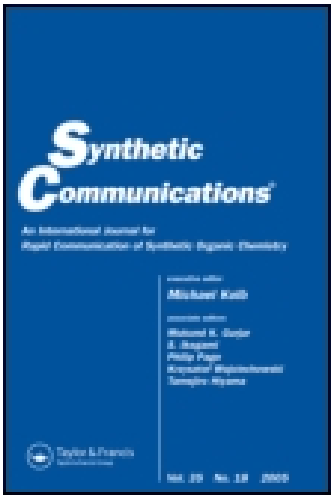


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

N-Methylpiperidine—A Useful Base Catalyst in the Morita-Baylis-Hillman Reaction

San-Hu Zhao [a b] & Zhao-Bin Chen [a]
[a] School of Chemistry and Chemical Engineering , Shanxi University , Taiyuan, China
[b] Xinzhou Teachers University , Xinzhou, China
Published online: 21 Aug 2006.

To cite this article: San-Hu Zhao & Zhao-Bin Chen (2005) N-Methylpiperidine—A Useful Base Catalyst in the Morita-Baylis-Hillman Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:23, 3045-3053

To link to this article: http://dx.doi.org/10.1080/00397910500278776

Synthetic Communications®, 35: 3045–3053, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500278776

N-Methylpiperidine—A Useful Base Catalyst in the Morita–Baylis–Hillman Reaction

San-Hu Zhao
School of Chemistry and Chemical Engineering, Shanxi University, Taiyuan, China and Xinzhou Teachers University, Xinzhou, China

Zhao-Bin Chen
School of Chemistry and Chemical Engineering, Shanxi University, Taiyuan, China

Abstract: N-methylpiperidine, a commercially available mild base, has effectively been utilized as a catalyst in the Morita–Baylis–Hillman reaction. Moderate to excellent yields (34–95%) and significant rate enhancement have been observed.

Keywords: Aldehyde, base catalyst, Morita–Baylis–Hillman reaction, dioxane–water, N-methylpiperidine

INTRODUCTION

The Morita–Baylis–Hillman reaction[1] has become increasingly important in synthetic organic chemistry because the resulting (α-methylene-β-hydroxy)-esters are versatile intermediates that allow for further functional-group manipulation. However, as a versatile carbon–carbon bond-forming reaction, Morita–Baylis–Hillman reaction is generally sluggish and has limited substrate scope[2]; many aromatic aldehydes and branched aliphatic aldehydes are reluctant to serve as substrates, which restricts its applications in organic

Received in Japan May 12, 2005
Address correspondence to Zhao-Bin Chen, School of Chemistry and Chemical Engineering, Shanxi University, Taiyuan 030006, China. Fax: 86351-7011688; E-mail: zhaosh@sxu.edu.cn

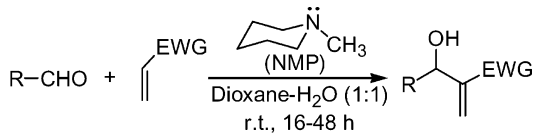
synthesis. To overcome these problems, several modifications have been attempted including novel solvent media,[3] ultrasound,[4] high pressure,[5] and new catalysts such as 4-(dimethylamino)pyridine,[6] N,N,N′,N′-tetramethylethylenediamine,[7] imidazole, lithium perchlorate,[8] hexamethylenetetramine,[9] N-methylmorpholine,[10] 1,8-diazabicyclo(5.4.0)-undec-7-ene,[11] azoles,[12] and so forth.[13] Although many physical as well as chemical attempts are known in literature, the development of an efficient Morita–Baylis–Hillman reaction is among the most challenging themes in organic synthesis. In this article, we report that a rapid rate and good product yield can be achieved using N-methylpiperidine (NMP) as the catalyst for the Morita–Baylis–Hillman reaction (Scheme 1).

RESULTS AND DISCUSSION

1,4-Diazabicyclo[2. 2. 2]octane (DABCO), first introduced by Baylis and Hillman,[1a] is arguably still the most widely used catalyst for the Morita–Baylis–Hillman reaction, so our recent interest has been in the development of new catalysts. N-methylpiperidine (NMP) is a readily available tertiary amine and was chosen as a catalyst for our study because it is either hitherto unexplored or the least-studied catalyst in the Morita–Baylis–Hillman reaction. Initially, standardization of reaction conditions was carried out using 3-nitrobenzaldehyde **2** and methyl acrylate **12** in different solvents using 0.5 equiv of NMP at room temperature (Table 1). An optimum yield of adduct **15b** (89%) was obtained when the reaction was run for 16 h in an 1:1 mixture of 1,4-dioxane–water.[5] The mixture 1,4-dioxane–water (1:1) was found to be an appropriate solvent and hence was used as the standard in all further reactions.

To broaden the scope of the Morita–Baylis–Hillman reaction catalyzed by NMP, this study was then extended to other Michael acceptors. Namely, the Morita–Baylis–Hillman reaction of acrylonitrile was performed in dioxane–water (1:1) at ambient temperature for 16 h to afford the desired product **15a** in the yields as mentioned in Table 2.

Encouraged by this result, we then carried out the NMP- and DABCO-catalyzed Morita–Baylis–Hillman coupling of 2-nitrobenzaldehyde with acrylonitrile. It was found that the reaction medium catalyzed by DABCO became dark and dirty after 4 h. Furthermore, the formation of Morita–Baylis–Hillman



Scheme 1.

Table 1. Morita–Baylis–Hillman reactions of **2** with **12** catalyzed by NMP in different solvents

Solvent	Time (h)	Product yield (%)
THF	36	10
CH_3CN	36	13
CH_2Cl_2	36	12
Dioxane	36	15
THF–H_2O	20	71
Dioxane–water (1:1)	16	89

adducts could be only detected in very low yield (by thin-layer chromatography gas chromatography). As compared with DABCO, the reaction medium catalyzed by NMP was very clean in all reaction times, and the yield of the desired product **14a** was found to be high (86%, see Table 2).

Table 2. Morita–Baylis–Hillman reaction of aldehydes with activated alkenes using NMP as catalyst[a]

Entry	Aldehyde	Alkene	Product	Time (h)	Yield (%)[b]
1	1	11	**14a**	16	86[c]
2	1	12	**14b**	16	84
3	1	13	**14c**	16	58
4	2	11	**15a**	16	91
5	2	12	**15b**	16	89
6	3	11	**16a**	16	95
7	3	12	**16b**	16	92.5
8	4	11	**17a**	20	83
9	4	12	**17b**	20	85
10	5	11	**18a**	24	76.5
11	6	11	**19a**	24	62
12	6	12	**19b**	24	58
13	7	11	**20a**	24	61
14	8	11	**21a**	24	60
15	8	12	**21b**	24	58
16	9	11	**22a**	48	34
17	10	12	**23a**	48	57

[a]All reactions were performed with aldehydes (3 mmol) and activated alkenes (9 mmol) in a mixture of 1,4-dioxane and water (1:1, v/v, 10 mL) in the presence of an appropriate catalyst, NMP (1.5 mmol), at ambient temperature for 16–48 h.

[b]Refers to isolated, pure products after silica-gel chromatography.

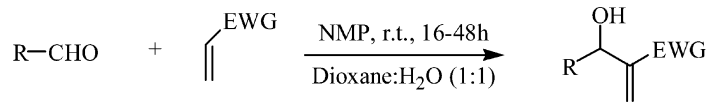
[c]Only trace amounts with catalyst DABCO (1.5 mmol).

The versatility of NMP as a catalyst for the Morita–Baylis–Hillman reaction was further strengthened when a variety of aldehydes such as 2-nitrobenzaldehyde **1**, 4-nitrobenzaldehyde **3**, 4-chloro-3-nitrobenzaldehyde **4**, 2,4-dichlorobenzaldehyde **5**, 4-chlorobenzaldehyde **6**, benzaldehyde **7**, 3-hydroxybenzaldehyde **8**, 4-(dimethylamino) benzaldehyde **9**, and acetaldehyde **10** were allowed to react with activated alkenes **11**, **12**, and **13** at room temperature to give the adducts **14a**, **14b**, **14c**, **16a**, **16b**, **17a**, **17b**, **18a**, **19a**, **19b**, **20a**, **21a**, **21b, 22a**, and **23a** (Scheme 2), respectively, in good to excellent yields (see Table 2). Interestingly, less-reactive benzaldehyde **7** and 3-hydroxybenzaldehyde **8** also, upon reaction with acrylonitrile and methyl acrylate, afforded the desired adducts **20a**, **21a**, and **21b** under the same reaction conditions in short reaction times.

In conclusion, the use of inexpensive and commercially available N-methylpiperdine as a new base catalyst for the Morita–Baylis–Hillman reaction at ambient temperature in aqueous dioxane (1:1) is demonstrated for the first time. Reactions of aromatic aldehydes and activated olefins in the presence of NMP provided the corresponding α-methylene β-hydroxy carbonyl derivatives with good to high yields in short reaction times (Table 2).

EXPERIMENTAL

Commercially available reagents were purchased from Aldrich and used without further purification. All melting points were recorded using



1 R=2-NO_2Ph
2 R=3-NO_2Ph
3 R=4-NO_2Ph
4 R=4-Cl-3-NO_2Ph
5 R=2, 4-Cl_2Ph
6 R=4-ClPh
7 R=Ph
8 R=3-OHPh
9 R=4-$(CH_3)_2$NPh
10 R=CH_3

11 EWG=CN
12 EWG=$COOCH_3$
13 EWG=$CONH_2$

14a R=2-NO_2Ph, EWG=CN
14b R=2-NO_2Ph, EWG=$COOCH_3$
14c R=2-NO_2Ph, EWG=$CONH_2$
15a R=3-NO_2Ph, EWG=CN
15b R=3-NO_2Ph, EWG=$COOCH_3$
16a R=4-NO_2Ph, EWG=CN
16b R=4-NO_2Ph, EWG=$COOCH_3$
17a R=4-Cl-3-NO_2Ph, EWG=CN
17b R=4-Cl-3-NO_2Ph, EWG=$COOCH_3$
18a R=2, 4-Cl_2Ph, EWG=CN
19a R=4-ClPh, EWG=CN
19b R=4-ClPh, EWG= $COOCH_3$
20a R=Ph, EWG=CN
21a R=3-OHPh, EWG=CN
21b R=3-OHPh, EWG= $COOCH_3$
22a R=4-$(CH_3)_2$N-Ph, EWG=CN
23a R=CH_3, EWG=$COOCH_3$

Scheme 2.

capillary melting-point apparatus and are uncorrected. The IR spectra were determined neat or as KBr plots on a Shimadzu FTIR-8300 spectrophotometer; ^{1}H NMR and ^{13}C NMR spectra were measured on a DRX300 NMR spectrometer using TMS as an internal standard in $CDCl_3$. The elemental analyses were performed in the Institute of Chemistry, Chinese Academy of Sciences. Analytical thin-layer chromatography (TLC) was carried out using MN Kieselgel G/UV_{254} (Art. 816320) glass-backed plates.

General Procedure

NMP (1.5 mmol) and the alkene (9 mmol) were added to a solution containing the aldehyde (3 mmol) in a 1:1 mixture (10 mL) of 1,4-dioxane–water. The reaction mixture was stirred for 16–48 h at room temperature; the reaction progress was monitored by TLC. Upon completion, the reaction mixture was neutralized with 0.5 N aqueous HCl and then partitioned with ether (50 mL) and water (30 mL). The organic phase was washed with brine (2 × 30 mL) and dried over anhydrous Na_2SO_4; solvent was removed on a rotary vacuum evaporator. The crude product thus obtained were purified by flash column chromatography (silica gel, 300–400 mesh; EtOAc–hexanes, 1:5–1:3) to afford adducts **14a**, **14b**, **14c**, **15a**, **15b**, **16a**, **16b**, **17a**, **17b**, **18a**, **19a**, **19b**, **20a, 21a**, **21b, 22a**, and **23a** in 34–95% yield. The structures of substances previously reported were confirmed by comparison with mp, IR, and ^{1}H NMR data.

Spectral Data of the Products

3-Hydroxy-2-methylene-3-(2-nitrophenyl)propanenitrile (14a).[7] Yellow solid; mp 40–41°C. IR (KBr): 3462.0, 2229.6, 1610.5, 1344.3 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.03$ (d, $J = 8.06$ Hz, 1H), 7.84 (d, $J = 8.06$ Hz, 1H), 7.73 (t, $J = 7.71$ Hz, 1H), 7.56 (t, 1H, $J = 7.71$ Hz), 6.15 (s, 1H), 6.12 (s, 1H), 5.96 (d, $J = 5.56$ Hz, 1H), 3.27 (br s, 1H).

3-Hydroxy-2-methylene-3-(2-nitrophenyl)propanoic acid, methyl easter (14b).[10] Yellow oil. IR (neat): 3449.4, 1714.1, 1530.9, 1352 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.96$ (d, $J = 8.01$ Hz, 1H), 7.76 (d, 1H, $J = 8.01$ Hz), 7.66 (t, $J = 7.41$ Hz, 1H), 7.48 (t, 1H, $J = 7.41$ Hz), 6.38 (s, 1H), 6.21 (s, 1H), 5.74 (s, 1H), 3.77 (s, 3H), 3.25 (br s, 1H).

3-Hydroxy-2-methylene-3-(2-nitrophenyl)propionamide (14c).[7] Yellow crystal; mp 59–60°C. IR (KBr): 3360, 1662, 1640, 1346.2 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.43$ (s, 1H), 8.13 (d, $J = 8.09$ Hz, 1H), 7.96 (d, $J = 8.09$ Hz, 1H), 7.80 (t, $J = 7.76$ Hz, 1H), 7.76 (t, $J = 7.76$ Hz, 1H), 6.19–6.34 (m, 2H), 5.73 (d, $J = 5.52$ Hz 1H), 5.53 (br s, 2H).

3-Hydroxy-2-methylene-3-(3-nitrophenyl)propanenitrile (15a).[9] Pale white solid; mp 64–66°C. IR (KBr): 3438.8, 2239.6, 1533.3, 1348.1 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.07$ (s, 1H), 8.02 (d, $J = 8.06$ Hz, 1H), 7.58 (d, $J = 7.71$ Hz, 1H), 7.40 (t, $J = 7.71$ Hz, 1H), 6.03 (s, 1H), 5.93 (s, 1H), 5.27 (s, 1H), 2.84 (br s, 1H).

3-Hydroxy-2-methylene-3-(3-nitrophenyl)propanoic acid, methyl easter (15b).[3b] Yellow oil. IR (neat): 3482, 1715.1, 1530.9, 1352 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.19$ (t, $J = 1.01$ Hz, 1H), 8.07 (d, $J = 8.01$ Hz, 1H), 7.72 (t, $J = 7.81$ Hz, 1H), 7.50 (t, $J = 7.81$ Hz, 1H), 6.38 (s, 1H), 5.94 (s, 1H), 5.63 (s, 1H), 3.77 (s, 3H), 3.55 (br s, 1H).

3-Hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile (16a). Pale yellow solid; mp 73.5–74°C (lit.[3d] mp 72–75°C). IR (KBr): 3424.2, 2865.6, 2229.6 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.26$ (d, $J =$ 8.56 Hz, 2H), 7.60 (d, $J = 8.02$ Hz, 2H), 6.18 (1s, 1H), 6.10 (s, 1H), 5.44 (s, 1H), 2.11 (br s, 1H)

3-Hydroxy-2-methylene-3-(4-nitrophenyl)propanoic acid, methyl easter (16b). Yellow solid; mp 71–73°C (lit.[3d] mp 71–73°C). IR (KBr): 3510, 2992, 1724, 1634, 1359 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.70$ (d, $J = 8.76$ Hz, 2H), 7.56 (d, $J = 8.76$ Hz, 2H), 6.40 (s, 1H), 5.88 (s, 1H), 5.64 (d, $J = 5.87$ Hz, 1H), 3.75 (s, 3H), 3.40 (br s, 1H).

3-Hydroxy-2-methylene-3-(4-chloro-3-nitrophenyl)propanenitrile (17a). Yellow oil. IR (neat): 3429.2, 2875.6, 2229.6, 1537 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 7.74$ (s, 1H), 7.39 (m, 2H), 6.00 (s, 1H), 5.92 (s, 1H), 5.20 (s, 1H), 3.00 (br s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 74.73$, 118.67, 126.01, 127.53, 129.72, 133.54, 133.94, 134.61, 142.14, 150.38. Anal. calcd. for $C_{10}H_7ClN_2O_3$: C, 50.31; H, 2.94; N, 11.74. Found: C, 50.26; H, 2.91; N, 11.72.

3-Hydroxy-2-methylene-3-(4-chloro-3-nitrophenyl)propanoic acid, methyl easter (17b). White solid; mp 84°C. IR (KBr): 3471.6, 1708.8, 1533.3 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 7.89$ (s, 1H), 7.48–7.55 (m, 2H), 6.39 (s, 1H), 5.89 (s, 1H), 5.55 (s, 1H), 3.73 (s, 3H), 3.01 (br s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 54.72$, 74.56, 126.04, 128.57, 128.88, 129.90, 133.58, 134.22, 143.01, 144.53, 168.69. Anal. calcd. for $C_{11}H_{10}ClNO_5$: C, 48.62; H, 3.68; N, 5.16. Found: C, 48.35; H, 3.71; N, 5.12.

3-Hydroxy-2-methylene-3-(2,4-dichlorophenyl)propanenitrile (18a). White solid; mp 74°C. IR (KBr): 3384.8, 2229.6, 1527.5, 1348.1 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 7.55$ (d, $J = 8.01$, 1H), 7.39 (s, 1H), 7.28 (d, $J = 7.5$, 1H), 6.05 (s, 1H), 5.67 (s, 1H), 3.07 (br s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 72.55$, 118.87, 126.70, 130.38, 131.37, 131.97, 134.09, 135.60, 137.60, 142.58. Anal. calcd. for $C_{10}H_7Cl_2NO$: C, 52.63; H, 3.07; N, 6.14. Found: C, 52.58; H, 3.05; N, 6.12.

3-Hydroxy-2-methylene-3-(4-dichlorophenyl)propanenitrile (19a).[3d] Yellow oil. IR (neat): 3431.1, 2227.5, 1490.9 cm^{-1}. ^1H NMR (300 MHz,

$CDCl_3$): $\delta = 7.38-7.29$ (m, 4H), 6.08 (s, 1H), 6.01 (s, 1H), 5.24 (s, 1H), 3.24 (br s, 1H, OH).

3-Hydroxy-2-methylene-3-(4-chlorophenyl)propanoic acid, methyl easter (19b). White solid; mp 40–42°C (lit.[3d] mp 42°C). IR (KBr): 3500, 2985, 1725 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.82$ (s, 2H), 7.30 (s, 2H), 6.35 (s, 1H), 5.85 (s, 1H), 5.52 (d, $J = 5.82$ Hz, 1H), 3.72 (s, 3H), 3.15 (d, $J = 5.84$, 1H).

3-Hydroxy-2-methylene-3-phenylpropanenitrile (20a).[3d] Yellow oil. IR (neat): 3445.0, 2229.5, 1605.8, 1340.3 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.40-7.16$ (m, 5H), 6.15 (s, 1H), 6.12 (s, 1H), 5.96 (d, $J =$ 5.56 Hz, 1H), 2.87 (br s, 1H).

3-Hydroxy-2-methylene-3-(3-hydroxyphenyl)propanenitrile (21a). Yellow oil. IR (neat): 3381.0, 2233.4, 1593.5, 1271.0 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$ (t, $J = 7.86$ Hz, 1H), 6.88 (d, $J = 7.06$ Hz, 2H), 6.80 (d, $J = 7.01$ Hz, 1H), 6.7 (br s, 1H), 6.10 (s, 1H), 6.04 (s, 1H), 5.90 (br s, 1H), 5.25 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 73.8$, 113.2, 113.5, 116.0, 116.8, 118.6, 128.8, 130.2, 140.7, 156.0. Anal. calcd. for $C_{10}H_9NO_2$: C, 68.57; H, 5.14; N, 8.01. Found: C, 68.51; H, 5.22; N, 7.86.

3-Hydroxy-2-methylene-3-(3-hydroxyphenyl)propanoic acid, methyl easter (21b). Pale yellow solid; mp 103°C. IR (KBr): 3411.8, 3090.6, 2852.5, 1708.8, 1589.2, 1047.3, 952.8 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.18$ (t, $J = 7.56$, 1H), 6.90 (d, $J = 7.32$, 2H), 6.78 (t, $J = 7.21$, 1H), 6.33 (s, 1H), 5.82 (s, 1H), 5.49 (s, 1H), 4.23 (s, 1H), 3.72 (s, 3H), 2.78 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 54.5$, 75.6, 115.2, 115.8, 116.4, 117.3, 121.5, 128.9, 132.0, 114.5, 158.2. Anal. calcd. for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77. Found: C, 63.41; H, 5.78.

3-Hydroxy-2-methylene-3-(4-dimethylaminophenyl)propanenitrile (22a).[2] Yellow oil. IR (neat): 3460.0, 2229.5, 1465.8 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.09$ (d, $J = 7.21$, 2H), 6.66 (s, 2H), 5.95 (s, 1H), 5.84 (s, 1H), 5.06 (s, 1H), 2.81 (s, 6H), 2.20 (br s, 1H).

3-Hydroxy-2-methylene-propanoic acid, methyl easter (23a).[3b] Yellow oil. IR (neat): 3469.5, 2937.1, 1720.8, 1638.5 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.15$ (d, $J = 1.5$ Hz, 1H), 5.8 (d, $J = 1.2$ Hz, 1H), 4.76 (m, 1H), 3.70 (s, 3H), 2.9 (br s, 1H), 1.25 (d, $J = 6.5$ Hz, 3H).

ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of China (No. 30000112), the Laboratory of Organic Solids, Chinese Academy of Sciences, and the Science Foundation of Taiyuan City of China; we are grateful to them.

REFERENCES

1. (a) Baylis, A. B.; Hillman, M. E. D. German Patent 2,155,113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q; (b) Drewes, S. E.; Roos, G. H. P. Synthetic potential of the tertiary-amine-catalysed reaction of activated vinyl carbanions with aldehydes. *Tetrahedron* **1988**, *44*, 4653–4670; (c) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. The Baylis–Hillman reaction: A novel carbon–carbon bond forming reaction. *Tetrahedron* **1996**, *52*, 8001–8062; (d) Ciganek, E. The Morita–Baylis–Hillman Reaction. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1997; Vol. 51, p. 201; (e) Langer, P. New strategies for the development of an asymmetric version of the Baylis–Hillman reaction. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049–3052; (f) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. Development of bis-thiourea-type organocatalyst for asymmetric Baylis–Hillman reaction. *Tetrahedron Lett.* **2004**, *45*, 5589–5592.
2. Basaviah, D.; Rao, A. J.; Satyanarayana, T. Recent advances in the Baylis–Hillman reaction and applications. *Chem. Rev.* **2003**, *103*, 811–891.
3. (a) Auge, J.; Lubin, N; Lubineau, A. Acceleration in water of the Baylis–Hillman reaction. *Tetrahedron Lett.* **1994**, *35*, 7947–7948; (b) Rosa, J. N.; Afonso, A. M.; Santos, A. G. Ionic liquids as a recyclable reaction medium for the Baylis–Hillman reaction. *Tetrahedron* **2001**, *57*, 4189–4193; (c) Yu, C.; Liu, B.; Hu, L. Efficient Baylis–Hillman reaction using stoichiometric base catalyst and an aqueous medium. *J. Org. Chem.* **2001**, *66*, 5413–5418; (d) Rose, P. M.; Clifford, A. A.; Rayner, C. M. The Baylis–Hillman reaction in supercritical carbon dioxide: Enhanced reaction rates, unprecedented ether formation, and a novel phase-dependent 3-component coupling. *Chem. Commun.* **2002**, 968–969; (e) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. Dramatic rate acceleration of the Baylis–Hillman reaction in homogeneous medium in the presence of water. *Org. Lett.* **2002**, *4*, 4723.
4. Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Silva Lopes, E. C.; Rossi, R. C.; Silveira, G. P. C.; Pavam, C. H. Ultrasound in Baylis–Hillman reactions with aliphatic and aromatic aldehydes: Scope and limitations. *Tetrahedron* **2002**, *58*, 7437–7447.
5. (a) Nolte, R. J.; Scheeren, H. W. Effect of branching in alkylgroups of tertiary amines on their performance as catalysts in the high pressure promoted Baylis–Hillman reaction. *Tetrahedron* **1996**, *52*, 8307–8314; (b) Hayashi, Y.; Okado, K.; Ashimine, I.; Shoji, M. The Baylis–Hillman reaction under high pressure induced by water-freezing. *Tetrahedron Lett.* **2002**, *43*, 8683–8686.
6. Rezgui, F.; El Gaied, M. M. DMAP-catalyzed hydroxymethylation of 2-cyclohexenones in aqueous medium through Baylis–Hillman reaction. *Tetrahedron Lett.* **1998**, *39*, 5965–5966.
7. Zhao, S.; Chen, Z. The N,N,N′,N′-teramethylethylenediamine mediated Baylis–Hillman reaction. *Synth. Commun.* **2005**, *35*, 121–127.
8. Kawamura, M.; Kobayashi, S. Lithium perchlorate–accelerated Baylis–Hillman reactions. *Tetrahedron Lett.* **1999**, *40*, 1539–1542.
9. de Souza, R. O. M. A.; Meireles, B. A.; Aguiar, L. C. S.; Vasconcellos, M. L. A. A. Hexamethylenetetramine as a cheap and convenient alternative catalyst in the Baylis–Hillman reaction: Synthesis of aromatic compounds with anti-malarial activity. *Synthesis* **2004**, *10*, 1595–1600.
10. Krishna, P. R.; Sekhar, E. R.; Kannan, V. N-methylmorpholine and urotropione as useful base catalysts in Baylis–Hillman reaction. *Synthesis* **2004**, *6*, 857–860.

11. Aggarwal, V. K.; Mereu, A. Superior amine catalysts for the Baylis–Hillman reaction: The use of DBU and its implication. *Chem. Commun.* **1999**, 2311–2312.
12. Luo, S.; Mi, X.; Wang, P. G.; Cheng, J. P. The azoles: Effective catalysts for Baylis–Hillman reaction in basic water solution. *Tetrahedron Lett.* **2004**, *45*, 5171–5174.
13. (a) Yamada, Y. M. A.; Ikegami, S. Efficient Baylis–Hillman reactions promoted by mild cooperative catalysts and their application to catalytic asymmetric synthesis. *Tetrahedron Lett.* **2000**, *41*, 2165–2169; (b) McDougal, N. T.; Schaus, S. E. Asymmetric Morita–Baylis–Hillman reactions catalyzed by chiral Brønsted acids. *J. Am. Chem. Soc.* **2003**, *125*, 12094–12096; (c) Shi, M.; Jiang, J.-K.; Li, C.-Q. Lewis base and L-proline co-catalyzed Baylis–Hillman reaction of arylaldehydes with methyl vinyl ketone. *Tetrahedron Lett.* **2002**, *43*, 127–130; (d) Sanzhong Luo, S.; Wang, P. G.; Cheng, J.-P. Remarkable rate acceleration of imidazole-promoted Baylis–Hillman reaction involving cyclic enones in basic water solution. *J. Org. Chem.* **2004**, *69*, 555–558.