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Domino Synthesis of Bridged Bicyclic Tetrahydro-1,2-oxazines: Access to Stereodefined 4-Aminocyclohexanols

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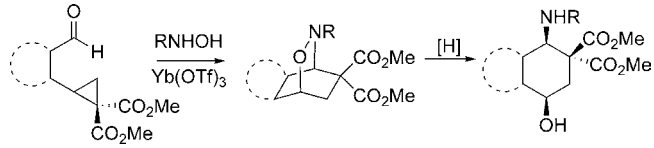
ABSTRACT



The intramolecular variant of the homo-[3 + 2]-dipolar cycloaddition of nitrones (generated in situ from an aldehyde and a hydroxylamine) with donor−acceptor cyclopropanes allows for the efficient synthesis of bridged tetrahydro-1,2-oxazines. This domino sequence produces adducts amenable to reductive N−O bond cleavage producing *cis*-1,4-aminocyclohexanols in excellent yields.

Domino reaction sequences, aside from their aesthetic appeal, are increasingly relied upon to generate complex structural motifs in an efficient and reliable manner. Their use as a practical synthetic tool is ever increasing, allowing ever more elaborate structures to be assembled through sometimes awe-inspiring cascades.[1]

Annulation reactions of donor−acceptor cyclopropanes with dipolarphiles have received considerable interest in recent years, allowing access to a variety of hetero- and carbocycles. A wide array of dipolar reagents (e.g., aldehydes,[2] imines,[3,4] nitriles,[5] azomethine imines,[6] diazenes,[7] and others) readily react with activated cyclopropanes[8] to form five- and six-membered heterocycles. Recently, we reported that nitrones **3** react with 1,1-cyclopropanediesters **4** in a stepwise annulative process[9] (via putative intermediate **5**) resulting in high yields of functionalized tetrahydro-1,2-oxazines **6** as single regioisomers with excellent diastereoselectivity (Scheme 1).[10] This process was improved by generating the nitrone in situ from hydroxylamines **1** and aldehydes **2**.[11] We recently employed this reaction sequence in the total synthesis of phyllantidine.[12] Cleavage of the N−O bond and subsequent ring closure results in the formation of pyrrolidines **7**,[13] a central tactic in our synthesis of nakadomarin A.[14]

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(9) With inversion of stereochemistry in the initial cyclopropane ring-opening event. See: Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 10251.

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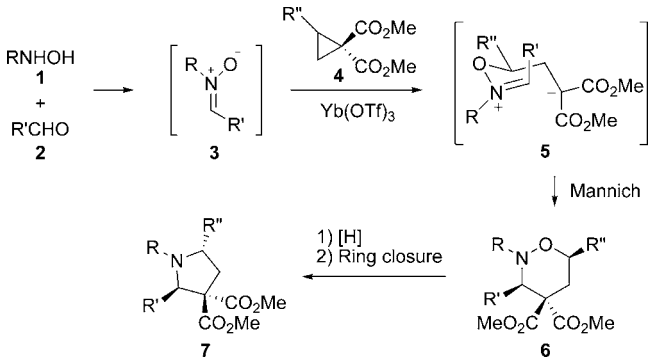
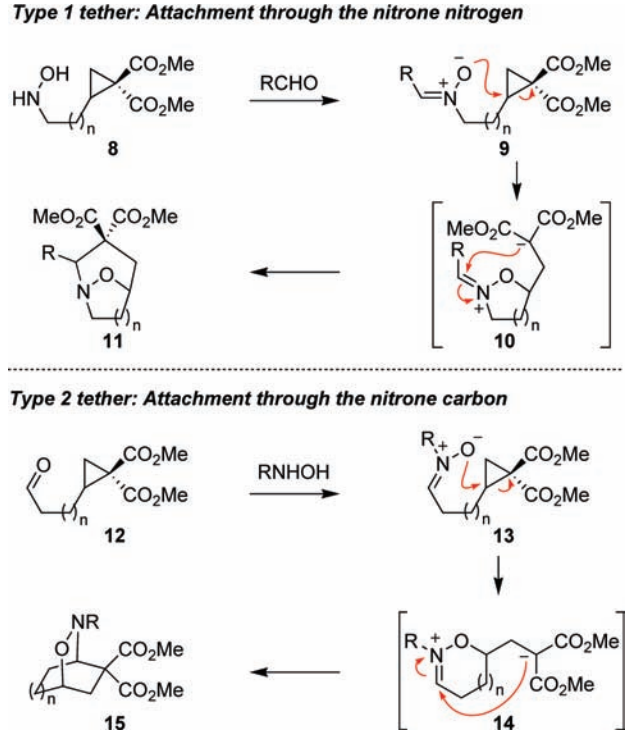
Scheme 1. Reaction of Nitrones with Cyclopropanediesters



As rewarding as these pursuits have been, we realized the potential to extend the utility of this reaction by designing an intramolecular variant. Tethering the cyclopropane to the nitrone should lead to a more facile reaction as well as incorporate an additional ring into the product. This is shown graphically in Scheme 2.

Scheme 2. Proposed Intramolecular Reactions



In one scenario, nitrone formation by condensation of a hydroxylamino-tethered cyclopropane **8** with an aldehyde would yield **9**, which would undergo nucleophilic cyclopropane ring opening to give **10**, followed by a Mannich-style ring closure. The net result would be a bridged bicycle such as **11**.[15] In an alternative sequence, the addition of a suitable hydroxylamine to cyclopropane tethered aldehyde **12** should be sufficient to trigger a domino sequence of events that starts with the formation of nitrone **13**. Cyclopropane ring opening by this short-lived intermediate would lead to zwitterion **14**, which in turn would undergo Mannich cyclization[16] to give oxazine **15**.

Bicyclic oxazines such as **15**, where $n = 1$, when subjected to reductive N−O bond scission, would lead to *cis*-1,4-aminocyclohexanols. This motif and derivatives thereof are ubiquitous in the natural product milieu with pancratistatin,[17] tetrodotoxin,[18] and 3-demethoxyerythratidinone[19] being but a few examples (Figure 1). In this Letter we disclose the realization of the successful implementation of the type 2 (vide supra) intramolecular formal homo-[3 + 2]-dipolar cycloaddition and its use in the synthesis of *cis*-1,4-aminocyclohexanols.

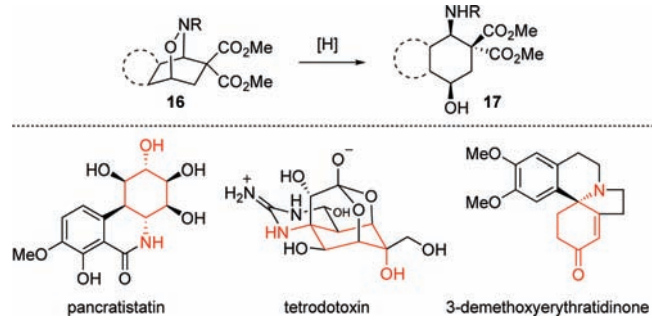


Figure 1. 1,4-Aminoalcohols present in natural products.

At the outset of this study, we faced two major issues. One was the necessity to generate the nitrone in the presence of the electrophilic cyclopropane. In our intermolecular studies involving the one-pot variant of this cycloaddition, it was necessary to preform the nitrone prior to addition of the cyclopropane. Failure to do so resulted in the competitive addition of hydroxylamine to the cyclopropanediester. For

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(14) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465.

(15) This mode of reactivity is currently under investigation. However, all attempts thus far have been unsuccessful.
(16) For previous examples of carbocycle construction by intramolecular Mannich reaction, see: (a) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* **2006**, *8*, 5311. (b) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4635. (c) Taber, D. F.; Liang, J.-L.; Chen, B.; Cai, L. *J. Org. Chem.* **2005**, *70*, 8739. (d) Thomas, J. B.; Gigstad, K. M.; Fix, S. E.; Burgess, J. P.; Cooper, J. B.; Mascarella, S. W.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *Tetrahedron Lett.* **1999**, *40*, 403. (e) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425. (f) Winkler, J. D.; Haddad, N.; Ogilvie, R. J. *Tetrahedron Lett.* **1989**, *30*, 5703.
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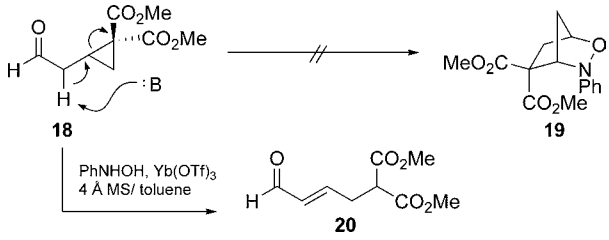
(19) (a) Tsuda, Y.; Nakai, A.; Ito, K.; Suzuki, F.; Haruna, M. *Heterocycles* **1984**, *22*, 1817. (b) Hosoi, S.; Ishida, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1992**, *40*, 3115.

the intramolecular variant to be successful, the nitrone formation must be significantly faster than hydroxylamine attack on the cyclopropane. A less worrisome issue was the tether length necessary to allow successful reaction of the nitrone moiety with the cyclopropane.

Our research began with the employment of a substrate with a one-carbon spacer between the aldehyde and the cyclopropane functionalities (Scheme 3). This compound

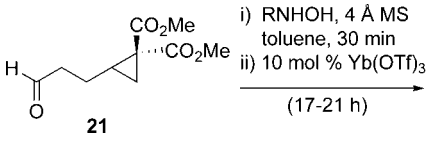
Scheme 3. Decomposition of **18** via β-Elimination



proved labile under the reaction conditions and merely decomposed via a β-eliminative ring opening of the cyclopropane.

The β-elimination pathway was obviated by preparing a substrate with an additional methylene unit in the linker.[20] We were delighted to observe that, upon addition of phenyl hydroxylamine and a catalytic amount of $Yb(OTf)_3$ to a mixture of aldeyde **21** and molecular sieves in toluene, the expected 2-oxa-3-azabicylo[2.2.2]octane was formed in 92% yield. Other hydroxylamines were surveyed and performed similarly, providing yields ranging from 82% to 92% (Scheme 4). Interestingly other tether lengths did not fare

Scheme 4. Preparation of [2.2.2] Bridged Bicyclic Systems

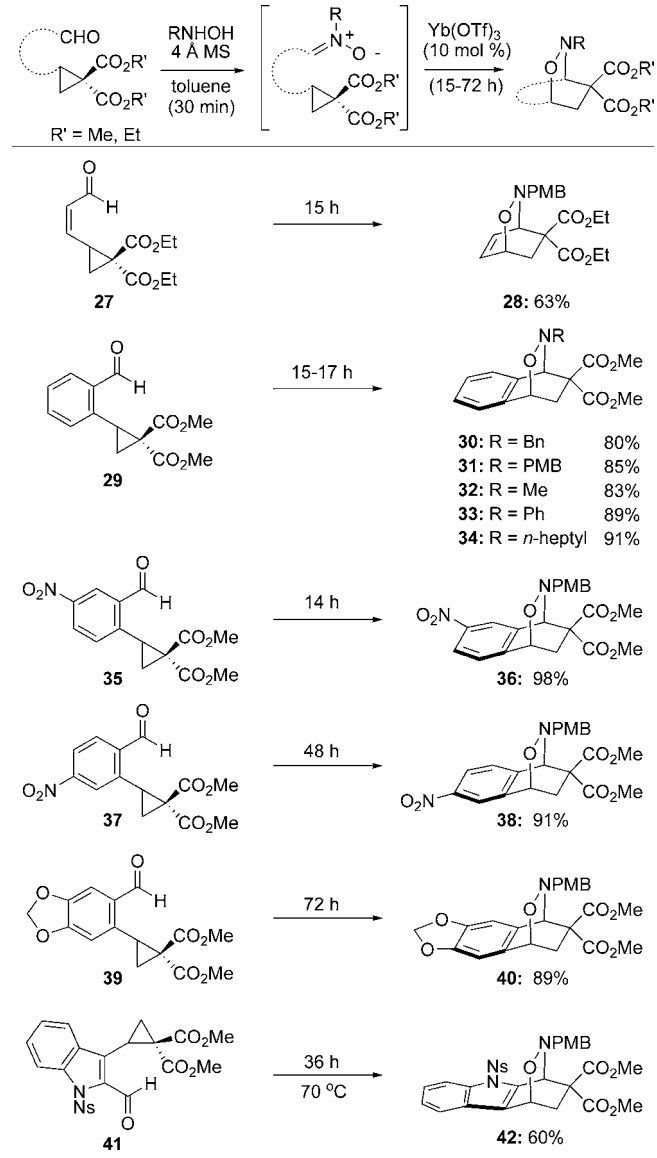


22: R = Ph 92%
23: R = *p*-tol 92%
24: R = Bn 89%
25: R = PMB 84%
26: R = *n*-heptyl 82%

as well, and so, at least for the time being, this process seems restricted to the formation of the [2.2.2] system.[21]

Our attention now turned to an investigation of substrate scope within this bicyclic framework (Scheme 5). Introduction of a *cis*-double bond in the tether (**27**) was well-tolerated and resulted in the formation of the bicyclic alkene **28** in

Scheme 5. Use of Alternative Tethers



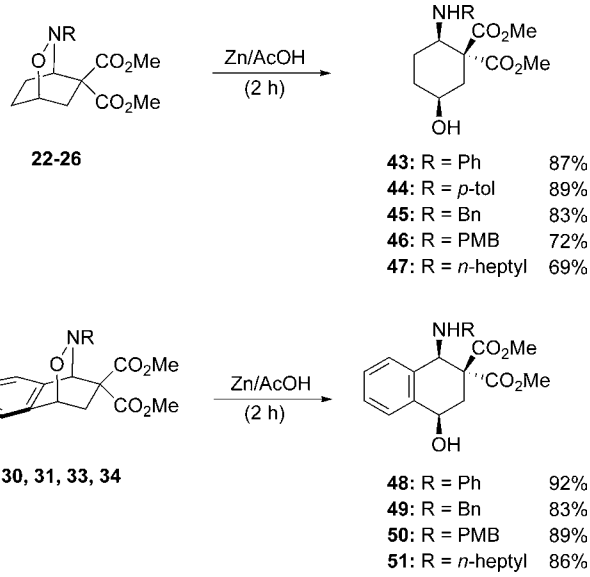
63% yield. Incorporation of a benzene ring as part of the linking moiety (**29**) was also well-behaved, and a variety of hydroxylamines produced adducts **30**−**34** in yields of 80−91%. Interestingly, the presence of a nitro group in conjugation with the electrophilic cyclopropane carbon (i.e., **35**) or the aldehyde (i.e., **37**) did not seem to affect the efficiency of the reaction, producing adducts **36** and **38** in excellent yields. It was suspected a priori that compound **35** would be a sluggish substrate since the nitro group should destabilize a developing positive charge on the electrophilic cyclopropane carbon. An electron-donating group in the form of a methylenedioxy moiety on the aromatic linker (**39**) neither hindered nor helped the reaction course. Finally, incorporation of a heteroaromatic group into the linker (**41**) resulted in the formation of the indole product **42** in a useful chemical yield.

With a variety of bicyclic tetrahydro-1,2-oxazines in hand, we examined the reductive rupture of the N−O bond with

(20) It is worth noting that geminal disubstitution a to the aldehyde in **18** would eliminate the β-elimination pathway and allow the desired reaction to proceed. However, this was not investigated.

(21) The use of three-carbon and five-carbon tethers were also investigated but were unsuccessful.

Scheme 6. Preparation of [2.2.2] Bridged Bicylic Systems



the goal of preparing cyclic 1,4-aminoalcohols. Scheme 6 illustrates the results. Two representative series, namely, the oxazines **22**−**26** derived from a saturated tether and those (**30**−**34**) derived from a phenyl tether, were subjected to reductive conditions. In contrast to many monocyclic tetrahydro-1,2-oxazines, we have encountered, the N−O bond reduction was easily accomplished by stirring the substrate with Zn dust in glacial acetic acid.[22] The reduction products are *cis*-4-aminocyclohexanols and *cis*-1-amino-4-hydroxytetrahydronaphthalenes. The yields were usually excellent ranging from 69−92%.

In summary, we have reported the first examples of an intramolecular nitrone/cyclopropane formal cycloaddition. The product bicyclic tetrahydro-1,2-oxazines are formed in excellent yields and when subjected to mild reduction conditions, produce *cis*-1,4-aminocyclohexanols in high yield. Application to target oriented challenges is currently underway in our laboratory.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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