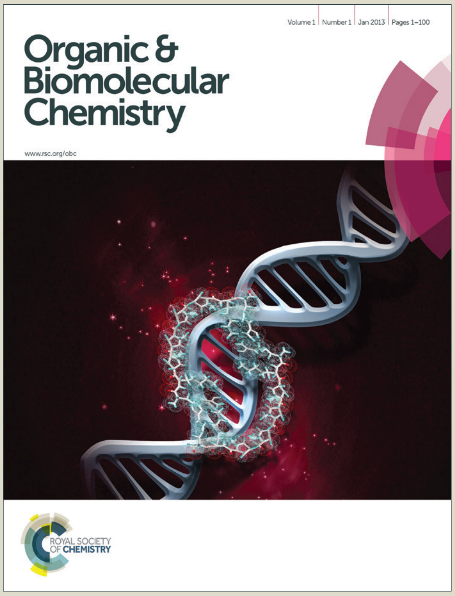

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ARTICLE TYPE

In situ intramolecular catalytic 1,2-addition of allenoates to cyclic ketones towards polycyclic allenoates

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Sequential déprotonation, isomerization of 3-alkynoates and subsequent 1, 2-addition led to bicyclic allenoate in the presence of a catalytic amount of Cs_2CO_3. Cyclization proceeds in a total stereoselective manner in the case of the two carbon linker chain. A one-pot reaction starting from alkynyl ketones afforded tricyclic fused ring systems with good yields.

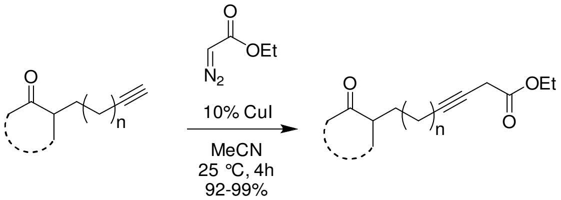
Introduction

Allenes are remarkably versatile intermediates in organic chemistry because of the cumulated diene system characteristic of this class of compounds. In particular, allenoates are interesting building blocks in various reactions.[1]

Crabbé *et al.* reported the first CuBr-mediated reaction to form terminal allenes from 1-alkynoates and formaldehyde in the presence of diisopropylamine.[2] Later Ma and coworkers[3] developed an efficient ZnI_2-mediated protocol for one-pot synthesis of 1, 3-disusbtituted allenes form 1-alkynes. Further, cumulated π- bonds can be obtained via isomerization. In this way, the Brønsted base catalyzed 1,3-prototropic shift reaction, which proceeds through déprotonation-protonation sequences, provides allenes directly from alkynes.[4] Based on these precedents, we wish to report the realization of such protocol on keto 3-alkynoates which uses catalytic amount of Cs_2CO_3. Thus, sequential déprotonation-isomerization of the latter led to an *in situ* 1,2-addition process providing bicyclic allenoates.

Results and discussions

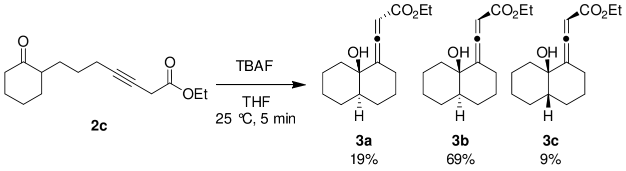
In order to functionalize our alkynyl ketones we utilized a convenient method developed by Fu and coworkers.[5] Coupling various terminal alkynes with ethyl diazoacetate in the presence of a catalytical amount of CuI produced the 3-alkynoate bearing a cyclic keto group (**scheme 1**).



1a-j **2a-j**

Scheme 1: Synthesis of 3-alkynoates 2a-j

With the 3-alkynoates in hand, we started our investigations by examining the treatment of the 3-alkynoates in the presence of TBAF. In fact, *in situ* 1,2 addition of the linear allenoate formed after sequential deprotonation-isomerization reaction occurred providing the formation of bicyclic allenoates.[6] This reaction led to a mixture of three compounds, *trans-cis*-allenoate **3b** being the major compound (**scheme 2**).



Scheme 2: Reactivity with TBAF

X-Ray crystal structures of allenoates **3a**, **3b** and **3c** provided evidence for the relative configuration of the compounds obtained.[7] Previous work[8] showed that starting from 2-alkynoates with a 4-carbon linker chain likewise provided those allenoates together with a mixture of compounds, although the selectivity was lower. Even treatment of trans-*cis* allenoate **3b** with TBAF afforded an almost equimolar mixture of *trans-trans* and *trans-cis* allenoates **3a** and **3b**.

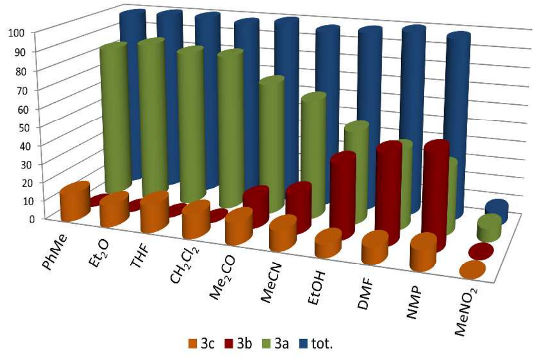
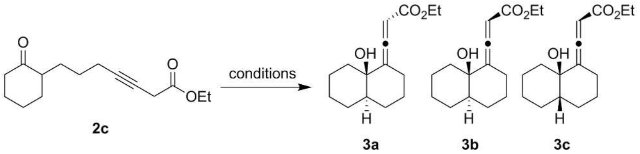


Figure 1: Screenings of different solvents

To check the outcome of the reaction in basic medium, compound **2c** was treated with several bases (**table 1**).

Table 1: Screenings of different bases



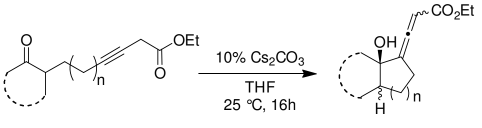
entry	base	solvent	allenoate 3a	allenoate 3b	allenoate 3c
1[a]	Et_3N,	$CHCl_3$	-	-	-
2	NaOEt	EtOH	38%	43%	10%
3	NaH	THF	-	74%	14%
4[b]	K_2CO_3	THF	-	36%	10%
5[c]	Rb_2CO_3	THF	-	72%	21%
6	Cs_2CO_3	THF	-	82%	10%
7[d]	CsF	THF	-	46%	11%
8	Cs_2CO_3 (10% mol)	THF	-	83%	16%

[a] Recovery of 16% of disubstituted allenoate together with 84% starting material. [b] 54% starting material was recovered. [c] 5% starting material was recovered. [d] Recovery of 18% of the disubstituted allenoate accompanied by 21% starting material.

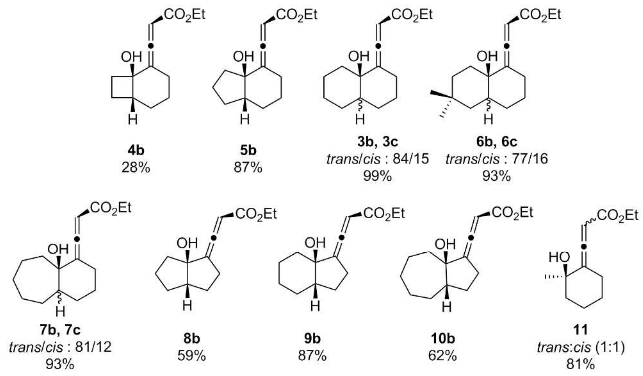
Whereas the reaction with Et_3N showed no sign of cyclization, only the formation of linear allenes (entry 1), the reaction with NaOEt and TBAF (entry 2) led to different proportions of cyclized allenes. However, NaH, Rb_2CO_3 and Cs_2CO_3 (entry 3, 5, 6) led preferentially to *trans-cis* allenoate **3b**. As the yield of *trans-cis* allenoate was improved using Cs_2CO_3, we tried a catalytic amount of the latter (entry 8). *Trans-cis* allenoate **3b** was obtained with almost the same yield as for 1 equivalent of the base together with 16% of allenoate **3c**.

The solvent effect was then examined (**figure 1**). In most cases, we observed a very good overall yield. Whereas PhMe, Et_2O, THF, and CH_2Cl_2 afforded similar selectivities for both allenoates, using polar aprotic solvents led to an important selectivity drop where both allenoates **3a** and **3b** were obtained in a nearly 1 to 1 ratio. The proportion of the bicyclic allenoate bearing a *cis* ring junction remains constant regardless of the polarity of the medium.

Having found that Cs_2CO_3 favors *in situ* 1,2 addition of the allenoate tether to the cyclic keto group, we evaluate the scope of the reaction by using various cyclic ketones as well as two and three carbon linker chain. Results are display in **scheme 3**.



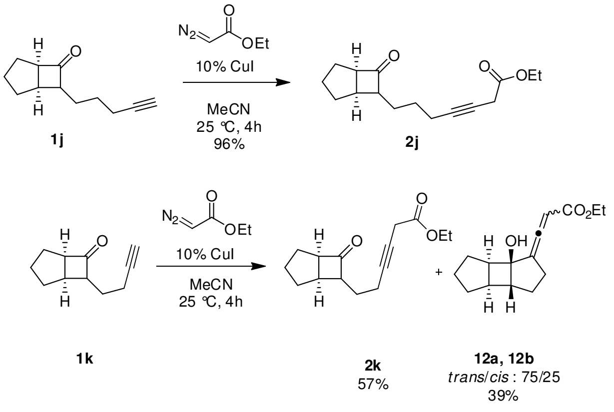
2a-i **4-11**



Scheme 3: Catalytic Cs_2CO_3 cyclization

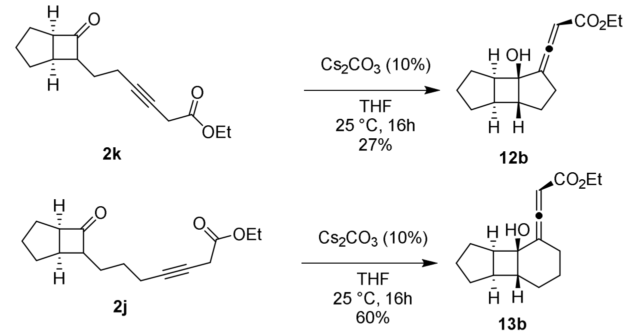
Through this investigation it transpired that Cs_2CO_3 provided almost completely the *trans-cis* allenoate regardless to the carbon linker chain and the starting cycloalkanone. The reaction is totaly stereoselective, in particular for the 4-6 (**4b**) and the 5-6 (**5b**) fused ring systems, the former being obtained in a low yield. Likewise for the two-carbon linker chain, in each case the *cis-cis* allenoate is exclusively obtained (**8b-10b**), while 2-alkynoates with a four-carbon linker chain tethered to cyclopentanone always led to a mixture of allenoates as well as spiro derivatives.[8] Linear 3-alkynoate led as well to cyclised allenoate **11** with good yield. 3-alkynoates bearing a four carbon linker chain led only to the corresponding linear allenoates without cyclization.

Next we focused on bicyclo[3.2.0]derivatives.[9] Fu's reaction conditions with a three carbon linker chain on alkynyl ketone **1j** provided the corresponding 3-alkynoate **2j**, whereas the two carbon linker chain derivative **1k** led directly to fused tricyclic ring system **12** in a diastereoselective manner with respect to the ring junction, together with the desired 3-alkynoate **2k** (**scheme 4**).



Scheme 4: Fu's reaction over bicyclo[3.2.0]derivatives

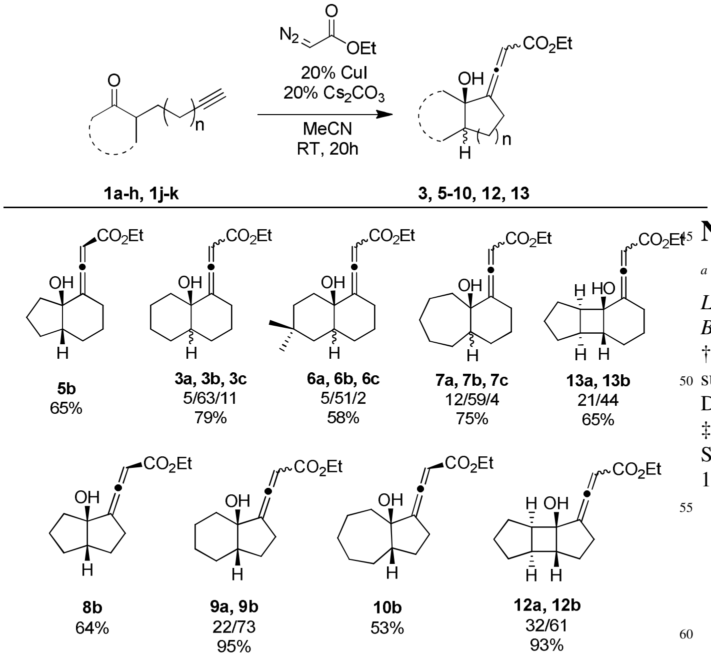
Cyclization of both alkynoates **2j** and **2k** in the presence of a catalytical amount of Cs_2CO_3 afforded tricyclic fused ring systems 5-4-5 (**12b**) and 5-4-6 (**13b**) respectively, with 27% and 60% yield (**scheme 5**).



Scheme 5: Obtention of tricyclic allenoate using catalytical amount of Cs_2CO_3

Taking into account the direct formation of the tricyclic allenoates observed for compound **12**, we examined the feasibility of a one-pot reaction starting from terminal alkynes.

Treatment of alkynyl ketones with ethyl diazoacetate, 20 mol% of CuI and 20 mol % of Cs_2CO_3 afforded directly polycyclic allenoates (**scheme 6**). Although in each case *trans-cis* allenoate remains the major product, there is a decrease of the selectivity with respect to the ring junction and the allenoate. However, the reaction is totally stereospecific for compounds **5b**, **8b** and **10b**, like for the two steps process. Moreover, the one pot reaction favors the synthesis of tricyclic fused ring systems **12** and **13** because the yield with respect to the two-step reaction has improved.

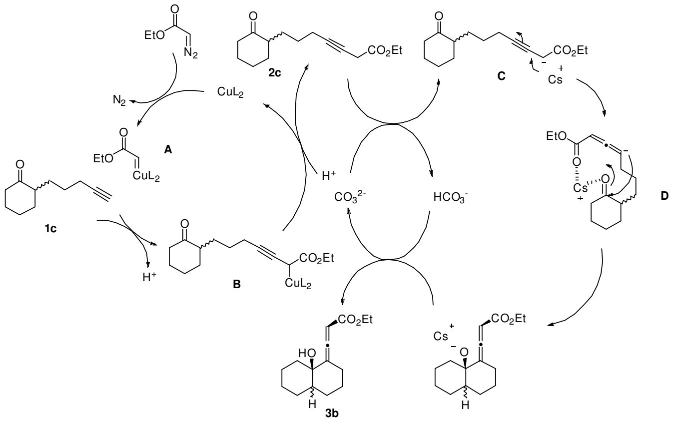


Scheme 6: One pot process starting from alkynyl ketones

A plausible reaction mechanism is shown in **scheme 7**. Carbenoid **A** obtained from the reaction ethyl diazoacetate and Cu-chelate reacts with the alkynyl ketone, providing intermediate **B**.[10] The latter undergoes protonation affording 3-alkynoate **2c**. In the presence of a base, anion **C** is generated and isomerizes to allenoate **D**. To explain the strong selectivity observed, we assume the existence of alkali-metal complex **D**,[11] which favors *trans-cis* allenoate **3b**, obtained via 1,2 addition of allenoate **D** to the keto group providing bicyclic allenoates.

Conclusions

In conclusion, an *in situ* catalytic process leading to bicyclic and tricyclic allenoates has been developed. The synthesis of bicyclic allenoate is operationally simple and takes place under mild conditions at room temperature, and a catalytic amount of Cs_2CO_3 was used. Cyclization proceeds in a total stereoselective manner, in particular in the case of the two-carbon linker chain. Polycyclic allenoates can be obtained directly through copper-catalyzed of diazo compounds with terminal alkynes by cesium carbonate; in this manner the yield of tricyclic fused ring systems could be improved.



Scheme 7: Mechanism proposal

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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1 (a) *Modern Allene Chemistry, Vols 1, 2* (Eds N. Krause, A.S.K. Hashmi), Willey-VCH, Weinheim, 2004.; (b) S. Ma, *Palladium Two- or Three Component Cyclization of Functionalized Allenes in Palladium in Organic Synthesis* (Ed.: J. Tsuji), Springer, Berlin, 2005, pp. 183-210.; (c) *Science of Synthesis, Vol 44* (Ed.: N. Krause), Thieme, Stuttgart, 2007.; (d) K.K. Wang, *Chem. Rev.*, 1996, **96**, 207.; (e) R. Zimmer, C. Dinesh, E. Nandanan, F.A. Khan, *Chem. Rev.*, 2000, **100**, 3067.; (f) A.S.K. Hashmi, *Angew. Chem.*, 2000, **112**, 3737.; (g) A.S.K. Hashmi, *Angew. Chem. Int. Ed.*, 2000, **39**, 3590.; (h) J.A. Marshall, *Chem. Rev.*, 2000, **100**, 3163.; (i) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.*, 2001, **34**, 535.; (j) R. Bates, V. Satcharoen, *Chem. Soc. Rev.*, 2002, **31**, 12.; (k) A. Hoffman-Röder, N. Krause, *Chem. Int. Ed.*, 2002, **41**, 2933.; (l) S. Ma, *Acc. Chem. Res.*, 2003, **36**¸ 701.; (m) L. Sydnes, *Chem. Rev.*, 2003, **103**, 1133.; (n) M. Tius, *Acc Chem. Res.*, 2003, **36**, 284.; (o) L.L. Wei, H. Xiong, R.P. Hsung, *Acc. Chem. Res.*, 2003, **36**, 773.; (p) S. Ma, *Eur. J. Org. Chem.*, 2004, **6**, 1175.; (q) A. Barbero, J.F. Pulido, *Synthesis*, 2004, **5**, 779.; (r) N. Krause, A. Hoffman-Röder, *Tetrahedron*, 2004, **60**, 11671.; (s) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.*, 2004, **16**, 3377.; (t) L.

Brandsma, N.A. Nedolya, *Synthesis*, 2004, **05**, 735.; (u) S. Ma, *Chem. Rev.*, 2005, **105**, 2829.; (v) L. Brandsma, N.A. Nedolya, *Synthesis*, 2005, **105**, 2829.; (w) S. Ma, *Aldrichimica Acta*, 2007, **40**, 91.; (x) K.M. Brumond, J.E. DeForrest, *Synthesis*, 2007, **7**, 795.; (y) S. Braverman, M. Cherkinsky, *Top. Curr. Chem.*, 2007, **275**, 67.; (z) H.H.A.M. Hassan, *Curr. Org. Synth.*, 2007, **4**, 413.; (aa) M. Jeganmohan, C.-H. Cheng, *Chem. Eur. J.*, 2008, **14**, 10876.; (ab) H. Kim, L.J. Williams, *Curr. Opin. Drug. Discovery Dev.*, 2008, **11**, 870.; (ac) M. Jeganmohan, C.-H. Cheng, *Chem. Commun.*, 2008, 3101.; (ad) T. Bai, S. Ma, G. Jia, *Coord. Chem. Rev.*, 2009, **253**, 423.; (ae) T.M.V.D. Pinho e Melo, *Curr. Org. Chem.*, 2009, **13**, 1406.; (af) S.R. Chemler, *Org. Biomol. Chem.*, 2009, **7**, 3009.; (ag) M. Brasholtz, H.U. Reissig, R. Zimmer, *Acc. Chem. Res.*, 2009, **42**, 45.; (ah) S. Ma, *Acc. Chem. Res.*, 2009, **42**, 1679.; (ai) M. Ogasawara, *Tetrahedron: Asymmetry*, 2009, **20**, 259.; (aj) A.S.K. Hashmi, M. Buehrle, *Aldrichimica Acta*, 2010, **43**, 27.; (ak) A. Deagostino, C. Prandi, S. Tabasso, P. Venturello, *Molecules*, 2010, **15**, 2667.; (al) B. Xu, G.B. Hammond, *Synlett*, 2010, 1442.; (am) M. Bandini, *Chem. Soc. Rev.*, 2011, **40**, 1358.; (an) N. Krause, C. Winter, *Chem. Rev.*, 2011, **111**, 1994.; (ao) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.*, 2011, **111**, 1954.; (ap) F. López, J.L. Mascareñas, *Chem. Eur. J.*, 2011, **17**, 418.; (aq) F. Inagaki, S. Kitagaki, C. Mukai, *Synlett*, 2011, 594.; (ar) B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano, *Top. Curr. Chem.*, 2011, **302**, 183.; (as) S. Yu, S. Ma, *Chem. Commun.*, 2011, **47**, 5384.; (at) S. Yu, S. Ma, *Angew. Chem. Int. Ed.*, 2012, **51**, 3074.; (au) B. Alcaide, P. Almendros, *Chem. Soc. Rev.*, 2014, **43**, 2886.; (av) W. Yang, A.S.K. Hashmi, *Chem. Soc. Rev.*, 2014, **43**, 2941.

2 (a) P. Crabbé, H. Fillion, A. André, J.L. Luche, *J.C.S. Chem. Comm.*, 1979, 859.; (b) P. Rona, P. Crabbé, *J. Am. Chem. Soc.*, 1969, **91**, 3289.; (c) J. Kunag, S. Ma, *J. Org. Chem.*, 2009, **74**, 1763.

3 J. Kuang, S. Ma, *J. Am. Chem. Soc.*, 2010, **132**, 1786.

4 (a) M.E. Jung, M. Node, R.W. Pfluger, M.A. Lyster, J.A. Lowe III, *J. Org. Chem.*, 1982, **47**, 1150.; (b) M.E. Jung, J.A. Lowe III, M.A. Lyster, M. Node, R.W. Pfluger, R.W. Brown, *Tetrahedron*, 1984, **40**, 4751.; (c), T. Yasukouchi, K. Kanemastu, *Tetrahedron Lett.*, 1989, **30**, 6559.; (d) B.M. Trost, U. Kazmaier, *J. Am. Chem. Soc*, 1992, **114**, 7933.; (e) C. Guo, X. Lu, *J. Chem. Soc. Perkin Trans. I*, 1993, 1921.; (f) C. Guo, X. Lu, *J. Chem. Soc., Chem. Commun.*, 1993, 394.; (g) M. Oku, S. Arai, K. Katayama, T. Shioiri, *Synlett*, 2000, 493.; (h) H. Liu, D. Leow, K.W. Huang, C.H. Tan, *J. Am. Chem. Soc.*, 2009, **131**, 7212.; (i) M. Sampath, T.P. Loh, *Chem. Sci.*, 2010, **1**, 739.; (j) (i) T. Inokuma, M. Furukawa, Y. Suzuki, T. Kimachi, Kobayashi, Y. Takemoto, *ChemCatChem*, 2012, **4**, 983.

5 Suárez, A.; Fu, G.C., *Angew. Chem. Int. Ed.*, 2004, **43**, 3580.

6 To described the relative stereochemistry of the obtained bicyclic allenoates the terms trans-trans; trans-cis; cis-cis will be used. The first term refering to the ring junction, the second term refering to the relative stereochemistry between the alcohol and the ester group on the allene.

7 (a) CCDC-1005688 contains the crystallographic data for compounds **3a**.; (b) CCDC-271435 contains the crystallographic data for compounds **3b**.; (c) CCDC-1005689 contains the crystallographic data for compounds **3c**. These data can be obtained free of charges form the Cambridge Crystallographic Data Center via www.ccdc.cam.a-c.uk./data_request/cif.

8 Mota, A.J.; Klein, A.; Wendling, F.; Dedieu, A.; Miesch, M., *Eur. J. Org. Chem*., 2005, 4346.

9 (a) Miesch, L.; Welsch, T.; Rietsch, V.; Miesch, M. *Chem. Eur. J.,* 2009, **15**, 4394.; (b) Miesch, M.; Welsch, T.; Rietsch, V.; Miesch, L., *Strategies and Tactics in Organic Synthesis*, 2013, **9**, 203.

10 (a) Hassink, M.; Liu, X.; Fox, J.M., *Org. Lett.,* 2011, **13**, 2388.; (b) Q. Xiao, Y. Xia, H. Li, Y. Zhang, J. Wang, *Angew. Chem. Int. Ed.*, 2011, **50**, 1114.

11 Dunbar, R.C.; Steill, J.D.; Oomens, J., *J. Am. Chem. Soc.*, 2011, **133**, 9376.