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Dual Iminium- and Lewis Base Catalyzed Morita–Baylis–Hillman Reaction on Cyclopent-2-enone

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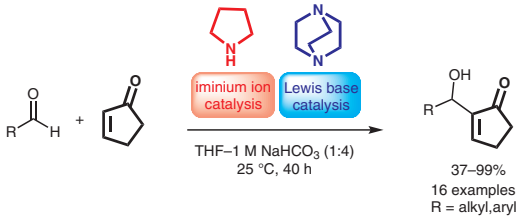

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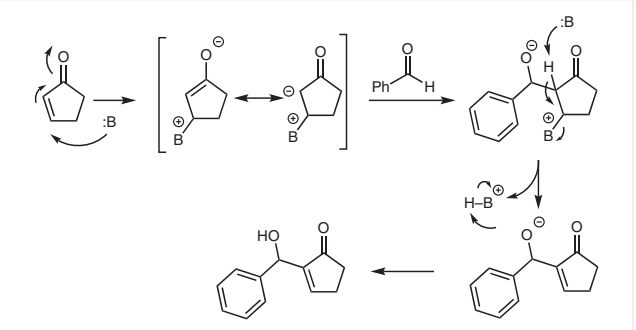
Abstract The application of iminium catalysis to the challenging Morita–Baylis–Hillman reaction on cyclopenten-2-one leads to the corresponding allylic alcohols in excellent yields. Experimental evidence shows that secondary amines act as co-catalysts activating the enone moiety towards the nucleophilic attack at the β-position by DABCO as the Lewis base catalyst, resulting in an augmented nucleophilic character towards the reaction with aldehydes.

Key words catalysis, enones, synthetic methods, C–C coupling, basicity

It is well recognized that the development of multibond-forming protocols, such as multicomponent reactions,[1] domino reactions,[2] or one-pot multistep processes[3] are important synthetic approaches in organic chemistry. The Morita–Baylis–Hillman (MBH) reaction[4] is an aldol-type chemical transformation used for the generation of C–C bonds. The first paper on this reaction was reported by Morita in 1968,[5] in which acrylonitrile was reacted with a range of aldehydes under phosphine catalysis. In 1972, Baylis and Hillman subsequently patented a similar reaction catalyzed by amines.[6] Typical substrates for these reactions are electron-poor alkenes, which react by their α-carbon with carbonyl compounds or imines as the electrophiles. In the latter case the reaction is called the 'aza-MBH'.[7] Interest in this reaction grew in the 1990s,[8] due to the high level of atom economy, the versatility in the use of aldehydes and α,β-unsaturated carbonyls, and the polyfunctional character of the reaction product. Accordingly, this reaction met our interest as an efficient synthetic tool addressing coupling reactions to achieve polyfunctional molecules for diversity-oriented synthesis strategies.[9]

The mechanism of the MBH reaction consists of the activation of the α,β-unsaturated compound at the β-position to form a zwitterionic compound, which subsequently attacks the electrophilic carbonyl carbon atom of the aldehyde. A final H-shift and elimination of the base furnishes the corresponding adduct (Scheme 1). Recent insight on the mechanism of alcohol-mediated MBH reaction have been reported by Plata and Singleton.[10]



Scheme 1 The MBH reaction mechanism between cyclopent-2-enone and benzaldehyde

The reactivity of α,β-unsaturated compounds is modulated by the potency of the electron-withdrawing group attached to the double bond; as the higher such character the higher the reactivity of the β-position for the base attack to generate the nucleophile. Cyclopent-2-enones are poorly reactive under MBH reaction conditions, although this moiety is represented in many natural product compounds,[11] such as prostaglandins and didemnenones, as illustrated in Figure 1. Furthermore, many synthetic processes allow for formation and functionalization of the cyclopentenone ring, such as the Pauson–Khand reaction, the Nazarov cyclization, the asymmetric allylic alkylation, and cross-coupling reactions, demonstrating the value of such cyclic structures in organic synthesis.[11] The MBH reaction plays a key role in the derivatization of cyclopentenones, because it allows for the generation of a stereocenter adiacent to the α-carbon of the α,β-unsaturated system, and several synthetic approaches have been reported in the literature.[12]

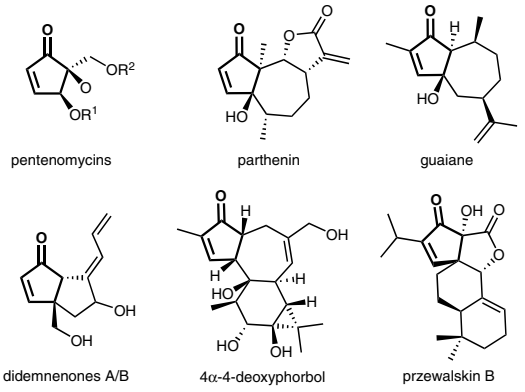
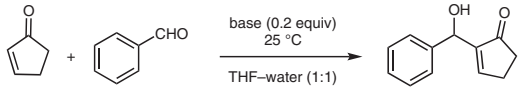


Figure 1 Representative natural products containing the cyclopent-2-enone ring

The application of iminium catalysis on the MBH reaction is somewhat recent. The first report, by Shi in 2002,[13] described the combined use of imidazole and L-proline for the reaction of methyl vinyl ketone and aromatic aldehydes; whereas no product was achieved without it. Tomkinson[14] subsequently reported the importance of water in the solvent system to enable efficient iminium catalysis. In 2003, the application of aqueous $NaHCO_3$ instead of water was reported by Cheng *et al.*,[15] and Gruttadauria[16] confirmed the role of $NaHCO_3$ in improving the MBH reactivity, due to a direct role in the mechanism. Iminium catalysis was also reported for the intramolecular MBH reaction.[17] Nevertheless, none of these approaches has been applied for the MBH on cyclopentenone thus far, which has been reported to occur only under Lewis base catalysis.[12] In this work we report our studies of the MBH on cyclopent-2-enone using iminium catalysis, demonstrating that a secondary amine is important in activating the poorly reactive cyclopentenone.

Diverse catalysts suitable for the MBH reaction were screened using different solvent systems (Table 1). Initially, DABCO failed to react in all solvents but aqueous THF.[18] Then, different MBH catalysts were screened using such a solvent system. Ph_3P and the tertiary amines Et_3N and *N*-Me-pyrrolidine did not work. DMAP and pyrrolidine proved to promote the reaction only in the presence of water, confirming its important role in the catalytic cycle. The use of DMAP in the reaction of α,β-unsaturated ketones and its limitations have been already reported in the literature.[12d,19] The finding of pyrrolidine as a secondary amine catalyst for the MBH reaction was interesting, as it suggested the possible dual role as a nitrogen nucleophile to activate the β-position of cyclopentenone and as a carbonyl activator through iminium catalysis to promote the reaction.[20] Interestingly, no Mannich-type adducts were observed in all cases, and starting material was recovered when the MBH did not occur. A noticeable improvement was observed when 1 M $NaHCO_3$ was used in place of water,[15] as the application of a 1:4 ratio of THF and 1 M $NaHCO_3$ improved the yield to 43%. The stoichiometry of the reaction was optimal when the aldehyde was used in a threefold excess, giving the product in 65% yield as compared to a stoichiometric amount (43%) or to a threefold excess in favor of the cyclopentenone (42%).[21]

Table 1 Study of the Base Catalyst in the MBH Reaction of Cyclopent-2-enone with Benzaldehyde[a]



1 2 3

Entry	Base	Time (h)	Yield (%)[b]
1	DABCO	168	0
2	N-Me-Py	168	0
3	imidazole	168	8
4	Ph_3P	168	0
5	DMAP	40	35
6	DMAP	168	37
7	Et_3N	168	0
8	pyrrolidine	40	23
9	pyrrolidine	168	22

[a] The reaction was carried out using cyclopent-2-enone (1 equiv), benzaldehyde (1 equiv), base (0.2 equiv), with 0.25 M concn for the cyclopentenone.
[b] Yields were calculated following product isolation and purification.

The concomitant application of pyrrolidine and DABCO as the base resulted in improved yields as, using catalytic DABCO (0.2 equiv), the yield was raised to 75%. Although the reaction worked in the presence of pyrrolidine as the sole catalyst, these results showed that a second nitrogen nucleophilic catalyst has a beneficial effect on the yield. In fact, DABCO alone is not able to attack the β-carbon of cyclopent-2-enone, but the formation of the iminium species by pyrrolidine results in the activation of the β-carbon as an electrophilic center allowing DABCO to react. Then, this intermediate attacks the aldehyde, and after oxygen protonation and DABCO elimination, the final unsaturated product is formed, releasing the amine on hydrolysis (Scheme 2).

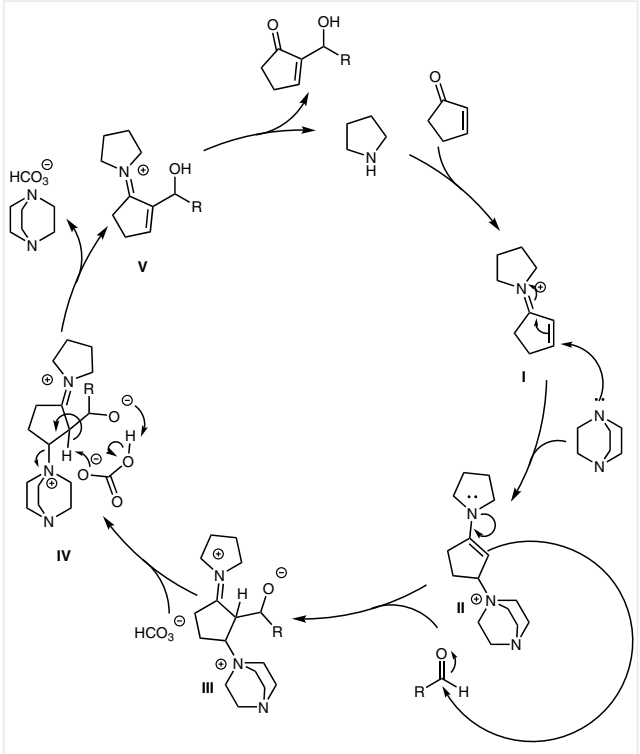
An attempt to carry out the reaction using L-proline in place of pyrrolidine reduced the yield from 75% to 32%. We considered a possible correlation of the yield with the pK_a of the secondary amine, as pyrrolidine possesses a higher value than proline (11.4 vs 10.6). Accordingly, we tested a range of secondary amines in the MBH reaction, and the results are shown in Table 2.

Indeed, the weaker the basic character of the amine, the lower the yield of the MBH reaction, possibly due to a role of the basicity of the nitrogen atom in the attack of intermediate **II** onto the aldehyde (Scheme 2, step II). Morpho-

line, possessing a pK_a around 8, failed to react, suggesting the inability of the iminium ion to proceed to the nucleophilic species as in step II in Scheme 2 (Table 2, entry 4). All proline derivatives showed reduced yields with respect to pyrrolidine, and a correlation between the pK_a and the yield could be established (Table 2, entries 5–8). The use of an imidazolidinone organocatalyst,[22] though well established in the formation of the iminium ion, did not give the expected reaction (Table 2, entry 9), suggesting that its low pK_a (5.8) could not facilitate the attack of the activated species to the aldehyde (step II of Scheme 2). Chiral (*R*)-*N*-benzyl-1-phenylethanamine and (*S*)-2-benzhydryl-pyrrolidine, although possessing a calculated pK_a value of 10 and 11, respectively, did not react under our MBH conditions, possibly due to steric hindrance impairing the formation of the iminium species with the cyclopentenone (Table 2, entries 10 and 12). Indeed, (*R*)-α-methyl-pyrrolidine reacted similarly to pyrrolidine, confirming that a high pK_a value is important for the iminium-catalyzed MBH reaction (Table 2, entry 11). When chiral amines were used, poor degrees of enantiomeric excess were obtained (Table 2, entries 5–8, 11). The optimized conditions consisted of the reaction of cyclopentenone with 3 equiv of aldehyde, using catalytic DABCO and pyrrolidine, in 1:4 THF–1 M $NaHCO_3$ at 25 °C for 40 h.[23] Insights on the mechanism were obtained with kinetics experiments, which allowed us to calculate pseudo-first-order rate constants and to establish linearity with catalyst concentration, along with ESI-MS identification of iminium intermediates, suggesting that only one secondary amine molecule is involved before the rate-limiting step (see Supporting Information).

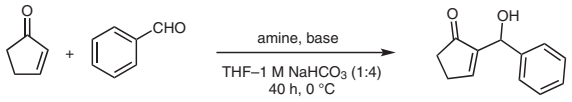
The scope of the iminium-catalyzed MBH reaction on cyclopentenone using pyrrolidine and DABCO as catalysts was studied for a range of aliphatic and aromatic aldehydes (Table 3).

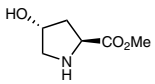
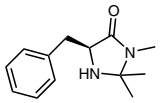
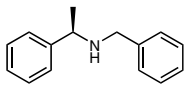
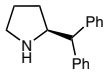
The MBH reaction on nitrobenzaldehydes proceeded in quantitative yields (products **4**–**6**), as the nitro group improved the electrophilic character of the aldehyde. A similar tendency was observed for halogen-substituted compounds **8** and **9**, which were obtained in 84% and 80% yield, respectively. Conversely, methoxy-substituted aldehydes showed reaction yields ranging from 37% to 70%, with the lowest



Scheme 2 Proposed mechanism of the MBH reaction mediated by a dual catalysis via iminium formation with pyrrolidine and DABCO as the Lewis base

Table 2 Screening of Amines as Iminium Ion Activators for the MBH Reaction

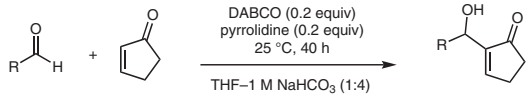


Entry	Amine	pK_a[a]	Yield, (%)[b,c]
1	pyrrolidine	11.4	75
2	piperidine	10.8	62
3	diethylamine	10.8	64
4	morpholine	8.3	0
5	proline	10.6	32 (9)
6	prolinol	10.7	52 (25)
7	proline methyl ester	8.3	20 (10)
8		9.4	24 (0)
9		5.8	0
10		10.0	0
11		11.5	81 (23)
12		11.0	0

[a] Calculated as the mean value between those obtained with ACD/pK_a DB v6.0, and Marvin v6.2.2. (see Supporting Information and ref.[24]).
[b] Yields were calculated following product isolation and purification.
[c] % ee in parentheses, calculated using GC with chiral BetaDex120 column.

outcome experienced for the preparation of **13**, possessing two methoxy groups on the phenyl ring. This was also found for the methyl-substituted compound **7**, which was obtained in 54% yield. Heterocyclic aldehydes showed reaction yields around 70%, as observed for compounds **14** and **15**, and the aliphatic isobutyraldehyde produced compound **16** in good yield as well.

Table 3 Scope of the Iminium-Catalyzed MBH on Cyclopent-2-enone



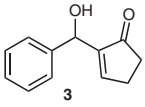
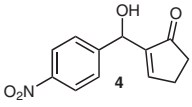
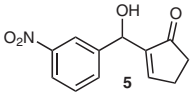
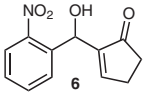
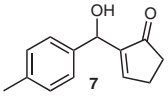
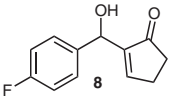
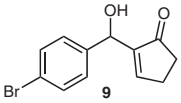
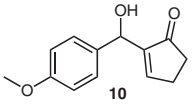
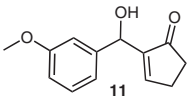
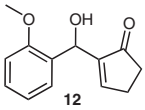
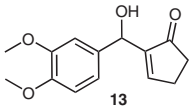
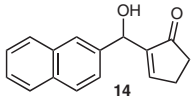
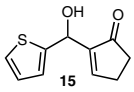
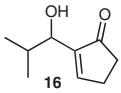
Product	Yield (%)
 **3**	75
 **4**	>99
 **5**	95
 **6**	>99
 **7**	54
 **8**	84
 **9**	80
 **10**	70
 **11**	63
 **12**	69

Table 3 (continued)

Product	Yield (%)
 **13**	37
 **14**	73
 **15**	69
 **16**	65

In conclusion, report the study of the Morita–Baylis–Hillman reaction on cyclopent-2-enone using dual iminium and Lewis base catalysis, demonstrating that a secondary amine is important in activating the poorly reactive enone. We have succeeded in demonstrating that the iminium-catalyzed MBH will occur on cyclopentenone with 1:4 THF–1 M $NaHCO_3$ solvent mixture, and using DABCO as the Lewis base catalyst and pyrrolidine as the iminium ion generator. The screening of a range of secondary amines showed a correlation of the reactivity to the basicity, quantified by the pK_a value of the conjugated acid and also to steric hindrance.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591521.

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(23) **General Procedure for the Morita–Baylis–Hillman Reaction**

In a flask containing a solution of DABCO (0.12 mmol, 14 mg) in THF (0.5 mL) and 1 M aqueous solution of $NaHCO_3$ (2 mL), pyrrolidine (0.12 mmol, 10 μL), cyclopent-2-enone (0.6 mmol), and the aldehyde (1.8 mmol) were successively added. The reaction was stirred at room temperature for 40 h. Then, ethyl acetate (20 mL) was added, and the organic phase was washed with 1 M HCl, sat. aqueous $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, filtered, concentrated under reduced pressure, and the crude product was purified by flash chromatography column (FCC).

2-[Hydroxy(3,4-dimethoxyphenyl)methyl]cyclopent-2-enone (13)

Obtained in 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95–6.81 (m, 4 H), 5.50 (s, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H) 2.58 (m, 2 H), 2.45 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.7, 159.3, 149.1, 148.6, 147.8, 133.9, 118.6, 110.9, 109.5, 69.7, 55.9 (2 C), 35.3, 26.6. ESI-MS: *m/z* (%) = 271.17 (100) $[M + Na]^+$. Anal. Calcd for $C_{14}H_{16}O_4$ (248.27): C, 67.73; H, 6.50. Found: C, 67.80; H, 6.58.

2-[Hydroxy(2-thienyl)methyl]cyclopent-2-enone (15)

Obtained in 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (m, 1 H), 7.27–7.23 (m, 1 H), 7.00–6.95 (m, 2 H), 5.81 (s, 1 H), 3.68 (br, 1 H), 2.65–2.62 (m, 2 H), 2.49–2.47 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 159.6, 146.9, 145.1, 126.7, 125.2 124.7, 66.2, 35.3, 26.7. ESI-MS: *m/z* (%) = 217.08 (100) $[M + Na]^+$. Anal. Calcd for $C_{10}H_{10}O_2S$ (442.52): C, 61.83; H, 5.19. Found: C, 62.00; H, 5.28.

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