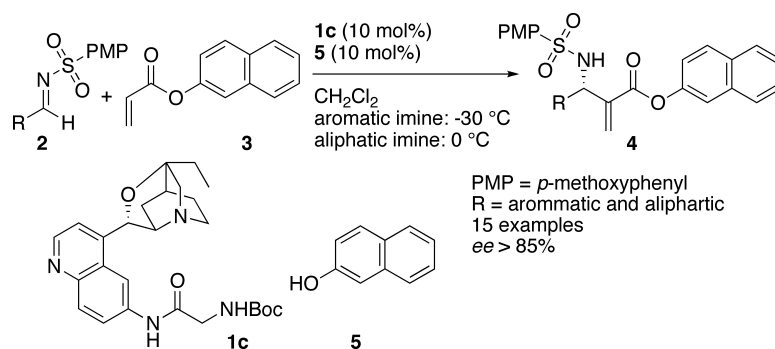Communication

Highly Enantioselective Aza Morita#Baylis#Hillman Reaction Catalyzed by Bifunctional #-Isocupreidine Derivatives

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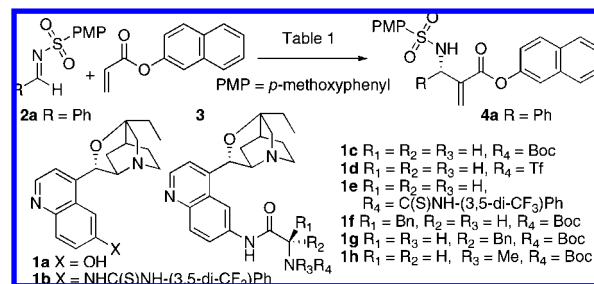
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The Morita−Baylis−Hillman (MBH) reaction and its aza counterpart (aza-MBH) have attracted considerable attention among synthetic chemists because of the utility of these adducts in organic synthesis.[1] Since one chiral center is created during these reactions, the search for enantioselective variants has been the main focus of the recent decades. However, the complexity of the reaction mechanism made the development of the asymmetric version particularly challenging, and only a few efficient catalyses have so far been developed.[2] For the aza-MBH reaction, the β-isocupreidine (β-ICD),[3,4] phosphinyl BINOLs,[5] and 3-(N-3′-pyridinylaminomethyl) BINOL[6] developed by Hatakeyama, Shi, and Sasai, respectively, stood out as the most efficient bifunctional catalysts. On the other hand, Jacobsen documented that a combined use of a chiral urea and DABCO can afford the aza-MBH adducts in excellent ee, albeit with moderate yields.[7] Despite these notable achievements, two problems persisted with the enantioselective aza-MBH:[8] (a) acrylates including the activated HFIP and naphthol acrylates were poor substrates providing the adduct in only moderate ee;[3b,9] (b) aliphatic imine failed to participate in this reaction.[9] We report herein a solution to these two issues by developing a novel catalysis that was applicable to the reaction of acrylate with both aromatic and aliphatic imines.

The 6′-OH group in β-ICD **1a** provided a handle for the introduction of other H-bond donors that were modulable both sterically and electronically. Consequently, a series of amides and thioureas were synthesized from **1a** and screened as catalysts using N-(p-methoxybenzenesulfonyl)imine **2a** and β-naphtyl acrylate **3** as model substrates.[10] As summarized in Table 1, the previously unknown 6′-N-Boc-glycine β-ICD (**1c**) gave much better results than 6′-N-thiourea β-ICD **1b**[11] in terms of yield and ee (entries 2 vs 1). Catalysts **1d** and **1e** incorporating a N-trifluorosulfonyl and N-thiourea glycinamide, respectively, afforded adduct **4a** with diminished ee (entries 3, 4). After a survey of reaction conditions by varying the solvents, the temperatures, the stoichiometries, and the additives, the optimal conditions consisted of performing the reaction in CH_2Cl_2 at −30 °C in the presence of 0.1 equiv of catalyst (cf. Supporting Information for details). Under these conditions, catalyst **1c** afforded the adduct **4a** in 87% yield with 91% ee, whereas the β-ICD **1a** provided **4a** in only 39% yield with 77% ee (entries 5 and 6). The superiority of **1c** over β-ICD **1a** is thus clearly demonstrated. Encouraged by these results, catalysts **1f** and **1g** incorporating the N-Boc D- and L-phenylalanine unit, respectively, were prepared. However, neither of them was as efficient as **1c** as catalyst (entries 7 and 8 vs 5). Serendipitously, when freshly prepared acrylate **3** instead of the commercial one was used, **4a** was isolated with significantly reduced enantiomeric excess (entries 9 vs 5) under otherwise identical conditions. Noticing that commercial acrylate **3** contained nearly 10% of β-naphthol, the influence of the additives with different acidic strength was next investigated. Analysis of these results (Supporting Information) showed that the acidity of the additives affected significantly the yield and the ee

Table 1. Aza-MBH Reaction: Survey of Catalysis

entry	catalyst	temperature (°C)	yield (%)[b]	ee (%)[c]
1[a]	**1b**	room temp	81	30[d]
2[a]	**1c**	room temp	99	76[d]
3[a]	**1d**	room temp	88	69[d]
4[a]	**1e**	room temp	64	55[d]
5	**1c**	−30	87	91[d]
6	**1a**	−30	39	77[d]
7	**1f**	−30	75	78[d]
8	**1g**	−30	57	86[d]
9	**1c**	−30	80	79[e]
10	**1c**	−30	95	92[f,g]

[a] Use of 20 mol % of catalyst **1**. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Use of commercially available β-naphtyl acrylate (2.0 equiv). [e] Use of freshly prepared β-naphtyl acrylate (2.0 equiv). [f] The reaction was carried out in presence of **1c** (10 mol %), β-naphtol **5** (10 mol %) and of freshly prepared β-naphtyl acrylate (2.0 equiv). [g] The absolute configuration of **4a** was determined to be (S)-enriched. For details see Supporting Information.

of **4a**, with β-naphtol **5** being optimal ($pK_a^{H2O} = 9.5$, $pK_a^{DMSO} = 17.2$). When **1c** along with β-naphthol (10 mol % each) were employed as a dual catalysts, **4a** was isolated in 95% yield with 92% ee. Too strong acids (PhCOOH) either reduced the yield of **4a** or completely inhibited the reaction (PhSO$_3$H) probably due to the acid−base quench of active catalyst.[12]

The scope of this enantioselective aza-MBH reaction was next examined (Table 2). For aromatic imines, the yield and the ee of adducts **4** were not sensitive to the electronic properties of the aromatic ring and the presence of strong electron withdrawing (NO$_2$, entry 3) or donating group (MeO, entry 4) were well tolerated. The ortho-substituted aromatic imines, known to be challenging substrates for the aza-MBH reaction, worked well. Indeed, **4h** derived from 2,6-dichlorobenzaldehyde was obtained in high yield and enantioselectivity (entry 7). 2-Naphthylimine, 2-furylimine, and 2-cinnamyl imine (entries 8−10) were suitable substrates providing aza-MBH products with excellent enantioselectivities (up to 98% ee).

All previous efforts to include aliphatic imines as electrophilic partner in the MBH reaction have met with failure.[13] It is thus remarkable to find that, under our catalytic conditions, aliphatic imines including α-unbranched imines readily participated in the aza-MBH reaction to yield adducts **4l−p** in moderate yields and

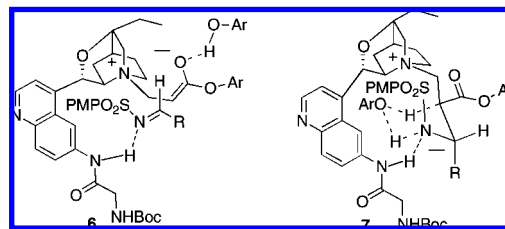**Table 2.** Enantioselective aza-MBH Reaction of Aromatic and Aliphatic Imines[a]

entry	R	time (h)	yield (%)[b]	ee (%)[c]
1	p-MeC$_6$H$_4$ (**4b**)	67	90	91
2	p-ClC$_6$H$_4$ (**4c**)	47	81	94
3	p-NO$_2$C$_6$H$_4$ (**4d**)	47	67	97
4	p-MeOC$_6$H$_4$ (**4e**)	80	84	93
5	m-BrC$_6$H$_4$ (**4f**)	72	84	92
6	m-MeC$_6$H$_4$ (**4g**)	68	95	92
7	2,6-dichloro-C$_6$H$_3$ (**4h**)	60	86	85
8	3-furyl (**4i**)	60	80	98
9	2-naphthyl (**4j**)	47	81	92
10	PhCH=CH (**4k**)	72	52	90
11	Ph(CH$_2$)$_2$ (**4l**)	24	39	86
12	n-pentyl (**4m**)	24	38	85
13	n-butyl (**4n**)	24	41	85
14	i-PrCH$_2$ (**4o**)	24	57(43)[d]	87(82)[d]
15	c-hexylCH$_2$ (**4p**)	24	45	84

[a] Reaction conditions: imine (1 mmol), β-naphtyl acrylate (2 mmol), β-naphtol (0.1 mmol), **1c** (0.1 mmol) in CH$_2$Cl$_2$ (0.35 mL) at −30 °C or aromatic imines and at 0 °C for aliphatic imines. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis. [d] Use of β-naphtyl acrylate (2.0 equiv) freshly prepared without β-naphtol.

good enantioselectivities (Table 2, entries 11−15). In this case, the reaction was best carried out at 0 °C in CH$_2$Cl$_2$. Naphthol had a lesser impact on the enantioselectivity in this case; however, higher yield was obtained in its presence (Table 2, entry 14).

Selective and rapid proton transfer of one of the diastereomers of the aldol adduct was thought to be crucial in determining the ee of the MBH process based on the reversibility of the aldol reaction.[14] This guideline has been considered as a key element in designing the catalyst for enantioselective MBH as well as aza-MBH reactions and the capability of selectively promoting intramolecular proton transfer has frequently been advanced to account for the success of bifunctional catalyst. Indeed, the Hatakeyama's and Sasai's catalysts gave much reduced enantioslectivity when the reaction was performed in the presence of an external proton source.[3,6,9] The positive effect of β-naphthol in the present catalytic system is thus intriguing. Considering the low reversibility of the Mannich reaction,[15] the coexistence of two H-bond acceptors (enoate oxygen, imine nitrogen) and two H-bond donors (naphthol, amide NH), we proposed following H-bond pairings to explain the observed enantioselectivity. Thus, the E-enolate formed upon addition of **1c** to acrylate, being more Lewis basic, would form a H-bond with the β-naphthol, which could in turn be stabilized by π−π interaction between two naphthyl groups. The less basic neutral imine would H-bonded to the less acidic amide NH.[16] These H-bonding pairs would be stronger and sterically less constrained than the alternative intramolecular H-bond. Among two possible transition states (only one was shown), that of **6** was less crowded and should lead, after the C−C bond formation, to the adduct **7**. The β-naphthol mediated proton transfer followed by β-elimination would afford then the observed (S)-adduct. It is interesting to note that enantioselectivity dropped significantly when MeOH having similar pK_a as amide NH was used as cosolvent, probably due to the break down of the H-bond pairs shown in **6**.

The catalyst **1c** was initially designed to have multiple H-bond donor capacity, as found in the Sasai's catalyst. The important role played by naphthol cast doubt on our designing principle. To evaluate this point, catalyst **1h** having a N-Boc sarcosine attached to C-6′ position was synthesized. Reaction of **2a** and **3** in the presence of **1h** under otherwise identical conditions afforded the adduct (S)-**4a** in comparable yield and ee as in the case of **1c**. This experiment indicated that the NHBoc in **1c** might not be involved in H-bonding in accord with the transition state models **6** and **7**.

Figure 1

In summary, β-ICD derived bifunctional catalyst **1c** in combination with β-naphtol served as a highly effective dual catalyst for the asymmetric aza-MBH reactions. High yield and enantioselectivity were uniformly observed in the case of aromatic imines. In addition, the aliphatic N-sulfinyl imines have been successfully employed in the aza-MBH reaction for the first time leading to the corresponding adduct in over 85% ee. The pairing of cooperative H-bonds was thought to be important in developing the present catalysis and we assumed that such approach could be of general implication in devising the novel catalytic systems.

Supporting Information Available: Catalysis optimization, spectroscopic data, ee measurement, and absolute configuration determination for **4a** and **4o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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