Tetrahedron Letters 51 (2010) 5943–5946

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Tandem three-component reaction of aldehyde, alkyl acrylate, and amide using ethyl diphenylphosphine as organocatalyst

Siang-en Syu, De-Wei Wang, Pei-yi Chen, Yi-Ting Hung, Yi-Wun Jhang, Tzu-Ting Kao, Yu-Ting Lee, Wenwei Lin *

Department of Chemistry, National Taiwan Normal University, 88, Section 4, Tingchow Road, Taipei 11677, Taiwan, ROC

ARTICLE INFO

Article history:
Received 4 May 2010
Revised 2 July 2010
Accepted 8 September 2010
Available online 21 September 2010

Keywords:
Multicomponent reaction
Morita–Baylis–Hillman
Chemoselectivity
Michael addition
Aldehyde

ABSTRACT

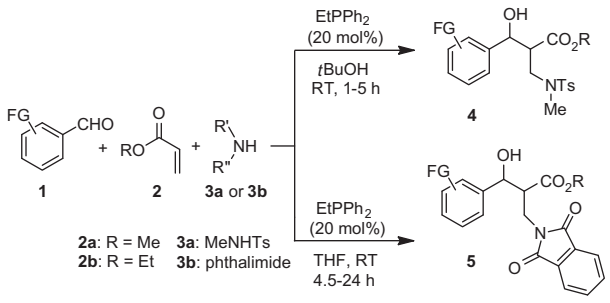
It is the first time that a chemoselective $EtPPh_2$-catalyzed three-component reaction of aromatic aldehyde, alkyl acrylate, and phthalimide or methyl toluenesulfonamide has been achieved. A variety of highly functional adducts can be generated efficiently in one step within 1–72 h in 38–93% yields. The reaction mechanism is proposed to undergo Morita–Baylis–Hillman reactions of aryl-substituted aldehydes and alkyl acrylates followed by Michael additions of amides. Our studies indicated that, in combination of $EtPPh_2$, alkyl acrylate also catalyzed this process.

Carbon–carbon or carbon–heteroatom bond formation is of importance in organic synthesis with numerous interesting studies concerning reactivity, chemoselectivity, and stereoselectivity.[1] Among all well-developed methodologies, the multicomponent reaction plays an important role due to its allowance of generation of an adduct in a single operation from three or more reactants with high atom economy and bond-forming efficiency.[2] Successful application of a multicomponent reaction highly relies on the good chemoselectivities in the presence of all the reactants.[3]

The Baylis–Hillman reaction adduct, resulting from alkyl acrylate and aldehyde is a good Michael acceptor according to the ester function activated by the neighboring hydroxy group.[4,5] Numerous successful applications for syntheses of highly functional compounds were achieved by the Michael addition of nucleophiles toward the Baylis–Hillman adducts as routine protocols.[5] However, the Baylis–Hillman reaction is notorious for its slow reaction rate with moderate to high yield[6] and, therefore, the whole process often takes several days to obtain the final Michael product. Further effort to simplify the whole process was taken by one-pot sequential Baylis–Hillman and Michael reactions with aldehyde, methyl acrylate, and nitroalkane in the presence of DBU (1.0 equiv) with 26–62% yields, albeit the one-step three-component reaction failed due to dominant Michael addition of DBU-deprotonated nitroalkane toward methyl acrylate.[7] Therefore, a strong demand remains to develop an efficient approach.

Instead of using a basic tertiary amine as organocatalyst, we assume that it should be possible to proceed a phosphine-catalyzed three-component reaction starting from the Baylis–Hillman reaction of aldehyde **1** and alkyl acrylate **2**, which is followed by the Michael addition of amide **3** toward the resulting adduct. To the best of our knowledge, there are no reports of successful reactions or related studies that utilize this strategy. Herein, we wish to report a highly efficient three-component reaction of aldehyde **1**, alkyl acrylate **2**, and amide **3** catalyzed by ethyl diphenylphosphine (Scheme 1).

Thus, 4-nitrobenzaldehyde (**1a**), methyl acrylate (**2a**) (1.2 equiv), and methyl tosylamine (**3a**) (1.2 equiv) in the presence of $EtPPh_2$ (20 mol %) in *t*BuOH reacted smoothly at room temperature



Scheme 1. A three-component reaction of aldehyde **1**, alkyl acrylate **2**, and amide **3** catalyzed by ethyl diphenylphosphine.

* Corresponding author. Tel.: +886 2 7734 6131; fax: +886 2 2932 4249.
E-mail address: wenweilin@ntnu.edu.tw (W. Lin).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.09.020

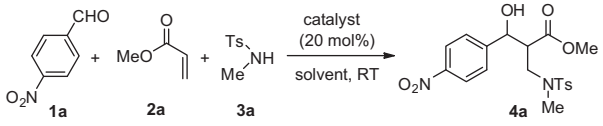
within 1 h, providing the highly functional three-component adduct **4a** in 80% yield (entry 1, Table 1). The inferior result was obtained when the reaction proceeded in *i*PrOH (**4a**: 66% yield) (entry 2). Interestingly, when polar aprotic solvent, such as THF was used, the significant reduced reaction rate was observed (**4a**: 71% yield; 20 h) (entry 3). Other catalysts like PPh_3, PBu_3, and DABCO were also examined in our optimized reaction condition. PPh_3, which has weaker nucleophilicity than that of $EtPPh_2$, catalyzed the three-component reaction of **1a**, **2a**, and **3a**, affording **4a** in 45% yield in 22 h (entry 4). Only the dimerization of **2a** occurred in the presence of PBu_3 (entry 5). DABCO, one of the best catalysts for Baylis–Hillman reaction, failed to catalyze the reaction of **1a**, **2a**, and **3a** and only the Baylis–Hillman adduct **6a** was obtained in 22 h without further addition of **3a** (entry 6). DMAP and DBU were also screened in the same condition, however, poor results were given even in the prolonged time (entries 7 and 8).

The broad reaction scope of our protocol was demonstrated by further studies disclosed in Table 2. It showed that highly chemoselective three-component reactions of various aromatic aldehydes **1a–g**, alkyl acrylate **2** (1.2 equiv), and **3a** (1.2 equiv) in the presence of $EtPPh_2$ (20 mol %) took place in 1–5 h, leading to the corresponding adducts **4a–j** in 52–93% yields (Table 2). The steric effect was observed when an *ortho*-substituted aromatic aldehyde participated in our designed reaction. For example, an aromatic aldehyde bearing a nitro group in *para*- or *meta*-position, like **1a** or **1b**, reacted with **2a** and **3a** within 1 h to provide the corresponding adduct **4a** or **4b** in 80% or 93% yield, respectively (entries 1 and 2). However, 2-nitrobenzaldehyde (**1c**) reacted with **2a** and **3a** more slowly, furnishing the adduct **4c** in 55% yield within 5 h (entry 3).

Remarkably, phthalimide (**3b**) (1.1 equiv), which is useful for transformation into the amine functionality, reacted successfully with a variety of aromatic aldehyde **1** and alkyl acrylate **2** (1.2 equiv) in the presence of $EtPPh_2$ (20 mol %) in THF at room temperature, yielding the corresponding adducts **5** as precursors of β^2-amino acids[8] (Table 3).[9] The formation of the Baylis–Hillman adduct **6** occurred together with the appearance of the corresponding adduct **5** during the reaction progress monitored by ^1H NMR analysis and the ratio of **5** to **6** increased as the reaction proceeded. Besides, the reaction rates highly depended on the reactivities of aromatic aldehydes **1**. Thus, **1a–d**, bearing a nitro or cyano function as a powerful electron-withdrawing group, reacted effectively with **2a** and **3b** within 4.5–6.5 h, giving the corresponding adducts **5a–d** in 80–86% yields (entries 1–4). Other aryl-substituted aldehyde, such as 4-trifluoromethylbenzaldehyde (**1e**), 2,4-dichlorobenzaldehyde (**1f**), 4- or 2-bromobenzaldehyde (**1g** or **1h**), or 4- or 2-chlorobenzaldehyde (**1i** or **1j**), reacted with **2a** and **3b** more slowly, affording the corresponding adducts **5e–j** in 68–86% yields within 10–24 h (entries 5–10). A heteroaromatic aldehyde, like nicotinaldehyde (**1k**), 2-furaldehyde (**1l**), or 2-naphthaldehyde (**1m**) was also suitable for the reaction with **2a** and **3b**, providing the adduct **5k**, **5l**, or **5m** in 85%, 70%, or 70% yield, respectively, within 8–24 h (entries 11–13). Benzaldehyde (**1n**) was less reactive, and its reaction with **2a** and **3b** underwent in the same reaction condition within 26 h, furnishing the adduct **5n** in 58% yield (entry 14). Poor results were obtained when an aromatic aldehyde bearing an electron-donating group, like **1o** or **1p**, was used (entries 15 and 16). Similiar reactivities were also observed when ethyl acrylate (**2b**) reacted with an aryl-substituted aldehyde **1a–e** or **1i** and **3b**, leading to the corresponding adduct **5q–v** within 4.5–19 h in moderate to good yields (66–88%) (entries 17–22). Additionally, DABCO (20 mol %) was examined with **1a**, **2a** (1.2 equiv), and **3b** (1.1 equiv) in the same reaction condition (rt, up to 3 days), mainly giving rise to **6a** without the formation of **5a**.

This excellent catalytic protocol was demonstrated again in our preliminary study. According to the traditional two-step process, the Morita–Baylis–Hillman adduct **6a** was synthesized in the presence of $EtPPh_2$ (20 mol %) in *t*BuOH (66% yield, 1 h) or in THF (67% yield, 24 h) in the first step (Scheme 2).[10] Only moderate yield of **6a** was obtained due to the decomposition of **6a** in the presence of $EtPPh_2$. In order to elucidate the role of $EtPPh_2$ in the addition of **2a** or **2b** toward the Morita–Baylis–Hillman adduct **6**, seven experiments were carried out (Scheme 3).[11] No reaction of **6a** and **3** (**3a** in *t*BuOH; **3b** in THF) occurred when $EtPPh_2$ was absent. Surprisingly, the most efficient addition of **3a** or **3b** toward **6a** underwent only when both of $EtPPh_2$ and **2a** were present (**4a**: 30 min in *t*BuOH, 88% yield; **5a**: 4.5 h in THF, 92% yield). Without the presence of **2a**, $EtPPh_2$ catalyzed the reaction of **3a** and **6a** or that of **3b** and **6a** less efficiently, leading to **4a** in 88% yield (2 h in *t*BuOH) or **5a** in 85% yield (12 h in THF), respectively.

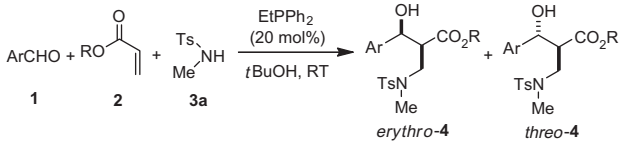
Table 1
Optimization of reaction conditions for an organocatalytic three-component reaction of 4-nitrobenzaldehyde (**1a**), methyl acrylate (**2a**), and MeNHTs (**3a**)[a]



Entry	Catalyst	Solvent	Time (h)	Yield of **4a**[b] (%)
1	$EtPPh_2$	*t*BuOH	1	80
2	$EtPPh_2$	*i*PrOH	1	66
3	$EtPPh_2$	THF	20	71
4	PPh_3	*t*BuOH	1 (22)	Trace[c]; (45)
5	PBu_3	*t*BuOH	1	Trace[c]
6	DABCO	*t*BuOH	1	Trace[c,d]
7	DMAP	*t*BuOH	1 (16)	Trace[c]; (41)
8	DBU	*t*BuOH	1 (16)	29; (44)

[a] Reactions were carried out using **1a** (0.5 mmol), **2a** (1.2 equiv), and **3a** (1.2 equiv) in the presence of catalyst (20 mol %) in solvent (0.5 mL) at rt.
[b] Yield of isolated product.
[c] Almost undetectable.
[d] There was no formation of **4a**, and significant amount of **6a** was observed in 22 h.

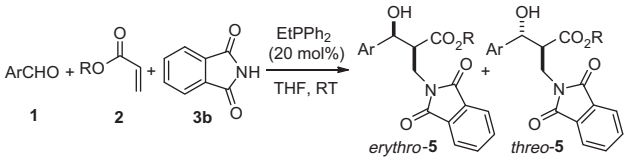
Table 2
A three-component reaction of aldehyde **1**, alkyl acrylate **2**, and methyl toluenesulfonamide (**3a**) catalyzed by $EtPPh_2$[a]



Entry	Ar	R	Time (h)	Yield of **4** (%)[b]; dr[c,d]
1	4-$NO_2C_6H_4$ (**1a**)	Me	1	**4a**, 80; 48:52[e]
2	3-$NO_2C_6H_4$ (**1b**)	Me	1	**4b**, 93; 48:52[f]
3	2-$NO_2C_6H_4$ (**1c**)	Me	5	**4c**, 55; 35:65[e]
4	4-CNC_6H_4 (**1d**)	Me	2	**4d**, 83; 53:47
5	4-$CF_3C_6H_4$ (**1e**)	Me	2.5	**4e**, 70; 48:52
6	2,4-$Cl_2C_6H_3$ (**1f**)	Me	1.5	**4f**, 60; 31:69[e]
7	4-BrC_6H_4 (**1g**)	Me	2	**4g**, 52; 48:52
8	4-$NO_2C_6H_4$ (**1a**)	Et	1	**4h**, 82; 47:53
9	3-$NO_2C_6H_4$ (**1b**)	Et	1	**4i**, 78; 47:53[f,g]
10	4-CNC_6H_4 (**1d**)	Et	2.5	**4j**, 82; 49:51

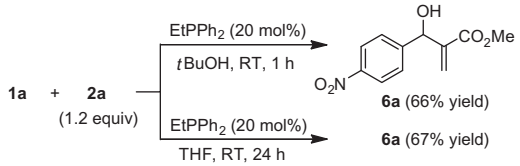
[a] Reactions were carried out using **1** (0.5 mmol), **2** (1.2 equiv), and **3a** (1.2 equiv) in the presence of $EtPPh_2$ (20 mol %) in *t*BuOH (0.5 mL) at rt.
[b] Yield of isolated product.
[c] Determined by ^1H NMR analysis of the crude product.
[d] The stereochemistry of **4** was determined by ^1H NMR analysis in comparison to **4a** and **4c**.
[e] The relative configuration was confirmed by X-ray crystallography.
[f] The relative configuration was not determined.
[g] Inseparable mixture of two diastereomers.

Table 3
A three-component reaction of aldehyde **1**, alkyl acrylate **2**, and phthalimide (**3b**) catalyzed by $EtPPh_2$[a]



Entry	Ar	R	Time (h)	Yield of **5** (%)[b]; dr[c,d]
1	4-$NO_2C_6H_4$ (**1a**)	Me	4.5	**5a**, 85; 28:72
2	3-$NO_2C_6H_4$ (**1b**)	Me	4.5	**5b**, 86; 32:68[f]
3	2-$NO_2C_6H_4$ (**1c**)	Me	6.5	**5c**, 85; 57:43[g]
4	4-CNC_6H_4 (**1d**)	Me	5.5	**5d**, 80; 29:71
5	4-$CF_3C_6H_4$ (**1e**)	Me	14	**5e**, 86; 32:68
6	2,4-$Cl_2C_6H_3$ (**1f**)	Me	11	**5f**, 73; 61:39[e]
7	4-BrC_6H_4 (**1g**)	Me	12	**5g**, 77; 39:61[e]
8	2-BrC_6H_4 (**1h**)	Me	24	**5h**, 71; 68:32[e]
9	4-ClC_6H_4 (**1i**)	Me	18	**5i**, 72; 38:62
10	2-ClC_6H_4 (**1j**)	Me	10	**5j**, 68; 67:33
11	3-Pyridyl (**1k**)	Me	8	**5k**, 85; 69:31[f]
12	2-Furyl (**1l**)	Me	10	**5l**, 70; 63:37[f]
13	2-Naphthyl (**1m**)	Me	24	**5m**, 70; 44:56[f]
14	C_6H_5 (**1n**)	Me	26	**5n**, 58; 45:55
15	4-$CH_3C_6H_4$ (**1o**)	Me	48	**5o**, 53; 45:55
16	4-$CH_3OC_6H_4$ (**1p**)	Me	72	**5p**, 38; 48:52
17	4-$NO_2C_6H_4$ (**1a**)	Et	4.5	**5q**, 88; 29:71
18	3-$NO_2C_6H_4$ (**1b**)	Et	6	**5r**, 88; 34:66[f]
19	2-$NO_2C_6H_4$ (**1c**)	Et	12	**5s**, 73; 54:46
20	4-CNC_6H_4 (**1d**)	Et	7.5	**5t**, 83; 31:69
21	4-$CF_3C_6H_4$ (**1e**)	Et	18	**5u**, 84; 34:66
22	4-ClC_6H_4 (**1i**)	Et	19	**5v**, 66; 41:59

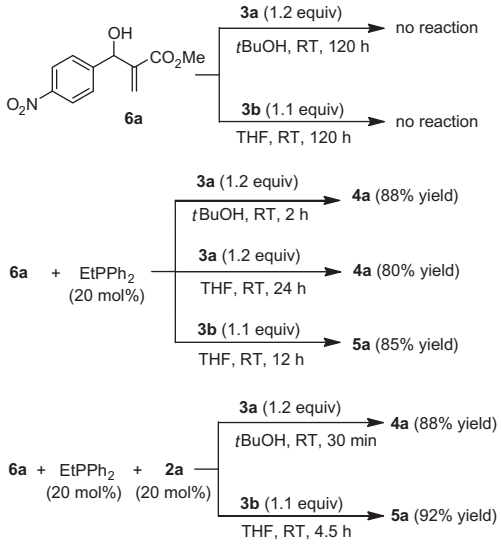
[a] Reactions were carried out using **1** (0.5 mmol), **2** (1.2 equiv), and **3b** (1.1 equiv) in the presence of $EtPPh_2$ (20 mol %) in THF (0.5 mL) at rt.
[b] Yield of isolated product.
[c] Determined by ^1H NMR analysis of the crude product.
[d] The stereochemistry of **5** was determined by ^1H NMR analysis in comparison to **5g** and **5h**.
[e] The relative configuration was confirmed by X-ray crystallography.
[f] The relative configuration was not determined.
[g] Inseparable mixture of two diastereomers.



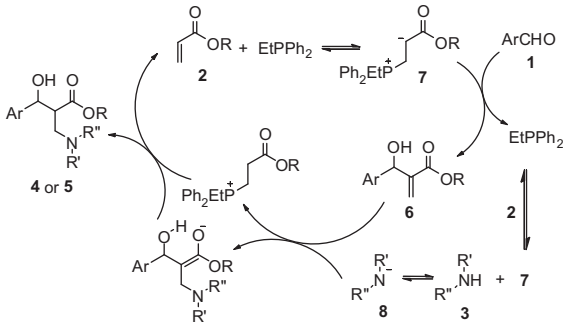
Scheme 2. An $EtPPh_2$-catalyzed Morita–Baylis–Hillman reaction of **1a** and **2a** in *t*BuOH or THF.

On the basis of experimental results (Tables 1–3 and Scheme 3) a plausible reaction mechanism for this highly chemoselective three-component reaction was proposed (Scheme 4). First, an $EtPPh_2$-catalyzed Morita–Baylis–Hillman reaction took place, giving rise to the corresponding adduct **6**. The in situ formed basic intermediate **7**, which was the nucleophile in the Morita–Baylis–Hillman reaction, deprotonated amide **3**, and then **8** underwent the Michael addition toward **6** followed by protonation, affording the corresponding adduct **4** or **5** with the regeneration of $EtPPh_2$.

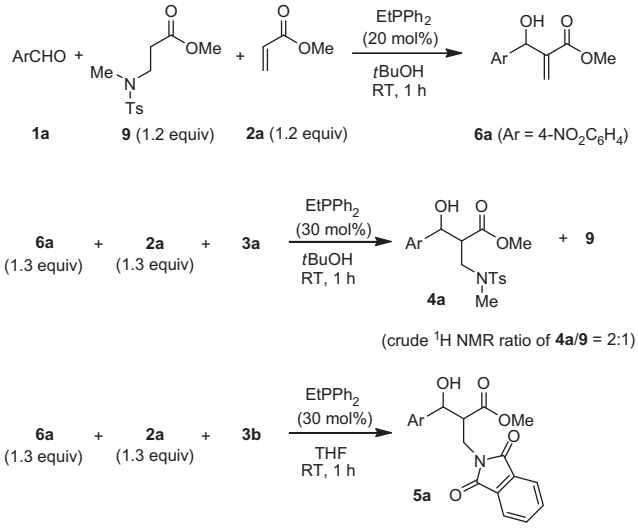
Furthermore, an additional experiment was carried out to exclude another possible pathway for the formation of **4** via the Michael addition of **3** to **2**, which was then followed by 1,2-addition of the corresponding adduct toward **1**. When the reaction of **1a**, the Michael adduct **9** (1.2 equiv) and **2a** (1.2 equiv) proceeded in the presence of $EtPPh_2$ (20 mol %) in *t*BuOH, only **6a** was observed



Scheme 3. Michael addition of **3a** or **3b** toward **6a** without catalyst, in the presence of $EtPPh_2$, or in the presence of $EtPPh_2$ and **2a**.

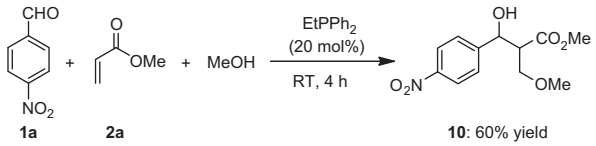


Scheme 4. A proposed mechanism of the three-component reaction of **1**, **2**, and **3** catalyzed by $EtPPh_2$.



Scheme 5. Further investigation of the reaction mechanism.

without the formation of **4a** (Scheme 5). Besides, a competitive experiment for the Michael addition of **3a** toward **2a** or **6a** has also been demonstrated, indicating that **6a** is the better Michael acceptor than **2a** (crude ^1H NMR ratio of **4a**:**9** = 2:1). The excellent



Scheme 6. An $EtPPh_2$-catalyzed three-component reaction of **1a**, **2a**, and MeOH.

chemoselectivity was shown in case of the Michael addition of **3b** toward **6a** in the presence of **2a**. Only the adduct **5a**, resulting from the addition of **3b** toward **6a** was observed without the occurrence of the addition of **3b** toward **2a**.

Interestingly, not only an amide, such as **3a** or **3b**, but also an alcohol like MeOH, was a suitable nucleophile. A highly chemoselective three-component reaction via the addition of MeOH toward **6a** resulting from **1a** and **2a** (1.5 equiv) was accomplished in 4 h in the presence of $EtPPh_2$, affording the corresponding product **10** in 60% yield without the competitive reaction of the Michael addition of MeOH toward **2a** (Scheme 6).[12,13]

In conclusion, we have developed a general procedure for a new type of chemoselective three-component reaction with aromatic aldehyde **1**, alkyl acrylate **2**, and amide **3** catalyzed by $EtPPh_2$. The reaction condition is very mild, and numerous aromatic aldehydes **1** can react efficiently with **2** and **3** in moderate to high yields. The reaction mechanism is proposed to undergo the Morita–Baylis–Hillman reaction of **1** and **2** followed by the Michael addition of **3** toward the corresponding adduct **6**. Our study indicated that in combination of $EtPPh_2$, alkyl acrylate also catalyzed this process. Further studies and the extensions of this work in imines or other activated alkenes, as well as the use of other nucleophilic reagents are currently underway.

Acknowledgments

We thank the National Science Council of the Republic of China (NSC Grant No. 97-2113-M-003-003-MY2) and National Taiwan Normal University (99031019) for financial support.

Supplementary data

Supplementary data (general experimental procedures, compound characterization data, X-ray crystallographic data (CCDC number: *threo*-**4a** (750223), *threo*-**4c** (744771), *threo*-**4f** (752968), *threo*-**5g** (744772), *erythro*-**5f** (753480), and *erythro*-**5h** (748316)) and NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.020.

References and notes

1. (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
2. (a) For an overview, see: *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; For excellent reviews, see: (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321; (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (e) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51; (f) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (g) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
3. (a) For an overview, see: *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K., Eds.; Wiley-VCH: Weinheim, 2006; Also see: (b) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831; (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.
4. Reviews for Morita–Baylis–Hillman reactions, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811, and references cited therein; (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049; (c) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581; (d) Menozzi, C.; Dalko, P. I. Organocatalytic Enantioselective Morita–Baylis–Hillman Reactions. In *Enantioselective Organocatalysis, Reactions and Experimental Procedures*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; Recent reviews for application of Baylis–Hillman adduct, see: (e) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614; (f) Batra, S.; Singh, V. *Tetrahedron* **2008**, *64*, 4511.
5. For selected literature about the addition of nitrogen nucleophile to Baylis–Hillman adduct, see: (a) Roy, A. K.; Pathak, R.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2006**, 1021; (b) Nag, S.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2007**, 911.
6. For selected reviews, see: (a) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759; (b) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841.
7. Wang, W.; Yu, M. *Tetrahedron Lett.* **2004**, *45*, 7141.
8. (a)For studies of β-peptides, see: *Pseudo-peptides in Drug Discovery*; Nielsen, P. E., Ed.; Wiley-VCH: Weinheim, 2004; (b) Seebach, D.; Kimmerlin, T.; Šebesta, R.; Campo, M. A.; Beck, A. K. *Tetrahedron* **2004**, *60*, 7455; (c) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *J. Am. Chem. Soc.* **2001**, *101*, 3219.
9. THF was used as solvent due to the poor solubility of **3b** in *t*BuOH.
10. The reaction rate of **1a** and **2a** catalyzed by $EtPPh_2$ (20 mol %) in *t*BuOH (full conversion; 1 h; 66% yield) or in THF (full conversion; 24 h; 67% yield) is much faster than that of DABCO-catalyzed reaction in *t*BuOH (60 h; 92% yield) or in THF (90 h; 90% yield). In addition, an experiment of **6a** in the presence of $EtPPh_2$ (20 mol %) in *t*BuOH or THF was examined, respectively; showing that the decomposition of **6a** occurred faster in *t*BuOH than in THF. See the Supplementary data.
11. For the detailed studies, please see the Supplementary data.
12. For addition of MeOH toward **2a** catalyzed by PMe_3 (36 h, 71% yield), please see: Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.
13. For Baylis–Hillman reaction of acrylamide with an aryl aldehyde catalyzed by DBU or PBu_3, which was accompanied with a highly competitive side reaction of MeOH adding toward acrylamide. See: Faltin, C.; Fleming, E. M.; Connon, S. J. *J. Org. Chem.* **2004**, *69*, 6496.