ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. Kontham, D. A. Kambale, S. S. Thorat, M. S. Pratapure and R. G. Gonnade, *Chem. Commun.*, 2017, DOI: 10.1039/C7CC03668J.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C7CC03668J

Journal Name

COMMUNICATION

Lewis acid catalyzed cascade annulation of alkynols with α-ketoesters: A facile access to γ-spiroketal-γ-lactones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Digambar A. Kambale,[a,b] Sagar S. Thorat,[a,b] Madhukar S. Pratapure,[a,b] Rajesh G. Gonnade[b,c] and Ravindar Kontham*[a,b]

A novel Lewis acid catalyzed intermolecular cascade annulation of alkynols with α-ketoesters has been developed. This simple and efficient cascade annulation proceeds through a 5-*exo*-dig cyclization of alkynols followed by annulation with α-ketoester to provide a wide variety of unsaturated γ-spiroketal-γ-lactones (1,6-dioxaspiro[4.4]non-3-en-2-ones) related to many natural products.

Spiroketals and oxa-spirolactones are frequently found structural units in biologically potent natural products.[1-2] In addition, it has been shown that simplified spiroacetals derived from natural products retain their biological properties. Hence, these scaffolds essentially contribute to pharmacological activities and represent privileged pharmacophores in drug discovery.[3] In the recent years, several bioactive natural products with unsaturated γ-spiroketal-γ-lactone (1,6-dioxaspiro[4.4]non-3-en-2-one) appendage were isolated and have become an important sub-group of spiroketals, which include tuberostemonamide,[4] massarinoline A,[5] aphagrandinoid A,[6] pyrenolide D,[7] crassalactone D,[8] levantenolide,[9] papyracillic acid C,[9] acutissimatriterpene A and many others (Figure 1).[8,10]

Despite their potential properties, only a few synthetic methods have been documented in the literature. For instance, Mitsunobu's protocol of photo-oxidation of unprotected prefunctionalized furyl-alkanols, which was further developed by Vassilikogiannakis *et al*.[11] and others.[12] Kitching *et al*. reported a strategy starting from 3-butyn-1-ol via saturated oxa-spirolactone in total number of 8 steps.[13] In 2006, Shi and co-workers reported using $SnCl_4$ (stoichiometric amount, 40 °C) mediated annulation of cyclopropyl-alkyl ketones and α-ketoesters.[14] Few other miscellaneous reports also present in the literature.[15] All of these approaches had limitations such as usage of prefunctionalized starting materials, protection and deprotection sequence, stoichiometric amount of Lewis acids and multiple steps. Thus, the development of a new intermolecular approach to unsaturated γ-spiroketal-γ-lactones from easily available fragments is of considerable importance from the point of view of diversity-oriented synthesis.[15]

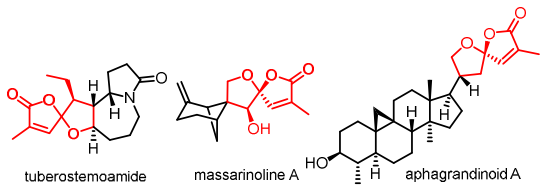


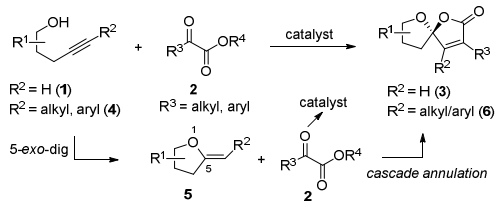
Figure 1. Unsaturated γ-spiroketal-γ-lactone containing bioactive natural products

Inspired by the emerging importance of cascade/domino reactions[16] involving alkynols[17,18] and as part of our research interest in Lewis acid-promoted cascade reactions involving alkynols,[19] we herein report a protocol for the construction of unsaturated γ-spiroketal-γ-lactones comprising $Bi(OTf)_3$ catalyzed cascade annulation of alkynols (4-pentyn-1-ol derivatives) and α-ketoesters, where hydroalkoxylation of alkynol **1** and/or **4** furnish the exocyclic enol ether **5** via 5-*exo*-dig mode of cyclization, which in the proximal presence of an activated α-ketoester **2** would undergo an annulation reaction to furnish the desired product **3** and/or **6** in a cascade manner (Scheme 1).

To explore the feasibility of this proposed strategy, the reaction between known alkynol **1a** (1.0 eq) and ethylpyruvate (**2a**, 1.0 eq) with commercially available $Bi(OTf)_3$ (99%, 20 mol %) in anhydrous CH_2Cl_2 at room temperature was performed (Table 1). Gratifyingly, both starting materials were completely consumed in 12 h at room temperature and gave the desired unsaturated γ-spiroketal-γ-lactone **3aa** in 80% yield (entry 1). Reaction in other solvents such as toluene, acetonitrile and tetrahydrofuran did not result in any improvement in the yield (entries 2-4). Notably, various Lewis (entries 5-15) and Brønsted acids (entries 16-18) were also

[a] Organic Chemistry Division, CSIR-National Chemical Laboratory Dr. Homi Bhabha Road, Pune-411008 (India).
[b] Academy of Scientific and Innovative Research (AcSIR), New Delhi, India.
[c] Centre for Materials Characterization, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune-411008 (India).
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C7CC03668J

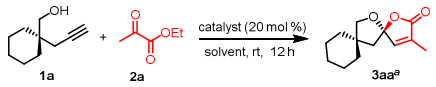


Scheme 1. Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols and α-ketoesters

tested in this reaction, where some of them found moderately active and gave 60-70% yields. To our delight, initially identified conditions of 20 mol % $Bi(OTf)_3$ in CH_2Cl_2 at rt was found to produce the best yield of the product **3aa** (entry 1).[21] Further tuning of the other parameters like molar ratios of the substrates, catalyst loading and temperature did not lead to any noticeable change in the outcome of the reaction (Table 1).[20]

With the optimal conditions in hand, we next investigated the scope of this annulation with respect to the alkynols possessing terminal alkyne functionality and α-ketoesters (Scheme 2). Reaction of cyclohexane and cyclopentane fused 4-pentyn-1-ols with several alkyl and aryl α-ketoesters gave corresponding oxa-spirolactones **3aa-be** in good yields (70-80%), which clearly states that the electronic nature of the phenyl substitution of α-ketoesters has a little influence on the outcome. Unsubstituted 4-pentyn-1-ol provided desired

Table 1. Optimization of the reaction conditions

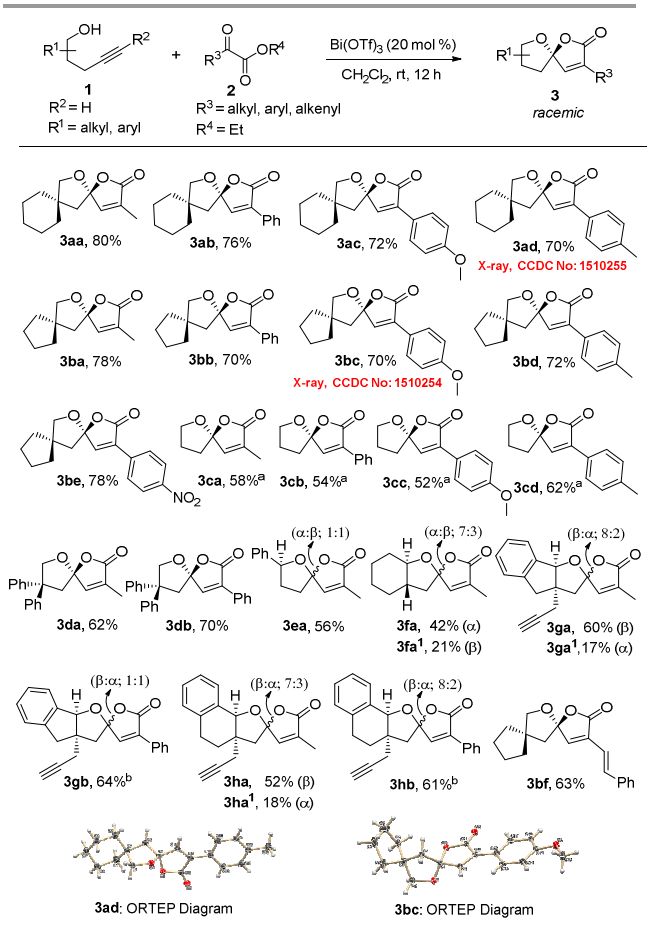


entry	catalyst	solvent	yield (%)[b]
1	$Bi(OTf)_3$	CH_2Cl_2	80
2	$Bi(OTf)_3$	toluene	70
3	$Bi(OTf)_3$	CH_3CN	64
4	$Bi(OTf)_3$	THF	65
5	$Cu(OTf)_2$	CH_2Cl_2	60
6	$Sc(OTf)_3$	CH_2Cl_2	-
7	$Fe(OTf)_2$	CH_2Cl_2	40
8	$In(OTf)_3$	CH_2Cl_2	68
9	$Hg(OTf)_2$	CH_2Cl_2	70
10	$Hg(OTf)_2$	CH_3CN	50
11	$Yb(OTf)_3$	CH_2Cl_2	-
12	$FeCl_3$	CH_3CN	50
13	$FeCl_3$	CH_2Cl_2	-
14	AgOTf	CH_2Cl_2	70
15	AgOTf	THF	60
16	PTSA	CH_3NO_2	-
17	PTSA	THF	62
18	TfOH	CH_2Cl_2	-

[a]Reaction condition unless otherwise specified: **1a** (1.0 mmol), **2a** (1.0 mmol), and catalyst (20 mol %) in the indicated solvent (anhydrous) at rt. [b]Isolated yields of **3aa**. rt = room temperature, Tf = triflate (CF_3SO_2), THF = Tetrahydrofuran.

products **3ca-cd** in moderate yields of 52-62%. 2,2-Diphenyl substituted alkynol furnished corresponding products **3da** and **3db** in 62% and 70% yield. Alkynol having benzylic-OH group was well tolerated in the reaction with ethylpyruvate and lead to the product **3ea** (*dr*, 1:1). *trans*-Cyclohexane fused alkynol possessing two alkyne functionalities gave **3fa** and **3fa**[1] (*dr*, 7:3). The reaction of indane-derived alkynol with ethylpyruvate gave the corresponding products **3ga** and **3ga**[1] (*dr*, 8:2), whereas with ethyl phenylglyoxylate provide **3gb** (*dr*, 1:1). Tetralin-fused alkynol (having two alkyne functionalities) with ethylpyruvate provided **3ha** and **3ha**[1] (*dr*, 7:3) in good yield, where as with ethyl phenylglyoxylate gave **3hb** (*dr*, 8:2). α,β-Unsaturated ketoester also proceeded smoothly and delivered the product **3bf** in good yield of 63%. The relative stereochemistry of diastereomers was assigned based on NOE analysis. Structures of **3ad** and **3bc** were rigorously confirmed by single crystal X-ray analysis, all other products were confirmed by analogy (Scheme 2).[20]

Taking our protocol a step further, we examined the reactivity of alkynols possessing internal alkyne functionality under standard reaction conditions. Cyclohexyl and cyclopentyl fused 4-pentyn-1-ols (with alkyl aryl substituents on alkyne termini) successfully reacted with various alkyl and



Scheme 2. Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (possessing terminal alkyne) . [a]48 h (reaction time); [b]inseparable diastereomers.

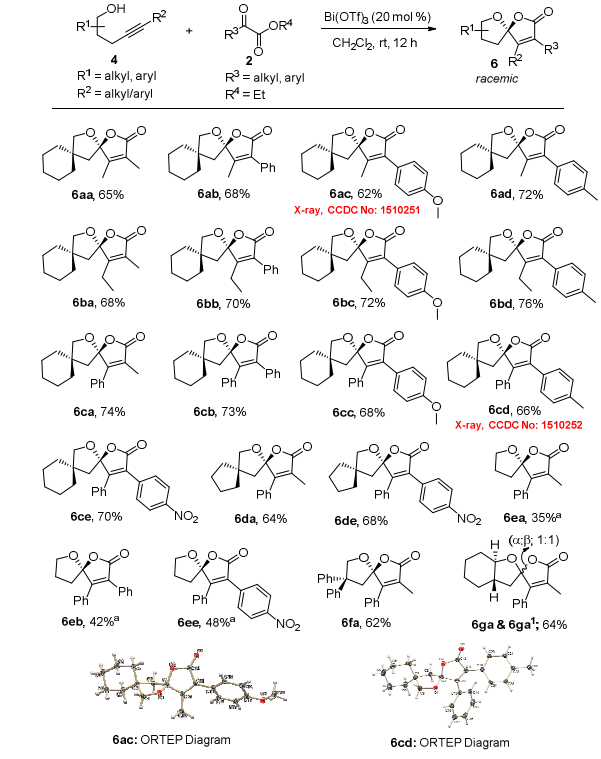
View Article Online
DOI: 10.1039/C7CC03668J

aryl-α-ketoesters, and furnished highly substituted and sterically demanding γ-spiroketal-γ-lactones (**6aa-6de**) in good yields. Phenyl substituted 4-pentyn-1-ol gave products **6ea-6ee** in moderate yields. Triphenyl substituted alkynol led to the product **6fa** in 62% yield. *trans*-Cyclohexane fused alkynol furnished **6ga** and **6ga**[1] (*dr*, 1:1). Products **6ac** and **6cd** were confirmed by single crystal X-ray diffraction analysis (Scheme 3).[20]

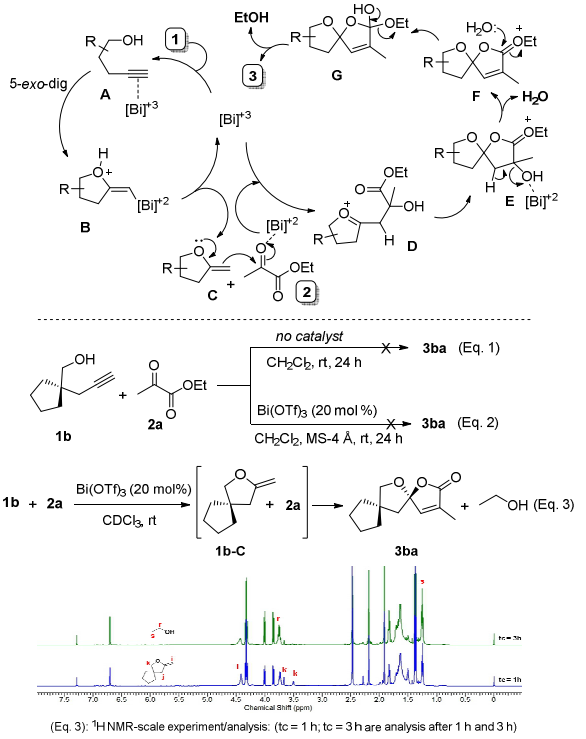
The reactivity of internal alkynols is little slower than those of the corresponding terminal alkynols. Best yields were observed for α or β-disubstituted alkynols as substrates compared to unsubstituted 4-pentyn-1-ols (**3ca**-**3cd** & **6ea-6ee**; Scheme 2 & Scheme 3) can be attributed by Thorpe-Ingold effect (angle compression).[22] All the 42 examples reported in this work were noteworthy, since the presence of α,β-unsaturated lactone functionality provides the platform for later product modification through reduction and oxidation (*vide infra*).

While the precise reaction mechanism requires further studies, a plausible mechanism based on recent reports [18-21] and the results obtained in this work is proposed (Scheme 4). Bismuth triflate mediated hydroalkoxylation (5-*exo*-dig; π-activation) of alkynol **1** to give **B** via **A,** followed by proto-debismuthination gives the corresponding enol-ether **C**, which then reacts with the activated (σ-activation) ketone group of α-ketoester **2** to give the oxocarbenium ion intermediate **D**. Intramolecular attack of ester oxygen on to the oxocarbenium ion **D** to give **E** followed by $Bi(OTf)_3$ facilitated release of water from **E** generates the intermediate **F**. Subsequent addition of *in situ* generated water on to **F** gives the intermediate **G**. Next, the release of EtOH from **G** leads to the formation of unsaturated γ-spiroketal-γ-lactone **3**.

To understand this proposed mechanistic pathway, few supporting experiments were performed (Scheme 4). Reaction of **1b** with **2a** in the absence of the catalyst failed to give the desired product (Eq. 1). The role of the *in situ* released water in lactone formation step (**E→F→G**) was confirmed by carrying out the reaction in the presence of activated MS-4 Å (Eq. 2). Formation of exocyclic-enol ether intermediate (**1b-C**) from **1b** and release of EtOH in the cascade annulation (**G→3**) were established by real-time ^{1}H NMR analysis (Eq. 3) (Scheme 4),[20] and these observations are consistent with earlier reports by Marks et al.[23]

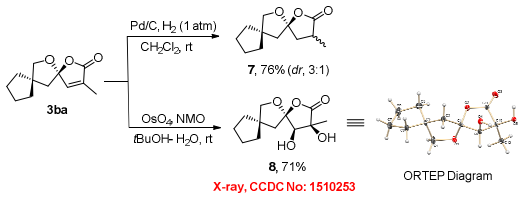


Scheme 3. Synthesis of unsaturated γ-spiroketal-γ-lactones from alkynols (possessing internal alkyne functionality). [a]48 h (reaction time).



Scheme 4. Postulated reaction mechanism and supporting experiments

The synthetic utility of this method was further explored by a couple of key transformations. Reduction of unsaturated γ-spiroketal-γ-lactone **3ba** using Pd/C, H_2 (1 atm, balloon) gave the saturated product **7** in 76% yield (*dr*, 3:1). Dihydroxylation of **3ba** with OsO_4-NMO gave the corresponding diol **8** as a single diastereomer, which structure was unambiguously confirmed by single crystal X-ray analysis (Scheme 5).[20]



Scheme 5. Synthetic utility

View Article Online
DOI: 10.1039/C7CC03668J

In summary, a simple access for the synthesis of diverse unsaturated γ-spiroketal-γ-lactones has been developed by employing $Bi(OTf)_3$ catalyzed cascade annulation of alkynols with α-ketoesters via dual (π and σ) activation process. Highly sterically demanding products, ambient reaction conditions, cost-effective catalytic system, good yields, operational simplicity, atom and step-economies are salient features of this strategy. Application of this method in total synthesis of related biologically active natural products is currently underway in our laboratory and will be reported in due course.

We thank Prof. Pierre Deslongchamps (University Sherbrooke/University Laval, Québec, Canada), Dr. J. S. Yadav (CSIR Bhatnagar Fellow, Former Director, CSIR-IICT, Hyderabad, India) for their constant encouragement. Financial support from SERB (Science & Engineering Research Board), New Delhi, India (Grant No. YSS/2015/000725) is gratefully acknowledged. D. A. K, S. S. T and M. S. P thank CSIR-India for the award of Junior Research Fellowships (JRF).

Notes and references

1 For reviews on spiroketals, see: (a) J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev*, 2005, **105**, 4406–4440; (b) K. T. Mead, B. N. Brewer, *Curr. Org. Chem*, 2003, **7**, 227–256; (c) M. F. Jacobs, W. B. Kitching, *Curr. Org. Chem*, 1998, **2**, 395–436; (d) F. Perron, K. F. Albizati, *Chem. Rev*, 1989, **89**, 1617–1661.

2 (a) K.-S. Yeung, I. Paterson, *Chem. Rev*, 2005, **105**, 4237–4313; (b) Y. Li, F. Zhou, C. J. Forsyth, *Angew. Chem., Int. Ed*, 2007, **46**, 279–282; (c) B. M. Trost, B. M. O'Boyle, D. Hund, *J. Am. Chem. Soc*, 2009, **131**, 15061–15074; (d) B. M. Trost, B. M. O'Blyle, *J. Am. Chem. Soc*, 2008, **130**, 16190–16192; (e) X. Li, A. R. Chianese, T. Vogel, R. H. Crabtree, *Org. Lett*, 2005, **7**, 5437–5440.

3 (a) O. Barun, K. Kumar, S. Sommer, A. Langerak, T. U. Mayer, O. Muller, H. Waldman, *Eur. J. Org. Chem*, 2005, 4773–4778; (b) S. Mitsuhashi, H. Shima, T. Kawamura, K. Kikuchi, M. Oikawa, A. Ichihara, H. Oikawa, *Bioorg. Med. Chem. Lett*. 1999, **9**, 2007–2012; (c) A. A. Birkbeck, S. V. Ley, J. C. Prodger, *Bioorg. Med. Chem. Lett*, 1995, **5**, 2637–2642.

4 L.-G. Lin, K. M. Li, C.-P. Tang, C.-Q. Ke, J. A. Rudd, G. Lin, Y. Ye, *J. Nat. Prod*, 2008, **71**, 1107–1110.

5 H. Oh, J. B. Gloer, C. A. Shearer, *J. Nat. Prod*, 1999, **62**, 497–501.

6 M. Kubo, Y. Nishikawa, K. Harada, M. Oda, J.-M. Huang, H. Domon, Y. Terao, Y. Fukuyama, *J. Nat. Prod*, 2015, **78**, 1466−1469.

7 (a) K. M. Engstrom, M. R. Mendoza, M. Navarro-Villalobos, D. Y. Gin, *Angew. Chem. Int. Ed*, 2001, **40**, 1128–1130; (b) M. Nukina, H. Hirota, *Biosci. Biotechnol. Biochem*, 1992, **56**, 1158–1159.

8 P. Tuchinda, B. Munyoo, M. Pohmakotr, P. Thinapong, S. Sophasan, T. Santisuk, V. Reutrakul, *J. Nat. Prod*, 2006, **69**, 1728-1733.

9 J. G. Urones, P. Basabe, I. S. Marcos, D. D. Martin, M. J. Sexmero, M. H. Peral, *Tetrahedron,* 1992, **48**, 10389-10398.

10 (a) Y. Hitotsuyanagi, H. Fukaya, E. Takeda, S. Matsuda, Y. Saishu, S. Zhu, K. Komatsu, K. Takeya, *Tetrahedron,* 2013, **69**, 6297-6304; (b) W. Steglich,; M. Klaar, L. Zechlin, H. Hecht, *J. Angew. Chem. Inl. Ed. Engl*. 1979, **18**, 698.

11 (a) D. Noutsias, I. Alexopoulou, T. Montagnon, G. Vassilikogiannakis, *Green Chem*. 2012, **14**, 601–604; (b) E. Pavlakos, T. Georgiou, M. Tofi, T. Montagnon, G. Vassilikogiannakis, *Org. Lett*, 2009, **11**, 4556-4559; (c) T. Montagnon, M. Tofi, G. Vassilikogiannakis, *Acc. Chem. Res*, 2008, **41**, 1001-1011; (d) M. Tofi, T. Montagnon, T. Georgiou, G. Vassilikogiannakis, *Org. Biomol. Chem*, 2007, **5**, 772–777; (e) H. Fukuda, M. Takeda, Y. Sato, O. Mitsunobu, *Synthesis*, 1979, 368–370.

12 (a) J. Robertson, S. Naud, *Org. Lett*, 2008, **10**, 5445-5448; (b) C. Crawford, A. Nelson, I. Patel, *Org. Lett*, 2006, **8**, 4231–4234; (c) P. J. McDermott, R. A. Stockman, *Org. Lett*, 2005, **7**, 27–29; (d) J. Robertson, P. Meo, J. W. P. Dallimore, B. M. Doyle, C. Hoarau, *Org. Lett*, 2004, **6**, 3861–3863; (e) S. Bartlett, R. Hodgson, J. M. Holland, M. Jones, C. Kilner, A. Nelson, S. Warriner, *Org. Biomol. Chem*, 2003, **1**, 2393–2402; (f) P. J. Kocienski,; R. C. D. Brown, A. Pommier, M. Procter, B. Schmidt, *J. Chem. Soc, Perkin Trans. 1*, 1998, 9–39; g) P. J. Kocienski, Y. Fall, R. Whitby, *J. Chem. Soc., Perkin Trans. 1*, 1989, 841–844; h) P. DeShong, R. E. Waltermire, H. L. Ammon, *J. Am. Chem. Soc*, 1988, **110**, 1901–1910; (i) B. L. Feringa, R. J. Butselar, *Tetrahedron Lett*, 1982, **23**, 1941–1942.

13 Y. Q. Tu, K. A. Byriel, C. H. L. Kennard, W. Kitching, *J. Chem. Soc. Perkin Trans. 1*, 1995, 1309-1315, and reference cited therein.

14 (a) X. –Y. Tang, M. Shi, *Tetrahedron*, 2009, **65**, 9336–9343; (b) Y.-H. Yang, M. Shi, *Org. Lett*, 2006, **8**, 1709–1712; (c) Y.-H. Yang, M. Shi, *Eur. J. Org. Chem*, 2006, 5394–5403.

15 (a) B. Ramakrishna, P. R. Sridhar, *RSC Adv*. 2015, **5**, 8142–8145; (b) A. B. Bueno, L. S. Hegedus, *J. Org. Chem*. 1998, **63**, 684-690; (c) J. M. Mellor, S. Mohammed, *Tetrahedron*, 1993, **49**, 1541-1556; (d) B. L. Feringa, W. Dannenberg, *Synth. Commun*, 1983, **13**, 509-514.

16 (a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed*, 2006, **45**, 7134–7186; (b) R. Robinson, *J. Chem. Soc. Trans*. 1917, 762–768.

17 General reviews: (a) K. Ouyang, W. Hao, W.-X. Zhang, Z. Xi, *Chem. Rev*, 2015, **115**, 12045-12090; (b) D. Bouyssi, N. Monteiro, G. Balme, *Beilstein J. Org. Chem*, 2011, **7**, 1387-1406; (c) N. T. Patil, R. D. Kavthe, Y. Yamamoto, *Adv. Heterocycl. Chem*, 2010, **101**, 75-95; (d) J. Barluenga, F. Rodríguez, F. J. Fañanás, *Chem. –Asian J*. 2009, **4**, 1036-1048; (e) K. Kruger, A. Tillack, M. Beller, *Adv. Synth. Catal*, 2008, **350**, 2153-2167; (f) G. Battistuzzi, S. Cacchi, G. Fabrizi, *Eur. J. Org. Chem*. 2002, 2671-2681.

18 (a) J. Barluenga, A. Mendoza, F. Rodríguez, F. J. Fañanás, *Angew. Chem. Int. Ed*, 2009, **48**, 1644; and references cited therein; (b) Qi-Lin. Zhou, *Angew. Chem. Int. Ed*, 2016, **55**, 5352-5353; (c) Y. Yamamoto, *J. Org. Chem*, 2007, **72**, 7817-7831; (d) A. Aponick, C.-Y. Li, J. A. Palmes, *Org. Lett*. 2009, **11**, 121-124; (e) J. Li, L. L. Lin, B. W. Hu, X. J. Lian, G. Wang, X. H. Liu, X. M. Feng, *Angew. Chem. Int. Ed*, 2016, **55**, 6075-6078.

19 (a) K. Ravindar, M. S. Reddy, P. Deslongchamps, *Org. Lett*. 2011, **13**, 3178–3181; (b) K. Ravindar, M. S. Reddy, L. Lindqvist, J. Pelletier, P. Deslongchamps, *J. Org. Chem*, 2011, **76**, 1269–1284; (c) K. Ravindar, M. S. Reddy, L. Lindqvist, J. Pelletier, P. Deslongchamps, *Org. Lett*, 2010, **12**, 4420–4423.

20 See the Electronic Supplementary Information (ESI) for details.

21 (a) T. Ollevier, *Org. Biomol. Chem*, 2013, **11**, 2740-2755; (b) J. M. Bothwell, S. W.Krabbe, R. S. Mohan, *Chem. Soc. Rev*, **2011**, *40*, 4649–4707; and references cited therein.

22 (a) S. M. Bachrach, *J. Org. Chem*, **2008**, *73*, 2466-2468; (b) R. M. Bessley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc., Trans*, 1915, **107**, 1081-1092.

23 S. –Y. Seo, X. Yu, T. J. Marks. *J. Am. Chem. Soc*. **2009**, *131*, 263-276 and references cited therein.