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Templated Assembly of Chiral Medium-Sized Cyclic Ethers via 8-endo-trig Nucleophilic Cyclization of Cyclopropenes

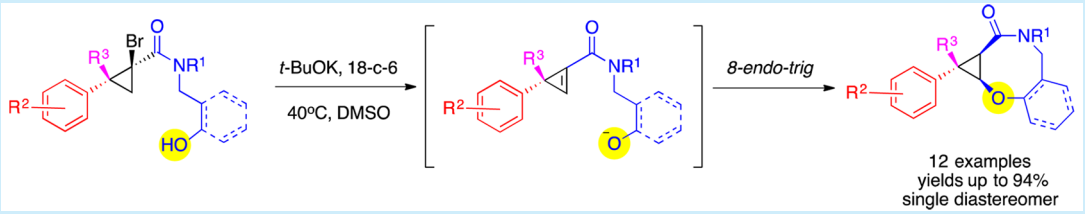
Pavel Ryabchuk,[†,‡] Jonathon P. Matheny,[†] Marina Rubina,[†] and Michael Rubin*[,†,§]

[†]Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States

[‡]Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein Straße 29a, Rostock 18059, Germany

[§]Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., Stavropol 355009, Russian Federation

Supporting Information

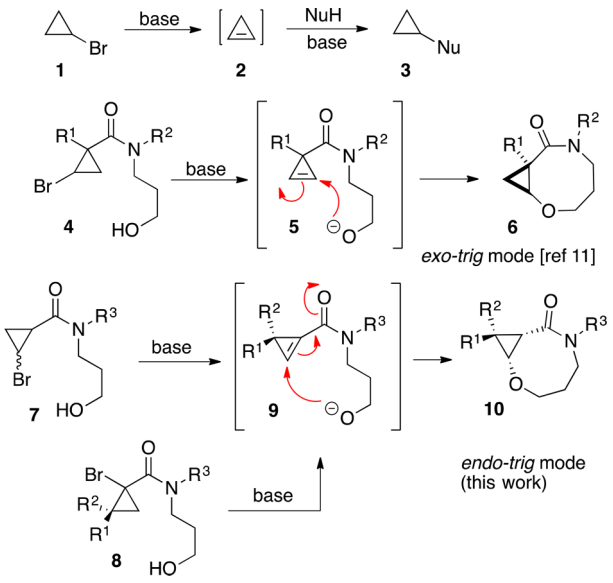


ABSTRACT: An efficient approach toward enantioenriched eight-membered heterocycles via the intramolecular formal substitution of bromocyclopropanes with oxygen-based nucleophiles has been developed. The reaction proceeds via a reactive cyclopropene intermediate, which undergoes a rapid 8-*endo-trig* cyclization affording *cis*-fused [6.1.0] bicyclic products exclusively. The quaternary chiral center in the cyclopropene governs the configuration of the other two stereocenters in the final product.

The occurrence of medium-sized heterocycles in nature[1] and their privileged position in drug discovery research[2] justify the unceasing interest in development of efficient synthetic routes for their assembly. Ring closures to form medium-sized rings can be achieved by employing various transition-metal-catalyzed[3] and free radical[4] methods, yet direct nucleophilic cyclizations remain underexplored. Synthetic approaches to 7−12-membered lactones involving intramolecular nucleophilic attack by an alkoxide on an activated carbonyl group are well documented.[5] However, analogous processes employing a less reactive alkene double bond are rare,[6] particularly, the thermodynamically challenging *n-endo-trig* closures[7] accompanied by a notable increase in ring strain and the stringent conformational requirement for the Bürgi−Dunitz angle. We envisioned that these challenges could be efficiently addressed by employing the strain release-driven nucleophilic addition of alkoxides and aryloxides to cyclopropenes developed in our laboratories.[8] This methodology takes advantage of a reactive cyclopropene intermediate **2** obtained *in situ* via a base-assisted 1,2-elimination of bromocyclopropanes **1**, which undergoes facile diastereoselective addition of oxygen,[9] nitrogen,[10] and sulfur-based[9c] nucleophiles. We have previously reported that racemic cyclic ethers **6** with a ring size of 7−10 can be readily accessed via the intramolecular *n-exo-trig* cyclization (Scheme 1).[11] Herein, we disclose a novel 8-*endo-trig* nucleophilic cyclization of cyclopropenes **9** allowing for expeditious assembly of chiral medium cyclic ethers **10** (Scheme 1).

As mentioned above, a base-assisted 1,2-elimination of HBr in bromocyclopropane **4** possessing a quaternary center next to the carboxamide function was shown to afford a 3,3-disubstituted cyclopropene **5** amenable to *exo-trig* cyclization (Scheme 1).[11] The nonconjugated cyclopropenes **5** are relatively stable and isolable, the downside of which is that

Scheme 1. Different Modes of Cyclizations Involving Nucleophilic Additions of Alkoxides to Cyclopropenes



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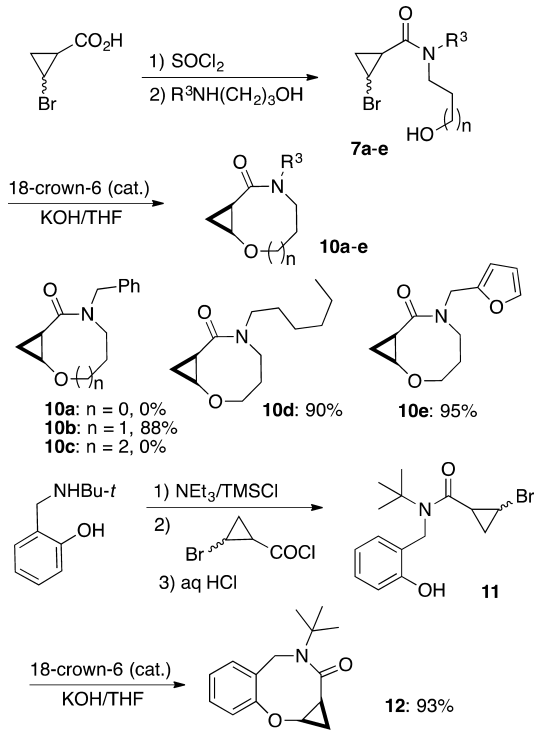
they undergo nucleophilic addition only with strong nucleophiles, such as primary alkoxides. This prompted us to explore complementary approaches to oxazabicyclo[6.1.0]-nonanes via a highly electrophilic cyclopropene **9** capable of reacting with a broader range of nucleophiles.[9,10] It was expected that, being strong Michael acceptors, conjugated cyclopropenes **9** would reinforce the addition via the mechanistically challenging *n-endo-trig* pathway. We envisioned the first approach to **10** via dehydrobromination of diastereomeric 2-bromocyclopropylcarboxamides **7**, in which deprotonation was expected to occur at the most acidic tertiary α-CH. To test this idea, we prepared several amides **7a**–**e** from 2-bromocyclopropylcarboxylic acid and aminoalcohols and subjected them to powdered KOH in the presence of 18-crown-6 ether. We were pleased to find that, in all three cases, eight-membered cyclic ethers **10b,d,e** were obtained in high yields as sole products (Scheme 2). However, substrates

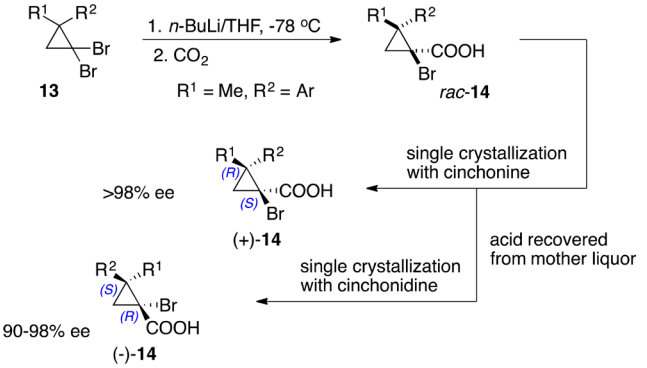
Scheme 2. Nucleophilic Ring Closures Involving Cyclopropenes Generated from 2-Bromocyclopropane Carboxylic Acid Derivatives



containing other than a three-carbon tether dramatically decreased the efficiency of cyclization. Neither seven- nor nine-membered products were detected in the corresponding reaction mixtures of **7a** and **7c**. We have also explored the possibility of an intramolecular addition of tethered aryloxides, as phenolates have been previously employed in the intermolecular nucleophilic addition to monosubstituted cyclopropenes.[9a] In accord with our expectations, treatment of bromocyclopropane **11** with a base afforded nearly quantitative yield of benzoxazocinone **12** (Scheme 2). Notably, all annulations described above were performed using crude mixtures of diastereomeric amides **7** at high concentration.

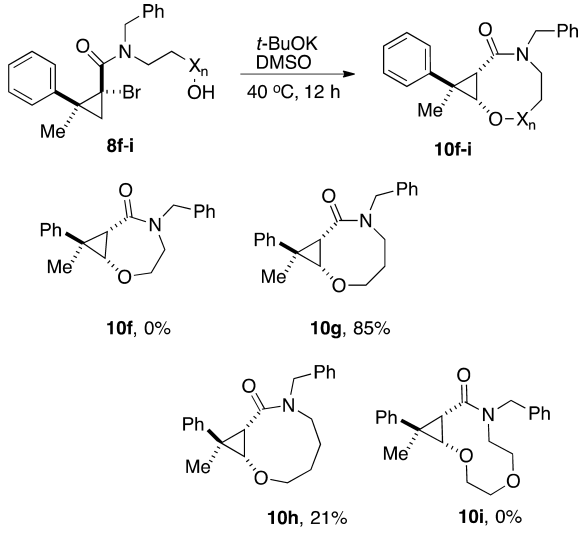
Inspired by these initial results, we moved on to probe a second approach employing more challenging, densely substituted cyclopropane precursors. In this mode, α-bromocyclopropylcarboxamides **8** possessing a quaternary center at C-2 would give rise to conjugated cyclopropenes **9**, bearing a stereogenic center at C-3 unless R^1 and R^2 are identical (Scheme 1). We anticipated that the facial selectivity of the intramolecular nucleophilic attack would be governed by steric factors, favoring the addition from the least hindered site. Furthermore, the ready availability of the parent α-halogenated cyclopropane carboxylic acids **14** in optically active form by an efficient chiral resolution method developed in our laboratories (Scheme 3)[12] starting from routinely accessible 2,2-dibromo-

Scheme 3. Synthesis and Efficient Chiral Resolution of α-Bromocyclopropylcarboxylic Acids



cyclopropanes **13**[13] makes this route very attractive for preparation of homochiral medium-sized heterocycles **10**. Accordingly, we tested a series of racemic α-bromocyclopropyl carboxamides **8f**–**i** with homologous side chains under the standard reaction conditions. Here again, bromide **8f** with a two-carbon linker (n = 0) failed to provide seven-membered cyclization product **10f** due to rapid polymerization (Scheme 4). In contrast, the bromocyclopropane possessing a three-carbon tether (**8g**, $X_n = CH_2$) underwent a very efficient 8-*endo-trig* cyclization cleanly producing the corresponding oxazacanone **10g** (Scheme 4). The 9-*endo-trig* cyclization of **8h** ($X_n = CH_2CH_2$) afforded a nine-membered cyclic product **10h** albeit

Scheme 4. Nucleophilic Ring Closures involving Cyclopropenes Generated from Racemic 1-Bromocyclopropane Carboxylic Acid Derivatives



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in low yield. Further elongation of the tether led to no success. Attempts to cyclize **8i** (X_n = OCH_2CH_2) resulted in polymerization of the starting material (Scheme 3). It should be mentioned that both cyclization products **10g** and **10h** were obtained as single diastereomers with *cis*-orientation of the alkoxy moiety with respect to carboxamide and methyl substituents, indicating very efficient control of the diastereoselectivity by the substituents on the quaternary center.

Having mapped out the scope of ring closures to form medium-sized rings, we proceeded to examine the 8-*endo-trig* cyclization employing a series of enantiomerically enriched substrates **8**.[12] It was found that a variety of substituents at the carboxamide nitrogen were tolerated rather well, including methyl, benzyl, *p*-methoxybenzyl, and furylmethyl groups (Figure 1). *N*-*p*-Methoxybenzyl- and *N*-methylsubstituted

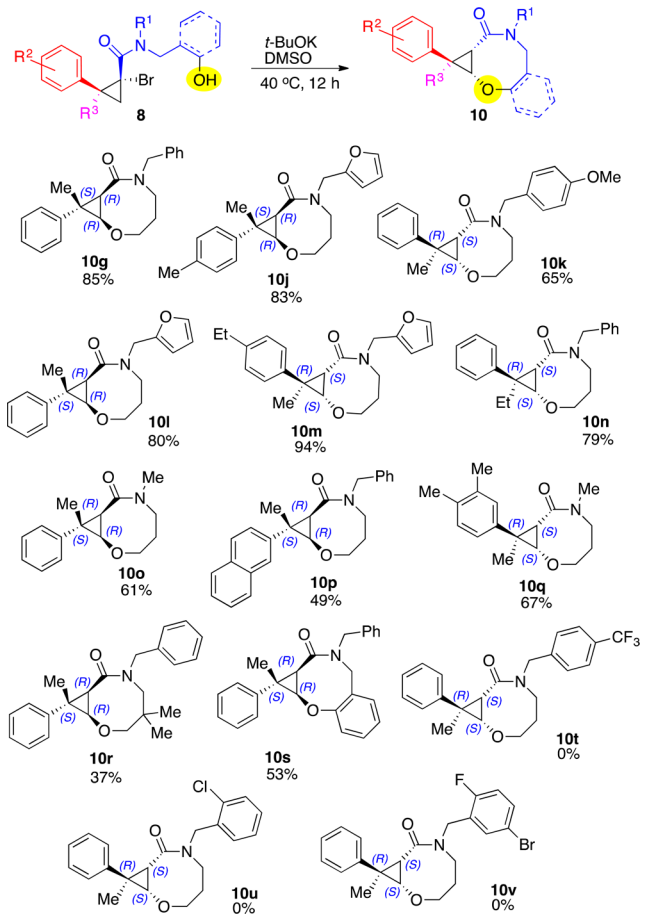

Figure 1. Intramolecular formal nucleophilic substitution of enantiomerically enriched 1-bromocyclopropane carboxylic acid derivatives.

analogs were somewhat less efficient giving lower yields of the corresponding cyclic products **10k**, **10o**, **10q**. The steric effect of substituents at the quaternary center of cyclopropane was tested as well (Figure 1), using the methyl or ethyl group as the "small" and an aryl group as the "large" substituent. In this series, a high degree of stereocontrol was achieved for all substrates. Even the most sterically challenging bromide **8n**, in which cyclization was forced to proceed *syn* to the ethyl group, provided a respectable yield of a single product **10n**.[14] Our next goal was to probe the addition of a tethered aryloxide under these conditions. Notably, our earlier efforts to add aryloxides to 3,3-disubstituted or 1,3,3-trisubstituted cyclopropenes in the intermolecular mode were unproductive. Although these nucleophiles were previously found to be inert in the *exo-trig* cyclization,[9c] we anticipated, however, that they would react more readily in the *endo-trig* fashion with a highly electrophilic, conjugate strained olefin. Indeed, the 8-*endo-trig* cyclization reaction of bromocyclopropane **8s** bearing a tethered phenol species proceeded uneventfully affording optically active benzazocane **10s**.

The results presented above indicate that the described 8-*endo-trig* ring closure has a specific, favorable trajectory of the nucleophilic attack, in contrast to the homologous seven- and nine-membered ring closures. In support of this hypothesis is also the observed more sluggish reaction of **8r** that can be rationalized on the basis of the notable distortion of the Bürgi–Dunitz angle imparted by the methyl substituents in the tether. Work is underway to support this rationale by computational methods.

Interestingly, reactions of amides generated from electron-deficient benzylamines **8t–v** did not afford cyclization products **10t–v**, providing complex mixtures of oligomers instead (Figure 1). Such a dramatic difference in reactivity of these electron-deficient substrates as compared to electron-neutral and electron-rich analogs, which readily provide the corresponding cyclization products (ca. **10g**, **10k**), is not completely understood. Further investigations of this phenomenon are currently underway in our laboratories.

In summary, we have developed a highly diastereoselective, intramolecular formal nucleophilic substitution of cyclopropanes proceeding via the 8-*endo-trig* addition of tethered oxygen-based nucleophiles to *in situ* generated cyclopropenes. This strategy, applied to readily available derivatives of nonracemic 1-bromocyclopropanecarboxylic acid, provided enantiomerically enriched oxazabicyclo[6.1.0]nonanes possessing a densely substituted cyclopropane moiety with three stereogenic centers. The disclosed protocol does not require purification of the precursors and afforded consistently good yields of chiral bicyclic products in the preparatively convenient 0.05 M concentration range.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03068.

Complete refs 2c and 2e; experimental procedures, characterization data, and NMR spectral charts (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mrubin@ku.edu.

ORCID

Michael Rubin: 0000-0002-1668-9311

Notes

The authors declare no competing financial interest.

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