RSC Advances

This article can be cited before page numbers have been issued, to do this please use: A. S. Edwards, T. Bennin, M. Rubina and M. Rubin, *RSC Adv.*, 2015, DOI: 10.1039/C5RA14077C.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C5RA14077C

RCS Advances

COMMUNICATION

Synthesis of 1,5-Dioxocanes via the Two-Fold C-O Bond Forming Nucleophilic 4+4-Cyclodimerization of Cycloprop-2-en-1-ylmethanols

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

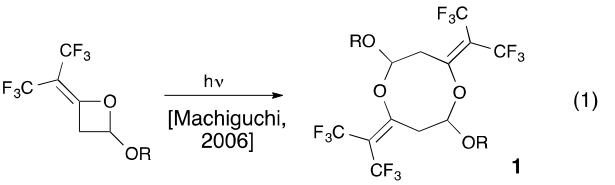
DOI: 10.1039/x0xx00000x

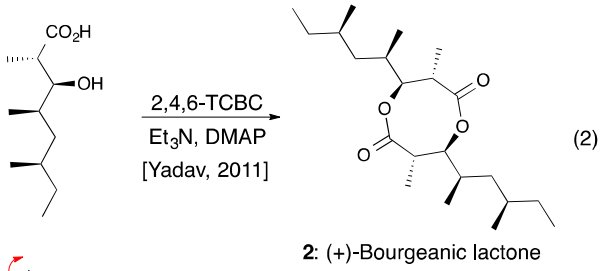
www.rsc.org/

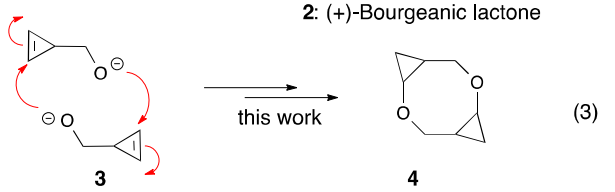
Andrew Edwards,[a] Trevor Bennin,[a,b] Marina Rubina,[a] and Michael Rubin*[a,c]

Abstract. An efficient [4+4] cyclodimerization of cyclopropenemethanols operating via a two-fold strain release-driven addition of alkoxides across the double bond of cyclopropenes was investigated. This chemo- and diastereoselective transformation provided previously unknown 2,7-dioxatricyclo[7.1.0.0^{4,6}]decane scaffolds.

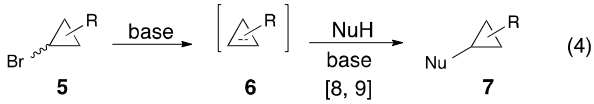
Transition metal-catalyzed[1] or photo-assisted[2] 4+4-cyclodimerizations with the simultaneous formation of two new C-C bonds are routinely used for assembly of eight-membered alicyclic compounds. However, analogous C-O bond-forming dimerization strategies for the preparation of eight-membered oxygen-based heterocycles remain much less explored. Nucleophilic closure of medium size rings is generally much more challenging than their five- and six-membered analogs due to a notable increase in ring strain (unfavorable enthalpic factor) and the accompanying significant loss of conformational freedom (unfavorable entropic factor). One of the few successful reported examples is the cyclodimerization of 2-alkoxyoxetanes, proceeding via acid-catalyzed or photo-induced reacetalization of ketals,[3] ortho-esters,[4] or enol ethers[5] (Scheme 1, eq. 1). Also, the assembly of eight-membered cyclic diesters via a double-fold Yamaguchi esterification of 3-hydroxypropanoic acids was employed during the total synthesis of (+)-bourgeanic lactone (eq. 2).[6] Somewhat less successful esterification under Steglich conditions providing cyclic trimers as major products was also reported.[7] While the above examples involved carbonyl derivatives, synthesis of the 1,5-dioxocane core via a 4+4-cyclodimerization accompanied by the installation of two *ethereal* C-O bonds has not been reported to date. Herein we demonstrate an efficient and selective formation of the 1,5-dioxocane core via a strain release-driven double-fold addition of alkoxides across the double bond of cyclopropenes **3**, providing access to peculiar 2,7-dioxatricyclo-[7.1.0.0^{4,6}] decanes **4** (eq. 3).

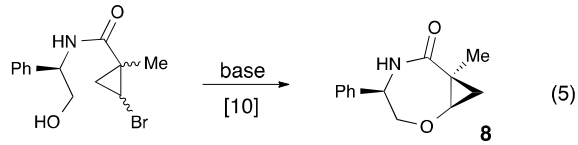






Scheme 1





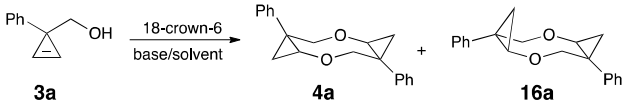
Scheme 2

In our previous work on the development of practical synthetic approaches to cyclopropyl ether[8] and cyclopropyl amine[9] derivatives **7** via the formal nucleophilic substitution of cyclopropylhalides **5** (Scheme 2, eq. 4),[8,9] we have shown that a variety of alkoxides, and amides can be added across the double bond of in situ generated cyclopropenes. It was also demonstrated that an intramolecular version of this reaction could efficiently

[a] Department of Chemistry, University of Kansas, 1251 Wescoe Hall Dr., Lawrence KS 66045-7582, USA.
[b] Department of Chemistry, Northland College, 1411 Ellis Avenue, Ashland, Wisconsin 54806-3999, USA.
[c] Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., Stavropol 355009, Russia.
Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C5RA14077C

Table 1. Optimization of 4+4-cyclization of alcohol **3a**

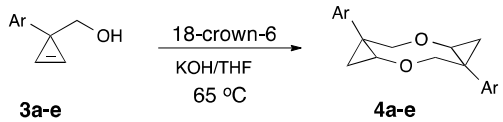


3a **4a** **16a**

#	Base (mass, mg)	Solvent (volume, mL)	Yield, %[a]	dr (**4a**:**16a**)[b]
1	**KOH (12)**	**THF (1)**	**74**	**99:1**
2	t-BuOK (24)	THF (1)	70	99:1
3	KOH (12)	THF (3)	0	-
4	t-BuOK (24)	THF (3)	0	-
5	KOH (12)	DMSO (1)	32	83:17
6	t-BuOK (24)	DMSO (1)	75	85:15
7	KOH (12)	DMSO (3)	57	81:19
8	t-BuOK (24)	DMSO (3)	78	82:18
9	t-BuOK (24)	DMSO (0.5)	57	84:16
10	KOH (12)	DMF (1)	36	89:11
11	t-BuOK (24)	DMF (1)	57	95:5
12	KOH (12)	DMA (1)	36	91:9
13	t-BuOK (24)	DMA (1)	68	90:10
14	KOH (12)	Et_2O (1)	60	99:1
15	t-BuOK (24)	Et_2O (1)	58	98:2
16	KOH (12)	PhMe (1)	28	99:1
17	t-BuOK (24)	PhMe (1)	43	98:2
18	KOH (12)	CH_2Cl_2 (1)	0	-
19	t-BuOK (24)	CH_2Cl_2 (1)	0	-
20	KOH (12)	CCl_4 (1)	0	-
21	t-BuOK (24)	CCl_4 (1)	0	-
22	KOH (12)	1,4-dioxane (1)	0	-
23	t-BuOK (24)	1,4-dioxane (1)	0	-

[a] NMR yieds. Test reactions were performed in 6.3 mg (43 μmol) mmol scale (based on **3a**) at 55 °C.[11]
[b] Determined by GC analyses of crude reaction mixtures

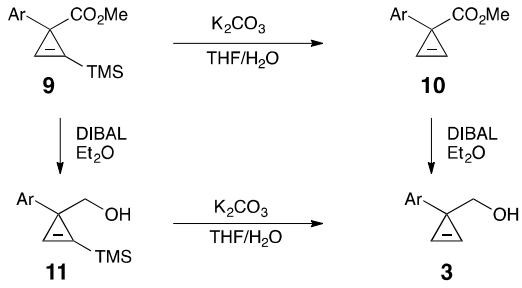
provide 2-oxabicyclo[5.1.0]octanes **8** (Scheme 2, eq. 5).[10] In our efforts toward expanding the scope of available strained substrates, we probed the reaction of (1-phenylcycloprop-2-en-1-yl)methanol (**3a**) under our standard reaction conditions with *t*-BuOK in THF in the presence of catalytic amount of 18-crown-6 ether (Table 1, entry 2).[8] Remarkably, homodimerization outcompeted addition of the external nucleophile (*t*-BuO^-) providing a single isomer of eight-membered cyclic ether **4a** in 70% NMR yield and *dr* of 99:1, as the only observable product. Optimization studies[11] proved powdered KOH to be a more efficient base than *t*-BuOK (Table 1, entry 1). It was also found that polar, aprotic, coordinating solvents were detr-



3a-e **4a-e**

3a, 4a: Ar = Ph; 66%, dr >99:1
3b, 4b: Ar = 4-FC_6H_4; 63%, dr >99:1
3c, 4c: Ar = 2,4-$F_2C_6H_4$; 59%, dr ~94:6
3d, 4d: Ar = 2-Cl-4-FC_6H_3; 75%, dr >99:1
3e, 4e: Ar = 2-Br-4-FC_6H_3; 63%, dr >99:1

Scheme 3



Scheme 4

imental to the diastereoselectivity (Table 1, entries 5-13). Reactions performed in diethyl ether and toluene were selective, but much less efficient (entries 14-17). No product was observed in dichloromethane (entries 18-19), carbon tetrachloride (entries 20-21), and 1,4-dioxane (entries 22-23).

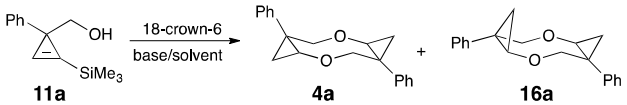
With the optimized procedure in hand we carried out preparative synthesis of **4a** and its 4-fluoro- (**3b**), 2,4-difluoro- (**3c**), 2-chloro-4-fluoro- (**3d**), and 2-bromo-4-fluoro- (**3e**) substituted analogs **4b**-**e**, all of which were obtained in good yields (Scheme 3).

The starting cyclopropene alcohols **3** are readily available by reduction of the corresponding 1-arylcycloprop-2-ene-1-carboxylates **10** (Scheme 4),[12] which are routinely obtained by Rh-catalyzed [2+1] cycloaddition of diazoarylacetates to trimethylsilylacetylene, followed by desilylation of the corresponding silylcyclopropenes **9**.[13] Alternatively, the reduction and the protodesilylation step can be swapped,[14] which usually provides better yields in DIBAL reduction (**9**→**11**), but at the expense of efficiency on desilylation step (**11**→**3**) (Scheme 4). We proposed that desilylation and subsequent nucleophilic addition (**3**→**4**) could be combined in a one-pot sequence to obtain 1,5-dioxocanes directly from TMS-protected precursor **11**. To test this idea, alcohol **11a** (Ar = Ph) was subjected to the reaction conditions for 4+4-cyclodimerization described above. Gratifyingly, the same dioxocane **4a** formed as sole isolable product in comparable yield (Table 2). Optimization of the reaction conditions revealed similar trends as the described above initial screening (Table 1); however, this one-pot transformation proceeded somewhat slower, requiring 5.5 equiv. of base (Table 2, entries 1-4) and slightly elevated temperature (entries 4-8) to achieve complete conversion.

With more easily accessed, silyl-protected alcohols **11**, we tested this reaction on fifteen other (1-aryl-2-silyl-cycloprop-2-en-1-yl)methanols possessing differently substituted aryl groups (Table 3). The first five examples shown in Table 3 (entries 1-5) allow for direct comparison of the one-pot desilylation/dimerization approach with the described above stepwise protocol (Scheme 3). In all cases the efficiency of the processes remained essentially the same. In the reactions of cyclopropenes **11c** and **11j** bearing two fluorine substituents competitive formation of two products was observed. These compounds were identified as diastereomers with *trans*- (1*R**,4*R**,6*S**,9*S**) (for major component) and *cis*-(1*R**,4*S**,6*R**, 9*S**) configurations, respectively. For all other examples the only isolable product was *trans*-2,7-dioxatricyclo-[7.1.0.$0^{4,6}$]decane **4**, which was unambiguously confirmed by single crystal X-Ray crystallography of *para*-tolyl-substituted dioxocane **4g** (Figure 1, CCDC #1408273). The high *trans*-selectivity observed in

View Article Online
DOI: 10.1039/C5RA14077C

Table 2. Optimization of 4+4-cyclization of alcohol **11a**



11a **4a** **16a**

#	Base (mass, mg)	Solvent (1 mL)	Temp, °C (time, h)	Yield, %[a]	dr (**4a**:**16a**)
1	KOH (4.5)	THF	65 (24)	72	98:2
2	KOH (9.5)	THF	65 (24)	68	98:2
3	**KOH (12)**	**THF**	**65 (24)**	**77**	**98:2**
4	KOH (24)	THF	65 (24)	73	98:2
5	KOH (12)	THF	75 (24)	49	97:3
6	KOH (12)	THF	55 (24)	56	98:2
7	KOH (12)	THF	45 (24)	21	98:2
8	KOH (12)	THF	35 (24)	0	-
9	t-BuOK (24)	THF	65 (24)	70	99:1
10	KOH (12)	DMSO	65 (24)	45	86:14
11	t-BuOK (24)	DMSO	65 (24)	67	87:13
12	KOH (12)	DMF	65 (24)	29[b]	94:6
13	t-BuOK (24)	DMF	65 (24)	29[b]	91:9
14	KOH (12)	DMF	65 (72)	34[b]	93:7
15	t-BuOK (24)	DMF	65 (72)	21[b]	92:8
16	KOH (12)	DMA	65 (72)	54	93:7
17	t-BuOK (24)	DMA	65 (72)	48	92:8
18	KOH (12)	Et_2O	65 (24)	59	99:1
19	t-BuOK (24)	Et_2O	65 (24)	61	99:1
20	KOH (12)	PhMe	65 (72)	71	98:2
21	t-BuOK (24)	PhMe	65 (72)	75	98:2

[a] NMR yields are listed. [b] Incomplete conversion: GC analysis showed presence of unreacted starting material **11a**. Test reactions were performed in 9.3 mg (43 µmol) mmol scale based on **11a**.[11]

the formation of these rigid tricyclic products can be rationalized as follows (Scheme 5). Initially, the intermolecular nucleophilic attack[8] of the primary alkoxide moiety in **12** at the double bond of the second cyclopropene molecule can potentially provide two intermediates: *trans*- (**14**) or *cis*-linear dimer (**15**), respectively. This strain release-driven step is highly exothermic and, therefore, essentially irreversible. Accordingly, the facial selectivity of this addition (in this case in the absence of efficient directing groups) should be exclusively governed by steric factors.[8] The considerably larger size of the aryl substituent as compared to hydroxymethyl group is, therefore, the main reason for *cis*-diastereomer **15** to be formed predominantly. The preference of the second nucleophilic attack at diastereotopic C-1 vs C-2 in the cyclopropene moiety of **15** leads to the highly selective formation of *trans*-cyclic dimer **4** with traces of *cis*-dimer **16** observed. Reasons affecting the stereodifferentiation in the intramolecular 8-*exo*-*trig* cyclization at this point are not completely understood. It is believed that the initial pre-coordination of the alkoxide moiety with potassium cation affords a more favorable transition state leading to C_2-symmetric product **4**. This hypothesis is supported by experiments carried out in coordinating aprotic solvents (DMSO, DMF, DMA), which provided notably lower diastereoselectivities (Tables 1,2). Computational investigations that could support or rule out this hypothesis are currently underway in our laboratories and will be reported in due course. It

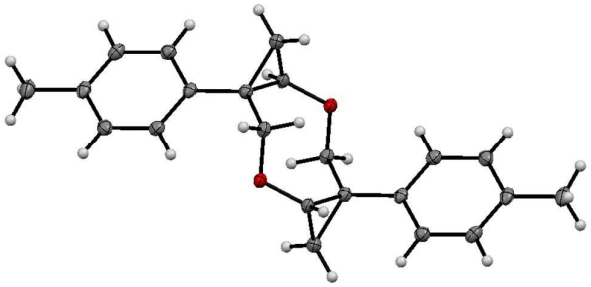
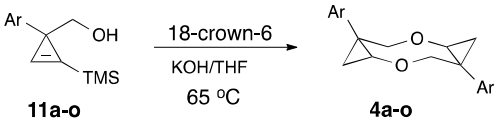


Figure 1. ORTEP drawing of 2,7-dioxatricyclo[7.1.0.0^{4,6}] decane **4g** showing 50% probability amplitude displacement ellipsoids.

should be mentioned that arguments pertaining to greater thermodynamic stability of cyclic dimer **4** vs **16**, can be ruled out since both steps (**15**→**4**) and (**15**→**16**) are irreversible (Scheme 5). Thus, our experiment showed that a sample of **4a** generated in DMSO and partially enriched with *cis*-cyclic dimer **16a** (**4a**:**16a** = 71:29), being re-subjected to the reaction conditions did not change its composition.

It is also important to mention that the fate of the minor linear intermediate, *trans*-**14** is completely different from that of *cis*-**15**, as it cannot undergo analogous cyclization. The cyclopropene and the alkoxymethyl moieties in *trans*-**14** are located away from each other on the opposite sides of the cyclopropyl ring and, as a result, an intermolecular nucleophilic attack takes place predominantly, leading to linear oligomers and polymers. This bimolecular process is much slower, and allows for accumulation of intermediate **14** at

Table 3. One-pot desilylation/4+4-cyclodimerization of (1-aryl-2-silylcycloprop-2-en-1-yl)methanols **11.**

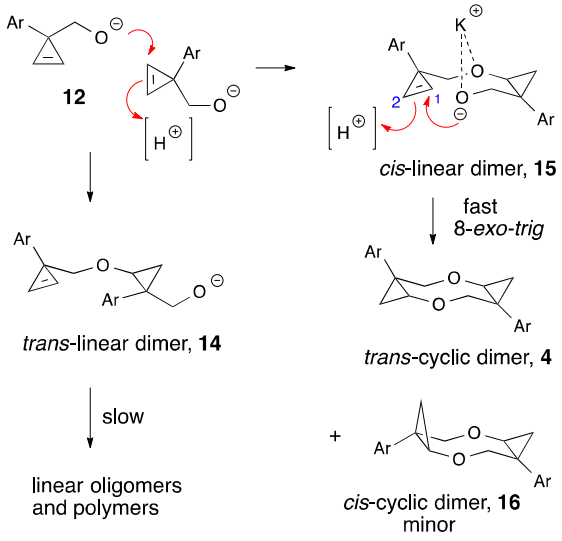


11a-o **4a-o**

#	**11**	Ar	**4**	Yield, % (dr)[a]
1	**11a**	Ph	**4a**	64 (98:2)
2	**11b**	4-FC_6H_4	**4b**	59 (>99:1)
3	**11c**	2,4-$F_2C_6H_3$	**4c**	62 (92:8)[b]
4	**11d**	2-Cl-4-FC_6H_3	**4d**	79 (>99:1)
5	**11e**	2-Br-4-FC_6H_3	**4e**	63 (>99:1)
6	**11f**	1-naphthyl	**4f**	55 (>99:1)
7	**11g**	4-MeC_6H_4	**4g**	78 (>99:1)
8	**11h**	2-Cl-6-FC_6H_3	**4h**	69 (>99:1)
9	**11i**	2-ClC_6H_4	**4i**	62 (>99:1)
11	**11j**	2,3-$F_2C_6H_3$	**4j**	57 (88:12)[b]
12	**11k**	3-BrC_6H_4	**4k**	83 (>99:1)
13	**11l**	4-BrC_6H_4	**4l**	67 (>99:1)
14	**11m**	2,4-$Cl_2C_6H_3$	**4m**	65 (99:1)
15	**11n**	3-$CF_3C_6H_4$	**4n**	70 (>99:1)
16	**11o**	2-Cl-4,5-$F_2C_6H_2$	**4o**	32 (98:2)

[a] Isolated yields of purified products are provided. Diastereomeric ratios were determined by GC analyses of crude reaction mixtures. Notation >99:1 indicates that minor diasereomer was below the detection limit. [b] Diastereomeric ratios were determined by ^{1}H NMR of crude reaction mixtures.

View Article Online
DOI: 10.1039/C5RA14077C



Scheme 5

initial stages of the reaction. By carrying out the reaction at slightly lower temperature, we were able to isolate **14a** (Ar = Ph) in low yield (9%) and confirm its structure by spectral methods. Being re-subjected to the typical reaction conditions, **14a** did not provide any cyclic products, but slowly polymerized instead. Polymerization of the alternate dimeric intermediate **14** under the reaction conditions significantly simplified isolation and purification of the tricyclic products **4**, as upon completion of the reaction the crude mixture contained only one chromatographically mobile component accompanied by small amounts of immobile polymers.

Conclusions

In conclusion, we have demonstrated an efficient 4+4-cyclodimerization of (cycloprop-2-en-1-yl)methanols allowing for a single step assembly of medium sized cyclic ethers via the simultaneous formation of two ethereal C-O bonds. The described base-assisted, strain release-driven transformation proceeds via a sterically-controlled, facially-selective, intermolecular nucleophilic addition of alkoxides across the double bond of cyclopropenes followed by a diastereoselective ring closure, furnishing an unusual 2,7-dioxatricyclo[7.1.0.0^{4,6}]decane core. To the best of our knowledge, this is the first example of a 4+4-cyclodimerization involving nucleophilic addition of oxygen-based nucleophiles to olefin moieties. Sterically controlled facial selectivity of the intermolecular attack in the first step of the reaction translates into the high chemoselectivity of the subsequent intramolecular cyclization. Such "natural selection", in which only the major intermediate, *cis*-linear dimer can participate in cyclization, while the minor *trans*-linear dimer polymerizes, results in the C_2-symmetric tricyclic compounds obtained exclusively in good yields and with excellent diastereoselectivities.

Financial support from International Collaboration Program, supported by the Ministry of Education and Science of the Russian Federation and the Ministry of Education of Perm Krai is gratefully acknowledged. We also are grateful for support by the Russian Fund for Basic Research (grant #15-03-02661) and NSF REU program grant #CHE-1263259 for student support (TB). Support for the NMR instrumentation was provided by NIH Shared Instrumentation Grant #S10RR024664 and NSF Major Research Instrumentation Grant #0320648.

Notes and references

1 For review, see: (a) J. Montgomery, *Sci. Synth.*, 2002, **1**, 11. See also: (b) R. Shintani, T. Tsuji, S. Park and T. Hayashi, *Chem. Commun.*, 2010, **46**, 1697; (c) P. H. Lee, K. Lee and Y. Kang, *J. Am. Chem. Soc.*, 2006, **128**, 1139; (d) P. H. Lee and K. Lee, *Angew. Chem., Int. Ed.*, 2005, **44**, 3253; (e) M. A. ElAmrani, I. Suisse, N. Knouzi and A. Mortreux, *Tetrahedron Lett.*, 1995, **36**, 5011; (f) A. Bendayan, H. Masotti; G. Peiffer, C. Siv and A. Archavlis, *J. Organomet. Chem.*, 1993, **444**, 41; (g) K. Masuda, K. Nakano, T. Fukahori, H. Nagashima and K. Itoh, *J. Organomet. Chem.*, 1992, **428**, C21; (h) K. U. Baldenius, H. Tom Dieck, W. A. Koenig, D. Icheln and T. Runge, *Angew. Chem., Int. Ed.*, 1992, **31**, 305.
2 (a) M. V. S. N. Maddipatla, M. Pattabiraman, A. Natarajan, K. Srivastav, J. T. Mague and V. Ramamurthy, *Org. Biomol. Chem.*, 2012, **10**, 9219; (b) A. Michaelides, S. Skoulika and M. G. Siskos, *Chem. Commun.*, 2011, **47**, 7140.
3 V. A. Petrov and W. Marshall, *Beilst. J. Org. Chem.*, 2010, **6**(46), doi:10.3762/bjoc.6.46.
4 N. J. Turro and J. R. Williams, *Tetrahedron Lett.*, 1969, **10**, 321.
5 T. Machiguchi, J. Okamoto, Y. Morita, T. Hagesawa, S. Yamabe and T. Minato, *J. Am. Chem. Soc.*, 2006, **128**, 44.
6 (a) J. S. Yadav, K. V. R. Rao, K. Ravindar and B. V. S. Reddy, *Eur. J. Org. Chem.*, 2011, 58; (b) J. S. Yadav, T. S. Rao, N. N. Yadav, K. V. R. Rao, B. V. S. Reddy and A. Al Khazim Al Ghamdi, *Synthesis*, 2012, **44**, 788.
7 H. J. Rogers, *J. Chem. Soc., Perkin Trans. 1*, 1995, 3073.
8 (a) P. Ryabchuk, A. Edwards, N. Gerasimchuk, M. Rubina and M. Rubin, *Org. Lett.*, 2013, **15**, 6010; (b) J. E. Banning, A. R. Prosser, B. K. Alnasleh, J. Smarker, M. Rubina and M. Rubin, *J. Org. Chem.*, 2011, **76**, 3968; (c) J. E. Banning, A. R. Prosser and M. Rubin, *Org. Lett.*, 2010, **12**, 1488.
9 (a) J. E. Banning, J. Gentillon, P. G. Ryabchuk, A. R. Prosser, A. Rogers, A. Edwards, A. Holtzen, I. A. Babkov, M. Rubina and M. Rubin, *J. Org. Chem.*, 2013, **78**, 7601; (b) P. Ryabchuk, M. Rubina, J. Xu and M. Rubin, *Org. Lett.*, 2012, **14**, 1752; (c) A. R. Prosser, J. E. Banning, M. Rubina and M. Rubin, *Org. Lett.*, 2010, **12**, 3968.
10 B. K. Alnasleh, W. M. Sherrill, M. Rubina, J. Banning and M. Rubin, *J. Am. Chem. Soc.*, 2009, **131**, 6906.
11 See Supporting Information for details.
12 M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2004, **126**, 3688.
13 A. Edwards and M. Rubin, *Tetrahedron*, 2015, **71**, 3237.
14 X. Liu and J. M. Fox, *J. Am. Chem. Soc.*, 2006, **128**, 5600.