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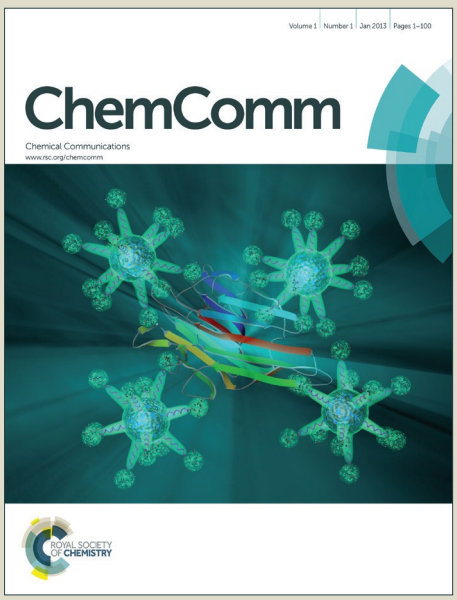

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View Article Online
DOI: 10.1039/C6CC02178F

Chemical Communications

COMMUNICATION

Templated Assembly of Medium Cyclic Ethers via *exo-trig* Nucleophilic Cyclization of Cyclopropenes

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

DOI: 10.1039/x0xx00000x

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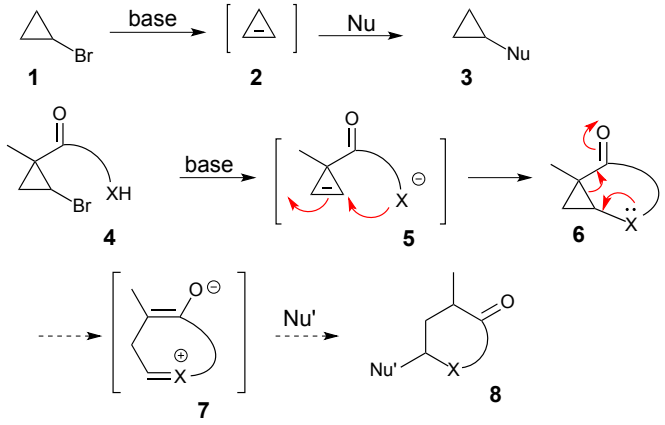
A novel method for the assembly of medium heterocycles via an intramolecular nucleophilic addition to cyclopropenes generated *in situ* from the corresponding bromocyclopropanes is described. The exo-trig nucleophilic cyclizations were shown to proceed very efficiently and in a highly diastereoselective fashion affording cis-fused bicyclic products possessing 7 to 10-membered medium rings; starting from a diastereomeric mixtures of bromocyclopropanes.

The abundance of medium heterocycles in nature[1] and their privileged position in drug discovery research[2] generate an increasing demand for efficient synthetic approaches to medium rings. Medium ring closure is typically achieved via transition metal-catalyzed[3] and free radical cyclizations,[4] whereas a direct cyclization via an intramolecular addition of a *nucleophilic entity* has not evolved into a practical synthetic tool. Several examples on ring closure via lactonization[5] towards 7-12 membered rings, involving a nucleophilic attack on an activated carbonyl group have been demonstrated. At the same time, analogous processes employing a less reactive C=C bond are scarce.[6] Although classical Baldwin's rules for ring closure[7] do not encompass rings larger than seven, it is commonly accepted that formation of these are disfavored. Indeed, the free energy of such cyclizations is typically positive due to a notable increase in the ring strain (enthalpic term) and loss of conformational freedom (entropic term). We envisioned that both these issues could be efficiently addressed by employing the formal nucleophilic substitution of bromocyclopropanes **1** (Scheme 1), which was recently developed in our labs.[8] This methodology allows for carrying out diastereoselective additions of oxygen,[9] nitrogen,[10] and sulfur-based[9b] nucleophiles to cyclopropene intermediates **2** generated in situ via a base-assisted 1,2-dehydro-bromination reaction.[11] We envisioned the intramolecular mode of this reaction as a convenient route for the construction of novel types of medium heterocycles and a useful tool for expanding the



Scheme 1

limits of the challenging nucleophilic *exo-trig* medium ring closures. The stringent enthalpic and enthropic requirements would be met in this cyclization as the rigid cyclopropyl moiety in the molecule backbone would endow the system with sufficient constraints, whereas the strain energy release would allow for effective ring closure via the nucleophilic attack of a tethered heteroatom moiety.[12] Thus, generation of cyclopropene species **5** from bromo-cyclopropane **4** bearing a pronucleophilic moiety tethered through the quaternary carbon would invoke an *exo-trig* cyclization, leading to bicyclic scaffold **6** (Scheme 1). Furthermore, the donor-acceptor cyclopropane with a heteroatom-based donor component in the resulting fused system **6** has a potential for further derivatization via ring-opening[13] to furnish expanded ring systems **8** (Scheme 1).

We began by probing the assembly of seven-membered rings, to which end we performed a test reaction of 2-ethanolamine-derived substrates **4a**,**b**. To our delight, both corresponding oxaz-epanones **6a**,**b** were formed as sole products in high yield (Scheme 2, eq 1). Similarly, 8-*exo-trig*, 9-*exo-trig*, and even 10-*exo-trig* ring closures occurred uneventfully providing the corresponding bicyclic oxazacanone (**6c**-**f**, Scheme 2, eq 2), oxazananone (**6g**,**h**, Scheme 3, eq 6), oxazecanone (**6i**-**j**, eq 3), and dioxazecanone (**6k**, eq 4). The unique feature of this sequential transformation, in which the

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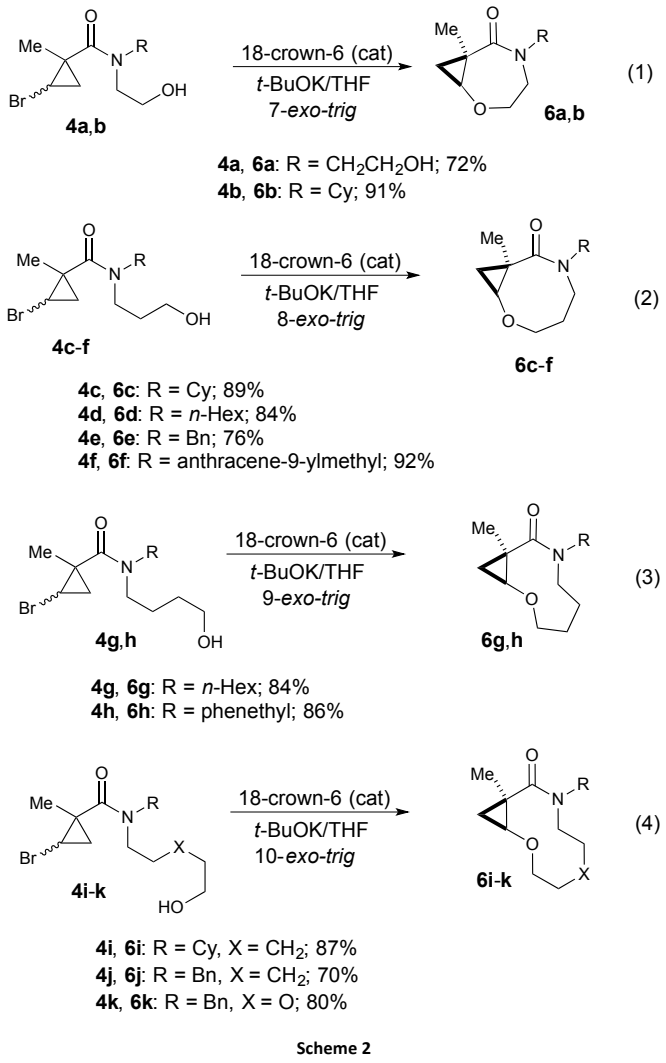
† Electronic Supplementary Information (ESI) available: Experimental procedures, physico-chemical and spectral data. See DOI: 10.1039/x0xx00000x



Scheme 2

reactive intermediate is generated in very low quantities, permitted carrying out the reaction at unusually high for medium ring closure concentrations of 0.05-0.20 M, with consistently high yields.[14] Starting from diastereomeric mixtures of bromocyclopropanes **4**, all cyclizations proceeded with very high *cis*-diastereoselectivity, including 9- and 10-membered ring closures of substrates bearing very flexible tethers with no additional selectivity-inducing elements. However, despite the efficient assembly of 7-10 membered cycles, to date, we failed to obtain 11 and 12-membered rings via this approach.

We have previously demonstrated in our intermolecular nucleophilic additions to cyclopropenes[9c] that potassium cation can efficiently coordinate to the carboxamide functionality and direct the addition of a nucleophilic species in *syn*-fashion. This directing effect was considered in our preliminary DFT computations of 7-exo-trig cyclization of cyclopropene **9** (Figure 1). The intermolecular reaction (i.e., linear oligomerization and polymerization) was also assessed by obtaining the activation barrier of the nucleophilic addition of methoxide to cyclopropene **11** (Figure 2). To simplify the computations, the coordination sphere of potassium, which during the reaction is occupied by solvent molecules, was left vacant. Considering the unusually low coordination number of the alkali metal in these computations, the obtained figures should only

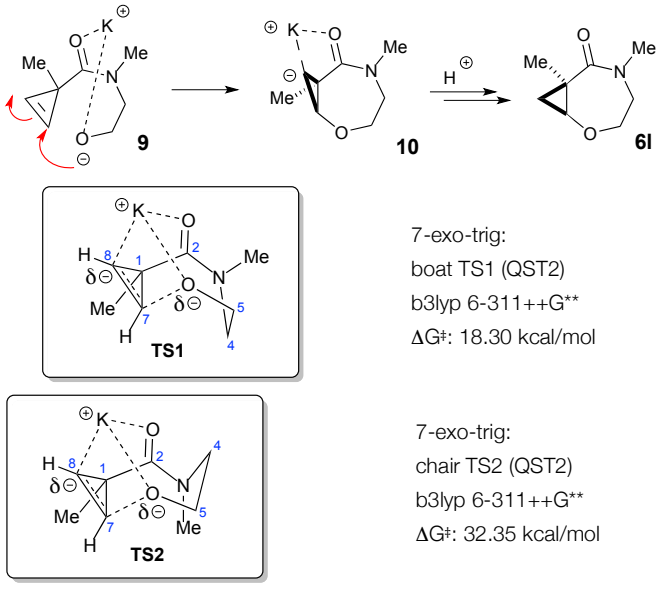


Figure 1. Geometry of two alternative transition states located for the intramolecular 7-exo-trig nucleophilic attack by tethered alkoxide **9** with pre-coordinated potassium cation. Activation barriers are assessed for THF.

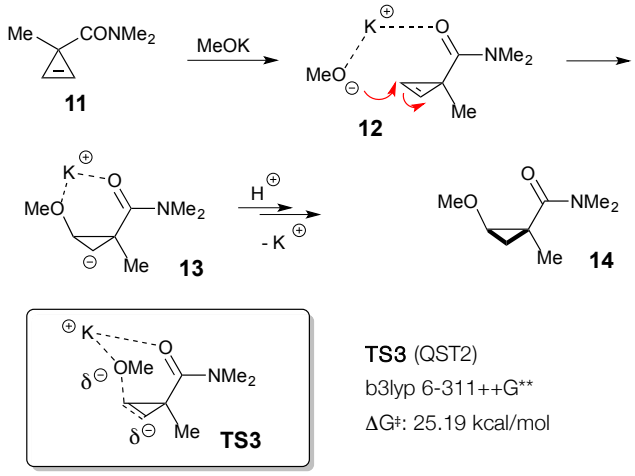


Figure 2. Geometry of transition state in the intermolecular nucleophilic attack of cyclopropene **11** by methoxide anion assisted by pre-coordinated potassium cation. Activation barrier is assessed in THF.

be used as an estimate for qualitative comparison of the two reaction pathways.

The nucleophilic addition of methoxide[8,9c] commences with the formation of coordination complex **12** and proceeds via transition state **TS3**, in which potassium cation is chelated to the alkoxide and carboxamide oxygens. The activation barrier for this process was found to be +25.19 kcal/mol (Figure 2), while the strain release-driven formation of zwitterionic intermediate **13** was moderately exothermic (ΔG_r = -17.58 kcal/mol). The final product, alkoxycyclopropane **14**, is obtained after protonolysis of **13** (Figure 2). Alternatively, the reaction of tethered nucleophilic alkoxide **9** produces a seven-membered zwitterionic intermediate **10**, which after protonolysis affords the corresponding oxazepanone **6l** (Figure

1). Two alternative transition states, **TS1** and **TS2** with coordinated potassium cation were located, as shown in Figure 1. The calculations show the lowest energy transition state **TS1** with a pseudo-boat conformation of the bicyclic core (Figure 1). Coordination of two oxygens to potassium does not cause any significant distortions of the nucleophile's trajectory in this case. The nucleophile approaches the π-bond at a 115° angle, a slightly larger than normal Bürgi–Dunitz angle for a trigonal attack, which is expected for the small cycle with an increased *s*-character of the strained double bond. Moreover, the shortened distance between the potassium cation and the anionic center at C8 of cyclopropene is responsible for an additional stabilization of this activated complex. The activation energy of the 7-exo-trig process is calculated to be 18.30 kcal/mol, while the ΔG° of this cyclization was found to be -5.68 kcal/mol. The significantly lower activation energy of the cyclization compared to that of the modeled intermolecular process (**12→TS3→13**, Figure 2) could explain the favorable formation of the medium rings and lack of oligomerization products even in relatively concentrated solutions. It should also be mentioned that the high activation energy of the pseudo-chair transition state **TS2** (32.35 kcal/mol, Figure 1) rules out this alternative pathway.

In conclusion, we have developed a novel method for the assembly of medium cyclic ethers via a formal nucleophilic substitution of bromocyclopropanes. An efficient *exo-trig* ring closure produced 7-10 membered heterocycles with excellent *cis*-selectivity. Favorable pre-organization of the acyclic precursor augmented by the strain energy release makes this cyclization approach highly efficient whilst offering a unique possibility for additional stabilization of the medium ring conformation in a fused bicyclic motif. The reaction proceeds in the unusually high for medium ring closure concentration range, rendering this method practical and easily scalable. DFT modeling of the 7-exo-trig cyclization suggested the pseudo-boat **TS1** as the likely structure of the reaction transition state. The three-prong coordinated potassium plays a crucial role in stabilization of the newly forming bicyclic core, making this model potentially suitable for predicting the results of diastereoselective cyclizations. Further studies are currently underway in our laboratories, aiming at (1) extending this methodology to the synthesis of larger ring systems; (2) employyment of tethered chiral nucleophilic entities for diastereoselective ring closure; (3) probing *N*-, *C*-, and *S*-based nucleophiles for furnishing other types of medium heterocycles; (4) evaluating *endo-trig* mode of the ring closure.

We are grateful for the financial support by the Russian Foundation for Basic Research (grant #15-03-02661). Support for NMR instruments used in this project was provided by NIH Shared Instrumentation Grant #S10RR024664 and NSF Major Research Instrumentation Grant #0329648.

Notes and references

1 For reviews, see: (a) H. M. C. Ferraz, F. I. Bombonato, L. S. Longo, Jr., *Synthesis* 2007, 3261. (b) H. M. C. Ferraz, F. I. Bombonato, M. K. Sano, L. S. Longo, Jr., *Quim. Nova* 2008, **31**, 885. (c) M. A. Ciufolini, *Farmaco* 2005, **60**, 627.

2 (a) J. G. Kettle, H. Alwan, M. Bista, J. Breed, N. L. Davies, K. Eckersley, S. Fillery, K. M. Foote, L. Goodwin, D. R. Jones, H. Kack, A. Lau, J. W. M. Nissink, J. Read, J. S. Scott, B. Taylor, G. Walker, L. Wissler, M. Wylot, *J. Med. Chem*. 2016, **59**, 2346. (b) M. R. Lambu, S. Kumar, S. K. Yousuf, D. K. Sharma, A. Hussain, A. Kumar, F. Malik, D. Mukherjee, *J. Med. Chem*. 2013, **56**, 6122.

3 See, for selected examples: (a) I. D. G. Watson, S. Ritter, F. D. Toste, *J. Am. Chem.* Soc. 2009, **131**, 2056. (b) A. Klapars, S. Parris, K. W. Anderson, S. L. Buchwald, *J. Am. Chem. Soc.* 2004, **126**, 3529. (c) A. T. Radosevich, V. S. Chan, H.-W. Shih, F. D. Toste, *Angew. Chem., Int. Ed.* 2008, **47**, 3755. (d) J. E. M. N. Klein, H. Muller-Bunz, Y. Ortin, P. Evans, *Tetrahedron Lett*. 2008, **49**, 7187. (e) K. C. Majumdar, B. Chattopadhyay, *Synlett* 2008, 979.

4 For reviews, see: (a) A. J. McCarroll, J. C. Walton, *Angew. Chem., Int. Ed*. 2001, **40**, 2224. (b) L. Yet, *Tetrahedron* 1999, **55**, 9349. For recent examples, see: (c) D. J. Wardrop, E. G. Bowen, R. E. Forslund, A. D. Sussman, S. L. Weerasekera, *J. Am. Chem. Soc.* 2010, **132**, 1188.

5 See, for example: (a) S. Magens, B. Plietker, *J. Org. Chem.* 2010, **75**, 3715. (b) M.-T. Dinh, S. Bouzbouz, J.-L. Peglion, J. Cossy, *Tetrahedron* 2008, **64**, 5703. (c) H. Kuno, M. Shibagaki, K. Takahashi, I. Honda, H. Matsushita, *Chem. Lett*. 1992, 571. (d) J. S. Yadav, R. Somaiah, K. Ravindar, L. Chandraiah, *Tetrahedron Lett*. 2008, **49**, 2848. (e) Y. Ohba, M. Takatsuji, K. Nakahara, H. Fujioka, Y. Kita, *Chem. Eur. J.* 2009, **15**, 3526. (f) L. Kaisalo, T. Hase, T. *Synlett* 1992, 503.

6 For recent examples of 7-*exo-trig* ring closure, see: (a) D. C. Leitch, P. R. Payne, C. R. Dunbar, L. L. Schafer, *J. Am. Chem. Soc.* 2009, **131**, 18246. (b) J. Saha, M. W. Peczuh, *Org. Lett*. 2009, **11**, 4482. For 8-*exo-trig*, see: (c) D. Tripathi, S. K. Pandey, P. Kumar, *Tetrahedron* 2009, **65**, 2226. (d) M. C. Carreno, R. Des Mazery, A. Urbano, F. Colobert, G. Solladie, *Org. Lett*. 2005, **7**, 2039. For 9-*exo-trig*, see: (e) J. Iqbal, B. Bhatia, N. K. Nayyar, *Tetrahedron* 1991, **47**, 6457. For 10-*exo-trig*, see: (f) M. Bartra, J. Vilarrasa, *J. Org. Chem*. 1991, **56**, 5132.

7 (a) J. E. Baldwin, R. C. Thomas, L. I. Kruse, L. Silberman, *J. Org. Chem*. 1977, **42**, 3846. (b) J. E. Baldwin, *J. Chem. Soc., Chem. Commun*. 1976, 734.

8 B. K. Alnasleh, W. M. Sherrill, M. Rubina, J. Banning, M. Rubin, *J. Am. Chem. Soc.* 2009, **131**, 6906.

9 (a) J. E. Banning, A. R. Prosser, M. Rubin, Org. Lett. 2010, **12**, 1488. (b) A. R. Prosser, J. E. Banning, M. Rubina, M. Rubin, *Org. Lett.* 2010, **12**, 3968. (c) J. E. Banning, A. R. Prosser, B. K. Alnasleh, J. Smarker, M. Rubina, M. Rubin, *J. Org. Chem*. 2011, **76**, 3968. (d) P. Ryabchuk, A. Edwards, N. Gerasimchuk, M. Rubina, M. Rubin, *Org. Lett.* 2013, **15**, 6010.

10 (a) P. Ryabchuk, M. Rubina, J. Xu, M. Rubin, *Org. Lett*. 2012, **14**, 1752. (b) J. E. Banning, J. Gentillon, P. Ryabchuk, A. R. Prosser, A. Rogers, A. Edwards, A. Holtzen, I. A. Babkov, M. Rubina, M. Rubin, *J. Org. Chem.* 2013, **78**, 7601.

11 For other closely related processes, see: (a) M. Zhang, J. Guo, Y. Gong, *Eur. J. Org. Chem*. 2014, 1942. (b) M. Zhang, F. Luo, Y. Gong, *J. Org. Chem*. 2014, **79**, 1335. (c) Z. Huang, J. Hu, Y. Gong, *Org. Biomol. Chem*. 2015, **13**, 8561. (d) Y. Zhu, Y. Gong, *J. Org. Chem.* 2015, **80**, 490. (e) A. Levin, I. Marek, *Chem. Commun*. 2008, 4300. (f) Y. Zhu, M. Zhang, H. Yuan, Y. Gong, *Org. Biomol. Chem.* 2014, **12**, 8828. (g) J. Hu, Y. Liu, Y. Gong, *Adv. Synth. Catal.* 2015, **357**, 2781.

12 For assembly of 8-membered heterocycles via 4+4 cyclodimerization of cyclopropenyl-3-methanols, see: A. Edwards, T. Bennin, M. Rubina, M. Rubin, *RSC Adv.* 2015, **5**, 71849.

13 See, for example: V. Maslivetc, M. Rubina, M. Rubin, *Org. Biomol. Chem.* 2015, **13**, 8993.

14 See Supporting Information for details.