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Dual Catalyst Control in the Enantioselective Intramolecular Morita–Baylis–Hillman Reaction

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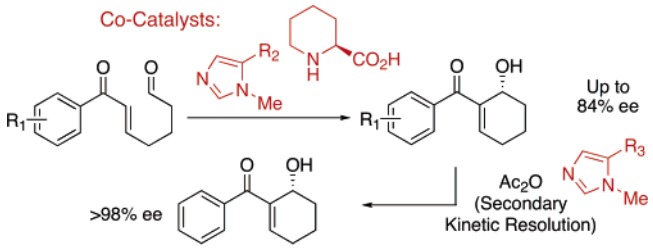
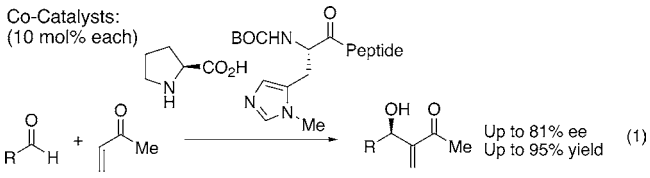
ABSTRACT



The intramolecular Morita–Baylis–Hillman (MBH) reaction has been achieved with unprecedented levels of enantioselectivity. Using a co-catalyst system involving pipecolinic acid and *N*-methylimidazole, cyclic MBH products have been obtained with enantiomer ratios of 92:8 (84% ee). In addition, reactions may be carried out with a "kinetic resolution quench" involving acetic anhydride and an asymmetric acylation catalyst such that ee enhancement occurs to deliver products with >98% ee with an isolated yield of 50%.

The Morita−Baylis−Hillman (MBH) reaction is a powerful transformation in organic synthesis.[1] It has been the subject of extensive mechanistic study,[2] in part due to the difficulty in the discovery of efficient and enantioselective variants. Among the many important contributions in this area are the development of cinchona alkaloid-based chiral nucleophiles for the ester-based MBH reaction,[3] as well as the development of chiral Bronsted acid-based catalysts for the MBH reaction of cyclic enones.[4] Particularly elusive in the search for highly enantioselective MBH reactions have been those variants that involve simple, acyclic ketones such as methyl vinyl ketone (MVK).[5] We recently reported a co-catalyst system for the MVK-based MBH reaction that resulted in state-of-the-art enantioselectivity for this process (eq 1).[6,7]



A class of MBH reactions where enantioselective catalysis has been nearly unexplored is the intramolecular version.[8,9]

(1) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049.

(2) (a) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147. (b) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706.

(3) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

(4) (a) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231. (b) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165.

(5) (a) Walsh, L. M.; Winn, C. L.; Goodman, J. M. *Tetrahedron Lett.* **2002**, *43*, 8219. (b) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241. (c) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533. (d) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015. (e) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941.

(6) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741.

(7) For a pioneering demonstration of a two-catalyst system for the ketone-based MBH reaction, see: Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2002**, *43*, 127.

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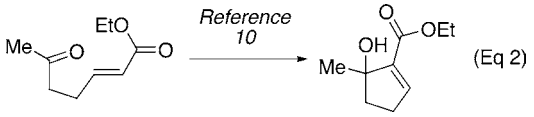
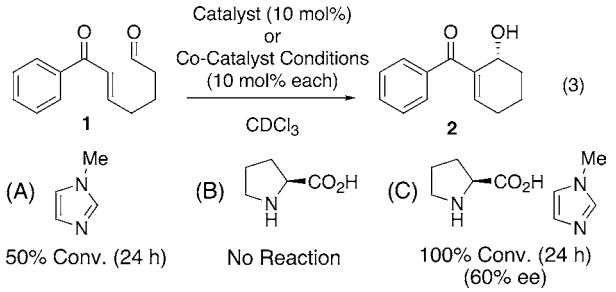
In the published reports to date, intramolecular MBH cases are plagued by not only low reactivity but also low chemo- and enantioselectivity. The only report of an enantioselective variant affords products with only 14% ee and 40% yield after a reaction time of 10 days (eq 2).[10] To address both methodology gaps, and to study the scope of co-catalysis in the MBH arena, we began a study of this reaction.



(Eq 2)

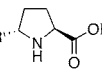
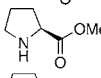
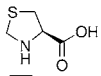
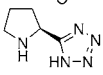
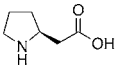
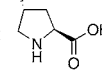
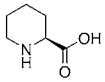
The reaction we set out to explore initially is the cyclization shown in eq 3. In analogy to our findings in the intermolecular MBH reaction with methyl vinyl ketone (cf. eq 1), we began by exploring co-catalysis with proline and *N*-methylimidazole (NMI). Control experiments revealed



some similarities but also significant differences between the two processes. First, NMI was a sluggish catalyst for both the intermolecular and intramolecular reactions. Second, proline alone was not a catalyst for either reaction. However, whereas the combination of NMI and proline provided good catalytic rates, but minimal ee, in the intermolecular reaction, this combination, *in the intramolecular case*, led to not only rate enhancement but also a product that exhibited an 80:20 enantiomeric ratio (60% ee). On the other hand, whereas oligopeptides could be readily found to enhance the ee of the intermolecular process, a screen of approximately 160 peptide-based co-catalysts did not lead to ee enhancement for the intramolecular reaction.

Given the distinctive features of the co-catalysis of the intramolecular reaction in contrast to the intermolecular process, we carried out new optimization studies that addressed the various components of the reaction. As shown

Table 1. Screen of Amino Acids as Co-catalysts with NMI for the Intramolecular MBH Reaction of Substrate **1**[a]

entry[b]	co-catalyst[b]	ee of **2**[b]	entry[b]	co-catalyst[b]	ee of **2**[b]
1		60%	6a, R = Me 6b, R = Ph 6c, R = vinyl		<10% <10% <10%
2		<10%	7		<10%
3		<10%	8		<10%
4		<10%	9		28%
5a, R = H 5b, R = *t*-Bu		17% 11%	10		60%

[a] All reactions were conducted at 25 °C in $CDCl_3$. [b] Determined by chiral HPLC. Reported ee values are the average of 2 runs. See the Supporting Information for details.

in Table 1, various analogues of proline prove to be less effective for chirality transfer (entries 2−9). On the other hand, pipecolinic acid (entry 10) provides the product with 60% ee, indistinguishable from the result with proline.

An important factor that reduces efficiency, in each of the experiments in Table 1, is the formation of a byproduct (**3**) derived from intermolecular aldol dimerization of **1**. (This product may be observed as the major product, depending upon the reaction solvent employed.)[11] However, through a screen of solvent effects, we were able to suppress completely its formation (Figure 1). Notably, *under protic*

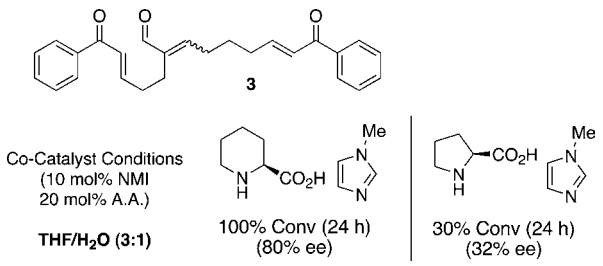


Figure 1.

conditions (THF/H_2O, 3:1), the pipecolinic acid−NMI co-catalyst system yields full conversion to **2**, with an attendant increase in product ee to 80%. (Under these conditions, proline−NMI is unambiguously less effective, yielding the product with only 32% ee at 30% conversion.)

We then sought to determine whether these conditions would be generalizable to other intramolecular MBH reac-

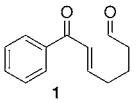
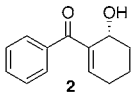
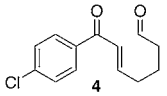
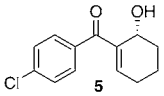
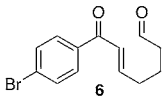
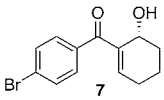
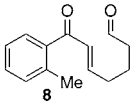
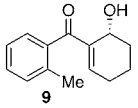
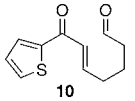
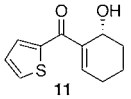
(8) For recent examples, see: (a) Yeo, J. E.; Yang, X.; Kim, H. J.; Koo, S. *Chem. Commun.* **2004**, 236. (b) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230. (c) Krishna, P. R.; Kannan, V.; Sharma, G. V. M. *J. Org. Chem.* **2004**, *69*, 6467. (d) Yagi, K.; Turitani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *18*, 3111. (e) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687. (f) Drewes, S. E.; Njamela, O. L.; Emslie, N. D.; Ramesar, N.; Field, J. S. *Synth. Commun.* **1993**, *23*, 2807. (g) Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, *57*, 7771.

(9) For recent examples of vinylogous variants, see: (a) Wang, L.-C.; Luis, A.-Z.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (b) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404. (c) Brown, P. M.; Käppel, N.; Murphy, P. J. *Tetrahedron Lett.* **2002**, *43*, 8707.

(10) Roth, F.; Gygax, P.; Fráter, G. *Tetrahedron Lett.* **1992**, *33*, 1045.

(11) The result is not surprising in light of the well-documented behavior of proline and its surrogates as an aldol reaction catalyst. See: List, B. *Tetrahedron* **2002**, *58*, 5573. The THF/H_2O solvent system was the unique medium that we examined that afforded exclusively intramolecular MBH product at high conversion.

Table 2. Substrate Screen for Pipecolinic Acid−NMI Catalysis of the Intramolecular MBH Reaction[a]

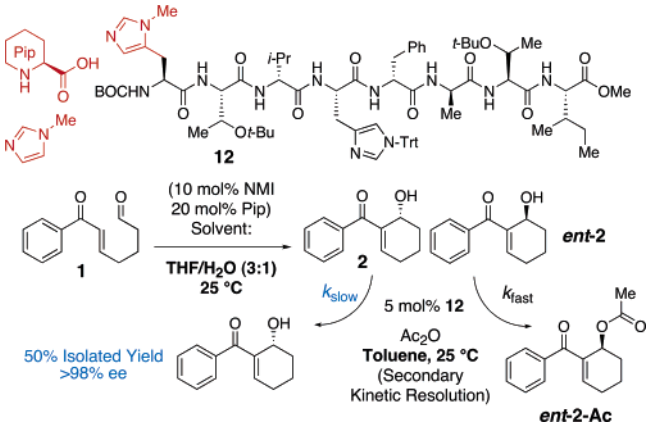
entry	substrate	product	isolated yield [b]	ee [c]
1a, 25 °C			82% (51%)	80%
1b, 4 °C	1	2	50% *conv.*	84%
2			92% (56%)	79%
	4	5		
3			88% (68%)	79%
	6	7		
4			94% (46%)	51%
	8	9		
5			83% (50%)	74%
	10	11		

[a] All reactions were conducted at 25 °C in THF/H_2O (3:1, 0.6 M in **1**) for 48 h. [b] After extraction (after silica gel chromatography). [c] Determined by chiral HPLC. Reported ee values are the average of two runs. See the Supporting Information for details.

tions in this class. As shown in Table 2, entry 1, substrate **1** may be run to full conversion under the THF/H_2O conditions such that product **2** may be isolated in 82% yield with 80% ee. The purity of the isolated material is >90% by TLC and NMR analysis. We found that the MBH products are not completely stable to silica gel chromatography and that after further purification by this method, product **2** is obtained in very high purity, but in a reduced isolated yield of 51%. We have also observed that the reaction selectivity is not strongly influenced by temperature. At 4 °C, the reaction proceeds to 50% conversion within 48 h, and the product ee is increased to 84% (entry 1b). A preliminary study of the scope of the process shows that it is tolerant of modest substitutions in the acyclic precursor. *p*-Chloro-substituted substrate **4** is converted to **5** with comparable ee and isolated yield (entry 2, 79% ee, 92% yield after extraction). The *p*-bromo-substituted analogue **6** performs similarly (entry 3, 79% ee, 88% yield after workup). *Ortho* substitution as in the case of compound **8**, on the other hand, has a deleterious effect on selectivity, with the product **9** being obtained with 51% ee (entry 4). The thiophene analogue **10** performs with slightly reduced ee, as MBH product **11** is obtained with 74% ee (entry 5).

While the enantioselectivity data reported in Table 2 represents a significant advance over that previously published for the intramolecular MBH, we wished to demonstrate that product ee could be enhanced through a strategic quench of the reaction mixture. At the conclusion of the enantioselective intramolecular MBH process, introduction of acetic anhydride along with a peptide-based asymmetric acylation catalyst[12] creates a scenario wherein the MBH reaction is coupled to a kinetic resolution of the nonracemic reaction mixture (Scheme 1). In practice, the co-catalyst system of

Scheme 1



pipecolinic acid, NMI, and peptide **12**[13,14] allows a sequential, one-pot enantioselective intramolecular MBH reaction−asymmetric acylation reaction to occur such that product **2** is obtained in 50% isolated yield (after chromatography) with >98% ee.

It is notable that in this context, the peptide-based catalyst may, in principle, perform multiple functions in this tandem asymmetric catalysis process. The optimization of this strategy toward even higher isolated yields of optically pure products is a future direction in which we hope to take this work. The mechanistic aspects of this process, although not established in detail at this time, are likewise among our current objectives.[15]

Acknowledgment. This research is supported by the National Science Foundation (CHE-0236591). We are also grateful to Merck Research Laboratories and Pfizer for support. We thank Christopher Gilmore for the preparation of starting materials.

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

OL0513544

(12) For a review of asymmetric acylation, see: Jarvo, E. R.; Miller, S. J. Asymmetric Acylation. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.: Springer-Verlag: Berlin Heidelberg, 2004; Chapter 43.

(13) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496.

(14) It is notable that the greater catalytic activity of **12** in comparison to NMI allows the resolution to be conducted in the presence of NMI.

(15) Fierman, M. B.; O'Leary, D. J.; Steinmetz, W. E.; Miller, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6967−6971.