*S*)-**5** from **3** and **4**.

We initially selected (*E*)-*N*-benzylidene-4-methoxybenzene sulfonamide (**3a**) and MVK **4a** as model substrates. Performing the reaction in the presence of β -ICD-amides (**1b**, *R* = BocNHCH₂, 0.1 equiv, CH₂Cl₂) and β -naphthol (**2a**, 0.1 equiv), the (*S*)-adduct **5a** was indeed isolated in 99% yield with 60% ee. Encouraged by this result, we screened β -ICD and various β -ICD-amides¹⁰ with β -naphthol as cocatalyst. The results are summarized in Table 1. In general, the β -ICD-amides gave higher yields of the aza-MBH product than β -ICD. The catalysts having an aromatic residue at the C-6' position (**1d**–**1f**) were found to be more efficient than those bearing an aliphatic chain (**1b**, **1c**), with **1e** (*R*¹ = 9-anthracenyl) being the most effective (ee: 89%, entry 9). It has to be noted that, in the absence of **2a**, all these β -ICD-based catalysts afforded the (*R*)-**5a**, albeit with reduced ee, indicating thus the crucial role of the achiral additive in achieving the *S*-selectivity.^{11,12} We have also briefly examined the effect of other achiral protic additives. As is seen, addition of 3,5-bis(trifluoromethyl)phenol (**2b**) and 4-methoxyphenol (**2c**) instead of naphthol (**2a**) into the catalytic reaction afforded (*S*)-**5a** in excellent yields but with diminished ee (entries 7, 8, vs 5). Both (*R*)- and (*S*)-BINOL were used in association with **1e**, and the (*S*)-adduct was obtained with reduced enantioselectivity regardless of the absolute configuration of the BINOL (entries 10 and 11). These experiments

Table 1. Dual Enantioselective aza-MBH Reaction: Survey of Catalysis^a



entry	cat.	temp	additive	yield ^b (%)	ee ^c (%)
1 ^d	1a	–30	none	26	–44 (<i>R</i>)
2	1a	–50	β -naphthol 2a	39	55 (<i>S</i>)
3	1b	–30	β -naphthol 2a	99	60 (<i>S</i>)
4	1c	–30	β -naphthol 2a	>99	72 (<i>S</i>)
5	1d	–30	β -naphthol 2a	>99	73 (<i>S</i>)
6 ^d	1d	–30	none	80	–69 (<i>R</i>)
7	1d	–30	3,5-CF ₃ -C ₆ H ₃ OH 2b	95	46 (<i>S</i>)
8	1d	–30	4-MeO-C ₆ H ₄ OH 2c	>99	59 (<i>S</i>)
9	1e	–30	β -naphthol 2a	>99	89 (<i>S</i>)
10	1e	–30	(<i>R</i>)-BINOL 2d	>99	51 (<i>S</i>)
11	1e	–30	(<i>S</i>)-BINOL 2e	>99	60 (<i>S</i>)
12 ^e	1e	–30	β -naphthol 2a	83	84 (<i>S</i>)
13 ^d	1e	–30	none	71	–39 (<i>R</i>)
14	1f	–30	β -naphthol 2a	>99	71 (<i>S</i>)
15 ^d	1f	–30	none	91	–52 (<i>R</i>)
16	1e	–50	β -naphthol 2a	>99	96 (<i>S</i>)

^a Reaction conditions: imine (**3a**) (0.1 mmol), MVK (**4a**) (0.2 mmol), additive **2** (0.01 mmol), **1** (0.01 mmol) in CH₂Cl₂ (0.35 mL) for 48 h.

^b Isolated yield after column chromatography. ^c Determined by chiral HPLC analysis. ^d Reaction time: 72 h. ^e With 5 mol % of **2a**.

enantioselective aza-MBH reaction between *N*-sulfonylimines and β -naphthyl acrylate and documented that the presence of an achiral additive β -naphthol (**2a**) can significantly improve the ee of the product **5**.¹⁰ A nucleophilic addition of the *Z*-enolate onto the Re-face of the *E*-imine was proposed to account for the observed *S*-enantioselectivity.

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(12) **1a**-catalyzed reaction between **3a** and MVK leading to (*R*)-adduct in 85% yield and 97% ee in DMF–MeCN. See ref 5.

indicated that the sense of asymmetric induction came from mainly the bifunctional catalyst **1e** rather than the chirality of protic additive. Overall, naphthol (**2a**) was identified as the best cocatalyst for this reaction. When the loading of **2a** was lowered to 5 mol %, both the yield and enantioselectivity decreased slightly (Table 1, entry 12). By performing the reaction at -50°C in the presence of **1e** and **2a** (10 mol % each), we were pleased to find that (*S*)-**5a** can be produced in quantitative yield with 96% ee (entry 16).

Having established that naphthol (**2a**) can inverse the enantioselectivity of **1e**-catalyzed aza-MBH reaction between **3a** and **4a**, we next examined the scope of the reaction using MVK and EVK as Michael acceptors and a range of sulfonylimines **3** as electrophiles. As shown in Table 2, the

Table 2. Enantioselective aza-MBH Reaction with Representative Aromatic and Aliphatic *N*-Sulfonylimines

entry	R ₁	R ₂	product	yield ^b (%)	ee ^c (%)
1 ^a	<i>p</i> -MeC ₆ H ₄ (3b)	Me (4a)	5b	>99	96
2 ^a	<i>p</i> -MeOC ₆ H ₄ (3c)	Me (4a)	5c	62	96
3 ^a	<i>p</i> -CF ₃ C ₆ H ₄ (3d)	Me (4a)	5d	>99	95
4 ^a	<i>p</i> -ClC ₆ H ₄ (3e)	Me (4a)	5e	>99	94
5 ^a	<i>m</i> -BrC ₆ H ₄ (3f)	Me (4a)	5f	>99	96
6 ^a	<i>m</i> -MeC ₆ H ₄ (3g)	Me (4a)	5g	>99	97
7 ^a	<i>o</i> -BrC ₆ H ₄ (3h)	Me (4a)	5h	>99	98
8 ^a	PhCH=CH (3i)	Me (4a)	5i	85	96
9 ^a	C ₆ H ₅ (3a)	Et (4b)	5j	>99(46) ^d	98(–68) ^d
10 ^a	<i>p</i> -MeC ₆ H ₄ (3b)	Et (4b)	5k	>99	98
11 ^a	<i>p</i> -ClC ₆ H ₄ (3e)	Et (4b)	5l	>99	97
12 ^e	<i>i</i> -PrCH ₂ (3j)	Me (4a)	5m	59	81
13 ^e	<i>c</i> -hexylCH ₂ (3k)	Me (4a)	5n	71	85
14 ^e	<i>n</i> -butyl (3l)	Me (4a)	5o	42	90
15 ^e	<i>n</i> -pentyl (3m)	Me (4a)	5p	46	92
16 ^e	Ph(CH ₂) ₂ (3n)	Me (4a)	5q	36	93
17 ^e	<i>n</i> -pentyl (3o)	Et (4b)	5r	37	93

^a Reaction conditions: imine (**3**) (0.1 mmol), **4** (0.2 mmol), β -naphthol (**2a**) (0.01 mmol), **1e** (0.01 mmol) in CH₂Cl₂ (0.35 mL) at -50°C for 48 h. ^b Isolated yield after column chromatography. ^c Determined by chiral HPLC analysis. ^d In the absence of β -naphthol (**2a**) with **1d** as catalyst in CH₂Cl₂ (*c* = 0.35) at -30°C . ^e Reaction conditions: aliphatic imine (**3a**) (0.1 mmol), **4** (0.2 mmol), β -naphthol (**2a**) (0.01 mmol), **1e** (0.01 mmol) in CH₂Cl₂ (0.35 mL) at 0°C for 12 h.

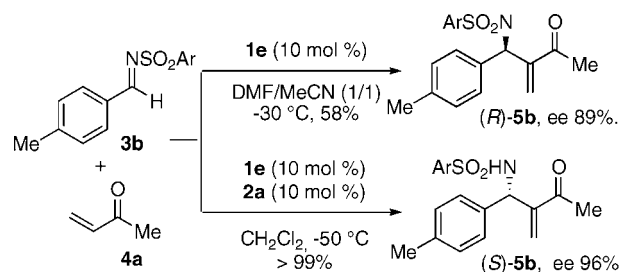
catalysis showed substantial generality resulting in broad substrate scope. Imines derived from aromatic aldehydes bearing electron-donating and electron-withdrawing substituents at the *para*, *meta*, and *ortho* positions were all tolerated to afford cleanly the corresponding (*S*)-adducts in excellent yields and enantioselectivities (entries 1–11). The α,β -unsaturated imine **3i** was also a suitable substrate providing (*S*)-**5i** in 85% yield and 96% ee. Under the identical reaction conditions (0.1 equiv of **1e**, 0.1 equiv of **2a**, CH₂Cl₂, -50°C), the reaction of ethyl vinyl ketone (EVK, **4b**) with sulfonylimines proceeded smoothly to afford the (*S*)-aza-MBH adducts in excellent yields and enantioselectivities (ee

> 97%). As expected, the (*R*)-enriched adduct was again obtained in the absence of **2a** (entry 9).

The use of aliphatic imines in an enantioselective aza-MBH reaction is a long-standing problem due to their rapid degradation under experimental conditions.^{5,9,13} Delightfully, reaction of aliphatic imines with MVK or EVK under our optimized conditions furnished, in the presence of 4 Å molecular sieves, the corresponding aza-MBH adducts **5m–r** in good to excellent enantioselectivities, albeit with moderate yields.

The invertible enantioselectivity in **1e**-catalyzed aza-MBH reaction between *N*-sulfonylimine **3** and MVK (**4**) is demonstrated in Scheme 1. Thus, reaction of sulfonylimine

Scheme 1. Dual Enantioselectivity of **1e**-Catalyzed MBH Reaction and Role of Naphthol **2a**



3b with MVK (**4a**) in DMF/CH₃CN⁵ in the presence of catalyst **1e** afforded the (*R*)-**5b** in 58% yield with 89% ee. The same reaction performed in CH₂Cl₂ in the presence of **1e** and cocatalyst **2a** provided (*S*)-**5b** in 99% yield with 96% ee (Scheme 1).

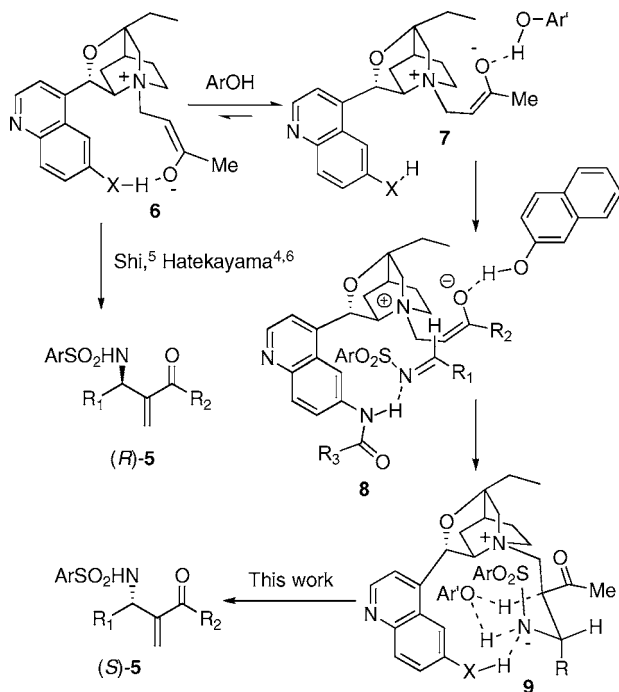
The ability of β -naphthol **2a** to inverse the enantioselectivity of β -ICD-amide-catalyzed reaction between sulfonylimines and MVK/EVK is intriguing.¹⁴ The *R*-selectivity

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in the β -ICD-catalyzed reaction between *N*-sulfonylimines and MVK was explained by evoking a nonselective Mannich reaction and a faster β -elimination of the (2*S*,3*R*)- vs (2*S*,3*S*)-Mannich adduct (Scheme 2).^{5–7,9k,15} This implied that the

Scheme 2. Dual Enantioselectivity: Role of Achiral Additive



proton migration step determined the enantioselectivity of the reaction and that the reaction itself could be regarded as a dynamic kinetic resolution. The ability of β -naphthol to inverse the kinetics of these two competitive β -elimination processes was not obvious. The recent mechanistic investigations carried out by Leitner¹⁶ and Aggarwal^{15b,c} showed that the addition of a Brønsted acid in aza-MBH reaction leads to a shift of the rate-determining step (RDS) from the proton migration to the Mannich-type coupling.¹⁷ We therefore

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hypothesized that the Mannich reaction may become highly stereoselective in the presence of β -naphthol (**2a**) to afford the (2*S*,3*S*) adduct **9** via a ternary Z-enolate complex **8**. Subsequent β -naphthol-assisted β -elimination via a plausible six-membered cyclic transition state **9** would then provide the observed (*S*)-aza-MBH adduct. When the *O*-triflate β -ICD (**1g**) lacking amide NH functionality was used in combination with naphthol (**2**), the reaction between **3a** and **4a** gave the aza-MBH (*S*)-**5a** adduct in 98% yield with much reduced ee (48%). This control experiment indicated that both the amide–NH in **1e** and phenol–OH in **2** were important for the high enantioselectivity observed in the present catalytic system.

In summary, we reported that an achiral protic additive was capable of inverting the β -ICD and β -ICD-amide-catalyzed enantioselective aza-MBH reaction between *N*-sulfonylimines and MVK/EVK, therefore providing a solution to the enantio-complementarity associated with this family of catalysts.^{18–20} Further studies to elucidate the role of β -naphthol are under active pursuit in our laboratory.

Acknowledgment. Financial support from CNRS and ICSN is gratefully acknowledged. N.A. thanks ICSN for a doctoral fellowship.

Supporting Information Available: Experimental procedures, product characterization, ee measurement, absolute configuration determination for **5a** and **5o**, and copies of the ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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