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COMMUNICATION

Organocatalytic tandem three-component reaction of aldehyde, alkyl vinyl ketone, and amide: one-pot syntheses of highly functional alkenes†

De-Wei Wang, Siang-en Syu, Yi-Ting Hung, Pei-yi Chen, Chia-Jui Lee, Ko-Wei Chen, Yu-Jhang Chen and Wenwei Lin*

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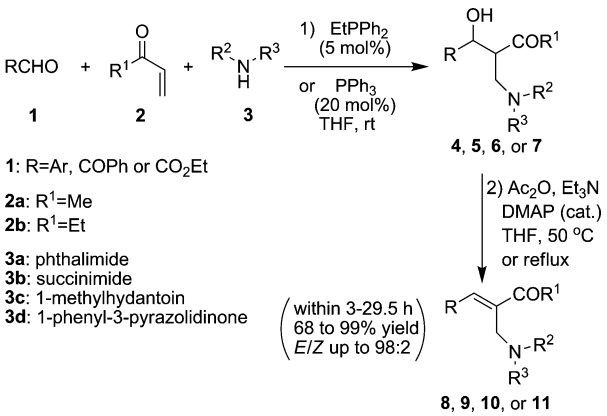
An $EtPPh_2$- or PPh_3-catalyzed tandem three-component reaction of aldehyde, alkyl vinyl ketone, and amide is developed. Its further application in one-pot syntheses of highly functional alkenes starting from aldehydes, alkyl vinyl ketones, and amides is realized. A wide variety of highly functional α,β-unsaturated ketones can be furnished in 68–99% yields with high stereoselectivity (*E*/*Z* up to 98 : 2) within overall 3–29.5 h.

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 adduct, starting from alkyl vinyl ketone and aldehyde, is a good Michael acceptor according to the ketone 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 with moderate to high yield,[6] and therefore the whole process often takes long time to obtain the final Michael product. Therefore, it remains a strong demand to develop an efficient approach.

Herein, we wish to report a phosphine-catalyzed three-component reaction starting from the Baylis–Hillman reaction of aldehyde **1** and alkyl vinyl ketone **2**, which is followed by Michael addition of amide **3** toward the resulting adduct. Efficient one-pot syntheses of highly functional alkenes **8–11** *via* $EtPPh_2$- or PPh_3-catalyzed tandem three-component reactions of **1**, **2** and **3** are also demonstrated (Scheme 1).



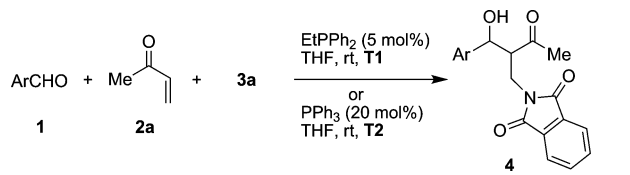
Scheme 1 One-pot syntheses of alkenes **8–11** *via* three-component reactions of aldehydes **1**, alkyl vinyl ketones **2** and amides **3** catalyzed by $EtPPh_2$ or PPh_3.

Practically, a more reactive catalyst than PPh_3, such as $EtPPh_2$, was seldom used in Morita–Baylis–Hillman reaction of an aldehyde and an α,β-unsaturated ketone due to a significant amount of side reaction resulting from the $EtPPh_2$-catalyzed Michael addition of the α,β-unsaturated ketone toward the corresponding Baylis–Hillman adduct. Besides, dimerization of α,β-unsaturated ketone occurred even when PPh_3 was used. Therefore, it is common to use excess amount of α,β-unsaturated ketone (at least 3.0 equiv) in Morita–Baylis–Hillman reactions.[7] Surprisingly, in the presence of $EtPPh_2$ (5 mol%), 4-nitrobenzaldehyde (**1a**) (2.0 mmol) reacted with merely 1.2 equivalent of methyl vinyl ketone (**2a**) and phthalimide (**3a**) (1.1 equiv) in dry THF (2.0 mL) smoothly at room temperature within 1 h, providing the highly functional three-component adduct **4a** in 95% yield (Table 1, entry 1). Even less reactive PPh_3 (20 mol%) can effectively catalyze this type of three-component reaction of **1a**, **2a** (1.5 equiv) and **3a** (1.4 equiv), furnishing **4a** in 97% yield within 4.5 h. The reactions of other aryl-substituted aldehydes **1b–i** as well as heteroaryl-substituted aldehydes **1k–n** underwent smoothly with **2a** and **3a** in the presence of $EtPPh_2$ (5 mol%), leading to the corresponding adducts **4b–i** and **4k–n** within 1–7 h (**T1**) in 54–98% yields (entries 2–9 and 11–14). The reactivity of an aldehyde had strong influence on the reaction time, and therefore **2a** (1.3 equiv) and **3a** (1.2 equiv) are necessary for the formation of **4f–h** and **4k–n**.[7,8] PPh_3 (20 mol%) also catalyzed the reactions of **1b–n**, **2a** (1.5 or 2.0 equiv) and

Department of Chemistry, National Taiwan Normal University, 88, Section 4, Tingchow Road, Taipei 11677, Taiwan, ROC. E-mail: wenweilin@ntnu.edu.tw; Fax: (+886)-2-29324249; Tel: (+886)-2-77346131

† Electronic supplementary information (ESI) available: Experimental section, X-ray crystallographic data and NMR spectra. CCDC reference numbers 769605, 770519, 775300, 778973 and 778974. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00644k

Table 1 A three-component reaction of **1**, **2a**, and **3a** catalyzed by EtPPh2 or PPh_3

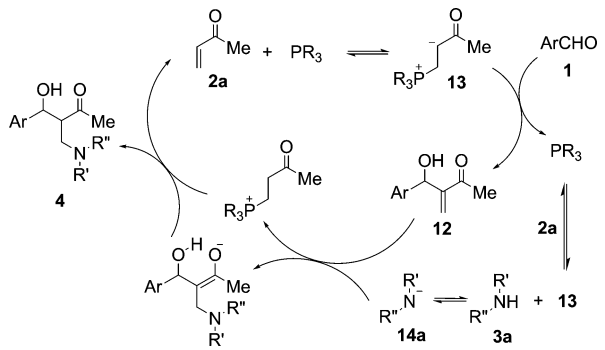


Entry	Ar	**T1**[a]; **T2**[b]/h	Yield of **4** (%)[c,d]
1	4-$NO_2C_6H_4$	1; 4.5	**4a**[e], 95; 97
2	3-$NO_2C_6H_4$	1; 4	**4b**, 95; 98
3	2-$NO_2C_6H_4$	1.5; 24	**4c**, 88; 96
4	4-CNC_6H_4	1.5; 5.5	**4d**, 90; 98
5	4-$CF_3C_6H_4$	1.5; 24	**4e**, 93; 97
6	4-BrC_6H_4	2[f]; 17[g]	**4f**, 87; 98
7	4-ClC_6H_4	3[f]; 18[g]	**4g**, 83; 96
8	2-ClC_6H_4	5[f]; 26[g]	**4h**[e], 91; 98
9	C_6H_5	7; 62[g]	**4i**, 54; 86
10	4-$CH_3C_6H_4$	–; 62[g]	**4j**, –[h]; 62
11	4-Pyridyl	1[f]; 7[g]	**4k**, 97; 95
12	3-Pyridyl	1[f]; 11[g]	**4l**, 98; 92
13	2-Pyridyl	5[f]; 48[g]	**4m**, 94; 87
14	2-Furyl	5[f]; 25[g]	**4n**, 77; 98

[a] Reactions were carried out with **1** (2.0 mmol), **2a** (1.2 equiv) and **3a** (1.1 equiv) catalyzed by $EtPPh_2$ (5 mol%) in THF (2.0 mL) at rt. [b] **1** (1.0 mmol), **2a** (1.5 equiv) and **3a** (1.4 equiv) were used in the presence of PPh_3 (20 mol%) in THF (1.0 mL) at rt. [c] Yield of isolated product. [d] For the diastereomeric ratios of **4**, see the ESI.† [e] The structures of *threo*-**4a** (CCDC no. 778973) and *erythro*-**4h** (CCDC no. 778974) were confirmed by X-ray analysis. [f] **2a** (2.0 equiv) and **3a** (1.3 equiv) were used. [g] **2a** (2.0 equiv) and **3a** (1.5 equiv) were used. [h] The trace amount of **4j** was observed.

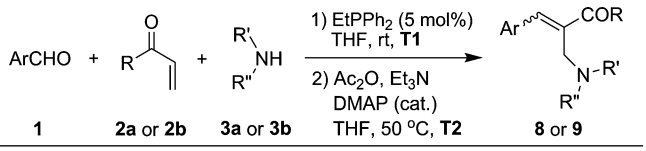
3a (1.4 or 1.5 equiv), providing the corresponding adducts **4b–n** within 4–62 h (**T2**) in 62–98% yields (entries 2–14). DABCO (20 mol%), one of the best catalysts for the Baylis–Hillman reaction, also catalyzed the reaction of **1a**, **2a** (1.3 equiv) and **3a** (1.2 equiv). However, the reaction rate was very slow (7 days, 86% conversion), indicating DABCO was not effective for our designed reaction.[9]

Based on experimental‡ results (Table 1), a plausible reaction mechanism for this highly chemoselective three-component reaction was proposed (Scheme 2). First, an $EtPPh_2$- or PPh_3-catalyzed Morita–Baylis–Hillman reaction took place, giving rise to the corresponding adduct **12**. The *in situ* formed basic intermediate **13**, which was the nucleophile in the Morita–Baylis–Hillman reaction, deprotonated an amide **3a**, and then **14a** underwent the Michael addition toward **12** followed by protonation, affording the corresponding adduct **4** with the regeneration of $EtPPh_2$ or PPh_3.



Scheme 2 A proposed mechanism of the three-component reaction of **1**, **2a** and **3a** catalyzed by $EtPPh_2$ or PPh_3.

Table 2 One-pot syntheses of **8** and **9**[a]



Entry	**1/2/3**	**T1**[a];**T2**[b]/h	Product **8** or **9**	*E*/*Z*[c]; Yield (%)[d]
1	**1a/2a/3a**	1[e]; 3	**8a**: R = 4-NO_2	92/8; 81[f]
2	**1b/2a/3a**	1[e]; 3	**8b**: R = 3-NO_2	91/9; 83
3	**1e/2a/3a**	1.5[g]; 4.5	**8c**: R = 4-CF_3	93/7; 81[h]
4	**1g/2a/3a**	3; 5	**8d**: R = 4-Cl	94/6; 77
5	**1h/2a/3a**	5; 4[i]	**8e**: R = 2-Cl	97/3; 76
6	**1k/2a/3a**	1; 2	**8f**: R = 4-pyridyl	92/8; 96
7	**1l/2a/3a**	1; 3	**8g**: R = 3-pyridyl	91/9; 99
8	**1m/2a/3a**	5; 6[i]	**8h**: R = 2-pyridyl	98/2; 90[f]
9	**1d/2b/3a**	1.5[e]; 5	**8i**	92/8; 76
10	**1a/2a/3b**	1[e]; 3	**9a**: R = 4-NO_2	88/12; 76[f]
11	**1d/2a/3b**	1.5[e]; 4.5	**9b**: R = 4-CN	90/10; 68[f]

[a] Reactions were carried out with **1** (2.0 mmol), **2** (2.0 equiv) and **3** (1.3 equiv) catalyzed by $EtPPh_2$ (5 mol%) in THF (2.0 mL) at rt. [b] Without further purification, reactions were carried out using Ac_2O (1.2 equiv), Et_3N (2.5 equiv), DMAP (10 mol %), and additional THF (2.0 mL) at 50 °C. [c] Determined by ^1H NMR analysis of the crude product. [d] Yield of isolated products. [e] **2a** (1.3 equiv) and **3b** (1.01 equiv) were used. [f] Yield of (*E*)-form isomer. [g] **2a** (1.5 equiv) and **3b** (1.01 equiv) were used. [h] The structure of (*E*)-form of **8c** (CCDC no. 769605) was confirmed by X-ray analysis. [i] Reactions were carried out in refluxing THF.

Highly functional α,β-unsaturated ketones are bioactive compounds as well as interesting building blocks for organic synthesis, and the three-component adduct such as **4a** can be further transformed into **8a** successfully in our preliminary study.[10,11] Encouraged by this result, we envisioned that it should be possible to develop one-pot procedure for the syntheses of polyfunctional α,β-unsaturated ketones *via* our designed three-component reactions and acylation of the corresponding adducts followed by elimination. Thus, the reaction of **1a** (2.0 mmol), **2a** (1.3 equiv) and **3a** (1.01 equiv) catalyzed by $EtPPh_2$ (5 mol%) proceeded in THF at rt within 1 h, followed by the addition of Ac_2O (1.2 equiv), Et_3N (2.5 equiv) and DMAP (10 mol%), and then underwent smoothly at 50 °C within 3 h, providing the highly functional alkene (*E*)-**8a** in 81% yield (Table 2, entry 1). Other aryl-substituted aldehydes, such as **1b**, **1d–e**, **1g–h**, and **1k–m**, worked nicely with **2a** (or **2b**)

Table 3 One-pot syntheses of **10** and **11**[a]

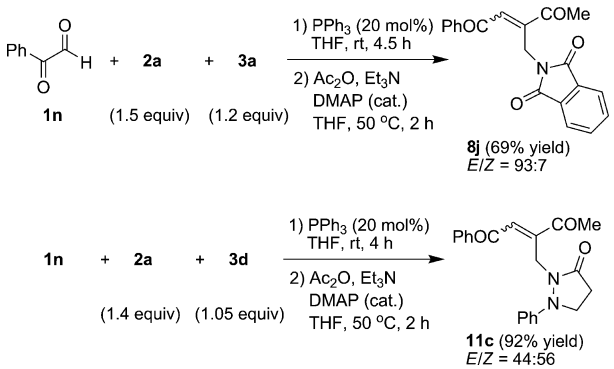
Entry	1/2/3	T1[a];T2[b]/h	Product 10 or 11	E/Z[c]; Yield (%)[d]
1	**1a/2a/3c**	3; 3.5	**10a**: R = 4-NO_2	84/16; 84
2	**1b/2a/3c**	3; 3.5	**10b**: R = 3-NO_2	83/17; 88
3	**1c/2a/3c**	15; 6	**10c**: R = 2-NO_2	92/8; 92
4	**1d/2a/3c**	4.5; 3.5	**10d**: R = 4-CN	89/11; 92
5	**1e/2a/3c**	23; 6.5	**10e**: R = 4-CF_3	90/10; 90
6	**1f/2a/3c**	24; 5[e]	**10f**: R = 4-Br	89/11; 83[f]
7	**1k/2a/3c**	12[g]; 4	**10g**	89/11; 92
8	**1a/2b/3c**	3.5; 3[e]	**10h**: R = 4-NO_2	86/14; 80
9	**1b/2b/3c**	6; 3[e]	**10i**: R = 3-NO_2	87/13; 86
10	**1d/2b/3c**	3.5; 4[e]	**10j**: R = 4-CN	85/15; 83
11	**1a/2a/3d**	1[h]; 2	**11a**	97/3; 83
12	**1k/2a/3d**	7[i]; 2	**11b**	92/8; 98

[a] Reactions were carried out with **1** (1.0 mmol), **2** (1.4 equiv) and **3** (1.05 equiv) catalyzed by PPh_3 (20 mol%) in THF (1.0 mL) at rt. [b] Without further purification, reactions were carried out using Ac_2O (1.2 equiv), Et_3N (2.5 equiv), DMAP (10 mol %), and additional THF (1.0 mL) at 50 °C. [c] Determined by ^1H NMR analysis of the crude product. [d] Yield of isolated products. [e] Reactions were carried out in refluxing THF. [f] The structure of (*E*)-**10f** (CCDC no. 770519) was confirmed by X-ray analysis. [g] **1j** (1.01 equiv) and **2a** (1.4 equiv) were used. [h] **1a** (1.05 equiv) and **2a** (1.4 equiv) were used. [i] **2a** (1.4 equiv) and **3d** (1.05 equiv) were used.

and **3a** according to our protocol, furnishing the corresponding adducts **8b–i** within 3–11 h (**T1**+**T2**) in overall 76–99% yields with high stereoselectivities (E/Z = 91/9 to 98/2) (entries 2–9). The other amide, like succinimide (**3b**), was also successfully applied in our one-pot procedure with **2a** and **1a** or **1d**, affording the corresponding alkene (*E*)-**9a** or (*E*)-**9b** within 4 or 6 h in overall 76% or 68% yields, respectively (entries 10 and 11).[12]

The broad reaction scope of our one-pot protocol was demonstrated by further studies disclosed in Table 3. It showed that the syntheses of **10** and **11** starting from the reactions of aldehydes **1**, **2a–b**, and amides, such as 1-methylhydantoin (**3c**) and 1-phenyl-3-pyrazolidinone (**3d**), in the presence of PPh_3 (20 mol%) were achieved in overall 3–29.5 h (**T1**+**T2**) with high yields (80–98%) and good stereoselectivities (E/Z = 83/17 to 97/3) according to our procedure (Table 3, entries 1–12). However, $EtPPh_2$, which showed better catalytic ability than PPh_3 for the three-component reaction of **1**, **2** and **3a–b**, gave poor results in case of **3c** and **3d**, and was not a suitable catalyst for the preparation of **10** and **11**.

Not only aryl-substituted aldehydes **1a–m** but also the other interesting aldehyde, like **1n**, reacted successfully with **2a** and **3a** according to our one-pot protocol, giving the corresponding highly functional alkene **8j** in 69% yield with good stereoselectivity (E/Z = 93 : 7) (Scheme 3). The amide **3d** worked also nicely with **1n** and **2a**, furnishing the corresponding alkene **11c** within 6 h in 92% yield (E/Z = 44 : 56).[13]



Scheme 3 One-pot syntheses of **8j** or **11c**.

In summary, we have developed a general procedure for one-pot syntheses of highly functional α,β-unsaturated ketones **8–11** *via* tandem $EtPPh_2$- or PPh_3-catalyzed three-component reaction of aldehydes **1**, alkyl vinyl ketones **2** and amides **3**, and acylation of the corresponding adducts followed by elmination. The reaction condition is very mild, and numerous polyfunctional alkenes **8–11** can be efficiently afforded in good yields with high stereoselectivities. The reaction mechanism of our tandem three-component reaction is proposed to undergo the Morita–Baylis–Hillman reaction of **1** and **2** followed by the Michael addition of **3** toward the corresponding adduct. Further studies and the extensions of this work in imines as well as the use of other nucleophilic reagents, are currently underway.

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Notes and references

‡ Experimental procedure: Preparation of **8a**: A dry and nitrogen-flushed 10-mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of **1a** (302 mg, 2 mmol) and **3a** (297 mg, 1.01 equiv) in dry THF (2 mL). MVK (**2a**) (211 μL, 1.3 equiv) and $EtPPh_2$ (20.4 μL, 5 mol%) were added, and the reaction mixture was stirred for 1 h (**T1**) at rt. Without further purification, Ac_2O (0.23 mL, 1.2 equiv), Et_3N (0.70 mL, 2.5 equiv), DMAP (24.4 mg, 10 mol%), and additional THF (2.0 mL) were added, and the resulting mixture was stirred at 50 °C for 3 h (**T2**) Thereafter, the solvent was removed by evaporation in vacuo. Purification by recrystallization (hexanes/CH_2Cl_2) furnished the alkene (*E*)-**8a** as a yellow solid (568 mg, 81%).

1 (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*b*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726; (*c*) *Handbook of functionalized organometallics*, ed. P. Knochel, Wiley-VCH, Weinheim, Germany, 2005.

2 For an overview, see: (*a*) *Multicomponent reactions*, ed. J. Zhu and H. Bienaymé, Wiley-VCH, Weinheim, Germany, 2005; for excellent reviews, see: (*b*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (*c*) H. Bienaymé, C. Hulme, G. Oddon and P. Schmitt, *Chem.–Eur. J.*, 2000, **6**, 3321; (*d*) R. V. A. Orru and M. de Greef, *Synthesis*, 2003, 1471; (*e*) C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51; (*f*) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602; (*g*) A. Dömling, *Chem. Rev.*, 2006, **106**, 17.

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4 Reviews for Morita–Baylis–Hillman reactions, see: (*a*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811, and references cited therein; (*b*) P. Langer, *Angew. Chem., Int. Ed.*, 2000, **39**, 3049; (*c*) D. Basavaiah, K. V. Rao and R. J. Reddy, *Chem. Soc. Rev.*, 2007, **36**, 1581; (*d*) C. Menozzi and P. I. Dalko, Organocatalytic Enantioselective Morita–Baylis–Hillman Reactions. In *Enantioselective Organocatalysis, Reactions and Experimental Procedures*, ed. P. I. Dalko, Wiley-VCH, Weinheim, Germany, 2007; recent reviews for application of Baylis–Hillman adduct, see: (*e*) G. Masson, C. Housseman and J. Zhu, *Angew. Chem., Int. Ed.*, 2007, **46**, 4614; (*f*) S. Batra and V. Singh, *Tetrahedron*, 2008, **64**, 4511; (*g*) D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev.*, 2010, **110**, 5447.

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6 For selected reviews, see: (*a*) E. A. C. Davie, S. M. Mennen, Y. Xu and S. J. Miller, *Chem. Rev.*, 2007, **107**, 5759; (*b*) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches and V. K. Aggarwal, *Chem. Rev.*, 2007, **107**, 5841; (*c*) D. Basavaiah, K. V. Rao and R. J. Reddy, *Chem. Soc. Rev.*, 2007, **36**, 1581.

7 For double transitional Morita–Baylis–Hillman reactions, please see: (*a*) G.-N. Ma, J.-J. Jiang, M. Shi and Y. Wei, *Chem. Commun.*, 2009, 5496, and references cited therein; for the *p*-$NO_2C_6H_4OH$ and PPh_3-catalyzed Baylis–Hillman reaction of **1a** and **2a** (3.0 equiv) (98% yield, rt, 18 h), see: (*b*) M. Shi and Y.-H. Liu, *Org. Biomol. Chem.*, 2006, **4**, 1468.

8 The dimerization of methyl vinyl ketone (**2a**) occurred during the reaction progress, and therefore it is necessary to use increasing amount of **2a** when the reaction time of the whole reaction progress was getting longer. In case of preparation of **4i**, there was no further improvement when increasing amount of **2a** was used.

9 The Baylis–Hillman adduct resulting from **1a** and **2a** was furnished efficiently (5 h, 100% conversion). However, the further addition of **3a** toward the Baylis–Hillman adduct in the presence of DABCO proceeded very slowly (7 days, 86% conversion), leading to the expected adduct **4a** in 84% yield.

10 For recent application of functionalized α,β-unsaturated ketones as inhibitors of specific classes of cysteine proteases, see: Z. Yang, M. Fonović, S. H. L. Verhelst, G. Blum and M. Bogyo, *Bioorg. Med. Chem.*, 2009, **17**, 1071.

11 In our preliminary study, the three-component adduct **4a** can be successfully converted into the corresponding α,β-unsaturated ketone **8a** in the presence of Ac_2O, Et_3N and DMAP at rt.

12 Interestingly, the alkenes, such as **8a–i**, were afforded with high stereoselectivities (E/Z = 91/9 to 98/2) after acylation of the three-component adducts **4a–b**, **4d–e**, **4g–h**, **4j–k**, and **4l** followed by elimination according to our one-pot protocol. However, **4a–b**, **4d–e**, **4g–h**, **4j–k**, and **4l** were furnished in poor diastereoselectivities (dr = 1 : 1 to 1 : 4.6).

13 The structure of (*E*)-form of **11c** (CCDC no. 775300) was confirmed by X-ray analysis.

