ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2015, **51**, 14797

Received 17th July 2015,
Accepted 14th August 2015

DOI: 10.1039/c5cc05967d

www.rsc.org/chemcomm

# A highly enantioselective, organocatalytic [3+2]-cycloannulation reaction towards the *de novo*-synthesis of 1-cyclopentenyl-α-keto esters†

Pradeep R. Nareddy and Christoph Schneider*

**We disclose herein a highly enantioselective *de novo*-synthesis of chiral 1-cyclopentenyl-α-keto esters starting from a simple bis-silyl-1,3-dienediolate and α,β-unsaturated aldehydes *via* a domino vinylogous Michael-intramolecular Knoevenagel-type condensation. The cyclopentenes proved to be highly versatile and were readily converted into various structural motifs.**

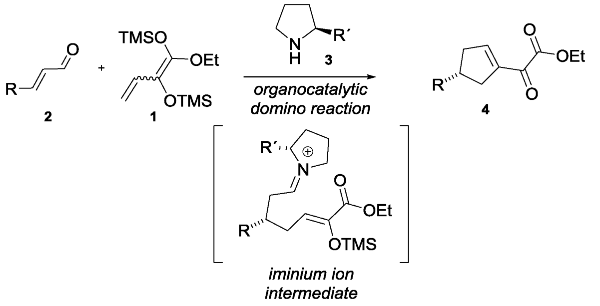
Asymmetric organocatalytic domino transformations have recently emerged as a powerful tool to rapidly assemble complex organic structures with defined absolute configuration.[1] This strategy can now be applied to a wide range of carbon–carbon bond-forming reactions employing different activation modes and organocatalysts.[2] Very prominent among such processes stands the coupled iminium-enamine activation mode using α,β-unsaturated carbonyls in concert with chiral amines in which an initial conjugate addition of a nucleophilic component is directly followed by electrophilic trapping of the *in situ*-generated enamine to generate an α,β-difunctionalized carbonyl compound.[3] Much less explored albeit very attractive as well is a different scenario in which the enal acts as a double 1,3-electrophile *via* initial conjugate and then direct 1,2-addition of two nucleophilic components. This concept, however, has thus far been largely limited to formal [3+3]-cycloaddition reactions of 1,3-dinucleophiles resulting in the synthesis of 6-membered rings.[4,5]

We have recently introduced a novel 1,2-dinucleophile for organic synthesis. The bis-silyl-1,3-dienediolate **1** smoothly underwent Lewis acid-catalyzed, domino-type vinylogous Mannich-*N,O*-acetalization reactions to produce pyrrolo[2,1-*b*]benzoxazoles[6] and pyrrolo[1,2-*a*] benzoxazinones[7] and was also employed in the direct and highly flexible synthesis of pyrrolo[3,2-*c*]quinolines *via* a domino-vinylogous Mannich-Mannich-Pictet-Spengler reaction.[8] Given the capacity of **1** to readily participate in sequential Lewis acid-catalyzed Mannich processes we reasoned that we could exploit the reactivity of **1** in other important carbon–carbon bond-forming reactions, namely the vinylogous Michael reaction.

We now report the amine-catalyzed, enantioselective [3+2]-cycloannulation of **1** with α,β-unsaturated aldehydes **2** to furnish chiral 1-cyclopentenyl-α-keto esters **4** directly with exceptional enantioselectivity (Scheme 1). In this process, bis-silyl-1,3-dienediolate **1** engages the aldehyde in an organocatalyzed vinylogous Michael reaction directly followed by an intramolecular Knoevenagel-type condensation of the silyl enol ether toward the intermediate iminium ion resulting both in ring-closure and regeneration of the chiral catalyst **3**.

We have previously established the first organocatalytic, enantioselective, vinylogous Michael reaction of acyclic dienol silyl ethers and enals producing highly versatile 1,7-dioxo compounds with exceptional enantio- and regiocontrol.[9] As chiral organocatalyst we employed diphenylprolinol silyl ether **3b** which Hayashi and Jorgensen had established independently for iminium ion-activated conjugate addition reactions.[10] Based upon this precedence we started our investigations with the model reaction shown in Table 1.

Thus, we treated bis-silyl-1,3-dienediolate **1** (2.0 equiv.) with cinnamaldehyde (**2a**) (1.0 equiv.), Jørgensen catalyst **3a** (20 mol%) and 2,4-dinitrobenzoic acid (1.0 equiv.) as cocatalyst



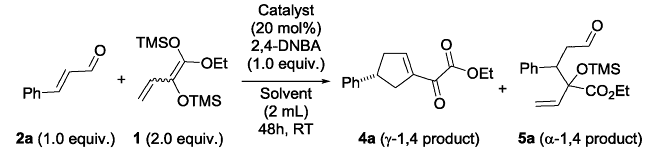
Scheme 1 Conceptual design.

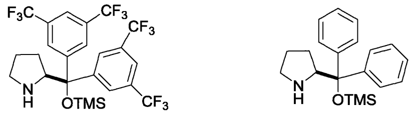
---

*Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, D-4103 Leipzig, Germany. E-mail: schneider@chemie.uni-leipzig.de*

† Electronic supplementary information (ESI) available: Experimental details, characterization and copies of $^1H$, $^{13}C$ NMR spectra and HPLC profiles for novel compounds. CCDC 1412686. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc05967d

Table 1 Optimiziation studies[a]



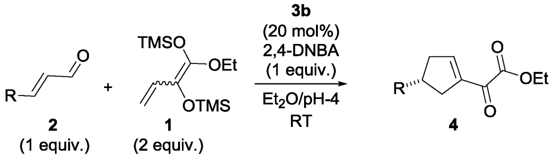


**3a** **3b**

| No. | Catalyst | Solvent (1/1) | **4a** : **5a**[b] | Yield[c,d] (%) | Er[e] |
|---|---|---|---|---|---|
| 1 | **3a** | THF/H$_2$O | 4 : 1 | 28 | 97 : 3 |
| 2 | **3a** | THF/pH-4 | 4 : 1 | 50 | 99 : 1 |
| 3 | **3a** | MTBE/pH-4 | 9 : 1 | 59 | 97 : 3 |
| 4 | **3a** | DME/pH-4 | N.D[f] | 25 | 97 : 3 |
| 5 | **3a** | Dioxane/pH-4 | — | N.R[g] | — |
| 6 | **3a** | Et$_2$O/pH-4 | 9 : 1 | 69 (57) | 98 : 2 |
| 7 | **3b** | Et$_2$O/pH-4 | 9 : 1 | 78 (63) | 99 : 1 |
| 8 | **3b** | Et$_2$O/pH-4 | 9 : 1 | 60[h] | 96 : 4 |
| 9 | **3b** | Et$_2$O/pH-4 | 9 : 1 | 24[i] | N.D[f] |

[a] Standard conditions: bis-silyl-1,3-dienediolate 1 (0.4 mmol), aldehyde **2a** (0.2 mmol), 20 mol% catalyst and 2,4-dinitrobenzoic acid (2,4-DNBA), solvent/pH-4 (1 : 1). [b] Determined by $^1$H NMR. [c] Combined yield of γ- and α-1,4-products. [d] Yield of chromatographically purified γ-1,4 product in brackets. [e] Determined by HPLC on a chiral stationary phase (see the ESI). [f] Not determined. [g] No reaction. [h] *p*-Nitrobenzoic acid (PNBA) was used as cocatalyst. [i] PhCO$_2$H was used as cocatalyst.

Table 2 Substrate scope[a]



| No. | Aldehyde (R) | Product | 4 : 5[b] | Yield[c,d] (%) | Er[e] |
|---|---|---|---|---|---|
| 1 | **2a** (Ph) | **4a** | 9 : 1 | 63 (78) | 99 : 1 |
| 2 | **2b** (4-Me-C$_6$H$_4$) | **4b** | 9 : 1 | 59 (70) | 98 : 2 |
| 3 | **2d** (4-*t*Bu-C$_6$H$_4$) | **4d** | 9 : 1 | 58 (67) | 99 : 1 |
| 4 | **2d** (4-NO$_2$-C$_6$H$_4$) | **4d** | 10 : 1 | 61 (73) | 97 : 3 |
| 5 | **2e** (4-F-C$_6$H$_4$) | **4e** | 5 : 1 | 57 (70) | 98 : 2 |
| 6 | **2f** (4-Cl-C$_6$H$_4$) | **4f** | 5 : 1 | 58 (72) | 98 : 2 |
| 7 | **2g** (4-Br-C$_6$H$_4$) | **4g** | 9 : 1 | 62 (70) | 98 : 2 |
| 8 | **2h** (2-NO$_2$-C$_6$H$_4$) | **4h** | 10 : 1 | 55 (64) | 98 : 2 |
| 9 | **2i** (2-Me-C$_6$H$_4$) | **4i** | 9 : 1 | 57 (68) | 99 : 1 |
| 10 | **2j** (2-Naphth) | **4j** | 5 : 1 | 57 (72) | 99 : 1 |
| 11 | **2k** (2-Furyl) | **4k** | 6 : 1 | 65 (77) | 98 : 2 |
| 12 | **2l** (2-Thienyl) | **4l** | 7 : 1 | 59 (69) | 98 : 2 |
| 13 | **2m** (PhMe$_2$Si) | **4m** | > 20 : 1 | 68 | 99 : 1 |
| 14 | **2n** (Cy) | **4n** | > 20 : 1 | 61 | 98 : 2 |
| 15 | **2o** (iPr) | **4o** | > 20 : 1 | 54 | 99 : 1 |
| 16 | **2p** (CO$_2$Et) | **4p** | 9 : 1 | 65 (73) | 88 : 12 |

[a] Standard conditions: bis-silyl-1,3-dienediolate **1** (2.0 mmol), aldehyde **2a–n** (1.0 mmol), 20 mol% catalyst **3b** and 2,4-dinitrobenzoic acid (2,4-DNBA), Et$_2$O/pH-4 (1 : 1). [b] Determined by $^1$H NMR. [c] Yield of chromatographically purified γ-1,4 product. [d] Combined yield of γ- and α-1,4-products in brackets. [e] Er determined through chiral HPLC analysis (see the ESI).

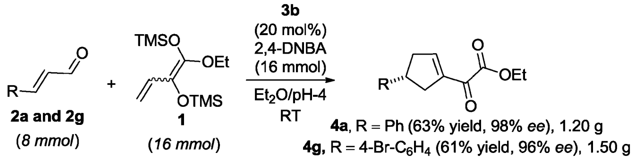
in the solvent mixture THF/H$_2$O (1/1) for 48 h at rt.[11] Under these conditions, a mixture of the desired γ-product **4a** and the regioisomeric α-product **5a** (4 : 1 of γ : α-ratio) was obtained with low yield, but with very high enantioselectivity for the γ-product (Table 1, entry 1). Increasing the acidity of the aqueous phase by using a solvent mixture of THF/pH-4 buffer solution (1 : 1) helped to turnover the reaction and gave rise to **4a** and **5a** (4 : 1 of γ : α-ratio) with 50% combined yield and with exceptional enantioselectivity for **4a** (entry 2).

Encouraged by this result, some more etheral solvents were evaluated in combination with pH-4 buffer solution in this transformation (entries 3–6). Whereas MTBE, DME, and 1,4-dioxane did not improve the yield significantly, the reaction conducted in Et$_2$O/pH-4 buffer solution (1 : 1) delivered the mixture of γ- and α-products with 69% combined yield, from which the desired pure γ-product **4a** could be separated with 57% yield and 98 : 2 er by silica gel chromatography after treatment with 1 N HCl-solution (entry 6, see ESI† for more details). Under identical reaction conditions, the Hayashi catalyst **3b** furnished an increased yield of 78% for the mixture of regioisomers from which the desired pure γ-product **4a** was isolated with 63% yield and 99 : 1-enantioselectivity suggesting this catalyst for further studies (entry 7). In addition we tested other acidic cocatalysts in combination with **3b** which led, however, to inferior results (entries 8 and 9).

With these reaction conditions in hand the generality of this new organocatalytic [3+2]-cycloannulation reaction of bis-silyl-1,3-dienediolate **1** and α,β-unsaturated aldehydes was investigated and the results are summarised in Table 2. A wide array of α,β-unsaturated aldehydes bearing electrondonating and electron-withdrawing groups on the aromatic ring could be coupled with bis-silyl-1,3-dienediolate **1**, and the corresponding products were obtained with generally moderate to good yields and excellent enantioselectivities. Alkyl-, halogen-, and nitro-groups were readily tolerated as aromatic substituents within the cinnamaldehydes (entries 1–10). Heteroaromatic substituents were found to be equally effective in furnishing the corresponding products with excellent enantioselectivities (entries 11 and 12). The ratio between γ- and α-product typically varied between 5 : 1 and 10 : 1, and the pure γ-regioisomers could be isolated in all cases studied. Remarkably, β-silyl-substituted aldehyde **2m** was successfully coupled with **1** and delivered the desired γ-product **4m** as a single regioisomer with good yield and excellent enantioselectivity (entry 13). Likewise, aliphatic α,β-unsaturated aldehydes **2n–o** gave rise to single γ-regioisomers **4n–o** again with very high enantioselectivities (entries 14 and 15). In addition, the ester-substituted enal **2p** furnished cyclopentene **4p** with good isolated yield, but with somewhat diminished enantioselectivity (entry 16).

To probe the applicability and robustness of this new process we carried out the large-scale synthesis of two new cyclopentenes. In the presence of 20 mol% of Hayashi catalyst **3b** the domino vinylogous Michael-intramolecular Knoevenagel-type condensation of **1** and the α,β-unsaturated aldehydes **2a** and **2g** proceeded to completion within three days at room temperature delivering the corresponding 1-cyclopentenyl-α-keto esters **4a** and **4g** with good isolated yields and excellent enantioselectivity (Scheme 2).

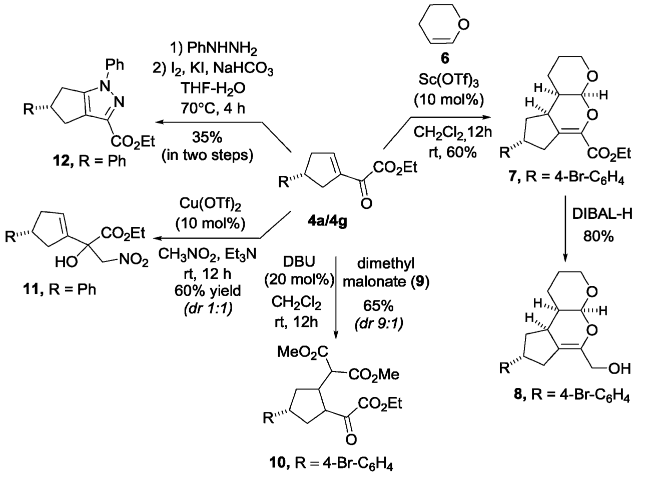
To demonstrate the synthetic utility of the highly functionalized cyclopentene products **4a** (R = Ph) and **4g** (R = *p*-Br-Ph) were taken as representative examples and converted into diversely



Scheme 2 Catalytic, enantioselective [3+2]-cycloannulation reaction of bis-silyl-1,3-dienediolate **1** and enals on large scale.

functionalized products *via* a series of simple transformations (Scheme 3). Thus, $Sc(OTf)_3$-catalyzed hetero-Diels Alder (HDA)[12] reaction of **4g** and 3,4-dihydro-2*H*-pyran (**6**) afforded the tricyclic α,β-unsaturated ester **7** as a single *endo*-diastereomer in good yield. Remarkably, only a single stereoisomer was formed in this reaction that created three new contiguous stereogenic centers documenting the large inherent substrate selectivity. The absolute and relative configuration of hetero Diels-Alder adduct **7** was unambiguously determined by an X-ray diffraction analysis[13] of the corresponding alcohol **8** (Fig. 1) which at the same time established the absolute configuration of the 1-cyclopentenyl-α-keto esters **4** as well.

In addition, β,γ-unsaturated α-keto ester **4g** underwent facile base-catalyzed 1,4-conjugate addition with dimethyl malonate (**9**) to afford the highly functionalized cyclopentane **10** with 65% yield (d.r. 9 : 1).[14] Moreover, cyclopentene **4a** and nitromethane reacted in a selective 1,2-addition[15] delivering the corresponding nitroaldol product **11** with 60% yield as a 1 : 1-mixture of diastereomers. Finally, we were delighted to find that cyclopentene **4a** could also be converted into pyrazole **12** with moderate yield in a two step-sequence comprising hydrazone formation and oxidative cyclization (Scheme 3).[16]



Scheme 3 Synthetic modifications of 1-cyclopentenyl-α-keto esters **4a** and **4g**, respectively.

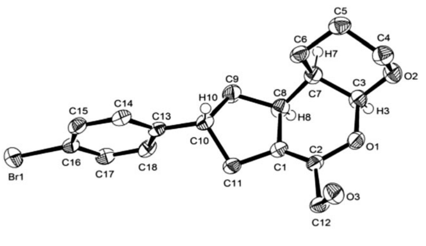


Fig. 1 Crystal structure of alcohol **8**.

In conclusion, we have developed a highly enantioselective, organocatalytic domino reaction of bis-silyl-1,3-dienediolate **1** and α,β-unsaturated aldehydes **2** furnishing 1-cyclopentenyl-α-keto esters **4** in moderate to good yields and excellent enantioselectivities of up to > 99 : 1 er. Using an operationally very simple protocol this process comprises an initial vinylogous Michael reaction followed by a Knoevenagel-type condensation reaction with concomitant ring-closure and regeneration of the chiral catalyst. The reaction has been shown to be quite general with respect to the enal component. The versatility of the cyclopentene products has been demonstrated by a series of synthetic transformations involving either the α-keto ester or the α,β-unsaturated carbonyl moiety. Studies to further improve and extend this process to other Michael acceptors are currently underway in our laboratory and will be reported in due course.

Generous financial support provided by the DFG (SCHN 441/10-1) is gratefully acknowledged. We thank K. Stockhausen (University of Leipzig) for preliminary experiments, Dr P. Lönnecke (University of Leipzig) for the crystal structure analysis and Evonik and BASF for the donation of chemicals.

## Notes and references

1 Select reviews: (*a*) H. Pellissier, in *Organocatalysis in Domino Processes in Domino Reactions*, ed. L. F. Tietze, Wiley-VCH, 2014, p. 325; (*b*) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237; (*c*) A. Grossmann and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 314; (*d*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*e*) D. Enders, C. Grondal and M. R. M. Huettl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; for a more general discussion of domino reactions see: (*f*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*g*) see complete book mentioned in ref. 1*a*.

2 Select reviews: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*b*) A. Berkessel and H. Groger, *Asymmetric Organocatalysis*, VCH, Weinheim, Germany, 2004, p. 1806; (*c*) J. Seayed and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (*d*) B. List, *Chem. Rev.*, 2007, **107**, 5413; (*e*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138; (*f*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (*g*) K. M. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht and K. A. Jørgensen, *Acc. Chem. Res.*, 2012, **45**, 248.

3 For leading contributions see: (*a*) J. F. Austin, S. G. Kim, C. J. Sinz, W. J. Xiao and W. C. MacMillan, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, 5482; (*b*) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051; (*c*) M. Marigo, T. Schulte, J. Franzen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 15710; (*d*) J. W. Yang, M. T. Hechavarria Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036; (*e*) D. Enders, M. R. M. Huttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861; (*f*) W. Wang, H. Li, J. Wang and L. Zu, *J. Am. Chem. Soc.*, 2006, **128**, 10354; (*g*) S. Brandau, E. Maerten and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 14986; (*h*) D. Enders, A. Greb, K. Deckers, P. Selig and C. Merkens, *Chem. – Eur. J.*, 2012, **18**, 10226; (*i*) X. Tian and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2013, **52**, 5360.

4 (*a*) A. Carlone, M. Marigo, C. North, A. Landa and K. A. Jørgensen, *Chem. Commun.*, 2006, 4928; (*b*) M. Marigo, S. Bertelsen, A. Landa and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 5475; (*c*) C. L. Cao, X. L. Sun, Y. B. Kang and Y. Tang, *Org. Lett.*, 2007, **9**, 4151; (*d*) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 9202; (*e*) Y. Hayashi, H. Gotoh, R. Masui and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 4012; (*f*) L. Zu, H. Xie, H. Li, J. Wang, X. Yu and W. Wang, *Chem. – Eur. J.*, 2008, **14**, 6333; (*g*) L. Albrecht, B. Richter,

C. Vila, H. Krawczyk and K. A. Jørgensen, *Chem. – Eur. J.*, 2009, **15**, 3093; (*h*) Y. Hayashi, M. Toyoshima, H. Gotoh and H. Ishikawa, *Org. Lett.*, 2009, **11**, 45; (*i*) Y. Liu, C. Mao, K. Jiang, T.-Y. Liu and Y.-C. Chen, *Org. Lett.*, 2009, **11**, 2848; (*j*) E. Alza, S. Sayalero, X. C. Cambeiro, R. M. Rapún, P. O. Miranda and M. A. Pericàs, *Synlett*, 2011, 464; (*k*) B.-C. Hong, N. S. Dange, C.-F. Ding and J.-H. Liao, *Org. Lett.*, 2012, **14**, 448; (*l*) S. Wang, Y. Zhang, G. Dong, S. Wu, S. Zhu, Z. Miao, J. Yao, H. Li, J. Li, W. Zhang, C. Sheng and W. Wang, *Org. Lett.*, 2013, **15**, 5570.

5 For a few syntheses of five-membered ring systems according to this principle which are limited exclusively to heteronucleophiles however see: (*a*) G. Talavera, E. Reyes, J. L. Vicario, L. Carrillo and U. Uria, *Adv. Synth. Catal.*, 2013, **355**, 653; (*b*) M. Fernández, E. Reyes, J. L. Vicario, D. Badía and L. Carrillo, *Adv. Synth. Catal.*, 2012, **354**, 371; (*c*) I. Ibrahem, R. Rios, J. Vesely, G. L. Zhao and A. Cordova, *Chem. Commun.*, 2007, 849; (*d*) S. Brandau, E. Maerten and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 14986.

6 M. Boomhoff and C. Schneider, *Chem. – Eur. J.*, 2012, **18**, 4185.

7 M. Boomhoff, R. Ukis and C. Schneider, *J. Org. Chem.*, 2015, **80**, DOI: 10.1021/acs.joc.5b01293.

8 M. Boomhoff, A. K. Yadav, J. Appun and C. Schneider, *Org. Lett.*, 2014, **16**, 6236.

9 (*a*) V. Gupta, S. Sudhir, T. Mandal and C. Schneider, *Angew. Chem., Int. Ed.*, 2012, **51**, 12609; (*b*) S. Basu, V. Gupta, J. Nickel and C. Schneider, *Org. Lett.*, 2014, **16**, 274.

10 (*a*) M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 794; (*b*) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212; reviews: (*c*) C. Palomo and A. Mielgo, *Angew. Chem., Int. Ed.*, 2006, **45**, 7876; (*d*) K. L. Jensen, G. Dickmeis, H. Jiang, L. Albrecht and K. A. Jørgensen, *Acc. Chem. Res.*, 2012, **45**, 248.

11 Solvent mixtures containing minor or even equal amounts of protic components had been found advantageous for amine-catalyzed Mukaiyama-Michael reactions to trap the cationic silicon species formed (see ref. 7).

12 (*a*) J. Lv, L. Zhang, S. Hu, J.-P. Cheng and S. Luo, *Chem. – Eur. J.*, 2012, **18**, 799; (*b*) Y. Zhu, M. Xe, S. Dong, X. Zhao, L. Lin, X. Liu and X. Feng, *Chem. – Eur. J.*, 2011, **17**, 8202; (*c*) Y. Zhu, X. Chen, M. Xe, S. Dong, Z. Qiao, L. Lin, X. Liu and X. Feng, *Chem. – Eur. J.*, 2010, **16**, 11963; (*d*) D. A. Evans, J. S. Johnson and E. J. Olhava, *J. Am. Chem. Soc.*, 2000, **122**, 1635; (*e*) L. F. Tietze, C. Schneider and A. Grote, *Chem. – Eur. J.*, 1996, **2**, 139.

13 CCDC 1412686.

14 S. Zhang, K. Xu, F. Guo, Y. Hu, Z. Zha and Z. Wang, *Chem. – Eur. J.*, 2014, **20**, 979.

15 (*a*) C. Christensen, K. Juhl and K. A. Jørgensen, *Chem. Commun.*, 2001, 2222; (*b*) C. Christensen, K. Juhl, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 4875.

16 H. Kenji, Y. Satoyuki, U. Sadayuki and S. Hideo, *Jpn. Kokai Tokkyo Koho.*, JP 06306053 A 19941101, 1994.