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Aqueous Morita–Baylis–Hillman Reaction of Unprotected Isatins with Cyclic Enones

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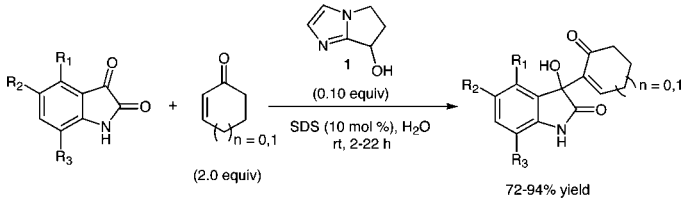
ABSTRACT



The readily available bicyclic imidazolyl alcohol 1 is a unique catalyst for the aqueous Morita–Baylis–Hillman (MBH) reaction between unprotected isatins and cyclic enones that gives access to a variety of potentially very useful 3-substituted 3-hydroxy-2-oxindoles in an operationally simple, efficient, and environmentally friendly way. The hydroxyl group of the catalyst is believed to stabilize the betaine intermediate formed in the first step of the MBH reaction.

The organocatalyzed Morita–Baylis–Hillman (MBH) reaction is unquestionably one of the most attractive methods for the construction of carbon–carbon bonds, due to its complete atom economy, mild reaction conditions, and functional group tolerance, as well as for its ability to generate densely functionalized structures (containing hydroxyl, olefin, and carbonyl groups in adjacent carbon atoms) that are important synthetic intermediates and/or exhibit useful biological activities.[1,2] Despite its interesting benefits, the MBH reaction suffers from several drawbacks, such as low reaction rates, moderate yields, high concentration of the nucleophilic catalyst, poor reactivities of β-substituted activated olefins and of cyclic enones, and use of hazardous organic solvents, that have hampered its industrial utilization. The use of water as solvent can improve the applicability of the MBH reaction and has been the object of much attention in the past few years.[3] While it is clear that water can both

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(1) For selected reviews on the Morita–Baylis–Hillman reaction, see: (a) Ciganek, E. *Org. React.* **1997**, *51*, 201–350. (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. T. *Chem. Rev.* **2003**, *103*, 811–892. (c) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574. (d) Mansilla, J.; Saá, J. M. *Molecules* **2010**, *15*, 709–734. (e) Shi, M.; Wang, F.-J.; Zhao, M.-X.; Wei, Y. *The Chemistry of the Morita–Baylis–Hillman Reaction*; RSC Publishing: Cambridge, U.K., 2011. (f) Basavaiah, D.; Veeraraghavaiah, G. *Chem. Soc. Rev.* **2012**, *41*, 68–78. (g) Liu, T. Y.; Xie, M.; Chen, Y. C. *Chem. Soc. Rev.* **2012**, *41*, 4101–4112.

(2) For applications of MBH adducts in the synthesis of natural products, see: (a) Reddy, Y. S.; Kadigachalam, P.; Basak, R. K.; John Pal, A. P.; Vankar, Y. D. *Tetrahedron Lett.* **2012**, *53*, 132–136. (b) Paioti, P. H. S.; Coelho, F. *Tetrahedron Lett.* **2011**, *52*, 6180–6184. (c) Kumar, V.; Das, P.; Ghosal, P.; Shaw, A. K. *Tetrahedron* **2011**, *67*, 4539–4546. (d) Reddy, R. L.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230–6231. (e) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030–2031. (f) Luna-Freire, K. R.; Tormena, C. F.; Coelho, F. *Synlett* **2011**, 2059–2063. (g) Gowrisankar, S.; Lee, H. S.; Kim, S. H.; Lee, Y. K.; Kim, J. N. *Tetrahedron* **2009**, *43*, 8769–8780.

(3) (a) Basavaiah, D.; Krishnamacharyulu, K.; Rao, A. J. *Synth. Commun.* **2000**, *30*, 2061–2069. (b) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413–5418. (c) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723–4725. (d) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369–7371. (e) Gatri, R.; El Gaïed, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835–7836. (f) Luo, S.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 555–558. (g) de Souza, R. O. M. A.; Pereira, V. L. P.; Esteves, P. M.; Vasconcellos, M. L. A. A. *Tetrahedron Lett.* **2008**, *49*, 5902–5905. (h) Schwartz, B. D.; Porzelle, A.; Jack, K. S.; Faber, J. M.; Gentle, I. R.; Willians, C. M. *Adv. Synth. Catal.* **2009**, *351*, 1148–1154. (i) Asano, K.; Matsubara, S. *Synthesis* **2009**, 3219–3226. (j) Pawar, B.; Padalkar, V.; Phatangare, K.; Nirmalkar, S.; Chaskar, A. *Catal. Sci. Technol.* **2011**, *1*, 1641–1644. (k) Shairgojray, B. A.; Dar, A. A.; Bhat, B. A. *Tetrahedron Lett.* **2013**, *54*, 2391–2394.

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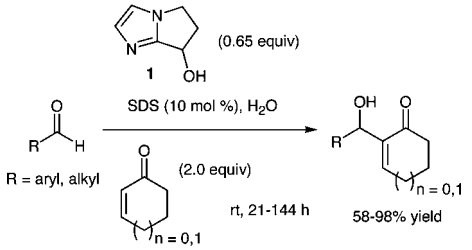
stabilize the betaine intermediate resulting from the initial Michael addition of the nucleophilic catalyst to the activated alkene[1a] and facilitate the proton transfer step (from C to O) necessary for the generation of the product and release of the catalyst,[4] it can also reduce the nucleophilicity of the catalyst, so that generally an excess of the nucleophilic promoter is necessary in an aqueous medium. On the other hand, the low solubility of the reactant may also reduce the reaction rate in water. We have recently shown[5] that the use of the bicyclic imidazolyl alcohol **1** as a catalyst overcomes most of these drawbacks, affording excellent results in the aqueous MBH reactions of aldehydes with cyclic enones, in the presence of SDS (sodium dodecyl sulfate) as an additive (Scheme 1).

Scheme 1. Aqueous MBH Reaction between Aldehydes and Cycloalkenones Catalyzed by the Bicyclic Imidazolyl Alcohol **1**



3-Substituted 3-hydroxy-2-oxindoles are privileged core structures from the point of view of biological activity and are present in many natural products and pharmaceuticals (Figure 1).[6] Accordingly, much effort has been devoted in the past years in the preparation of these compounds.[7] Given the easy availability of isatins, the nucleophilic addition of carbon nucleophiles to these compounds provides a straightforward method for the preparation of 3-substituted 3-hydroxy-2-oxindoles.[8] By taking advantage of the high electrophilic character of the keto carbonyl group of isatins, the MBH reaction has been considered as a convenient entry to highly functionalized 3-substituted

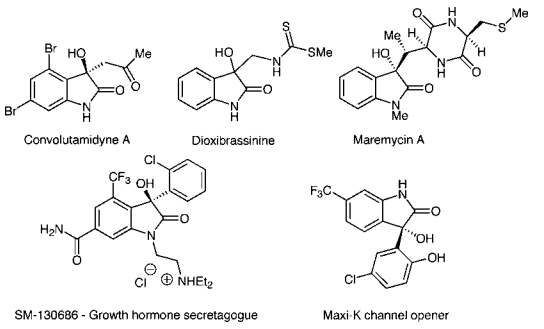
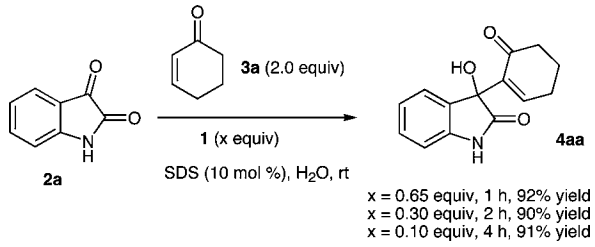


Figure 1. Representative natural products and bioactive compounds with 3-substituted 3-hydroxy-2-oxindole framework.

Scheme 2. Aqueous MBH Reaction between Isatin **2a** and Cyclohexenone (**3a**) Catalyzed by the Imidazolyl Alcohol **1**



3-hydroxy-2-oxindoles, and the reaction of isatin derivatives with electron-defficient alkenes, either in racemic[9] or in asymmetric[10] fashion, has been achieved under catalysis of tertiary amines or phosphines. These procedures however are restricted to highly reactive electron-deficient alkenes (acrylates, acrolein, methyl vinyl ketone, allenoates, maleimides), often require the use of *N*-protected isatins, and generally take place in anhydrous, nonaqueous media. On the other hand, there are only two reports on the MBH reaction between isatins and the relatively inert cyclic enones that involve the use of either strong Lewis bases (50 mol % sodium methoxide in anhydrous methanol)[11] or strong Lewis acids (100 mol % titanium tetrachloride in anhydrous dichloromethane)[12] as promoters.

(4) (a) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706–1708. (b) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513–15525.

(5) Gomes, J. C.; Rodrigues, M. T., Jr.; Moyano, A.; Coelho, F. *Eur. J. Org. Chem.* **2012**, 6861–6866.

(6) For reviews, see: (a) Peddibhotla, S. *Curr. Bioact. Cmpd.* **2009**, *5*, 20–38. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8478–8578. (c) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219.

(7) Selected recent reviews: (a) Moyano, A.; Companyó, X. In *Studies in Natural products Chemistry*; Atta-ur-Rahman, Ed.; 2013; Vol. 40 pp 71−132. (b) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327–334. (c) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407. For recent examples, see: (d) Xiao, Z.-K.; Yin, H.-Y.; Shao, L.-X. *Org. Lett.* **2013**, *15*, 1254–1257. (e) Ren, Q.; Huang, J.; Wang, L.; Li, W.; Liu, H.; Jiang, X.; Wang, J. *ACS Catal.* **2012**, *2*, 2622–2625. (f) Lu, S.; Poh, S. B.; Siau, W.-Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 1731–1734. (g) Saidalimu, I.; Fang, X.; He, X.-P.; Liang, J.; Yang, X.; Wu, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5566–5570. (h) Cassani, C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 5590–5593. (i) Kumar, A.; Chimni, S. S. *Eur. J. Org. Chem.* **2013**, 4780–4786.

(8) For reviews on the chemistry of isatins, see: (a) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104–6155. (b) Flores, M.; Peña, J.; García-García, P.; Garrido, N. M.; Diez, D. *Curr. Org. Chem.* **2013**, *17*, 1957–1985.

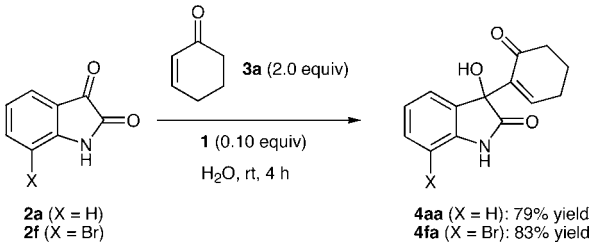
(9) (a) Garden, S. J.; Skakle, J. M. *Tetrahedron Lett.* **2002**, *43*, 1969–1972. (b) Chung, Y. M.; Im, Y. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 1651–1654. (c) Rad-Mogadham, K.; Youseftabar-Miri, L. *ARKIVOC* **2011**, *xi*, 43–50. (d) Khalafi-Nezhad, A.; Mohammadi, S. *Synthesis* **2012**, *44*, 1725–1735. (e) Zhao, Q.-Y.; Lian, Z.; Wei, Y.; Shi, M. *Tetrahedron* **2012**, *68*, 4899–4905.

(10) (a) Guan, X.-Y.; Wei, Y.; Shi, M. *Chem.—Eur. J.* **2010**, *16*, 13617–13621. (b) Liu, Y.-L.; Wang, B.-L.; Cao, J.-J.; Chen, L.; Zhang, Y.-X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, *132*, 15176–15178. (c) Zhong, F.; Chen, G.-Y.; Lu, Y. *Org. Lett.* **2011**, *13*, 82–85. (d) Wang, C.-C.; Wu, X.-Y. *Tetrahedron* **2011**, *67*, 2974–2978. (e) Qian, J.-Y.; Wang, C.-C.; Sha, F.; Wu, X.-Y. *RSC Advances* **2012**, *2*, 6042–6048. (f) Duan, Z.; Zhang, Z.; Qian, P.; Han, J.; Pan, Y. *RSC Advances* **2013**, *3*, 10127–10130. (g) Chauhan, P.; Chimni, S. S. *Asian J. Org. Chem.* **2013**, *2*, 586–592. (h) Pearson, A. J.; Panda, S.; Bunge, S. D. *J. Org. Chem.* **2013**, *78*, 9921–9928.

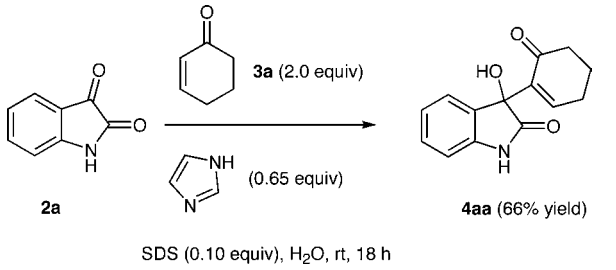
(11) Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 8413–8422.

(12) Basavaiah, D.; Roy, S.; Das, U. *Tetrahedron* **2010**, *66*, 6612–5622.

Scheme 3. Testing the MBH Reaction of Isatins in the Absence of SDS



Scheme 4. Use of Imidazole As a Catalyst in the Aqueous MBH Reaction between Isatin and 2-Cyclohexenone

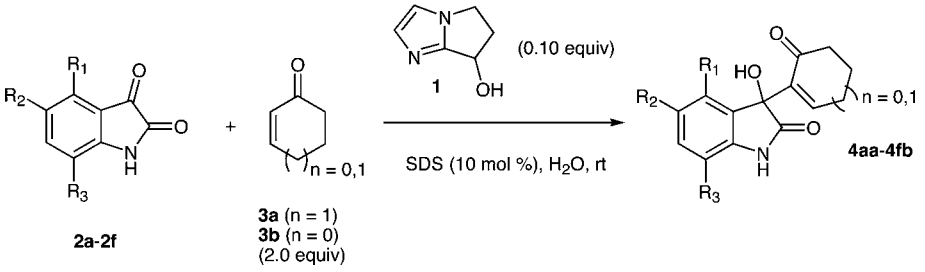


In light of these precedents, we anticipated that the use of the bicyclic imidazole **1** as a catalyst would offer a unique solution for the direct MBH reaction between unprotected isatins and cyclic enones in mild and environmentally friendly conditions.

We were pleased to find that, under the conditions that we had previously developed for aldehydes (0.65 equiv of **1**, 0.10 equiv of SDS, water, rt; see Scheme 1),[5] isatin **2a** readily reacted with 2-cyclohexenone (**3a**; 2.0 equiv) to furnish the previously unknown MBH adduct **4aa** in excellent yield (Scheme 2). The progress of the reaction was easily monitored, since the initially orange- or red-colored solution (or suspension) was gradually converted into a colorless hetereogeneous reaction mixture from which the insoluble adduct **4aa** was isolated by filtration.[13] In these conditions the reaction was complete in only 1 h, and we accordingly diminished the amount of catalyst **1**, finding that with 0.30 and 0.10 equiv the times necessary for full conversion were 2 h and 4 h, respectively, with the yield of the isolated MBH adduct being unaffected.

In order to test the scope of this procedure, we examined the MBH reaction of isatin (**2a**) and of a series of unprotected aryl-substituted isatins (**2b**–**2f**) either with 2-cyclohexenone (**3a**) or with 2-cyclopentenone (**3b**), under catalysis with 0.10 equiv of **1** (Table 1). As it can be seen, the MBH adducts **4aa**–**4fb** were obtained in all instances, with moderate to good yields. Some reactivity trends are readily apparent. First, reactions involving cyclopentenone **3b** (entries 7 to 12 in Table 1) are generally somewhat faster than those carried out with cyclohexenone **3a** (entries 1–6). Second, the electron-withdrawing or -donating nature of the aromatic moiety in the isatin derivatives does not have a significant effect on the rate of the addition, and only in

Table 1. Scope of the Aqueous MBH Reaction of Unprotected Isatins (**2a**–**2f**) with Cyclic Enones (**3a**,**3b**) under Catalysis with **1**[a]



entry	isatin	R_1	R_2	R_3	enone	time (h)[b]	product	yield (%)[c]
1	**2a**	H	H	H	**3a**	4	**4aa**	91
2	**2b**	H	Me	H	**3a**	5	**4ba**	87
3	**2c**	H	OMe	H	**3a**	6	**4ca**	85
4	**2d**	Cl	H	H	**3a**	22	**4da**	85
5	**2e**	H	Br	H	**3a**	8	**4ea**	79
6	**2f**	H	H	Br	**3a**	3	**4fa**	85
7	**2a**	H	H	H	**3b**	4	**4ab**	86
8	**2b**	H	Me	H	**3b**	3	**4bb**	88
9	**2c**	H	OMe	H	**3b**	2	**4cb**	82
10	**2d**	Cl	H	H	**3b**	15	**4db**	72
11	**2e**	H	Br	H	**3b**	6	**4eb**	94
12	**2f**	H	H	Br	**3b**	5	**4fb**	73

[a] General reaction conditions: 2.0 mmol of isatin, 4.0 mmol of enone, 0.20 mmol of **1**, 0.20 mmol of SDS in 2 mL of H_2O, rt. [b] Time necessary for total conversion of the starting isatin. [c] Yield of isolated product after filtration.

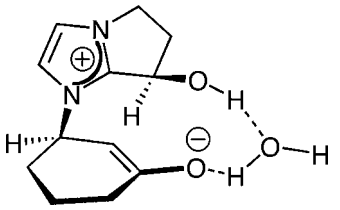


Figure 2. Possible role of the hydroxyl group of compound **1** in the stabilization of the initial betaine intermediate of the MBH reaction in aqueous solution.

the case of the 4-chloroisatin **2d** reaction times are longer than 8 h (see entries 4 and 10 in Table 1), probably due to steric hindrance around the carbonyl group. The MBH reaction can also be performed without SDS as a phase-transfer additive, but in this case the efficiency of the process is somewhat diminished, leading for instance to lower yields in the case of the isatin−cyclohexenone adduct **4aa** (Scheme 3). It is worth noting that, in the case of aldehydes, the aqueous MBH reaction with enones did not work at all in the absence of SDS (or the absence of other surfactants, such as cetyltrimethylammonium bromide or Triton-X100).[5]

The unique ability of the bicyclic imidazolyl alcohol **1** as a catalyst for this process is showcased by the fact that imidazole, which has been reported as a promoter of the MBH reaction in aqueous systems,[14] is a rather poor catalyst, even when used in a 65 mol % amount, for the MBH reaction between isatin **2a** and 2-cyclohexenone (Scheme 4).

On the other hand, compound **1** is not able to catalyze the MBH reaction in nonaqueous solvents, such as dichloromethane, *N*,*N*-dimethylformamide (in which both the reactants and the catalyst are very soluble), or methanol. Since in an aqueous medium the rate-determining step of the MBH reaction cannot be the proton transfer from carbon to oxygen in the adduct,[4] we believe that the hydroxyl group in **1** may assist in the stabilization of the betaine intermediate resulting from the initial Michael addition of the nucleophilic catalyst to the activated alkene (Figure 2). In summary, we have found that the readily available (one step reaction from imidazole and acrolein)[15] bicyclic imidazolyl alcohol **1** is a unique catalyst for the aqueous MBH reaction between unprotected isatins and cyclic enones that gives access to a variety of potentially very useful 3-substituted 3-hydroxy-2-oxindoles in an extremely simple, efficient, and environmentally friendly way. Further applications of compound **1** and of related bifunctional catalysts containing both imidazole and hydroxyl groups, as well as mechanistic studies, are currently underway in our laboratories, and results will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) An alternative workup involving extraction with 1:1 hexane/ethyl acetate, drying over $MgSO_4$, and evaporation of the solvent under reduced pressure afforded **4aa** in 56% yield.

(14) (a) Gatri, R.; El Gaïed, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835–7836. (b) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369–7371. (c) Luo, S.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 555–558. (d) Porzelle, A.; Williams, C. M.; Schwartz, B. D.; Gentle, I. R. *Synlett* **2005**, 2923–2926. (e) Schwartz, B. D.; Porzelle, A.; Jack, K. S.; Faber, J. M.; Gentle, I. R.; Williams, C. M. *Adv. Synth. Catal.* **2009**, *351*, 1148–1154.

(15) (a) Weintraub, P. M.; Tiernan, P. L.; Huffman, J. C. *J. Heterocycl. Chem.* **1987**, *24*, 561–563. (b) Zhang, Z. F.; Xie, F.; Jia, J.; Zhang, W. B. *J. Am. Chem. Soc.* **2010**, *132*, 15939–15941.

The authors declare no competing financial interest.