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Lewis base and L-proline co-catalyzed Baylis–Hillman reaction of arylaldehydes with methyl vinyl ketone

Min Shi,* Jian-Kang Jiang and Chao-Qun Li

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

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Abstract—In the Baylis–Hillman reaction of arylaldehydes with methyl vinyl ketone, we found that, in the presence of a catalytic amount of L-proline, weak Lewis bases such as imidazole and triethylamine as well as the stronger Lewis base DABCO, can promote the Baylis–Hillman reaction to give the normal Baylis–Hillman adduct in good yields. Substituent effects were also examined and a plausible reaction mechanism is proposed. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, the Baylis–Hillman reaction has made great progress,[1] and now includes a catalytic asymmetric version.[2] Baylis and Hillman first reported the reaction of acetaldehyde with ethyl acrylate and acrylonitrile in the presence of catalytic amounts of strong Lewis bases such as 1,4-diazabicyclo[2,2,2]octane (DABCO) in 1972.[3] During our own investigation on this very simple and useful reaction, we disclosed many new results.[4] Herein, we wish to report that in the reaction of arylaldehydes with methyl vinyl ketone (MVK) weak Lewis bases such as imidazole and triethylamine can also promote this reaction in the presence of L-proline to give high yields of **1**.

Imidazole and triethylamine are weak Lewis bases and cannot promote the reaction of arylaldehydes with MVK at all by themselves (Scheme 1). However, we found that, in the presence of a catalytic amount of L-proline, this reaction takes place smoothly to give high yields of **1**. For example, in the reaction of *p*-nitrobenzaldehyde (1.0 equiv.) with MVK (3.0 equiv.), **1a** can be obtained in 60% yield in the presence of 10 mol% of imidazole and 10 mol% of L-proline in DMF for 24 h.[5] By increasing the amount of imidazole and L-proline to 30 mol%, the yield of **1a** reaches 91% under the same conditions (Scheme 1). Similar results were obtained by carrying out the reaction in DMSO, tetrahydrofuran (THF) or chloroform (Scheme 2, Table 1, entries 2–4). Using benzimidazole or triethylamine as Lewis base reduced the yields of **1a** under the same reaction conditions (Table 1, entries 5 and 7). Using pyridine or 1*H*-benzotriazole as a Lewis base, no reaction occurred (Table 1, entries 6 and 8). Using other amino acids such as glycine (30 mol%) or L-phenylalanine (30 mol%) as a promoter, only 20–30% of **1a** was obtained.

For *m*-nitrobenzaldehyde, *o*-nitrobenzaldehyde, *p*-bromo or *p*-chlorobenzaldehyde and pyridylaldehydes, similar results were obtained under the optimized reaction conditions (Scheme 3, Table 2, entries 1–4). However, for benzaldehyde, *trans*-cinnamaldehyde, valeraldehyde or *p*-ethylbenzaldehyde, adducts **1** were obtained only in moderate yields. It should be pointed out that, in all cases, the adducts **1** were obtained with very low ees (5–10%), although L-proline was used as the co-catalyst.

Concerning the additives used for Baylis–Hillman reactions, $LiClO_4$ and $NaBF_4$ have been used as Lewis acids with Lewis bases DABCO and pyrrolizidine, respectively, to accelerate the reaction rate.[6] However, in these systems, DABCO or pyrrolizidine itself are sufficient to promote the reaction. In our system, coexistence of Lewis base and L-proline is required to promote the Baylis–Hillman reaction. We examined the imidazole and $LiClO_4$ co-catalyzed Baylis–Hillman reaction of *p*-nitrobenzaldehyde (1.0 equiv.) with MVK (3.0 equiv.) under our conditions (Scheme 4). The reaction was sluggish and the yield of **1a** was only 30%. We believe that L-proline acts as a Lewis acid in this reaction. Recently, many L-proline-catalyzed condensa-

Keywords: Baylis–Hillman reaction; Lewis base; methyl vinyl ketone (MVK); L-proline; imidazole; triethylamine.

* Corresponding author. E-mail: mshi@pub.sioc.ac.cn

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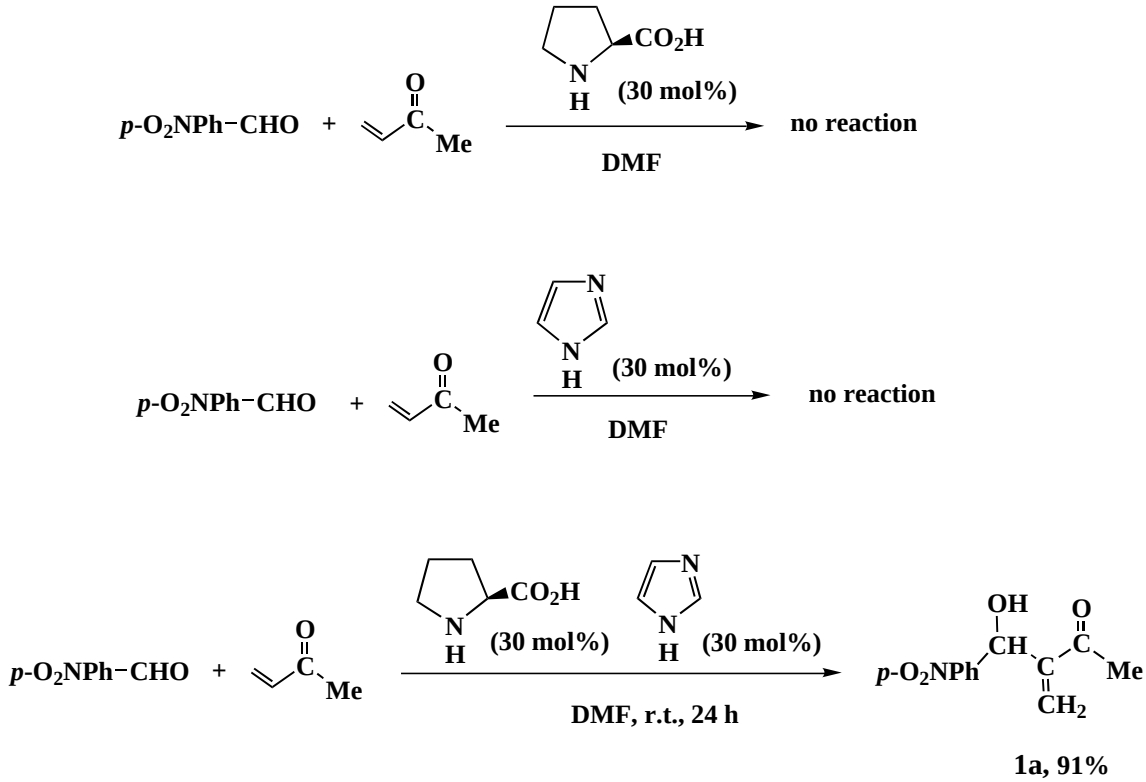
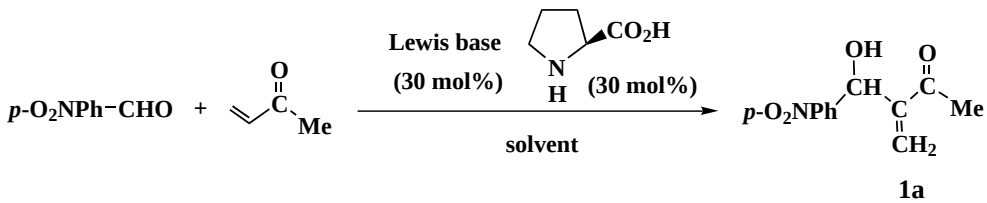


Scheme 1.



Scheme 2.

tion reactions have been reported.[7] List reported a very exciting L-proline-catalyzed direct asymmetric aldol reaction with an elegant mechanism.[7c] Based on his aldol reaction mechanism and the traditional Baylis–Hillman reaction mechanism, we would like to postulate the mechanism for the above L-proline and imidazole (Lewis base and Lewis acid) co-catalyzed Baylis–Hillman reaction shown in Scheme 5. In order

Table 1. Baylis–Hillman reactions of *p*-nitrobenzaldehyde (1.0 equiv.) with methyl vinyl ketone (MVK) (3.0 equiv.) in the presence of Lewis base (0.3 equiv.) and proline (0.3 equiv.)

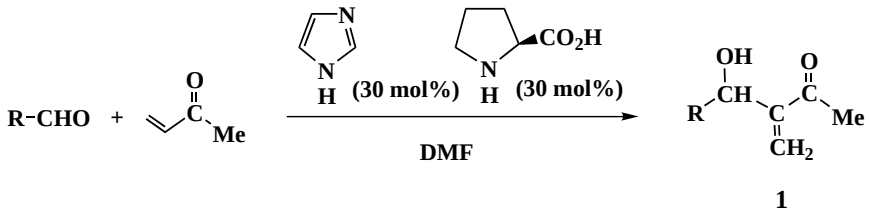
Entry	Lewis base	Solvent	Time (h)	Yield (%)[a] **1a**
1	Imidazole	DMF	24	91
2	Imidazole	DMSO	24	90
3	Imidazole	THF	24	87
4	Imidazole	Chloroform	24	88
5	Benzimidazole	DMF	24	45
6	1*H*-Benzimidazole	DMF	36	–
7	Et_3N	DMF	36	66
8	Pyridine	DMF	40	–

[a] Isolated yields.

Table 2. Baylis–Hillman reactions of aldehydes (1.0 equiv.) with methyl vinyl ketone (3.0 equiv.) in the presence of imidazole (0.3 equiv.) and proline (0.3 equiv.)

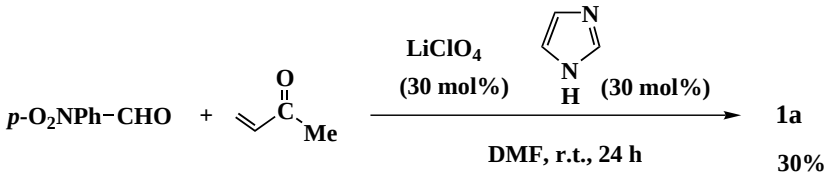
Entry	R	Time (h)	Yield (%)[a] **1**
1	*m*-NO_2Ph	24	90
2	*o*-NO_2Ph	24	86
3	*p*-BrPh[b]	48	85
4	*p*-ClPh[b]	60	67
5	Ph[b]	72	45
6	*p*-EtPh[b]	80	30
7	2-Pyridyl	24	90
8	3-Pyridyl	24	80
9	*trans*-PhCH=CH[b]	72	43
10	$CH_3(CH_2)_2$[b]	80	46

[a] Isolated yields.
[b] Arylaldehyde:methyl vinyl ketone = 1:5.

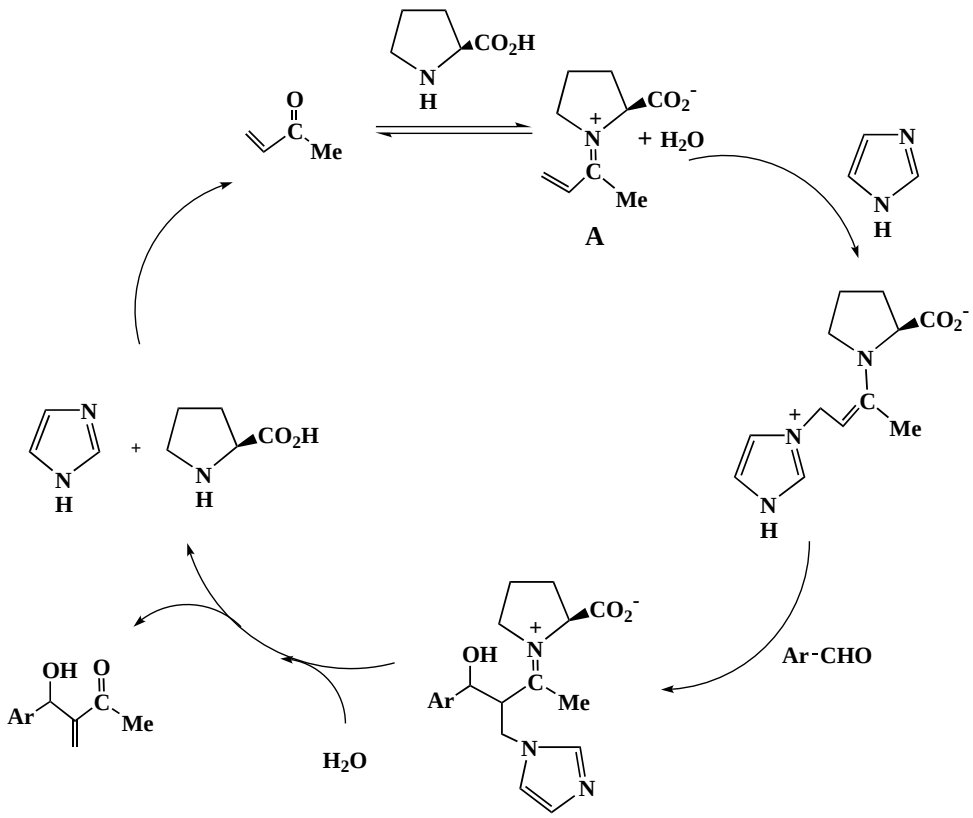


b: R= *m*-NO_2Ph, c: R= *o*-NO_2Ph, d: R= *p*-BrPh, e: R= *p*-ClPh, f: R= Ph, g: R= *p*-EtPh, h: R= 2-pyridyl, i: R= 3-pyridyl, j: R= PhCH=CH, k: R= $CH_3(CH_2)_3$.

Scheme 3.



Scheme 4.



Scheme 5.

to obtain evidence for this mechanism, we measured the ^{1}H NMR of MVK, L-proline and the mixture of MVK and L-proline (1:2) in CD_3OD and $CD_3S(O)CD_3$, but no useful information was obtained. This may mean that the concentration of intermediate **A** is very low, and it is difficult to find its NMR signal.

In conclusion, we have found that in the Baylis–Hillman reaction of arylaldehydes with methyl vinyl ketone (MVK), weak Lewis bases can promote the reaction in the presence of a catalytic amount of L-proline. It should be emphasized here that although the Baylis–Hillman adducts **1** obtained had very low optical activ-

ity, we believe this finding could open a new way for the design and synthesis of chiral ligands that will catalyse the asymmetric version of the Baylis–Hillman reaction. Efforts are underway to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

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References

1. (a) Ciganek, E. *Org. React*. **1997**, *51*, 201; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001; (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653; (d) Brzezinski, L. J.; Rafel, S.; Leahy, J. M. *J. Am. Chem. Soc*. **1997**, *119*, 4317; (e) Miyakoshi, T.; Saito, S. *Nippon Kagaku Kaishi* **1983**, *1623*; *Chem. Abstr*. **1984**, *100*, 156191g; (f) Marko, I. E.; Giles, P. G.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015; (g) Richter, H.; Jung, G. *Tetrahedron Lett*. **1998**, *39*, 2729; (h) Kunidig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett*. **1993**, *34*, 7049; (i) Aggarwal, V.; Mereu, A.; Tarver, G. J.; MaCague, R. *J. Org. Chem*. **1998**, *63*, 7183; (j) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S. *Tetrahedron* **1998**, *54*, 11813; (k) Kataoka, T.; Iwama, T.; Kinoshita, S.; Tsujiyama, Y.; Iwamura, T.; Watanabe, S. *Synlett* **1999**, 197; (l) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Kanematsu, K.; Iwamura, T.; Watanabe, S. *Chem. Lett*. **1999**, 257; (m) Kataoka, T.; Iwama, T.; Tsujiyama, S. *Chem. Commun*. **1998**, 197; (n) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett*. **1999**, *40*, 1509; (o) Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett*. **2000**, *41*, 1; (p) Kataoka, T.; Kinoshita, H.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S.; Muraoka, O.; Tanabe, G. *Tetrahedron* **2000**, *56*, 4725; (q) Li, G.; Gao, J.; Wei, H.-X.; Enright, M. *Org. Lett*. **2000**, *2*, 617.
2. Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc*. **1999**, *121*, 10219.
3. (a) Baylis, A. B.; Hillman, M. E. D. *Ger. Offen*. **1972**, *2*, 155, 113; *Chem. Abstr*. **1972**, *77*, 34174q; Hillman, M. E. D.; Baylis, A. B. US Patent 1973, 3,743,669; (b) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn*. **1968**, *41*, 2815.
4. (a) Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett*. **2000**, *2*, 2397; (b) Shi, M.; Feng, Y.-S. *J. Org. Chem*. **2001**, *66*, 406; (c) Shi, M.; Jiang, J.-K.; Cui, S.-C.; Feng, Y.-S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390; (d) Shi, M.; Jiang, J.-K. *Tetrahedron* **2000**, *56*, 4793; (e) Shi, M.; Li, C.-Q.; Jiang, J.-K. *Chem. Commun*. **2001**, 833; (f) Shi, M.; Xu, Y.-M. *Chem. Commun*. **2001**, 1876.
5. The spectral data of **1a**: Mp 76–77°C; IR (KBr) ν 1658 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.37 (3H, s, Me), 3.34 (1H, d, $J=5.3$ Hz, OH), 5.69 (1H, d, $J=5.3$ Hz), 6.04 (1H, s), 6.28 (1H, s), 7.56 (2H, d, $J=8.6$ Hz, Ar), 8.25 (2H, d, $J=8.6$ Hz, Ar); MS (EI) m/z 220 (M^+-1, 20.9), 204 (M^+-17, 100), 174 (M^+-47, 88.1).
6. (a) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett*. **1999**, *40*, 1539; (b) Barrett, A. G.; Cook, A. S.; Kamimura, A. *Chem. Commun*. **1998**, 2533.
7. Recent papers about L-proline-catalyzed reactions: (a) Bui, T.; Barbas, C. F., III, *Tetrahedron Lett*. **2000**, *41*, 6951; (b) Hanessian, S.; Pham, V. *Org. Lett*. **2000**, 2, 2975; (c) List, B.; Lerner, R. A.; Barbas, C. F., III, *J. Am. Chem. Soc*. **2000**, *122*, 2395; (d) Notz, W.; List, B. *J. Am. Chem. Soc*. **2000**, *122*, 7386.