MgI_2-accelerated enantioselective Morita–Baylis–Hillman reactions of cyclopentenone utilizing a chiral DMAP catalyst†

Alejandro Bugarin and Brian T. Connell*

Received (in College Park, MD, USA) 29th January 2010, Accepted 25th February 2010
First published as an Advance Article on the web 12th March 2010
DOI: 10.1039/c001977a

Fu's planar chiral DMAP catalyst efficiently promotes the asymmetric Morita–Baylis–Hillman reactions of cyclopentenone with a variety of aldehydes in the presence of MgI_2 as a cocatalyst.

The Morita–Baylis–Hillman (MBH) reaction, first reported in 1968, is an important carbon–carbon bond-forming reaction between electron-deficient alkenes, such as α,β-unsaturated ketones, and aldehydes or activated ketones.[1] It is usually catalyzed by suitable nucleophilic tertiary amines or phosphines.[2] This transformation has attracted attention because it can be a selective (chemo-, regio-, diastereo-, and enantio-) and atom economical method for converting simple starting materials into more densely functionalized products.[3] Because of the easy accessibility of starting materials and the potential of the poly-functionalized adducts, the development of a suitable asymmetric version of this reaction has attracted considerable interest in recent years.

Various attempts to accelerate this reaction through the use of chiral catalysts, cocatalysts, and a chiral medium have been studied.[4] Hatakeyama *et al.* reported a chiral quinidine-derived catalyst for the reaction of a highly activated acrylate with aldehydes, providing the adducts with ee values up to 99%.[5] Maher and Connon were the first to use thioureas to accelerate the DABCO-promoted MBH reaction.[6] Recently, several other thiourea-derived[7] and BINOL-derived[8] systems have been reported. Each of these methods has been limited in substrate scope to varying extents.

The mechanism of the MBH reaction allows the use of a Lewis acid cocatalyst to increase reaction rates.[9] For example, we recently reported a mild reaction system employing a 1 : 1 : 1 ratio of catalytic amounts (10 mol%) of MgI_2, TMEDA and DMAP to accelerate the rates of the MBH reaction between cyclic enones and enoates with aldehydes in methanol.[10] We were interested in an enantioselective process based on this protocol utilizing cyclopentenone as a substrate. MBH adducts of cyclopentenone have potential utility towards the total synthesis of natural products containing cyclopentenone or cyclopent(en)yl moieties, including Lathyranoic acid A and Euphorbia factor L_{11},[11] as well as Acutaxyline A and B.[12]

Our initial studies identified chiral nucleophiles (Fig. 1), which were capable of catalyzing the reaction of *trans*-cinnamaldehyde with cyclopentenone in the presence of catalytic

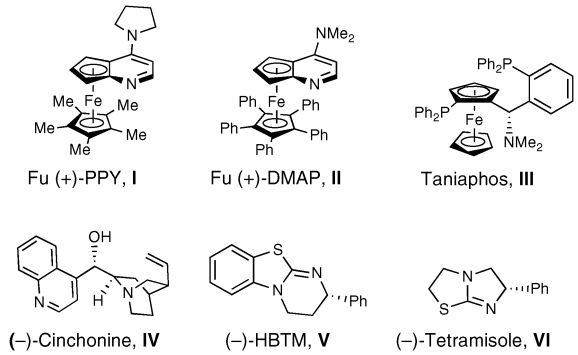
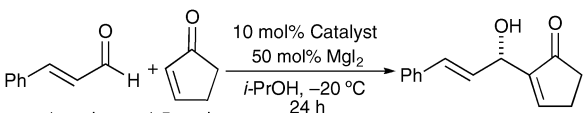


Fig. 1 Amine catalysts examined as nucleophiles.

MgI_2 (Table 1). TMEDA and several chiral TMEDA-equivalent ligands[13] were also screened, but they resulted in low enantioselectivity due to a reasonably high background reaction rate. Lewis acids other than MgI_2, including $NiCl_2$, $SnCl_4$, LiCl, $LiClO_4$, $Cu(OTf)_2$, and $Zn(OTf)_2$, showed poor or no reactivity under these conditions.

Table 1 depicts the catalytic activity of several enantioselective nucleophiles (**I–VI**)[14] towards the asymmetric MBH coupling of *trans*-cinnamaldehyde with cyclopentenone in the presence of 50 mol% MgI_2. The reaction mediated by the most nucleophilic catalyst (Fu's chiral PPY **I**) occurred with the highest yield (98%) but lower ee (81%) (Table 1, entry 1) than Fu's less nucleophilic **II**, which delivered the product in a 96% yield and 94% ee (Table 1, entry 2). Other catalytic nucleophiles showed lower enantioselectivity and reactivity (Table 1, entries 3–6). The chiral thiourea derived [(–)-HBTM **V** and (–)-tetramisole **VI**] were also notably less reactive (Table 1, entries 5 and 6) than the DMAP derivatives **I** and **II**.

Table 1 Enantioselective MBH reaction between cyclopenten-2-one and *trans*-cinnamaldehyde



Entry	Catalyst	Yield[a] (%)	ee[b] (%)
1	I	98	81
2	**II**	**96**	**94**
3	III	45	54
4	IV	89	45
5	V	5	63
6	VI	19	48

[a] Isolated yield after purification by silica gel chromatography. [b] Enantiomeric excess determined by chiral HPLC (see the ESI†).

Department of Chemistry, Texas A&M University, PO Box 30012, College Station, TX 77842-3012, USA.
E-mail: connell@chem.tamu.edu; Tel: +1 979-845-5746

† Electronic supplementary information (ESI) available: Experimental procedures for the preparation of Morita–Baylis–Hillman adducts; copies of ^1H and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/c001977a

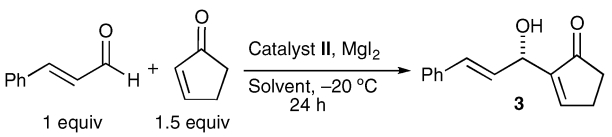
With these data in hand, optimization of the reaction conditions utilizing catalyst **II** was carried out (Table 2). At −20 °C, no reaction was observed between *trans*-cinnamaldehyde and cyclopentenone in the absence of MgI_2 (Table 2, entry 1). However, increasing the amount of MgI_2 from 10 mol% to 50 mol% increased the yield of the reaction from 45% to 96% yield without having a dramatic effect on the ee (92% *vs.* 94%) (entries 2 and 5). Intermediate quantities of MgI_2 provided intermediate yields (entries 3 and 4). *i*-PrOH proved to be the best solvent, delivering the product in excellent yield while maintaining a high level of enantioselectivity compared to MeOH and EtOH (entries 6 and 7). The use of less catalyst **II** (5 mol%) afforded a slower reaction but no loss of ee (entry 8), while 20 mol% of catalyst **II** was no better than 10 mol% (entry 5 *vs.* 9). Higher reaction concentration had a negligible effect on the reaction (entry 10) while higher temperatures eroded the observed ee (entries 11 and 12). Lower temperature slowed the reaction with no marked increase in enantioselectivity (entry 13).

We investigated the scope of this MBH reaction by examining a variety of electrophiles (Table 3). For aromatic aldehydes, the system is very efficient. The MBH reaction of 1-naphthaldehyde and cyclopentenone delivers the product in 94% yield and 98% ee (Table 3, entry 1). The adduct of electron-rich *p*-methoxybenzaldehyde is obtained in 73% yield and 95% ee (Table 3, entry 2). The electron-poor *p*-nitrobenzaldehyde afforded a lower yield (75%), likely due to solubility of the aldehyde in *i*-PrOH (Table 3, entry 8).[15] Additionally, this chiral DMAP/MgI_2 mixture afforded reasonable yields and moderate ees for the aliphatic aldehydes. The lower yields obtained in these cases are the result of incomplete reaction, and extended reaction times will likely provide increased yields.

To further examine the scope and utility of these reaction conditions, a variety of cyclic and acyclic α,β-unsaturated ketones and esters were treated with benzaldehyde, but no significant reaction occurred. Similar to other reported MBH catalytic systems (*vide supra*), the present system demonstrates a limited scope with respect to the nucleophilic component, so a careful analysis of substrates is necessary when evaluating various MBH reaction catalysts.

In summary, we have developed an effective asymmetric MBH reaction involving the addition of cyclopentenone to

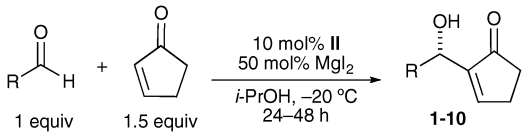
Table 2 Optimization of the MBH reaction

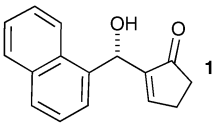
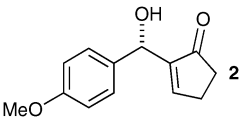
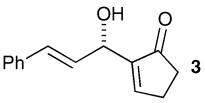
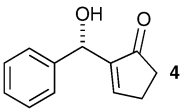
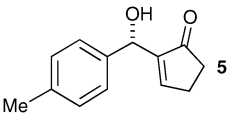
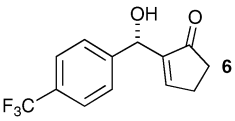
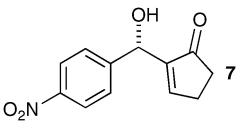
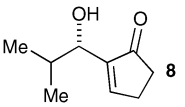
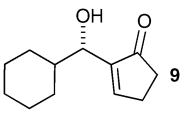
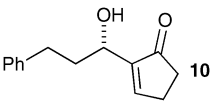


Entry	MgI_2 (mol%)	**II** (mol%)	Solvent	Yield[a] (%)	ee[b] (%)
1	0	10	*i*-PrOH	NR	NA
2	5	10	*i*-PrOH	21	80
3	10	10	*i*-PrOH	45	92
4	20	10	*i*-PrOH	57	93
5	**50**	**10**	**i-PrOH**	**96**	**94**
6	50	10	EtOH	89	77
7	50	10	MeOH	98	53
8	50	5	*i*-PrOH	60	94
9	50	20	*i*-PrOH	93	94
10[c]	50	20	*i*-PrOH	92	94
11[d]	50	10	*i*-PrOH	97	70
12[e]	50	10	*i*-PrOH	94	91
13[f]	50	10	*i*-PrOH	39	95

[a] Isolated yield after purification by silica gel chromatography. [b] Determined by chiral HPLC (see ESI†). [c] [*c*] = 0.1 M instead of 0.05 M. [d] Reaction performed at 20 °C. [e] Reaction performed at 0 °C. [f] Reaction performed at −50 °C.

Table 3 Enantioselective MBH reaction with various aldehydes



Entry	Product	Time/h	Yield[a] (%)	ee[b] (%)
1	 **1**	24	94	98
2	 **2**	24	73	95
3	 **3**	24	96	94 (*S*)
4[c]		24	93	94 (*R*)
5	 **4**	24	87	94
6	 **5**	24	81	92
7	 **6**	24	92	89
8	 **7**	24	75	89
9	 **8**	48	59	63
10	 **9**	48	54	58
11	 **10**	48	68	53

[a] Isolated yield after purification by silica gel chromatography. [b] Determined by chiral HPLC (see the ESI†). [c] The (−)-enantiomer of catalyst **II** was used.

aromatic and aliphatic aldehydes catalyzed by Fu's planar chiral DMAP derivative **II** in conjunction with readily available MgI_2 as a cocatalyst. The products are obtained in good to excellent yields and moderate to excellent enantiomeric excesses. Perhaps more importantly, the work described here shows that the scope of reactions catalyzed by Fu's planar chiral DMAP catalysts can be increased by employing a simple cocatalyst, a concept which, to our knowledge, has not been documented previously. Efforts are underway to further elucidate the mechanistic details of this reaction system which should in turn allow for future advances in scope and selectivity.

The Norman Hackerman Advanced Research Program and the Robert A. Welch Foundation (A-1623) are gratefully acknowledged for support of this research.

Notes and references

1 (*a*) K. Morita, Z. Suzuki and H. Hirose, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2815; (*b*) A. B. Baylis and M. E. D. Hillman, *German Patent*, 2155113, 1972 (*Chem. Abstr.*, 1972, **77**, 34174q).

2 (*a*) in *Organic Reactions*, ed. L. A. Paquette, John Wiley & Sons, New York, 1997, vol. 51, p. 201; (*b*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811–892; (*c*) S. France, D. J. Guerin, S. J. Miller and T. Lectka, *Chem. Rev.*, 2003, **103**, 2985–3012; (*d*) G. Masson, C. Housseman and J. Zhu, *Angew. Chem., Int. Ed.*, 2007, **46**, 4614–4628; (*e*) Y. L. Shi and M. Shi, *Eur. J. Org. Chem.*, 2007, 2905–2916; (*f*) V. Singh and S. Batra, *Tetrahedron*, 2008, **64**, 4511–4574.

3 (*a*) B. M. Trost, O. R. Thiel and H. C. Tsui, *J. Am. Chem. Soc.*, 2002, **124**, 11616–11617; (*b*) B. M. Trost, O. R. Thiel and H. C. Tsui, *J. Am. Chem. Soc.*, 2003, **125**, 13155–13164.

4 (*a*) J. E. Imbriglio, M. M. Vasbinder and S. J. Miller, *Org. Lett.*, 2003, **5**, 3741–3743; (*b*) R. Gausepohl, P. Buskens, J. Kleinen, A. Bruckmann, C. W. Lehmann, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2006, **45**, 3689–3692; (*c*) A. Nakano, K. Takahashi, J. Ishihara and S. Hatakeyama, *Org. Lett.*, 2006, **8**, 5357–5360.

5 Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.*, 1999, **121**, 10219–10220.

6 D. J. Maher and S. J. Connon, *Tetrahedron Lett.*, 2004, **45**, 1301–1305.

7 (*a*) A. Berkessel, K. Roland and J. M. Neudörfl, *Org. Lett.*, 2006, **8**, 4195–4198; (*b*) A. Lattanzi, *Synlett*, 2007, 2106–2110; (*c*) J. Wang, H. Li, X. Yu, L. Zu and W. Wang, *Org. Lett.*, 2005, **7**, 4293–4296; (*d*) X.-G. Liu and M. Shi, *Org. Lett.*, 2008, **10**, 1043–1046; (*e*) Y. Sohtome, N. Takemura, R. Takagi, Y. Hashimoto and K. Nagasawa, *Tetrahedron*, 2008, **64**, 9423–9429.

8 (*a*) N. T. McDougal and S. E. Schaus, *J. Am. Chem. Soc.*, 2003, **125**, 12094–12095; (*b*) N. T. McDougal, W. L. Trevellini, S. A. Rodgen, L. T. Kliman and S. E. Schaus, *Adv. Synth. Catal.*, 2004, **346**, 1231–1240; (*c*) K. Matsui, S. Takizawa and H. Sasai, *Tetrahedron Lett.*, 2005, **46**, 1943–1946.

9 (*a*) V. K. Aggarwal, D. K. Dean, A. Mereu and R. Williams, *J. Org. Chem.*, 2002, **67**, 510–514; (*b*) A. Barrett, A. Cook and A. Kamimura, *Chem. Commun.*, 1998, 2533–2534; (*c*) R. Robiette, V. K. Aggarwal and J. N. Harvey, *J. Am. Chem. Soc.*, 2007, **129**, 15513–15525; (*d*) Y. M. A. Yamada and S. Ikegami, *Tetrahedron Lett.*, 2000, **41**, 2165–2169.

10 A. Bugarin and B. T. Connell, *J. Org. Chem.*, 2009, **74**, 4638–4641.

11 S.-G. Liao, Z.-J. Zhan, S.-P. Yang and J.-M. Yue, *Org. Lett.*, 2005, **7**, 1379–1382.

12 I. S. Ismail, Y. Nagakura, Y. Hirasawa, T. Hosoya, M. I. M. Lazim, N. H. Lajis and H. Morita, *Tetrahedron Lett.*, 2009, **50**, 4830–4832.

13 I. Coldham, P. O'Brien, J. J. Patel, S. Raimbault, A. J. Sanderson, D. Stead and D. T. E. Whittaker, *Tetrahedron: Asymmetry*, 2007, **18**, 2113–2119.

14 (*a*) J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1996, **61**, 7230–7231; (*b*) G. C. Fu, *Acc. Chem. Res.*, 2004, **37**, 542–547; (*c*) V. B. Birman and L. Guo, *Org. Lett.*, 2006, **8**, 4859–4861; (*d*) V. B. Birman, X. Li and Z. Han, *Org. Lett.*, 2007, **9**, 37–40; (*e*) V. B. Birman and X. Li, *Org. Lett.*, 2008, **10**, 1115–1118.

15 *p*-Nitrobenzaldehyde was reduced to (4-nitrophenyl)methanol under these reaction conditions in 10 min at RT. Fortunately, at −20 °C, the MBH reaction occurred.

