Asymmetric catalytic aza-Morita–Baylis–Hillman reaction (aza-MBH): an interesting functional group-caused reversal of asymmetric induction†

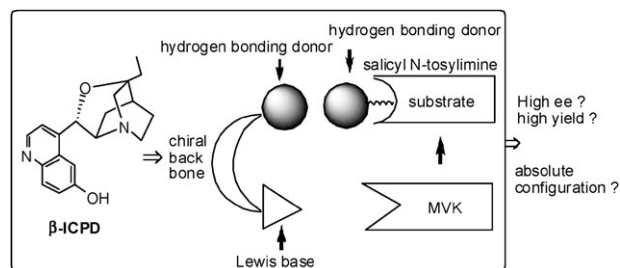Min Shi,* Ming-Juan Qi and Xu-Guang Liu

A highly efficient aza-Morita–Baylis–Hillman reaction (aza-MBH reaction) of N-tosyl salicylaldehyde imines with α,β-unsaturated ketones has been achieved by using β-isocupreidine (β-ICPD) as the catalyst (10 mol%) to give the corresponding adducts in good to high yields (90%–quant.) and excellent ee's (up to 99% ee), with adducts showing the opposite absolute configuration to that of those obtained in the similar aza-MBH reaction of N-tosyl aldimines with α,β-unsaturated ketones.

Asymmetric catalysis by the use of bifunctional organo-catalysts via hydrogen bonding has become one of the most active research areas in the past decade.[1] A synergistic activation by the functionalities on the catalyst can lead to specific control of the transition state and result in chiral products with high enantioselectivity. Recently, the aza-Morita–Baylis–Hillman (aza-MBH) reaction of N-sulfonated imines (ArCH = NTs) with various Michael acceptors such as methyl vinyl ketone (MVK) has received much attention.[2] We and others have successfully developed several excellent catalytic systems by using chiral nitrogen and phosphine Lewis bases as multifunctional organocatalysts and have achieved high enantioselectivities for this reaction.[3] Another interesting finding is that the absolute configuration of the adducts derived from the asymmetric aza-MBH reaction of N-sulfonated imines with MVK or ethyl vinyl ketone (EVK) is opposite to that obtained by reaction with acrolein, methyl acrylate, phenyl acrylate and α-naphthyl acrylate in the presence of β-isocupreidine (β-ICPD) under similar reaction conditions.[3g] Since the hydrogen bonding interactions between imines and bifunctional organocatalysts have been proven to be powerful, it is conceivable that by introducing functionalities on the aryl groups of the imine substrates, such as in salicyl N-tosylimines 1 (Scheme 1), high yields, ee's and reversible asymmetric induction would be realized. In this paper, we are pleased to report that an interesting reversal of absolute configuration can be achieved by introducing an ortho-phenol group onto imine substrates for aza-MBH reaction using β-isocupreidine (β-ICPD)[4] as the catalyst.

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China. E-mail: Mshi@mail.sioc.ac.cn; Fax: +86-21-64166128
† Electronic supplementary information (ESI) available: ^{13}C and ^{1}H NMR spectroscopic and analytical data for **3** and X-ray crystal data of **6a** and **7a** as well as chiral HPLC traces. CCDC 601323 and 632081. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b814500h

Scheme 1 Proposed asymmetric aza-MBH reaction of salicyl N-tosylimines with MVK catalyzed by bifunctional organocatalyst β-**ICPD**.

An initial examination was carried out using β-**ICPD** in this reaction. Gratifyingly, by adding β-**ICPD** (10 mol%) to the reaction of imine **1a** with MVK **2a** in THF at −30 °C, the product **3a** was obtained in a quantitative yield and 91% ee as the S-configuration (Scheme 2).[5] The resulting stereochemistry of the product **3a** was found to be opposite to that obtained in the previous system in which N-tosyl imines (such as **1a′**) were employed to react with **2a** in the presence of β-**ICPD**, providing the corresponding aza-MBH adducts (such as **3a′**) in R-configuration (Scheme 2).[3a,g]
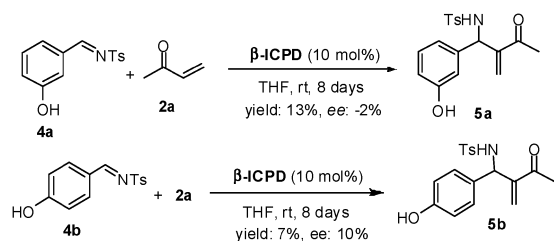
As for the aza-MBH reaction of N-tosylimines **4a** and **4b** with **2a** in the presence of β-**ICPD** in THF at 20 °C, we found that all these reactions were sluggish, affording the corresponding adducts **5a** and **5b** in low yields and ee's after the reaction was conducted for 8 days (Scheme 3).[6] These results
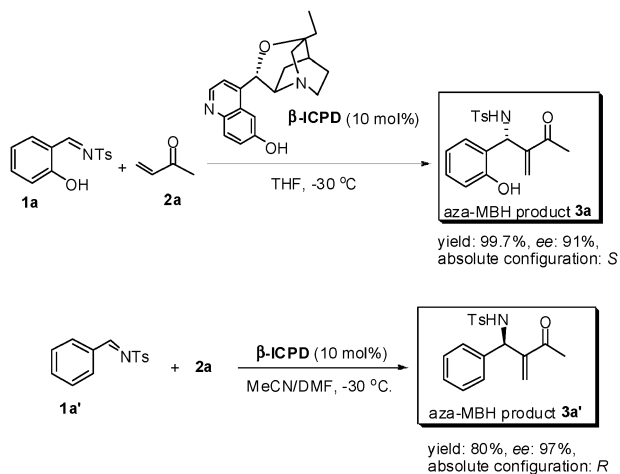
Scheme 2 aza-MBH reaction of salicyl N-tosylimine **1a** with MVK **2a** as well as aza-MBH reaction of N-sulfonated imine **1a′** with MVK **2a**.

Scheme 3 aza-MBH reaction of *N*-tosylimines **4a** and **4b** with MVK **2a** catalyzed by β-**ICPD** (10 mol%) in THF at room temperature.

suggest that the *ortho*-phenolic hydroxy group adjacent to the C=N double bond in salicyl *N*-tosylimine plays a key role in the aza-MBH reaction with **2a**, providing the corresponding adduct in high yield and ee.

In optimization studies, aza-MBH reactions of imine **1a** with **2a** catalyzed by β-**ICPD** (10 mol%) were carried out in a series of solvents such as dichloromethane (DCM), acetonitrile (MeCN), ethyl acetate (EA) and dioxane as well as at various temperatures. We found that the best reaction conditions are to carry out the reaction in THF at −30 °C. All these results have been outlined in the ESI† (Table SI-1) and indicate that solvents DCM, MeCN, EA and dioxane are not as effective as THF for this reaction. With these optimized reaction conditions in hand, we next investigated the substrate scope of the reaction of **1** with Michael acceptors **2a** and ethyl vinyl ketone (EVK, **2b**). The results of these experiments are summarized in Table 1. As shown in Table 1, the asymmetric induction is satisfactory and the reaction can tolerate various substituents on the aromatic rings of **1** for acceptors **2a** and **2b**. Most of the reactions proceeded smoothly to give the corresponding adducts **3** in good to high yields (90%–99.5% yields) and excellent ee's (90%–99.9% ee) with *S*-configuration under these optimal conditions, whether they are electron-rich or -poor aryl groups (Table 1, entries 1–8 and 10–13). As for salicyl *N*-tosylimine **1j** (R^1 = H, R^2 = R^4 = Me, R^3 = Cl),

Table 1 aza-MBH reaction of salicyl *N*-tosylimines **1** with activated alkenes catalyzed by β-**ICPD** (10 mol%) in THF at −30 °C
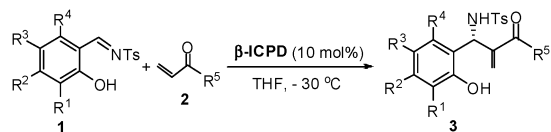
Entry	R^1	R^2	R^3	R^4	1	R^5	Time/h	Yield (%)[a]	ee (%)[b]
1	OMe	H	H	H	**1b**	Me	48	**3b**: 99.5	93 (*S*)
2	H	OMe	H	H	**1c**	Me	96	**3c**: 98	92 (*S*)
3	H	H	OMe	H	**1d**	Me	24	**3d**: 95	99.9 (*S*)
4	H	H	Me	H	**1e**	Me	30	**3e**: 96	92 (*S*)
5	Br	H	H	H	**1f**	Me	72	**3f**: 95	90 (*S*)
6	Cl	H	Cl	H	**1g**	Me	72	**3g**: 90	95 (*S*)
7	Cl	H	H	H	**1h**	Me	72	**3h**: 96	90 (*S*)
8	H	F	H	H	**1i**	Me	96	**3i**: 93	94 (*S*)
9	H	Me	Cl	Me	**1j**	Me	96	**3j**: Trace	—
10	H	H	H	H	**1a**	Et	64	**3k**: 99.9	92 (*S*)
11	H	H	OMe	H	**1d**	Et	64	**3l**: 97	95 (*S*)
12	OMe	H	H	H	**1b**	Et	64	**3m**: 96	94 (*S*)
13	Br	H	H	H	**1f**	Et	96	**3n**: 95	92 (*S*)

[a] Isolated yields. [b] Determined by chiral HPLC after acylation.
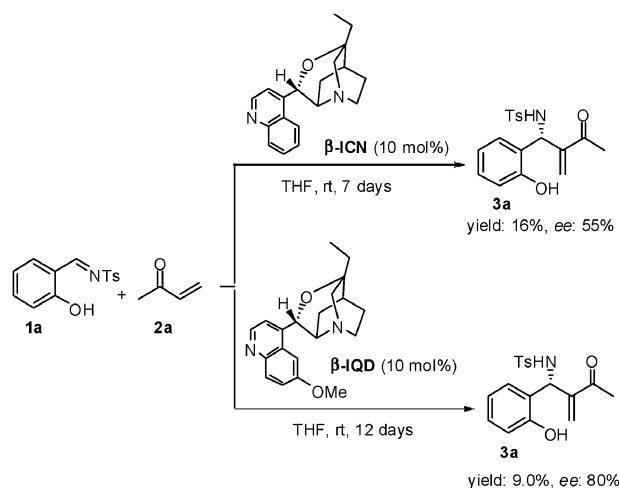

Scheme 4 aza-MBH reaction of salicyl *N*-tosylimine **1a** with MVK **2a** catalyzed by β-**ICN** (10 mol%) and β-**IQD** (10 mol%) in THF at room temperature.

the reaction was sluggish and the corresponding adduct **3j** was obtained in a trace amount under the standard conditions (Table 1, entry 9). The ee's of **3a–3i** and **3k–3n** were determined by chiral HPLC analyses after converting to the corresponding acetates **6** upon treatment with acetyl chloride in the presence of Et₃N in DCM as shown in the ESI.†

It should be noted that using salicyl *N*-tosylimine **1a** as the substrate, we examined its reaction with **2a** in the presence of β-**ICN** (10 mol%) and β-**IQD** (10 mol%) as the mono-functional organocatalysts, which have similar chiral scaffolds to the bifunctional counterpart β-**ICPD** (Scheme 4). Unfortunately, these reactions were sluggish at room temperature (20 °C) and the corresponding adducts **3a** were obtained in poor chemical yields (16% and 9%) and moderate to good enantiomeric excesses (55% ee and 80% ee) after 7 and 12 days in tetrahydrofuran (THF), respectively, as the *S*-configuration, suggesting that the bifunctional counterpart β-**ICPD** is essential for this reaction to achieve high yields and ee's.

A plausible reaction mechanism is shown in Scheme 5. Michael addition of β-**ICPD** to α,β-unsaturated ketone **2a** gives enolate **A** which is in equilibrium with enol **B** prior to Mannich reaction with *N*-sulfonated imine **1a** or **1a′** to furnish an equilibrium mixture of several diastereomers. In the case of *N*-sulfonated imine **1a′**, as we described in our previous papers,[3a,g] two betaine intermediates in an equilibrium which are stabilized by intramolecular hydrogen-bonding between the amidate ion and phenolic OH are nearly ideal for the subsequent E2 or E1cb elimination for stereoelectronic reasons.[3g] As indicated in a Newman projection of intermediate **C**, according to the generally accepted mechanism of Morita–Baylis–Hillman reaction this affords adduct **3a′** in *R*-configuration,[1] which has been strongly consolidated by Santos's finding on the basis of ESI/MS/MS spectroscopic investigation recently.[7] Therefore, the formation of intermediate **C′** is disfavored. In the case of salicyl *N*-tosylimine **1a**, the corresponding intermediate **D** would be more stable than intermediate **E**, because the *ortho*-phenol containing aromatic moiety in the chiral pocket can form a stronger net type or branched hydrogen bonding system,[8] which affords the
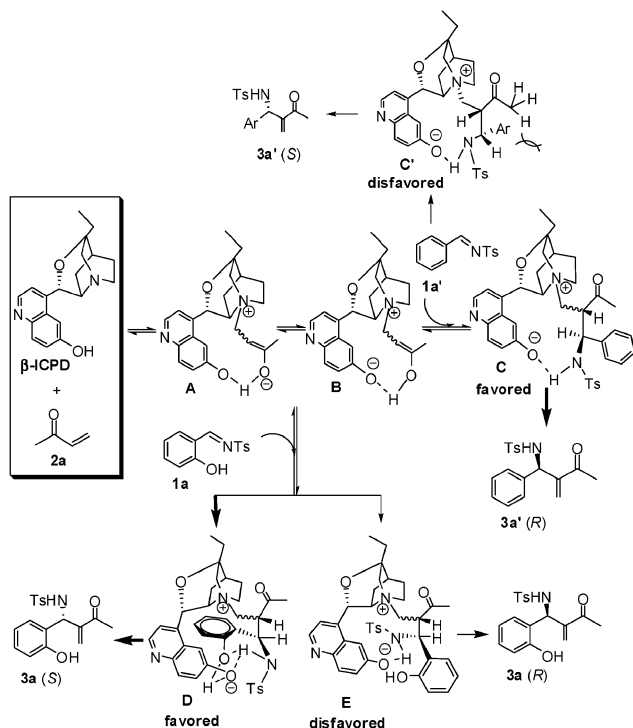
Scheme 5 Proposed reaction mechanism.

corresponding aza-MBH adduct in the *S*-configuration. However, in intermediate **E**, the *ortho*-phenol group is unable to join in the transition state to influence the reaction since it takes up a position outside of the chiral environment. As for *N*-tosylimines **4a** or **4b**, the phenolic hydroxy group is located at a position outside the hydrogen bonding network system and only acts as an electron-donating group on the benzene ring, retarding the reaction rate.

It should be noted that when using acrolein, acrylate, or acrylonitrile as the Michael acceptor in this reaction, none of the corresponding aza-MBH adducts could be obtained in the presence of **DABCO** or β-**ICPD** under identical conditions.[9] Therefore, we could not examine the absolute configuration with these Michael acceptors.

In conclusion, we have succeeded in an effective β-isocupreidine Lewis base-catalyzed asymmetric aza-MBH reaction of *N*-tosyl salicylaldehyde imines **1** with α,β-unsaturated ketones under mild conditions. The aza-MBH adducts have been obtained in good to high yields and high enantioselectivities. More importantly, an interesting reversal of asymmetric control has been achieved by introducing an *ortho*-phenol group to the imine substrates. Further study on the mechanism and scope of this asymmetric reaction is underway in our laboratories.

Notes and references

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5 The absolute configuration of **3** was determined by X-ray diffraction of its acetate **6a** and ester **7a** as shown in the ESI.† The crystal data of **6a** have been deposited in the CCDC with number 601323. Empirical Formula: $C_{20}H_{21}NO_2S$; formula weight: 387.44; crystal color, habit: colorless, prismatic; crystal system: monoclinic; lattice type: primitive; lattice parameters: $a = 8.8105(13)$ Å, $b = 9.4689(13)$ Å, $c = 12.1148(17)$ Å, $\alpha = 90°$, $\beta = 103.853(2)°$, $\gamma = 90°$, $V = 981.3(2)$ Å^3; space group: $P2(1)$; $Z = 2$; $D_{calc} = 1.311$ g cm^{-3}; $F_{000} = 408$; diffractometer: Rigaku AFC7R; residuals: R; Rw: 0.0636, 0.1529. The crystal data of **7a** have been deposited in the CCDC with number 632081. Empirical Formula: $C_{25}H_{22}BrNO_5S$; formula weight: 528.41; crystal color, habit: colorless, prismatic; crystal system: orthorhombic; lattice type: primitive; lattice parameters: $a = 8.9781(11)$ Å, $b = 10.3536(12)$ Å, $c = 25.647(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2384.0(5)$ Å^3; space group: $P2(1)2(1)2(1)$; $Z = 4$; $D_{calc} = 1.472$ g cm^{-3}; $F_{000} = 1080$; diffractometer: Rigaku AFC7R; residuals: R; Rw: 0.0407, 0.0785.

6 Electron-donating groups on the benzene ring can significantly retard the reaction rate of the MBH reaction.

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