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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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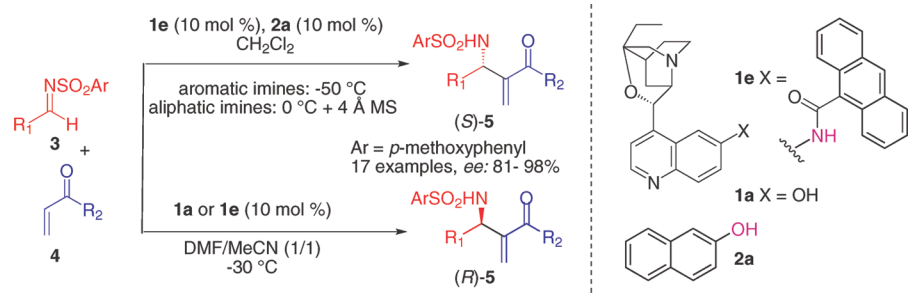
ABSTRACT



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 inversed 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 version[2] due to the high synthetic value of its adduct. The β-isocupreidine (β-ICD **1a**), originally synthesized by Hoffmann[3] 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] Notwithstanding 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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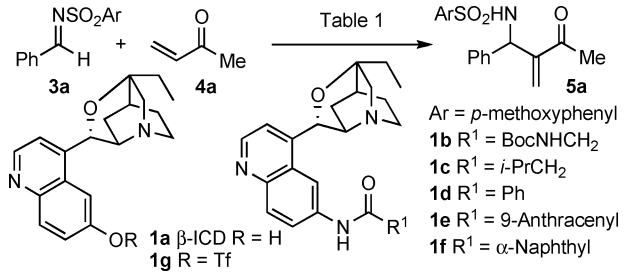
able,[8] making the access to both enantiomers of aza-MBH adducts difficult.[9] Intriguingly, it was noticed that the sense of asymmetric induction in the β-ICD-catalyzed aza-MBH reactions depended on the structure of electron-poor alkenes. Indeed, the aza-MBH reaction of methyl or ethyl vinyl ketone (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 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.

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 (*R*)
2	**1a**	−50	β-naphthol **2a**	39	55 (*S*)
3	**1b**	−30	β-naphthol **2a**	99	60 (*S*)
4	**1c**	−30	β-naphthol **2a**	>99	72 (*S*)
5	**1d**	−30	β-naphthol **2a**	>99	73 (*S*)
6[d]	**1d**	−30	none	80	−69 (*R*)
7	**1d**	−30	3,5-CF_3−C_6H_3OH **2b**	95	46 (*S*)
8	**1d**	−30	4-MeO-C_6H_4OH **2c**	>99	59 (*S*)
9	**1e**	−30	β-naphthol **2a**	>99	89 (*S*)
10	**1e**	−30	(*R*)-BINOL **2d**	>99	51 (*S*)
11	**1e**	−30	(*S*)-BINOL **2e**	>99	60 (*S*)
12[e]	**1e**	−30	β-naphthol **2a**	83	84 (*S*)
13[d]	**1e**	−30	none	71	−39 (*R*)
14	**1f**	−30	β-naphthol **2a**	>99	71 (*S*)
15[d]	**1f**	−30	none	91	−52 (*R*)
16	**1e**	−50	β-naphthol **2a**	>99	96 (*S*)

[a] Reaction conditions: imine (**3a**) (0.1 mmol), MVK (**4a**) (0.2 mmol), additive **2** (0.01 mmol), **1** (0.01 mmol) in CH_2Cl_2 (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**.

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 = $BocNHCH_2$, 0.1 equiv, CH_2Cl_2) 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-amides[10] 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

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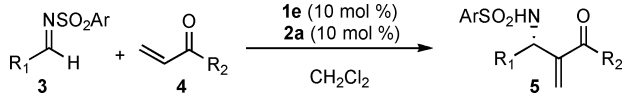
(12) **1a**-catalyzed reaction between **3a** and MVK leading to (*R*)-adduct in 85% yield and 97% ee in DMF−MeCN. See ref 5.

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 enantioselectivty 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]	*p*-MeC_6H_4 (**3b**)	Me (**4a**)	**5b**	>99	96
2[a]	*p*-$MeOC_6H_4$ (**3c**)	Me (**4a**)	**5c**	62	96
3[a]	*p*-$CF_3C_6H_4$ (**3d**)	Me (**4a**)	**5d**	>99	95
4[a]	*p*-ClC_6H_4 (**3e**)	Me (**4a**)	**5e**	>99	94
5[a]	*m*-BrC_6H_4 (**3f**)	Me (**4a**)	**5f**	>99	96
6[a]	*m*-MeC_6H_4 (**3g**)	Me (**4a**)	**5g**	>99	97
7[a]	*o*-BrC_6H_4 (**3h**)	Me (**4a**)	**5h**	>99	98
8[a]	PhCH=CH (**3i**)	Me (**4a**)	**5i**	85	96
9[a]	C_6H_5 (**3a**)	Et (**4b**)	**5j**	>99(46)[d]	98(−68)[d]
10[a]	*p*-MeC_6H_4 (**3b**)	Et (**4b**)	**5k**	>99	98
11[a]	*p*-ClC_6H_4 (**3e**)	Et (**4b**)	**5l**	>99	97
12[e]	*i*-$PrCH_2$ (**3j**)	Me (**4a**)	**5m**	59	81
13[e]	*c*-hexylCH_2 (**3k**)	Me (**4a**)	**5n**	71	85
14[e]	*n*-butyl (**3 L**)	Me (**4a**)	**5o**	42	90
15[e]	*n*-pentyl (**3m**)	Me (**4a**)	**5p**	46	92
16[e]	$Ph(CH_2)_2$ (**3n**)	Me (**4a**)	**5q**	36	93
17[e]	*n*-pentyl (**3o**)	Et (**4b**)	**5r**	37	93

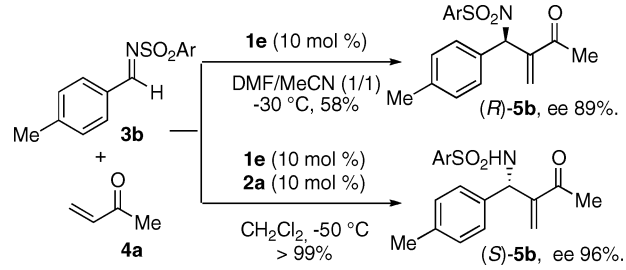
[a] Reaction conditions: imine (**3**) (0.1 mmol), **4** (0.2 mmol), β-naphthol (**2a**) (0.01 mmol), **1e** (0.01 mmol) in CH_2Cl_2 (0.35 mL) at −50 °C for 48 h. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] In the absence of β-naphthol (**2a**) with **1d** as catalyst in CH_2Cl_2 ($c = 0.35$) 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 CH_2Cl_2 (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**, CH_2Cl_2, −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/CH_3CN[5] in the presence of catalyst **1e** afforded the (*R*)-**5b** in 58% yield with 89% ee. The same reaction performed in CH_2Cl_2 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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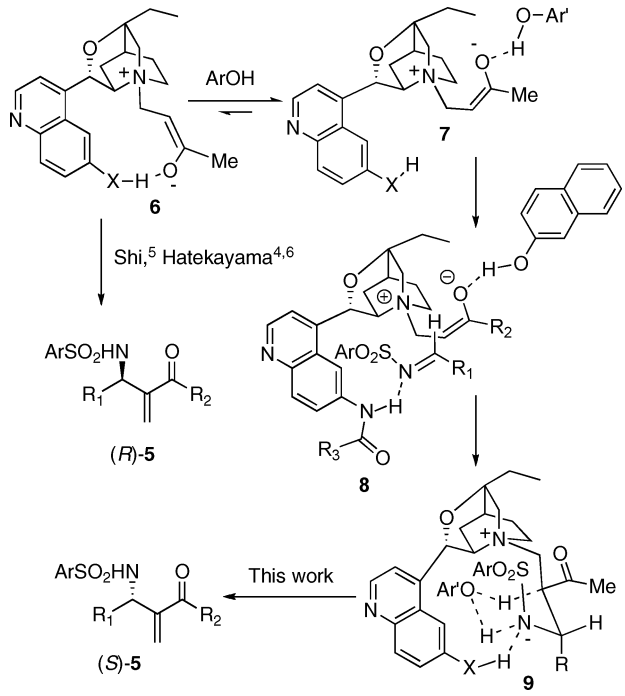
in the β-ICD-catalyzed reaction between *N*-sulfonylimines and MVK was explained by evoking a nonselective Mannich reaction and a faster β-elimination of the (2*S*,3*R*)- vs (2*S*,3*S*)-Mannich adduct (Scheme 2).[5−7,9k,15] This implied that the proton migration step determined the enantioselectivity 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 Leitner[16] 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 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.

Scheme 2. Dual Enantioselectivity: Role of Achiral Additive



In summary, we reported that an achiral protic additive was capable of inversing 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.

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

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