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Improved catalysis of Morita–Baylis–Hillman reaction. The strong synergic effect using both an imidazolic ionic liquid and a temperature

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ABSTRACT

The effect of different catalytic conditions for the Morita–Baylis–Hillman reaction has been evaluated both experimentally and by chemometry. The use of either ultrasound at 0 °C, ultrasound with an imidazolic ionic liquid at 0 °C or the ionic liquid catalyst at 0 and 50 °C was systematically tested. A strong synergic effect, which significantly increases the reaction rates and yields, was observed when the reactions were performed using an imidazolic ionic liquid catalyst at both 0 and 50 °C.

The Morita–Baylis–Hillman (MBH) reaction is an exquisite chemical transformation, and represents an interesting alternative to form new carbon–carbon bonds.[1] MBH reaction has many advantages as it presents a high atom economy, is organocatalyzed, requires mild conditions, and is compatible with multiple functional groups. Furthermore, this reaction provides highly functionalized substrates, which can be used as substrate for the synthesis of complex molecules such as natural products and drugs.[2] The MBH reaction can be broadly defined as a condensation reaction between an activated olefin and an aldehyde catalyzed by a Lewis base (tertiary amine or a phosphine) (Scheme 1).

In spite of their synthetic advantages, MBH reactions often suffer from poor reaction rates and long reaction times. Searching to circumvent this drawback different alternatives have been successfully tried, such as the use of microwaves,[3] ultrasound (US),[4] Lewis acids,[5] salts and metals,[6] an aqueous medium[7], and organocatalysts.[8]

Ionic liquids have also been used as catalysts for the MBH reaction.[9] Substantial increases in the rate and yield of MBH reactions have been observed.[10] The usefulness of MBH reactions to form new C–C bonds continues to encourage the development of improved catalysts or catalytic systems to perform this reaction properly.[1b,c]

In a study directed toward the synthesis of superior order sugars, it was necessary to prepare rapidly some MBH adducts derived from carbohydrates. Sugars as electrophiles work quite well; however, it often take several hours to achieve a good conversion.[11] To optimize this transformation, we decide to investigate the effect on rate and yield of combining different additives/catalysts (routinely employed in MBH reactions) and the possible synergism occurring among them. As far as we know, this issue has never been addressed for MBH reactions. In this Letter, we disclose the preliminary results of this study.

To start our work, two classic additives/catalysts were chosen for this reaction [ultrasound (US) and an ionic liquid (IL)], combined with different temperatures in the presence of DABCO. Leahy and Rafel have reported a significant increase in rate when they performed the MBH reaction at 0 °C.[12] They have rationalized this in terms of the greater stability at 0 °C of the *Z*-aza-enolate TS as compared to the *E*-TS. On the other hand, MBH reaction can be accelerated at 50 °C.[1c] The present study thus evaluated the combined use of (a) US with an IL at room temperature and 0 °C, (b) an IL at 0 °C, (c) an IL with US at 50 °C, and (d) IL at 50 °C.

First, the type of IL catalyst was chosen. It is well known that IL is presented in all steps of the MBH catalytic cycle, and stabilizes the intermediates of this reaction by increasing its rate.[10d] IL can be roughly divided into two categories: imidazolic and non-imidazolic. Both types had already been used as catalysts for the MBH reaction,[9] but we decided to use an imidazolic ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate, [bmimPF_6]),

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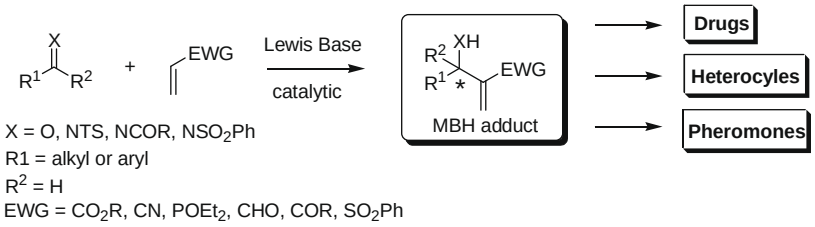


Scheme 1. Morita–Baylis–Hillman reaction and its synthetic versatility.

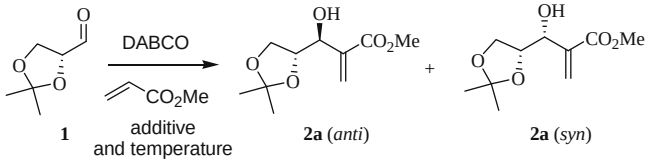
since imidazolic ionic liquids are known to be effective catalysts for MBH reactions and can be easily obtained from commercial sources.

The reaction between isopropylidene-D-glyceraldehyde[13] and methyl acrylate was selected as a model MBH reaction. Several experimental combinations were tested, and Table 1 summarizes the main results.

As shown in Table 1, when US was used at room temperature (rt) or in combination with the IL at 0 °C, a good conversion was attained (entries 1 and 4). However, when US was combined with the IL catalyst at rt or at 0 °C without the IL, the conversion was very poor (entries 2 and 3).[14] At 0 °C under stirring, the reaction displayed the lowest conversion (entry 5). To our surprise, however, the use of IL with 0 °C with no US (just stirring) provided the best result, a yield as high as 95% in just 30 min of reaction (entry 6).

This intriguing experimental result led us to evaluate the influence of each catalyst, separately or in combination, using chemometric tools.[15] The influences of the three catalysts are described as a function named response surface, in which we hope to deter-

Table 1
MBH reaction with different catalytical combinations[16]



Entry	Conditions	Yield[a] (%)	Time[b,c] (min)
1	US, rt	82	30
2	US, rt, IL	25	30
3	US, 0 °C	30	30
4	US, 0 °C, IL	92	30
5	Stirring, 0 °C	7	30
6	Stirring, 0 °C, IL	95	30

IL = $(Bmim)PF_6$.
[a] All yields refer to the sum of the isolated and purified products.
[b] For proper comparison, reactions were stopped after 30 min.
[c] Diastereoselectivity was determined by NMR, and the relative stereochemistry was determined by comparison with reported data.[14] For all cases, the observed diastereoselectivity was very poor (65:35; *anti*:*syn*).

Table 2
Experimental design for the MBH reaction between methyl acrylate and isopropylidene-D-glyceraldehyde

Factors[a]	+[b]	−[b]
US	With	Without
IL	With	Without
Temperature	0 °C	rt

[a] All experiments were carried out in duplicate; the responses observed were recorded considering eight possible combinations of the chosen factors.
[b] Signs (−) and (+) were attributed to the experimental conditions.

Table 3
Results from the experimental planning[a]

Entry	US	IL	Temperature	Yield[*,b,c] (%)	
1	−	−	−	50	53
2	+	−	−	82	80
3	−	+	−	55	55
4	+	+	−	25	24
5	−	−	+	7	5
6	+	−	+	30	30
7	−	+	+	95	96
8	+	+	+	92	89

[*] Yields from duplicate experiments.
[a] The experimental errors were estimated since their extents could be important to evaluate if significant effects exist and if these errors could be attributed to the interaction among the factors.
[b] All yields refer to the sum of isolated and purified products.
[c] All reactions were stopped after 30 min.

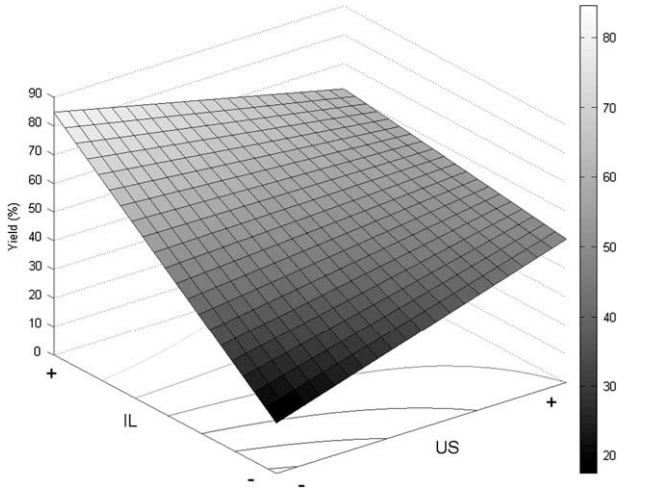
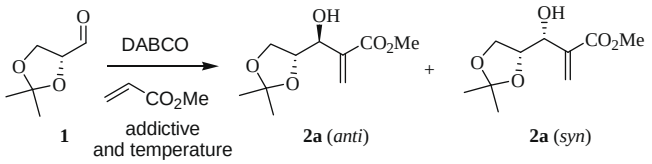


Figure 1. Contour surface for the experimental design with IL and US at 0 °C and room temperature.

Table 4
New experimental design with aldehyde **1** and methyl acrylate



Entry	US	IL	Temperature (°C)	Yield[*,a,b] (%)	
1[c]	−	−	50	17	18
2	+	−	50	48	52
3[c]	−	+	50	86	83
4	+	+	50	62	60

[*,a] Yields in duplicate. All yields refer to the sum of isolated and purified products.
[b] All reactions were stopped after 30 min.
[c] Stirring was done.

Table 5
Comparative results of the Morita–Baylis–Hillman reaction in different conditions

Entry	Aldehyde	IL at 0 °C		IL at 50 °C		Room temperature[a]	
		Time (h)	Yield[b] (%)	Time (h)	Yield[b] (%)	Time[c] (h)	Yield[b,c] (%)
1	4-NO_2-Benzaldehyde	4	>99	4	>99	72	45
2	4-Methylbenzaldehyde	96	80	96	28	720	20
3	3-Pyridylcarboxaldehyde	1	95	1	90	4	90
4	2-Chloroquinolylcarbaldehyde	4	87	4	87	8	89
5	Benzaldehyde	24	71	24	36	144	25
6	2-Bromobenzaldehyde	96	60	96	95	102	12
7	Heptanaldehyde	96	34	96	15	168	15
8	Propionaldehyde	96	70	96	82	120	71

[a] Room temperature means that the reactions were carried out under stirring without IL or US.
[b] All spectroscopic data for the MBH adducts are compatible for the structure proposed, and yields refer to purified and isolated products.
[c] See Ref. 4.

mine at which levels the three catalysts produce the best responses. An eight experiment factorial design factorial (2^3) was conducted for the model MBH reaction. Table 2 depicts the planning matrix used, while Table 3 summarizes results from these factorial experiments.

It is clear from these results that interaction effects are very significant, and the following conclusions could be made: IL increases the yield (and rate), but IL effect is more important at 0 °C (Table 3, compare entries 1 and 3 with 5 and 7), and this experimental observation justifies the high value found for IL + 0 °C (see statistical analysis in Supplementary data); at rt we observe an increase in the yield of the reaction when the IL was added, and the reaction was only stirred (Table 3, entries 1 and 3); however, the use of IL plus US significantly decreases the yield (see Table 3, entries 3 and 4); hence US + IL have a negative sign, despite their importance (the negative sign results from the good yield in the absence of US).

In Figure 1, we depict a contour surface obtained after statistical analysis of our results (the statistical analysis is available in Supplementary data).

The presence of both IL and US causes an increase on the yield of the reaction (presence of IL and US is signaled as 1 in the Figure and their absences as −1); however, the influence on yield is more pronounced when only IL is used. However, the association of IL with low temperature (0 °C) shows a synergism greater than that between US and low temperature.

These data lead to another question. What is the effect on rate and yield if higher temperatures are associated with catalyst combination? To answer this question, a new experimental design was planned. Using the same model reaction, the additive/catalyst was combined with temperature: (a) IL at 50 °C; (b) US at 50 °C. The results are summarized in Table 4.

At 50 °C, to our surprise a reaction profile quite similar to that described for reactions carried out at 0 °C was observed.[17] Both US and IL increased the rate and yield of reaction; however, the latter seems to be more efficient. The yields are slightly lower than those obtained using IL at 0 °C, perhaps a difference that could be attributed to the increase in disorder in the IL supramolecular structure, at the higher temperature.[18]

To test the generality of these results, several MBH reactions using aromatic (having electron-donor and electron-withdrawing substituents) and aliphatic aldehydes were carried out. Both temperatures (0 and 50 °C) were used, associated with IL. The results are summarized in Table 5.

Based on data summarized in Table 5 the synergic effect seems to be general. For all, a clear improvement of the reaction rate and yield is observed, when both conditions (IL at 0 °C and IL at 50 °C) are compared with room temperature. Even deactivated aldehydes as 4-methylbenzaldehyde (see entry 2) provide the corresponding adduct in good yield and relatively short reaction times if we compare with the same reaction performed at room temperature.

In some cases, the use of IL at 50 °C is less efficient and can be replaced advantageously by using a lower temperature. Most probably these reactions should occur within the lamellar structure of the ionic liquid and its better organization at lower temperature could contribute to increase yield.

In summary, we demonstrate that the association of additives/catalysts can render the Morita-Baylis-Hillman reaction faster and efficient. The chemometric analysis shows clearly the occurrence of a synergic interaction between IL and US, IL and temperature and US and temperature. Although, the synergic effects are more pronounced when IL is associated with temperature.[19]

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Supplementary data

The statistical analysis of all experiments and the contour surface for the experiment using IL and US at 50 °C are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.089.

References and notes

1. (a) Almeida, W. P.; Coelho, F. *Quim. Nova* **2001**, *23*, 98–101; (b) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581–1588; (c) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574; (d) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330–4333.
2. (a) Masunari, A.; Ishida, E.; Trazzi, G.; Almeida, W. P.; Coelho, F. *Synth. Commun.* **2001**, *31*, 2127–2136; (b) Coelho, F.; Veronese, D.; Pavam, C. H.; de Paula, V. I.; Buffon, R. *Tetrahedron* **2006**, *62*, 4563–4572; (c) Dunn, P. J.; Fournier, J.-F.; Hughes, M. L.; Searle, P. M.; Wood, A. S. *Org. Process Res. Dev.* **2003**, *7*, 244–253; (d) Reddy, L. R.; Fournier, J.-F.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2005**, *7*, 2699–2701; (e) Silveira, G. P. C.; Coelho, F. *Tetrahedron Lett.* **2005**, *46*, 6477–6481; (f) Mateus, C. R.; Coelho, F. *J. Braz. Chem. Soc.* **2005**, *16*, 386–396.
3. Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444.
4. Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Lopes, E. C. S.; Rossi, R. C.; Silveira, G. P. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437–7447. and references cited therein.
5. Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem.* **2005**, *1*, 45–58. and references cited therein.
6. Shi, M.; Jiang, J. K.; Cui, S. C. *Tetrahedron* **2001**, *57*, 7343–7347. and references cited therein.
7. He, K.; Zhou, Z.; Zhao, G.; Tang, C. *Heteroat. Chem.* **2006**, *17*, 317–321. and references cited therein.
8. Pellissier, H. *Tetrahedron* **2007**, *63*, 9267–9331.
9. (a) Rosa, J. N.; Afonso, C. A. M.; Santos, A. G. *Tetrahedron* **2001**, *57*, 4189–4193; (b) Dupont, J. *J. Braz. Chem. Soc.* **2004**, *15*, 341–350.
10. (a) Zhang, Z. C. *Adv. Catal.* **2006**, *49*, 153–237; (b) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McGague, J. *J. Org. Chem.* **1998**, *63*, 7183–7189; (c) Aggarwal, V. K.;

Emme, I.; Mereu, A. *Chem. Commun.* **2002**, 1612–1613; (d) Santos, L. S.; da Silveira Neto, B. A.; Consorti, C. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Dupont, J.; Eberlin, M. N. *J. Phys. Org. Chem.* **2006**, *19*, 731–736; (e) Afonso, C. A. M.; Branco, L. C.; Candeias, N. R.; Gois, P. M. P.; Lourenco, N. M. T.; Mateus, N. M. M.; Rosa, J. N. *Chem. Commun.* **2007**, 2669–2679.

11. (a) Krishna, P. R.; Narsingam, M. *J. Comb. Chem.* **2007**, *9*, 62–69; (b) Krishna, P. R.; Kannan, V.; Sharma, G. V. M.; Rao, M. H. V. R. *Synlett* **2003**, 888–890.
12. Rafel, S.; Leahy, S. W. *J. Org. Chem.* **1997**, *62*, 1521–1522.
13. Kumar, V.; Dev, S. *Tetrahedron* **1987**, *43*, 5932–5948.
14. (a) Papageorgiu, C.; Benezra, C. *J. Org. Chem.* **1985**, *50*, 157–158; (b) Nair, V.; Sinhababu, A. K. *J. Org. Chem.* **1980**, *45*, 1893–1897.
15. Bruns, R. E.; Scarminio, I. S.; de Barros Neto, B. In *Statistical Design—Chemometrics*; Elsevier: Amsterdam, 2006.
16. *A representative general procedure:* To a mixture of aldehyde **1** (0.26 g, 2 mmol) and DABCO (0. 15 g, 1.3 mmol, 0.65 equiv) in methyl acrylate (10 mL, used as both reagent and solvent) was added the ionic liquid (0.57 g, 2 mmol, 1 equiv, Bmim[PF_6]). The resulting mixture was cooled at 0 °C and stirred for 30 min. Then the mixture was diluted with dichloromethane (20 mL), and the organic phase was washed with a 10% HCl solution (10 mL), a saturated solution of $NaHCO_3$ (10 mL), brine (10 mL), and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography. Yield: 95%; **2a** *anti*; $[\alpha]_D^{20}$ −17 (*c* 1.5, acetone); lit.[12] $[\alpha]_D^{20}$ −17.0 (*c* 1.5, acetone); IR (λ_{max}, film): 3485; 2994; 2953; 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.44 (s, 3H), 3.79 (s, 3H), 3.92 (d, 2H, *J* = 5.9 Hz), 4.34 (dd, 1H, *J* = 5.9 Hz and *J* = 5.1 Hz), 4.53 (d, 1H, *J* = 5.1 Hz), 5.99 (t, 1H, *J* = 1.5 Hz), 6.36 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.4; 137.8; 127.6; 109.7; 76.5; 71; 66.5; 52; 27.8; 24.9; HRMS (70 eV, *m/z*) calcd for $C_{10}H_{16}O_5$: 216.0997; found: 216.0996; **2b** *syn*; $[\alpha]_D^{20}$ +8.5 (*c* 1.5, acetone); IR (λ_{max}, film): 3475, 2989; 2955; 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.46 (s, 3H), 3.78 (s, 3H), 3.89 (m, 2H), 4.31 (m, 1H), 4.45 (d, 1H, *J* = 4.4 Hz), 5.79 (s, 1H), 6.38 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.4; 138.1; 126.9; 109.2; 82.8; 71; 66.2; 52; 26; 24.5; HRMS (70 eV, *m/z*) calcd for $C_{10}H_{16}O_5$: 216.0997; found: 216.0999.
17. Due to the similarity we do not show in the text the statistical analysis and the contour surface of this second experimental design. All data concerning this experiment are available on Supplementary data.
18. Dupont, J.; Spencer, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5296–5297.
19. Pegot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 6425–6428.