ORGANIC LETTERS

2012
Vol. 14, No. 21
5562–5565

Gassman's Cationic [2 + 2] Cycloadditions Using Temporary Tethers

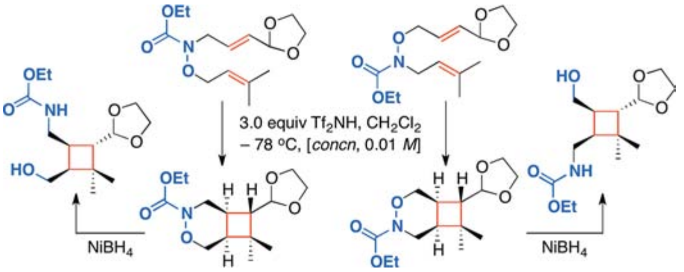
Jun Deng, Richard P. Hsung,* and Changhong Ko

Division of Pharmaceutical Sciences and Department of Chemistry, Rennebohm Hall,
777 Highland Avenue, University of Wisconsin, Madison, Wisconsin 53705-2222,
United States

rhsung@wisc.edu

Received September 28, 2012

ABSTRACT



An intermolecular equivalent of Gassman's cationic [2 + 2] cycloaddition through the use of temporary tethering is described. Notably, hydrazine and hydroxyamide proved to be robust under the acidic conditions required for the cycloaddition, leading to unique cyclobutane manifolds in a highly regio- and stereoselective manner. This development represents a rare usage of hydrazine and hydroxyamide in the capacity as temporary tethers.

While intramolecular reactions can bring forth complex structural motifs expeditiously via highly regio- and stereoselective reaction pathways, intermolecular reactions often lack regio- and/or stereochemical control despite being equally important. An elegant solution to this problem has been the use of a temporary and removable tether that renders intermolecular reactions intramolecular in nature, thereby allowing improved regio- and/or stereochemical control in addition to an enhanced reaction rate.[1] In particular, intermolecular [2 + 2] cycloadditions, photochemically[2−5] or thermally driven,[5−7] are known to suffer from poor regiochemical control. Our long-standing interest[8] in developing synthetically useful thermal−[2 + 2] cycloadditions led us to uncover a Lewis acid catalyzed intramolecular version of Gassman's cationic [2 + 2] cycloaddition [**1**→**2**→**3** in Scheme 1][9,10] amenable for the synthesis of raikovenal.[10a,11] To date, Gassman's work and ours

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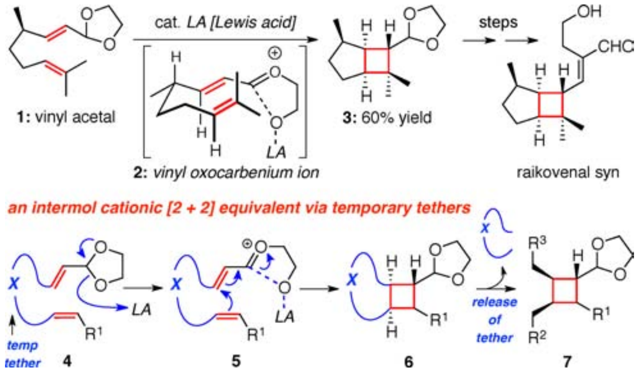
10.1021/ol3026796

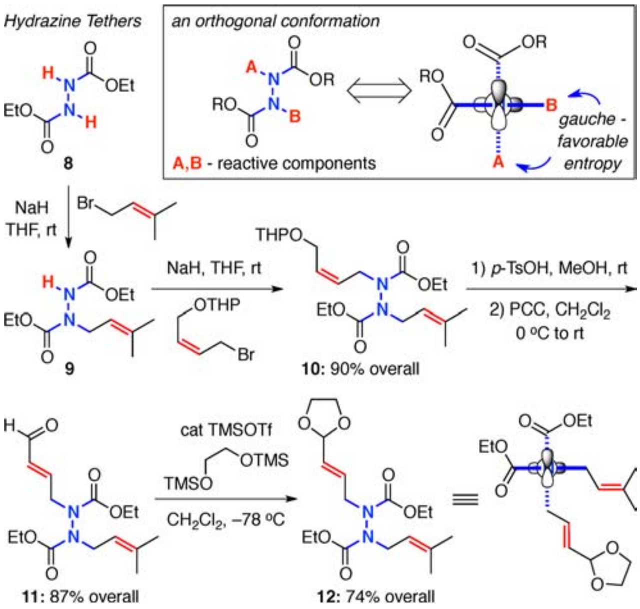
Scheme 1. Temporary Tethered Cationic [2 + 2] Cycloaddition



represent the only examples of such cycloadditions that involve vinyl oxocarbenium ion **2**.[12] Given the prevalence of cyclobutanes among alkaloids,[13] and that a cationic [2 + 2] pathway has a biosynthetic origin,[14] developing a temporary tethered manifold would be of great significance in providing a thermally driven intermolecular equivalent of the [2 + 2] cycloaddition [**4**→**5**→**6**→**7**]. While many different tethering systems have been documented with siloxane tethers being the most well-known especially in Diels–Alder cycloadditions,[1,15] we intended to explore unusual temporary tethers that can (1) sustain acidic conditions required for these cationic cycloadditions and (2) bring in unique functionalities. We wish to report here our success in achieving temporary tethered Gassman's cationic [2 + 2] cycloadditions.

Inspired by Lee's elegant work for hydrazine-tethered ring-closing metathesis,[16,17] we elected to first examine hydrazines as a possible tether for the Gassman's cationic [2 + 2] cycloadditions. We were intrigued by hydrazines because they are pharmacologically important structural entities[18] and because of our interest in cyclobutane containing alkaloids.[13] It is noteworthy that, based on calculations and X-ray structure, bis-*N*-acyl-hydrazines [right box in Scheme 2] possess a dihedral or torsional angle of ~90° with respect to the C(O)–N–N–C(O) bond sequence.[18] Therefore, although deceptively far apart when drawn two-dimensionally, reactive partners **A** and **B** on the hydrazinyl nitrogen atoms would assume a *gauche-like* conformational relationship. With the rotational barrier around the N–N bond being $\Delta E = 19$ kcal mol^{-1},[19] this *gauche-like* conformational preference should entropically promote the reactivity between **A** and **B**.

Scheme 2. Hydrazine Tether Cycloaddition Precursor



Toward this goal, we assembled the Gassman's cationic [2 + 2] cycloaddition precursor **12** from bis-*N*-ethoxycarbonyl hydrazine **8** in five steps [Scheme 2].[20] Selective monofunctionalization on one of the two hydrazinyl nitrogen atoms was readily achieved with a very high overall efficiency [see **10**], and Noyori's conditions[21] remain the best for the acetal formation from aldehyde **11**. The ensuing cationic [2 + 2] cycloaddition of **12** was successfully carried out as shown in Scheme 3. After screening some Lewis and Brønsted acids,[10] $SnCl_4$ proved to be the most effective here, leading to the desired cycloadduct **13** as a single diastereomer. $FeCl_3–SiO_2$,[22] used quite successfully in our intramolecular study,[10] is also feasible

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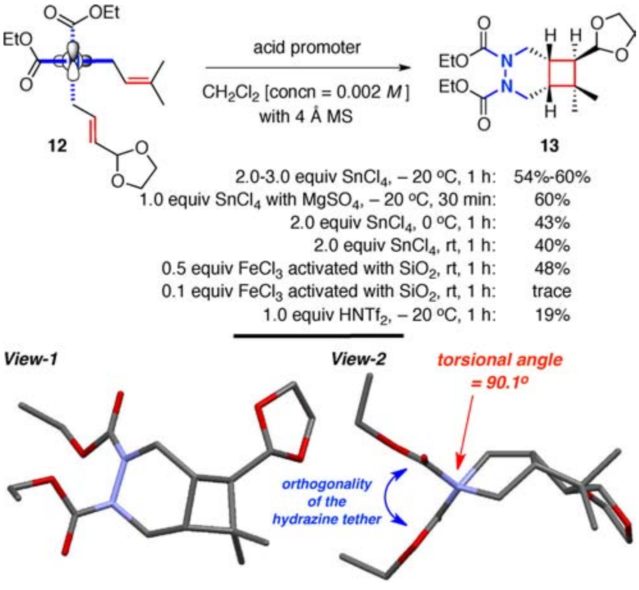
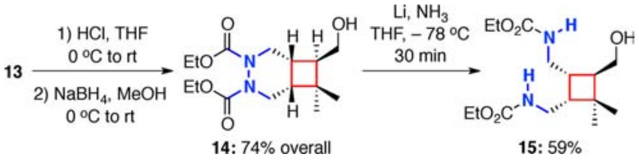
Scheme 3. A Hydrazine Tethered Cationic [2 + 2] Cycloaddition



here at 0.5 equiv, while HNTf$_2$[23,24] was essentially ineffective.

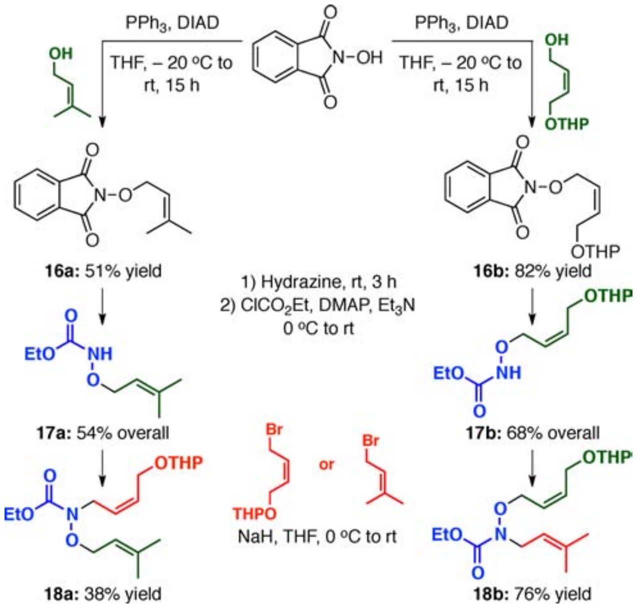
Relative stereochemistry in the cyclic hydrazine fused cyclobutane **13** was unambiguously assigned using the single crystal X-ray structure [Scheme 3]. It is noteworthy that the torsional angle for the (O)C–N–N–C(O) bond sequence here in the cycloadduct is also precisely at 90.1°, thereby suggesting a 90° dihedral angle is also present in the cycloaddition precursor **12**. To complete the concept of temporary tethering, we were able to first hydrolyze the acetal motif and then reduce the intermediate aldehyde to afford alcohol **14** [Scheme 4]. The final reductive cleavage of the hydrazine tether was best exercised using dissolving metal reduction[16,25] to afford diaminomethyl cyclobutane **15**, while standard hydrogenation conditions were not effective.

Scheme 4. A Diaminomethyl Cyclobutane Manifold



Having established the feasibility of hydrazine as a temporary tether for the Gassman's cationic [2 + 2] cycloaddition, we were compelled to expand the scope of the tethering system for this study, as this would be more significant than expanding the substrate scope for one tether. We contemplated adopting hydroxyamides as another unique tether for this cycloaddition because this design (1) could lead to an orthogonal approach to constructing cyclobutane manifolds and (2) would represent a rare usage of hydroxyamide as a temporary tether.[26,27]

Scheme 5. A Diversified Assembly of Hydroxyamide Tethers



As shown in Scheme 5, this orthogonal design can be achieved through the synthesis of hydroxyamide containing bis-olefins **18a** and **18b** with *N*-hydroxy-phthalamide serving as the diverging point. The assembly features two opposite sequences of *O*-allylation via Mistunobu reaction and *N*-allylation with the use of hydrazine to liberate the hydroxyl-amine followed by acylation in between. The cycloaddition precursors **20a** and **20b** could then be prepared, respectively, from **18a** and **18b**, using the same sequence for the hydrazine tether [Scheme 6]. The anticipated cationic [2 + 2] cycloadditions of **20a** and **20b** were the most successful when using 3.0 equiv of HNTf$_2$,[23,24] leading to bicyclic cyclobutanes **21a** and **21b** as single diastereomers. The latter yielded a single crystal that allowed us to obtain an X-ray structure to unambiguously assign the relative stereochemistry of the three contiguous carbon centers. On the other hand, the use of SnCl$_4$ or FeCl$_3$ activated with SiO$_2$ led to recovery of the starting material along with products resulting from hydrolysis of the starting material. We are not sure of the precise

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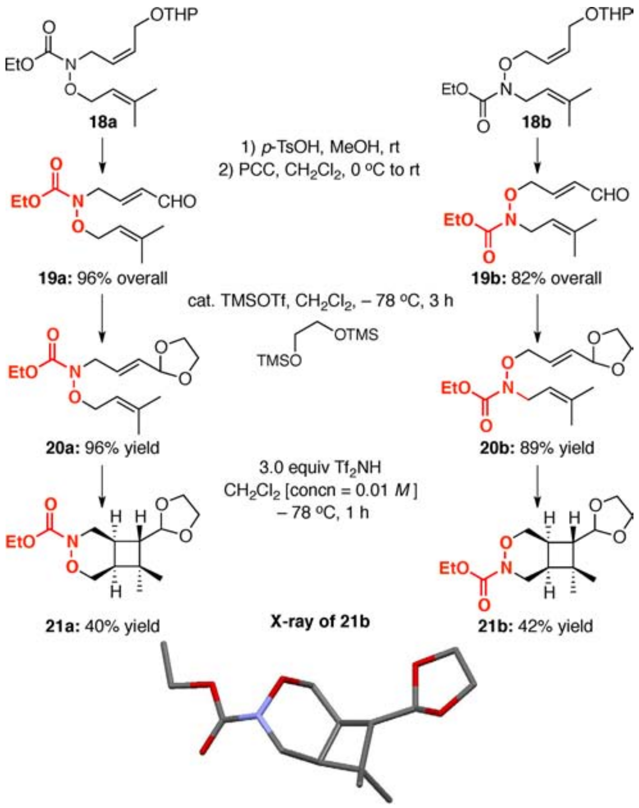
Scheme 6. Hydroxyamide Tethered [2 + 2] Cycloadditions



Scheme 7. Aminomethyl-Hydroxymethyl Cyclobutanes

rationale for this contrast with the reaction conditions used for the hydrazine-tethered system **12**.

Although these two hydroxyamide-tethered cycloadditions afforded lower yields than the hydrazine tether, these two cycloadditions provide a useful strategy for constructing orthogonally substituted cyclobutane manifolds in a highly stereo- and regioselective manner that is otherwise difficult for an intermolecular [2 + 2] cycloaddition. As demonstrated in Scheme 7, the N–O tether could be released in good yields through reductive cleavage using $NiCl_2{-}6H_2O$ and $NaBH_4$,[28] while the acetal motif could be preserved here for further transformations.

We have described here the concept of an intermolecular equivalent of Gassman's cationic [2 + 2] cycloaddition through temporary tetherings. In particular, hydrazine and hydroxyamide tethering systems proved to be tolerant of the Lewis and Brønsted acidic conditions required for the cycloaddition, leading to substituted cyclobutane manifolds in a highly regio- and stereoselective manner. This work represents a rare adaptation of hydrazine and hydroxyamide as temporary tethers. Applications of this unique intermolecular cationic [2 + 2] cycloaddition equivalent specifically in the synthesis of cyclobutane-containing alkaloids are currently underway.

Acknowledgment. We thank The National Science Foundation [NSF-CHE1012198] for support of this work and Dr. Vic Young and Mr. Gregory T. Rohde of the University of Minnesota for providing X-ray structural analysis.

Supporting Information Available. Experimental procedures as well as ^{1}H NMR spectra, X-ray structural data, and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.