Brucine *N*-oxide-catalyzed Morita–Baylis–Hillman reaction of vinyl ketones: a mechanistic implication of dual catalyst system with proline†

Kyungsoo Oh,* Jian-Yuan Li and Jinhyang Ryu

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The brucine *N*-oxide promoted Morita–Baylis–Hillman (MBH) reaction of vinyl ketones with aldehydes has been achieved. The corresponding asymmetric version of MBH reaction was also investigated, and the electron-deficient aryl aldehydes have emerged as suitable reaction partners for vinyl ketones; where proline was employed as a co-catalyst. In this dual catalyst system, proline is believed to form iminium intermediates with electron-deficient aryl aldehydes, while the *N*-oxide activates vinyl ketones to provide enolates through conjugate addition. Upon the combination of these two intermediates, the MBH products with high enantioselectivities are obtained by controlling of the rate-determining step through H-bridged chair-like transition state. Intrinsically, the resulting MBH products, alcohols, are found to interfere with the formation of both intermediates, enolates and proline iminium intermediates, thus the observed enantioselectivity of products attenuates upon further reaction conversion, possibly due to autocatalysis. This current study sheds lights on the synthetic utility of iminium species, derived from electron-deficient aryl aldehydes and proline.

Introduction

The Morita–Baylis–Hillman (MBH) reaction, an aldol condensation of electron-deficient alkenes with aldehydes in the presence of nucleophiles, is one of the most synthetically useful carbon–carbon bond forming reactions, resulting in highly functionalized carbonyl compounds with a newly created chiral center.[1] Although the recent development of asymmetric MBH reactions underscores the importance of chiral nucleophilic catalysts, the substrate scope of both reacting partners, alkenes and aldehydes, is rather limited, perhaps due to the complex nature of the mechanism of MBH reactions. In particular, the asymmetric MBH reaction of vinyl ketones still remains a great challenge.[2] The state-of-the-art in the enantioselective MBH reaction of methyl vinyl ketone involves the use of cyclohexane-based aminothiourea, achieving the MBH products in the range of 90–94% ee's with electon-deficient aromatic aldehydes.[2b] Prior to this work, the enantioselective MBH reaction of methyl vinyl ketone with electron-deficient aromatic aldehydes was reported in the range of 63–78% ee's from the laboratory of Miller *et al.* using a dual catalytic system of peptides and proline.[2g] The use of proline in the asymmetric MBH reaction of methyl vinyl ketone was intriguing since the asymmetric MBH reactions utilizing additives as a co-catalyst were less successful in the past.[2h] The co-catalyst, proline, was first introduced by the Shi group in 2002;[3] however, the exact nature of the co-catalyst has not been understood. One possible reaction mechanism of the proline/$NaHCO_3$-catalyzed MBH reaction has been recently proposed by Gruttadauria *et al.*, where proline acts as a bifunctional catalyst *via* a bicyclic enaminolactone species.[4] Nevertheless, the mechanistic implication for the potential asymmetric origin was not established due to the univocal formation of racemic MBH products. Herein, we report our mechanistic investigation of the proline-catalyzed asymmetric MBH reactions of vinyl ketones in the presence of brucine *N*-oxide as a co-catalyst. One particular noteworthy aspect of the current study is that the asymmetric induction of MBH products in our dual catalyst system could be dictated by a judicious choice of proline with a specific configuration.

Results and discussion

In our continuing effort to utilize chiral tertiary amine *N*-oxides in asymmetric reactions, we have recently reported the stereoselective oxygen transfer reaction of brucine *N*-oxide (BNO) **2b** with chalcone derivatives **1**, *albeit* with modest enantioselectivities (Scheme 1).[5] From our studies it was clearly evident that the bridgehead amine *N*-oxide offers an intrinsic asymmetric environment as well as an enhanced nucleophilicity of the oxygen atom of the *N*-oxide. Interestingly, our attempts to apply this oxygen transfer protocol to other α,β-unsaturated carbonyl systems were met with stringent resistance from several classes of substrates under our optimized reaction conditions. In particular, methyl vinyl ketone (MVK), a well known Michael acceptor,[6] did not participate in the proposed oxygen transfer reaction. We initially postulated that the intermediate **3b** from a conjugate addition of *N*-oxides might not adopt the favorable conformation for a subsequent nucleophilic attack of an α-carbanion to the oxygen atom in **3b**. Given the possibility of the asymmetric environment created by the conjugate addition intermediate **3**, we elected the Morita–Baylis–Hillman reaction to further examine the synthetic utility of such species.

We first examined the MBH reaction of methyl vinyl ketone **6** with *o*-nitrobenzaldehyde **7a** in the presence of catalytic amounts of chiral nucleophiles (Scheme 2). While our initial investigation

Department of Chemistry and Chemical Biology, Indiana University Purdue University Indianapolis, Indianapolis, Indiana 46202, USA. E-mail: ohk@iupui.edu

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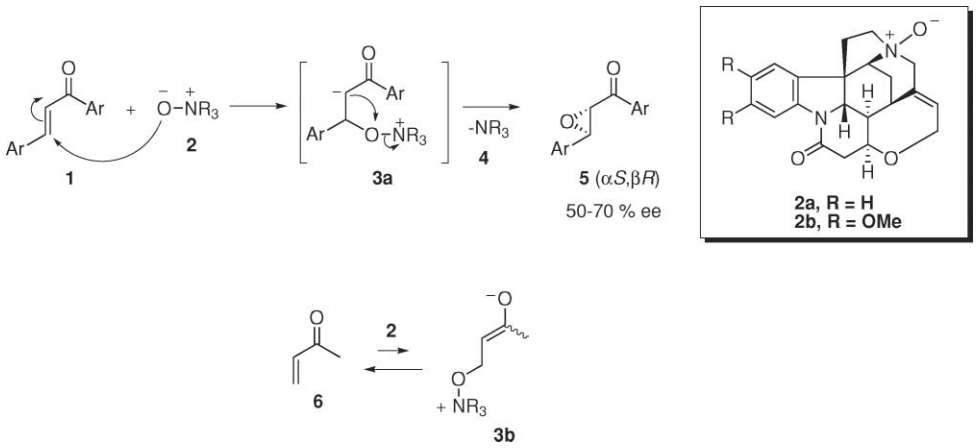
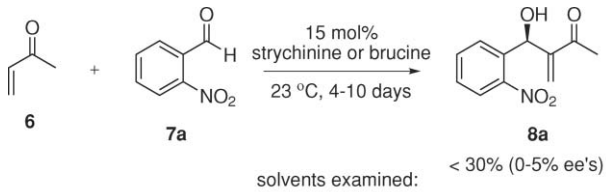


Scheme 1 Asymmetric oxygen transfer reaction using brucine *N*-oxide **2b**.



Scheme 2 The tertiary amine-catalyzed MBH reaction.

examined the tertiary amine-catalyzed MBH reactions, such as brucine and strychnine, the results were rather disappointing. The reaction conversions remained very low, providing **8a** in at best 10–30% yields, even with prolonged reaction times (typically 4–10 days). Furthermore, the observed enantioselectivities of **8a** were negligible, in the range of 0–5% ee's, regardless of reaction conditions involving various solvents and varied amounts of reaction components (catalysts, **6** and **7a**). Our experimental results closely mirrored the previous findings by Drewes[7] and Shi,[2g] respectively.

Thus, we turn our attention to the tertiary amine *N*-oxides of the alkaloids due to their weakened basicity (Table 1).[8] Our initial experimental results employing 15 mol% of **2a** or **2b** in a variety of solvents were similar to those of the parent alkaloids, providing racemic **8a** with <10% yields (entry 1–2). However, to our surprise, the reaction conversion drastically improved beyond 36 h reaction time *in the absence of solvent*, thus racemic **8a** was isolated in 90% yield after a total of 110–120 h reaction time (entry 6). This optimal reaction condition was identified by the use of 3 equivalents of methyl vinyl ketone **6**, since some of **6** was consumed in a self dimerization.[9] We interpreted the current MBH reaction with two plausible reaction mechanisms; (1) the BNO-promoted mechanism at the beginning of the reaction, (2) the reaction mechanism involving a synergistic action of BNO and **8a** to facilitate the product formation beyond 10% reaction conversion, typically after 36 h reaction time. We ruled out the possibility of autocatalysis of **8a** by performing the experiment using 20 mol% of **8a** in the absence of BNO, where a negligible reaction conversion was observed after a prolonged reaction time. Furthermore, we added 20 mol% of **8a** from the beginning of reaction and observed the total reaction time could be reduced to about 72 h, which clearly indicated the potential synergistic action of amine *N*-oxide and **8a**.

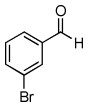
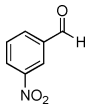
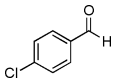
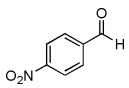
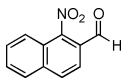
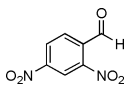
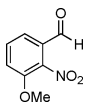
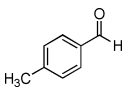
Table 1 The amine *N*-oxide catalyzed MBH reaction[a]

Entry	Catalyst[b]	Reaction time/h	**8a** yields (%)[c]	Comments
1	**2a**	120	<5	Protic/aprotic solvents
2	**2b**	120	<10	Protic/aprotic solvents
3	**2b**	36	<10	No solvent
4	**2b**	120	41	No solvent
5	**2b**	120	60	No solvent, **6** (2 eq)
6	**2b**	120	90	No solvent, **6** (3 eq)
7	**2b**	120	88	No solvent, **6** (5 eq)
8	**2b**	36	<10	No solvent, **6** (3 eq)

[a] Unless stated otherwise, reactions were performed with methyl vinyl ketone **6** (0.65 mmol) and *o*-nitrobenzaldehyde **7a** (0.65 mmol) at ambient temperature. [b] 15 mol% of catalysts **2** (0.098 mmol) were used. [c] Isolated yields after column chromatography.

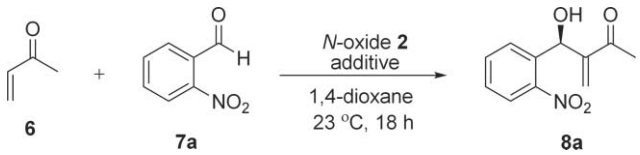
Having established the reaction conditions for the amine *N*-oxide-catalyzed MBH reaction, we further explored the reactivity of other aldehydes under our optimized conditions (Table 2). Electron-deficient aldehydes, in particular nitro group-containing aldehydes, readily reacted to afford the MBH products in good to excellent yields (entries 1–6). Halogen-substituted benzaldehydes were less efficient, providing modest yields of the MBH products (entries 7–9). Heteroaromatic aldehydes were also suitable substrates for our amine *N*-oxide-catalyzed MBH reaction (entries 10–11); however, the isolated yields of products were somewhat low, possibly due to the instability of the products during the reaction (entry 11) and upon purification on silica column chromatography (entries 10–11). The MBH reactions employing electron-rich arylaldehydes such as 4-methylbenzaldehyde and aliphatic aldehyde such as cyclohexanecarboxaldehyde proceeded less efficiently (entries 12–14). Our attempts to improve the reaction conversion or to reduce the reaction time by increasing the amounts of amine *N*-oxide catalyst were unsuccessful. Surprisingly, the varied amount of amine *N*-oxides did not affect the reaction yields and the reaction times for the electron-rich aldehydes, not only at the initial stage of reaction but also the overall reaction time.

Table 2 Substrate scope of the brucine *N*-oxide-catalyzed MBH reaction[a]

Entry	Aldehyde	Reaction time/d	Yield [b](%)	Entry	Aldehyde	Reaction time/d	Yield [b](%)
1		5	90	8		5	55
2		3	96	9		6	55
3		5	77	10		5	63
4		5	61	11		5	37
5		4	80	12		6	47
6		4	82	13		6	25
7		5	44	14		8	26

[a] Reactions were performed with methyl vinyl ketone **6** (1.95 mmol) and aldehydes **7** (0.65 mmol) using 15 mol% (0.098 mmol) **2b** in the absence of solvent at ambient temperature. [b] Isolated yields after column chromatography.

Table 3 Asymmetric MBH reaction of methyl vinyl ketone[a]



6 **7a** **8a**

Entry	*N*-oxide (eq)	Additive (eq)	ee (%)[b]
1	**2a** (0.1)	—	nr
2	**2b** (0.1)	—	8 (*R*)
3	**2b** (0.1)	Imidazole (0.1)	8 (*R*)
4	**2b** (0.1)	$LiClO_4$ (0.1)	nr
5	**2a** (0.1)	L-Pro (0.1)	39 (*R*)
6	**2b** (0.1)	L-Pro (0.1)	57 (*R*)
7	**2c** [c](0.1)	L-Pro (0.1)	nr
8	**2d** [d](0.1)	L-Pro (0.1)	16 (*R*)
9	**2e** [e](0.1)	L-Pro (0.1)	29 (*R*)
10	—	L-Pro (0.1)	nr
11	**2b** (0.1)	L-Pro (0.2)	40 (*R*)
12	**2b** (0.1)	L-Pro (0.3)	34 (*R*)
13	**2b** (0.1)	L-Pro (0.4)	27 (*R*)
14	**2b** (0.1)	L-Pro (0.5)	32 (*R*)
15	**2b** (0.2)	L-Pro (0.1)	62 (*R*)
16	**2b** (0.3)	L-Pro (0.1)	82 (*R*)
17	**2b** (0.4)	L-Pro (0.1)	83 (*R*)
18	**2b** (0.5)	L-Pro (0.1)	85 (*R*)

[a] Reaction performed with methyl vinyl ketone **6** (0.65 mmol) and *o*-nitrobenzaldehyde **7a** (0.65 mmol) in 1,4-dioxane (0.77 mL/0.1 mmol of amine *N*-oxide) in the presence of varied amounts of **2** and additives at ambient temperature for 18 h (0–20% conversion by ^{1}H NMR). [b] Determined by chiral HPLC (absolute configuration of **8a** was determined by comparison with the HPLC retention times in ref. 13). [c] **2c** (4-phenyl pyridine *N*-oxide). [d] **2d** (4-methylmorpholine *N*-oxide). [e] **2e** (*N*,*N*-dimethylundecylamine *N*-oxide).

Although our initial postulation regarding the conjugate addition of amine *N*-oxides to methyl vinyl ketone (MVK) was vindicated by the facile MBH reactions with a variety of aldehydes, the asymmetric induction using such intermediate species was not apparent from our BNO-catalyzed MBH reactions. The poor asymmetric induction was first attributed to the slow and non-selective BNO-catalyzed MBH reaction, which is believed to be a primary reaction pathway at the early stage of reaction *in the presence or absence of solvents*. Secondly, the BNO-MBH product catalyzed reaction mechanism is also believed to be non-selective, which might be a major reaction pathway for beyond 10–20% reaction conversion. Fortunately, our experiments implied that the BNO-MBH product catalyzed reaction pathway could slow down, if not completely shut down, *in the presence of solvents*, such as 1,4-dioxane. Therefore, we further examined the possibility of asymmetric induction in the BNO-catalyzed MBH reaction (Table 3). Similar to our previous studies, strychinine *N*-oxide **2a** did not catalyze the reaction (<5%); however, to our delight, employing BNO **2b** as a chiral nucleophilic catalyst led to the slow formation of MBH product **8a** with low ee (entry 2). Although further effort was made to improve enantioselectivity, due to the complex nature of MBH reaction mechanisms, our optimization attempts were unsuccessful regardless of changing reaction parameters: varied temperatures, solvents, and amounts of **2b**. We next turned our attention to systems employing a co-catalyst, using **2b** in combination with imidazole, lithium perchlorate, and L-proline (entry 3–6).[2h] Although imidazole and $LiClO_4$ delivered no obvious improvements in enantioselectivity, the presence of L-proline markedly enhanced the observed enantioselectivity to 57% in combination with BNO **2b** (entry 6). Interestingly, no reaction was observed with 4-phenyl pyridine *N*-oxide (entry 7), while other tertiary amine *N*-oxides were significantly less selective (entries 8–9). After confirming that L-proline alone did not catalyze the reaction (entry 10), further reaction optimization was conducted with varied amounts of both catalysts; **2b** and L-proline (entry 11–18). While increasing the amount of L-proline was detrimental to the observed enantioselectivity, the excess amount of **2b** led to further improvements in the observed enantioselectivities up to 85%. Considering the cost benefit of amounts of catalysts used against a minimal difference in the observed enantioselectivities (entry 16 *vs.* 18), the optimal catalyst combination was chosen as a 3 : 1 mixture of **2b** and L-proline. Although at this juncture we also investigated potential effects of various solvents and molar ratios of the reagents, no further improvement of enantioselectivity was obtained (see the Supplementary Information†).

Interestingly, during our investigation, we found that the enantiomeric excess of the MBH products **8a** was inversely proportional to the overall reaction conversion (Fig. 1). Indeed, our studies on the variation of enantiomeric excess against the reaction conversion clearly indicated that the observed enantiomeric excess was maximized at the beginning of the reaction and gradually

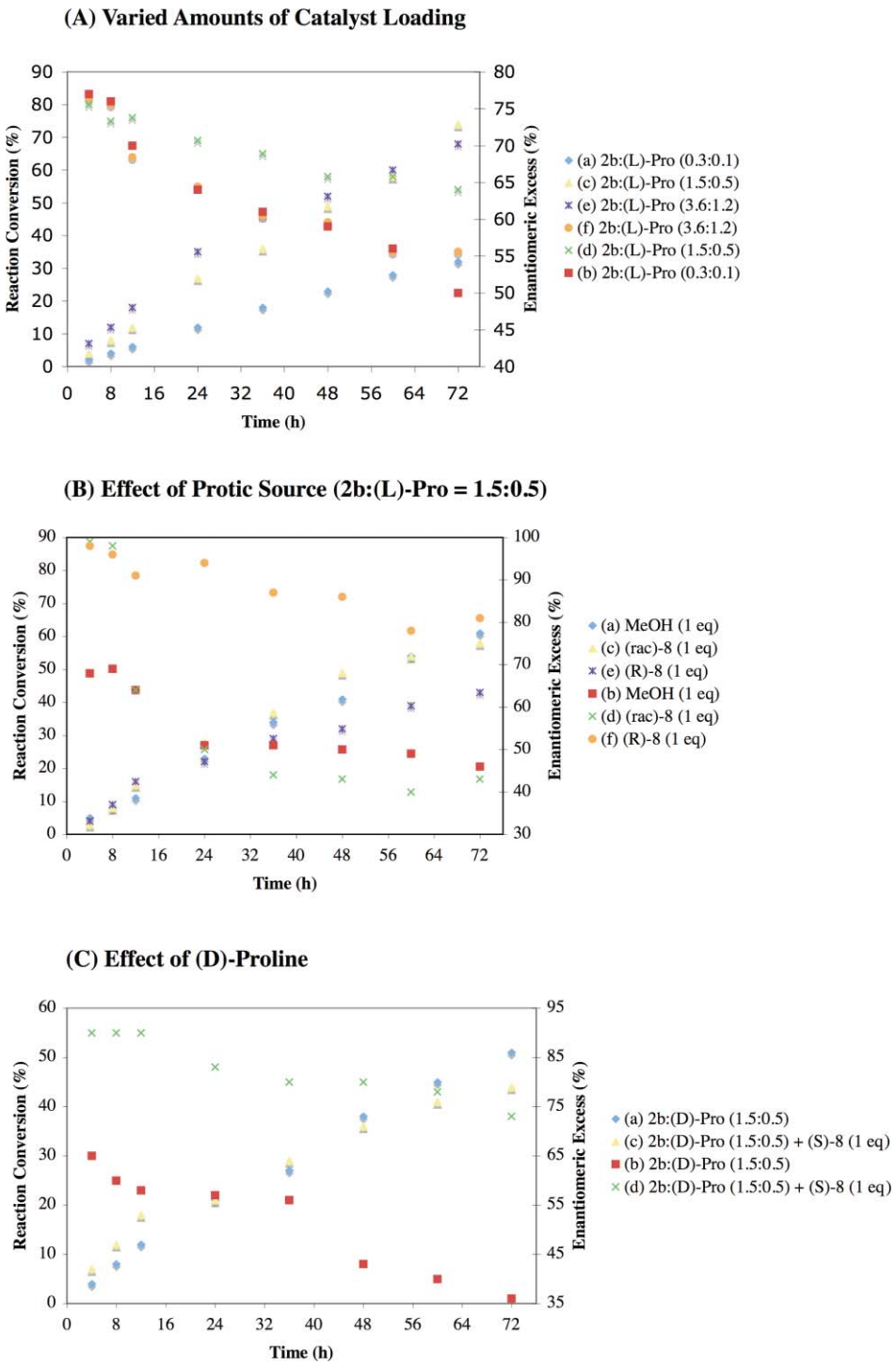


Fig. 1 Proline-catalyzed asymmetric MBH reaction: a, c, e refer to the reaction conversion *versus* time and b, d, f refer to the enantiomeric excess *versus* time.

lowered upon further reaction conversion (Fig. 1A-b, d and f). It should be noted that our experimental data sets involved frequent aliquot removals from a reaction, which are filtered using a short pad of silica gel and analyzed using ^{1}H NMR and HPLC. In doing so, the observed conversions were slightly higher than experiments involving direct isolation of MBH products. Subsequently, the observed ee values were slightly lower. We believe that this is due to the uneven removal of solid components, *N*-oxides and proline, upon taking out frequent aliquots. Nevertheless, the trend of reaction conversion *versus* enantioselectivity persisted throughout our experiments. The effect of catalyst loading showed that the increment of dual catalyst loading positively influenced the reaction rate; however, the optimal condition was achieved upon the employment of 1.5 equivalents of **2b** and 0.5 equivalents

of (L)-proline (Fig. 1A-a, c and e).[10] Next, we investigated the potential effect of added protic sources (Fig. 1B). The presence of 1 equivalent of MeOH slightly lowered the reaction rate and enantioselectivity; 61% conversion with 46% ee, compared to 74% conversion with 54% ee in the absence of added protic source after 72 h at ambient temperature (Fig. 1B-a and b).[11] Furthermore, we performed the reaction with added MBH product (*rac*)-**8a** and found that the reaction was slower as in the case of MeOH, and the corrected enantiomeric excess of the reaction products suggested that a similar decrease of enantioselectivity persisted upon further reaction conversion (Fig. 1B-c and d). In the presence of enantiomerically enriched **(*R*)-8**, the MBH reaction significantly slowed down (Fig. 1B-e and f), for example, it took 72 h for 43% conversion, while it took only 36 h in the absence of added protic source. However, the corrected enantiomeric excess of reaction products indicated a high level of enantioselectivity (81% ee at 43% conversion). Interestingly, the reaction was completely shut down in the presence of 1 equivalent of enantiomerically enriched **(*S*)-8**. In order to probe the nature of the dual catalyst system, we examined the catalyst combination of **2b** with (D)-proline for the cooperative catalyst activity as noted in classical double stereodifferentiation (Fig. 1C).[12] Consistent with the results reported by Miller *et al.*,[2g] the MBH products with opposite configuration, **(*S*)-8**, were observed with a slightly lower reaction rate, possibly a mis-matched case (Fig. 1C-a and b). Once again, the presence of enantiomerically enriched **(*S*)-8** displayed a similar reactivity and enantioselectivity as in combination of (D)-proline (Fig. 1C-c and d). The reversal of enantioselectivity clearly suggested that the stereochemistry of MBH products was dictated by the proline stereochemistry.

While proline and BNO **2b** are capable of undergoing conjugate addition to MVK,[13] our preliminary NMR studies (in 1,4-dioxane-D_8) did not show any evidence of such species. However, since the MBH reaction typically shows extremely slow reaction kinetics, the NMR time scale might not be suitable for detecting a low concentration of the intermediates from the conjugate addition of proline or BNO. The possibility of ionic interaction between catalysts has been ruled out by our NMR study, where no noticeable change in chemical shifts was observed in a mixture of **2b** and proline.[14] Although further research is required to establish the identity of the catalyst, one possible mechanistic implication has been derived from the NMR studies of proline and aldehyde **7a** (Fig. 2). The ^{1}H NMR analysis of a mixture of proline and *o*-nitro benzaldehyde **7a** showed an extremely low concentration of oxazolidinone species, *exo*-**9a**, at ambient temperature, while diastereomeric *endo*-**9a** was only observable upon raising the

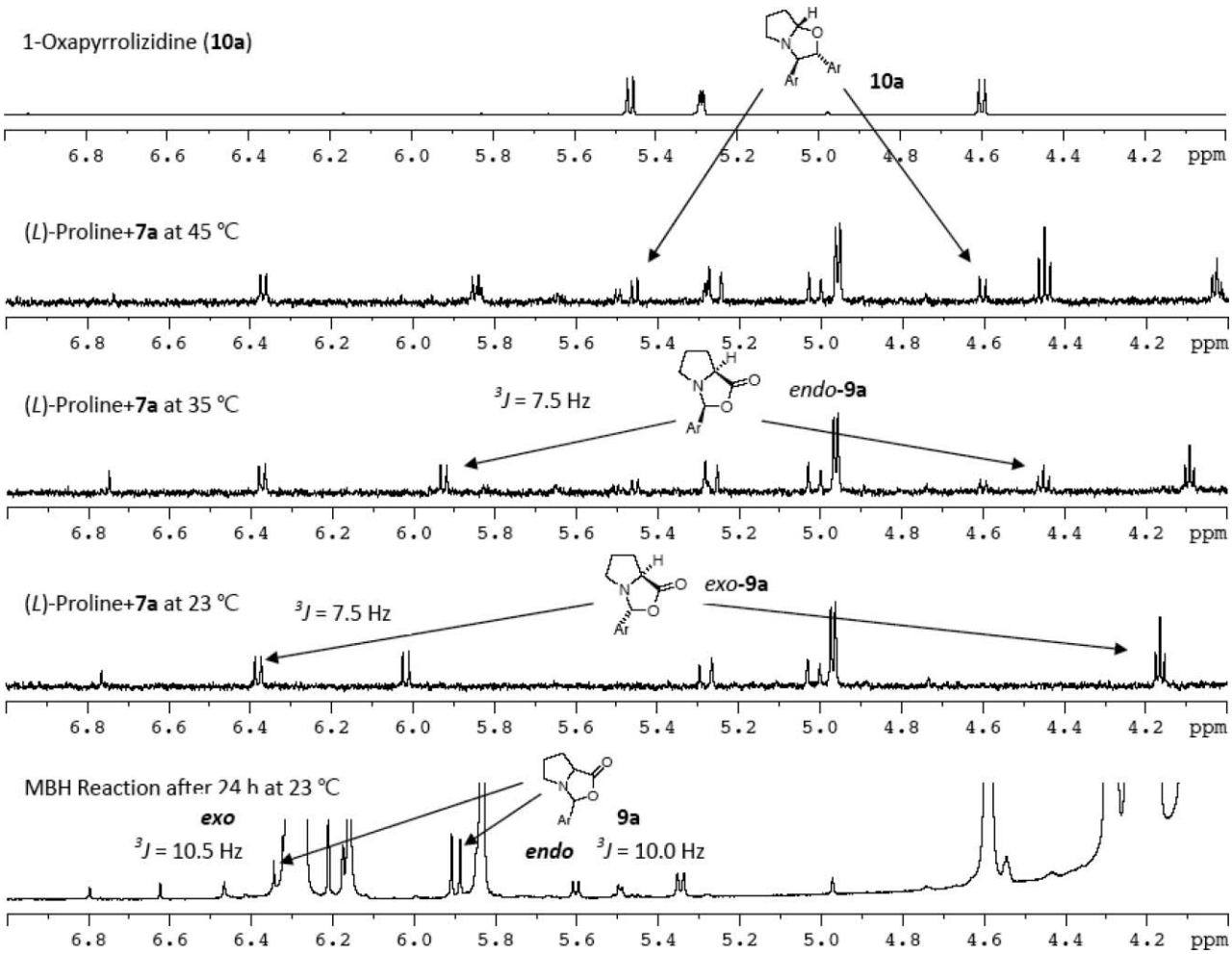


Fig. 2 ^{1}H NMR studies of a mixture of proline and aldehyde **7a**.

temperature.[15] The observation of oxazolidinones is very interesting, since this strongly indicates the presence of iminium species in the proline-catalyzed MBH reactions. Although our synthetic effort was made to isolate such oxazolidinone intermediates as possible catalyst precursors, in our hands, the isolation of oxazolidines from the reaction of proline and aromatic aldehydes was not successful. This was not surprising, since the only known proline-derived oxazolidinones in literature were derived from aliphatic aldehydes such as pivaldehyde,[16] trichloroacetaldehyde and 2-methylbutanal,[17] subsequently, oxazolidinones derived from aromatic aldehydes have only been NMR-detectable species in the course of proline-catalyzed transformations.[18] The formation of single diastereomeric 1-oxapyrrolizidine **10a** from our synthetic studies, as an isolable chemical entity, illustrates the potential thermodynamic sink for oxazolidinones and the transient nature of iminium species using aromatic aldehydes. 1-Oxapyrrolizidines **10** were typically obtained either from a prolonged exposure of proline and aromatic aldehydes at ambient temperature or a brief mixing of proline and aromatic aldehydes at elevated temperatures. The formation of 1-oxapyrrolizidines **10** could be explained by spontaneous decarboxylation of **9** to generate azomethine ylides followed by cycloaddition.[19] Upon a close inspection of ^{1}H NMR of our MBH reaction (in 1,4-dioxane-D_8), considerably higher concentrations of oxazolidinones, **9**, seem to be present at ambient temperature, similar to the mixture of proline and **7a** at elevated temperatures, while the formation of 1-oxapyrrolizidine **10a** was completely suppressed. Two isomeric oxazolidinones **9a** in the MBH reaction mixture were assigned by using chemical shifts, since the observed coupling constants for **9a** in the reaction mixture were somewhat different from that of **9a** in a mixture of **7a** and (L)-proline. This difference in coupling constants could be attributed to the conformational variation of **9a** due to the presence of a large amount of **2b** and (L)-proline, as well as the MBH product.[20]

Although there is plenty of room for alternative interpretations of our experimental findings, the formation of oxazolidinone **9a** might provide valuable mechanistic insights for the proline-catalyzed MBH reaction.[21] Recently, McQuade *et al.* proposed the mechanism of MBH reactions, in which the rate-determining step (RDS) is the elimination of the α-proton by a hemiacetal intermediate, by kinetic isotope studies (Fig. 3 (*a*)).[22] Moreover, the kinetic studies by Aggarwal and Lloyd-Jones concluded that the α-proton-transfer (or RDS) could be facilitated in the presence of protic species (Fig. 3 (*b*)),[23] thus the MBH products are dominant species for autocatalysis beyond 20% conversion. These two mechanistic pathways are consistent with our experimental results, where iminium intermediate **11** can be proposed to participate in the formation of the *N*,*O*-hemiacetal intermediate (Fig. 3 (*c*)) giving rise to the MBH products with high enantioselectivity after preferential α-H elimination (*via* H-bridged chair-like transition

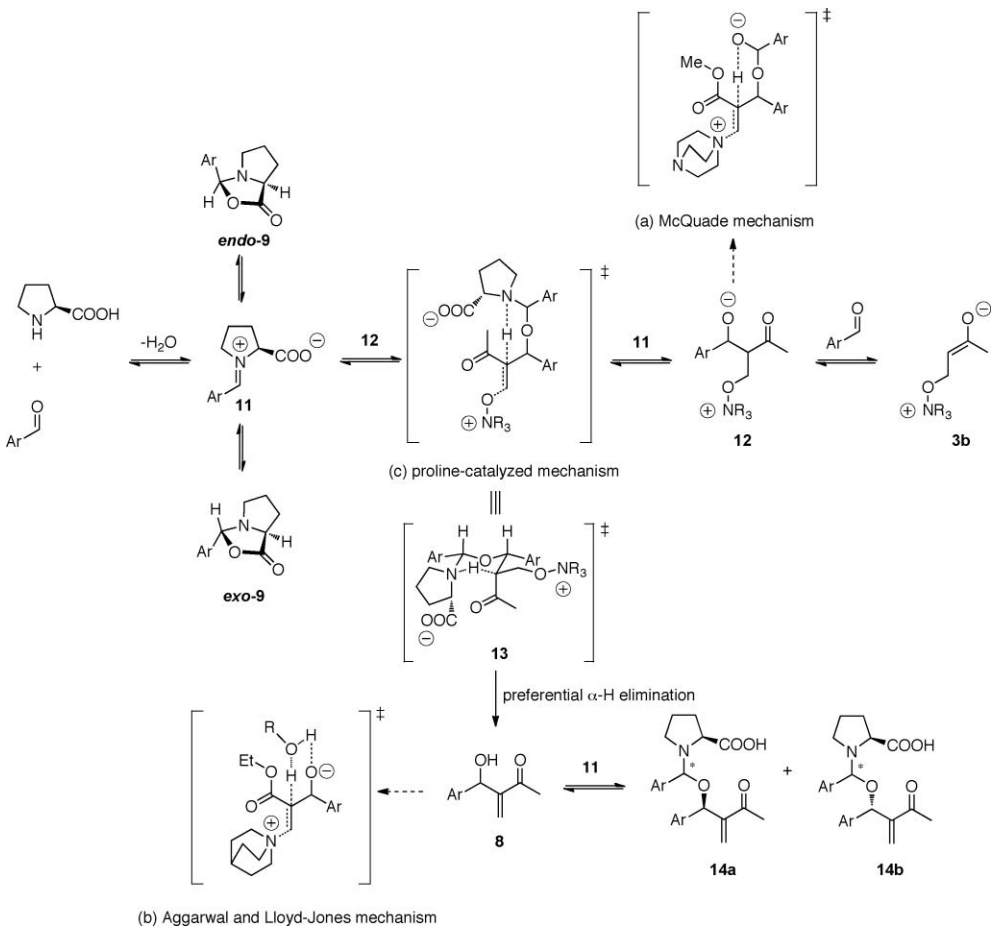
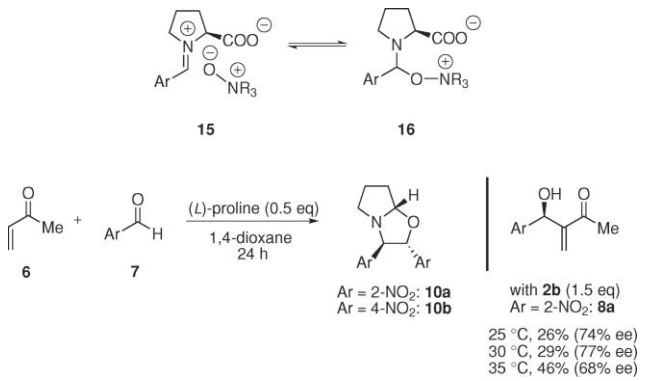


Fig. 3 Proposed reaction mechanism of the MBH reaction.

state **13**) at the initial stage of reaction. The presence of three stereogenic centers in the transition state **13** renders 8 possible diastereomeric species. However, considering the most stable chair-like transition state, where proline, two aromatic substituents, and $–CH_2O–NR_3$ groups[24] occupy equatorial positions, the proposed transition state should effectively discriminate all possible diastereomers for the one shown in Fig. 3. Furthermore, the stereochemistry of the iminium species **11** is expected to influence the stereochemical outcome of the *N*,*O*-acetal **13**, possibly through a preferential dissociative ring opening of *exo*-oxazolidinone ***exo*-9a**.[15] Thus, our proline-catalyzed MBH reaction appears to control the stereoselectivity of the proton-transfer step.

However, as the reaction progresses, the accumulation of MBH products **8** will compete with alkoxide intermediate **12** on the consumption of the iminium species **11** to give new *N*,*O*-acetals **14**. Our observation of slow MBH reaction rates in the presence of added protic species coincides with this interpretation. Aggarwal's alcohol-catalyzed autocatalysis could also compete with our proline-catalyzed reaction; however, the fact that our MBH reactions showed a high level of enantioselectivity in the presence of a small amount of protic species (MeOH or (*rac*)-**8**) suggests that the rate of autocatalysis might be lower than that of the proline-catalyzed reaction. Alternatively, it can be viewed that Aggarwal's autocatalysis phenomenon is somewhat selective, since there is a matched case (Fig. 1A and 1B) and a mis-matched case (in the presence of (*S*)-**8a** and (L)-Pro). The total shutdown of the mis-matched MBH reaction is not expected from our proposed role of MBH products in consuming the iminium intermediate since the *N*,*O*-acetals **14** should be able to revert back to re-generate the iminium intermediate **11**. This result, therefore, implies that alternative mechanisms for either proline or aldehyde consumption by the MBH products might exist. To investigate this notion further, we examined ^{1}H NMR spectra of a mixture of (L)-proline, aldehyde, and **(*S*)-8**, a mis-matched case, for possible molecular recognition between them. Although no significant information could be obtained in this regard, we observed a slow formation of 1-oxapyrrolizidine **10a** from the MBH reaction mixture of this mis-matched case, a potential inhibitory pathway during the MBH reaction (see the Supplementary Information†). We believe that Miller's highly successful asymmetric MBH reaction effectively controls this unproductive **(*S*)-8**-promoted consumption of (L)-proline and aldehydes in the presence of chiral peptide.[25]

The exact role of brucine *N*-oxide in the asymmetric induction is not clear at this time; however, it is possible to speculate that **2b** could be involved in stabilizing the iminium species **11** for a subsequent *N*,*O*-acetal formation **13**,[26] possibly through either a contact ion pair **15** or a *N*,*O*-acetal formation **16** (Scheme 3). To substantiate the positive role of **2b**, we conducted our proline-catalyzed reactions at 30 and 35 °C in the absence of **2b**. No MBH product was observed at either temperature, while the formation of 1-oxapyrrolizidine **10** was observed. The formation of **10** was significantly suppressed in the presence of **2b** at both temperatures, resulting in the exclusive formation of the MBH product **8a** with diminished enantioselectivity. Furthermore, it is reasonable to assume that the amine *N*-oxide **2b** undergoes conjugate addition to MVK to generate enolates **3b** (Fig. 3) as evidenced in our BNO-promoted MBH reactions (see Table 2–3),[27] although this might not be a major role of BNO in the proline-catalyzed MBH



Scheme 3 The proposed roles of brucine *N*-oxide.

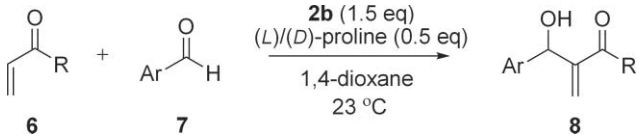
reaction; the BNO-promoted MBH reactions proceed with very low reaction rates and enantioselectivities in 1,4-dioxane (~10% conversion with 10 mol% **2b** after 30 h at 23 °C).

Next, we examined the scope of aldehyde substrates with different vinyl ketones (Table 4). As expected, the reaction at the 24 h mark appeared to be highly dependent on the aldehyde substrates in terms of observed reactivity and enantioselectivity. For example, 2-nitro-substituted aromatic aldehydes collectively showed good enantioselectivities with reasonable reactivities (entry 1–5), while other less electron-deficient aldehydes showed significantly diminished reactivities and enantioselectivities (entry 6–10). In addition, there was no reaction upon the use of aliphatic aldehydes and acrylates, as well as *N*-tosyl imine[28] derived from 2-nitrobenzaldehyde in place of vinyl ketones. These results were not so surprising, since no iminium intermediates are possible with acrylates and imines, and the oxazolidinones derived from aliphatic aldehydes are known to be stable, in fact isolable, thus, the concentration of iminium intermediates could be significantly low.[16,19] The substitution pattern on aryl aldehydes also influences the enantioselectivity of MBH products, and this could be attributed to the different activation energies of proline-catalyzed and alcohol-catalyzed (autocatalysis) processes. However, the general trend of the dual catalyst system regarding the formation of MBH products with opposite configuration in the presence of an appropriate proline persisted throughout substrates. Furthermore, the asymmetric MBH reactions of ethyl vinyl ketone with 2-nitro-substituted aromatic aldehydes also confirmed the generality of our reaction, providing the MBH products with good enantioselectivities (entry 11–15).

Conclusion

Our studies have shown that brucine *N*-oxide is a nucleophilic catalyst for the Morita–Baylis–Hillman reaction of methyl vinyl ketone. In particular, the presence of co-catalyst, brucine *N*-oxide, proline catalyzes the asymmetric Morita–Baylis–Hillman reactions of electron-deficient aryl aldehydes through iminium intermediates. Although the proline-catalyzed MBH reaction appears to control the proton-transfer step with high stereoselectivies, the observed enantioselectivity of the products varies on the nature of aldehyde substrates. The alcohol-catalyzed (autocatalysis) process is believed to become a competing reaction pathway as the reaction progresses; however, various MBH products with modest to good enantioselectivities can be achieved with electron-deficient aryl

Table 4 Asymmetric MBH reaction of vinyl ketones[a]



6 7 8

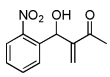
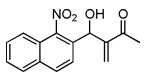
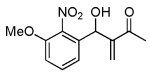
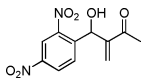
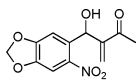
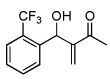
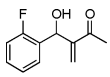
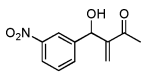
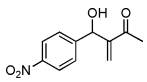
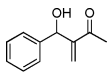
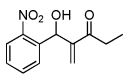
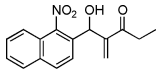
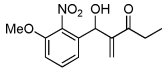
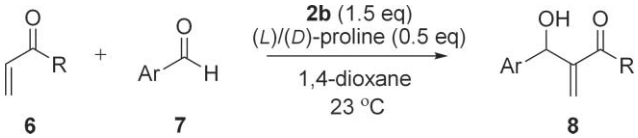
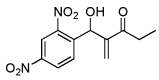
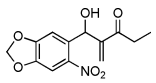
Entry	8	Additive	ee (%) at 24 h	Reaction time/d	Yield [b](%)	ee (%)[c]
1	 8a	(L)-Pro (D)-Pro	74 (*R*) 56 (*S*)	4 5	42 30	63 (*R*) 40 (*S*)
2	 8b	(L)-Pro (D)-Pro	78 (*R*) 81 (*S*)	3 4	45 49	44 (*R*) 39 (*S*)
3	 8c	(L)-Pro (D)-Pro	75 (*R*) 45 (*S*)	8 4	49 51	49 (*R*) 21 (*S*)
4	 8d	(L)-Pro (D)-Pro	35 (*R*) 44 (*S*)	4 3	72 67	55 (*R*) 32 (*S*)
5	 8e	(L)-Pro (D)-Pro	80 (*R*) 81 (*S*)	7 7	20 27	45 (*R*) 43 (*S*)
6	 8f	(L)-Pro (D)-Pro	60 (*R*) 84 (*S*)	6 6	16 16	59 (*R*) 37 (*S*)
7	 8g	(L)-Pro (D)-Pro	44 (*R*) 33 (*S*)	6 6	21 22	50 (*R*) 29 (*S*)
8	 8h	(L)-Pro (D)-Pro	29 (*R*) 36 (*S*)	7 6	38 43	48 (*R*) 16 (*S*)
9	 8i	(L)-Pro (D)-Pro	20 (*R*) 49 (*S*)	5 4	34 49	26 (*R*) 42 (*S*)
10	 8j	(L)-Pro (D)-Pro	10 (*R*) 19 (*S*)	7 7	12 16	8 (*R*) 11 (*S*)
11	 8k	(L)-Pro (D)-Pro	74 (*R*) 74 (*S*)	5 5	38 30	58 (*R*) 54 (*S*)
12	 8l	(L)-Pro (D)-Pro	79 (*R*) 82 (*S*)	5 5	30 39	54 (*R*) 61 (*S*)
13	 8m	(L)-Pro (D)-Pro	67 (*R*) 78 (*S*)	5 5	54 62	72 (*R*) 64 (*S*)

Table 4 *(Contd.)*



6 7 8

Entry	8	Additive	ee (%) at 24 h	Reaction time/d	Yield [b](%)	ee (%)[c]
14	 8n	(L)-Pro	66 (*R*)	3	47	57 (*R*)
		(D)-Pro	69 (*S*)	3	61	65 (*S*)
15	 8o	(L)-Pro	80 (*R*)	8	55	60 (*R*)
		(D)-Pro	87 (*S*)	8	40	56 (*S*)

[a] Reactions were performed with vinyl ketone **6** (0.65 mmol) and aldehydes **7** (0.65 mmol) in 1,4-dioxane (5.0 mL) in the presence of *N*-oxide **2b** (0.98 mmol) and (L)/(D)-proline (0.32 mmol) at ambient temperature. [b] Isolated after flash chromatography. [c] Determined by chiral HPLC (absolute configuration of **8** was determined by comparison of the HPLC retention times with known data).

aldehydes. While the synthetic potential of iminium intermediates derived from aryl aldehydes and proline in proline catalysis has not been well recognized, our studies clearly showed a high potential of such species, where a judicious choice of proline and electron-deficient aryl aldehydes could lead to the formation of both enantiomerically enriched MBH products. We are currently investigating the generality of our dual catalyst system in other asymmetric reactions, and our result will be reported in due course.

Experimental section

Typical experimental procedure for the enantioselective MBH reaction of aldehydes

To a stirred solution of 2-nitroaldehyde **7a** (100 mg, 0.65 mmol), brucine *N*-oxide **2b** (404 mg, 0.98 mmol), and (L)-proline (37 mg, 0.32 mmol) in dry 1,4-dioxane (5.0 mL) at ambient temperature, was added ethyl vinyl ketone **6b** (63 µl, 0.65 mmol) in one portion. The resulting suspension was stirred at 25 °C for 5 days, after which the mixture was directly loaded to silica gel for flash column chromatography (eluent 33 : 67 diethyl ether–hexanes) to give Morita–Baylis–Hillman product **8k**[29] (58 mg, 38% (58% ee)). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (dd, 8.0, 1.0 Hz, 1H), 7.77 (dd, 8.0, 1.5 Hz, 1H), 7.64 (td, 7.7, 1.0 Hz, 1H), 7.44 (td, 7.7 1.5 Hz, 1H), 6.20 (s, 1H), 6.14 (s, 1H), 5.72 (d, 1.0 Hz, 1H), 3.61 (br s, 1H), 2.77–2.71 (m, 2H), 1.07 (t, 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.7, 148.3, 147.9, 136.4, 133.4, 128.8, 128.4, 125.1, 124.6, 67.7, 31.1, 8.0; IR (film, cm^{-1}) 3431, 1675, 1525, 1350; HRMS calcd for $C_{12}H_{13}NO_4Na$ 258.0742, found 258.0729 [MNa]$^+$. HPLC (CHIRALPAK OD-H, hexane–2-propanol 95 : 5, 0.75 mL min^{-1}) t_R(minor) = 23.60 min, t_R(major) = 26.21 min.

Acknowledgements

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25 A more pronounced mis-matched case with (D)-proline and Miller's peptide catalyst has been evidenced, see: ref. 2*g* and 13.

26 Addition of water is known to suppress the formation of oxazolidinone **9** in proline-catalyzed aldol reactions, see: ref. 18.

27 The solubility of brucine *N*-oxide improved in the presence of methyl vinyl ketone and proline, see the Supporting Information†.

28 Racemic MBH product, **8a**, was obtained after 5 days in 10–20% yields due to the hydrolysis of imines to 2-nitrobenzaldehyde.

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