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Lewis Acid Catalyzed Formal Intramolecular [3 + 3] Cross-Cycloaddition of Cyclopropane 1,1-Diesters for Construction of Benzobicyclo[2.2.2]octane Skeletons

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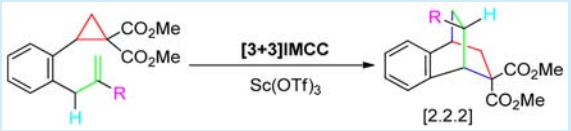
Supporting Information

ABSTRACT: A novel Lewis acid catalyzed formal intramolecular [3 + 3] cross-cycloaddition (IMCC) of cyclopropane 1,1-diesters has been successfully developed. This supplies an efficient and conceptually new strategy for construction of bridged bicyclo[2.2.2]-octane skeletons. This [3 + 3]IMCC could be run up to gram scale and from easily prepared starting materials. This [3 + 3]IMCC, together with our previously reported [3 + 2]IMCC strategy, can afford either the bicyclo[2.2.2]octane or bicyclo[3.2.1]octane skeletons from the similar starting materials by regulating the substituents on vinyl group.



Developing efficient and general strategies to construct skeletally complex and diverse polycyclic skeletons is important for the synthesis of natural products and biologically active compounds but still remains a big challenge in organic synthesis. The bicyclo[2.2.2]octane skeleton broadly exists in biologically important natural and unnatural products (Figure 1).

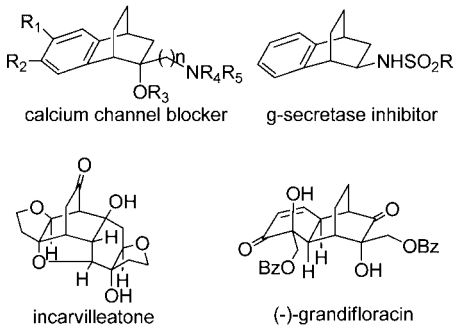
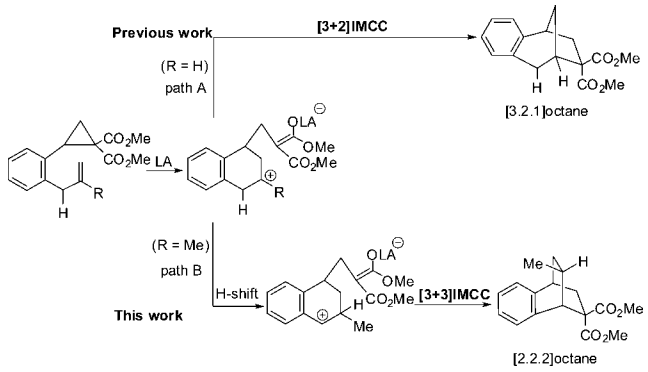


Figure 1. Representative natural and unnatural products with bicyclo[2.2.2]octane skeletons.

Additionally, due to its inherent stereochemistry, this skeleton is also a powerful building block for the stereoselective synthesis of natural products with other types of skeletons, for example, cis-1,4-disubstituted cyclohexanes via cleavage of a carbon−carbon bond. Stepwise strategies are the most commonly used ones to access the bridged bicyclo[2.2.2]octane skeleton. However, there are only a few step-efficient strategies for this skeleton, and the Diels−Alder [4 + 2] cycloaddition of cyclohexadienes might be the only commonly used one. Thus, developing efficient and conceptually new strategies to afford such a bicyclo[2.2.2]octane skeleton still remains an important and challenging task.[1]

Donor−acceptor cyclopropanes have been proven to be versatile building blocks in acid-promoted formal cycloadditions for construction of various cyclic skeletons.[2] We have developed intramolecular [3 + 2] and [4 + 2] cross-cycloadditions ([3 + 2]IMCC and [4 + 2]IMCC) of donor−acceptor cyclopropanes with various 2-atom moieties for construction of bridged [*n*.2.1] and [*n*.3.1] skeletons.[2f,3] During our recent research on the [3 + 2]IMCC of cyclopropane 1,1-diesters with C═C (Scheme 1, A),[3b] to our great surprise, we found that when substituent R was changed from H to Me, the reaction pathway was switched to [3 + 3]IMCC, a novel type of cycloaddition. This [3 + 3]IMCC afforded a bicyclo[2.2.2]octane skeleton (Scheme 1, path B). The switch of the [3 + 2]IMCC (R = H) to [3 + 3]IMCC (R = Me) was ascribed to a 1,2-shift of an allylic H, in which steric hindrance of R might be involved (Scheme 2). Although many formal [3 + 3] cycloadditions of donor−acceptor cyclopropanes

Scheme 1. [3 + 2]IMCC versus [3 + 3]IMCC of Cyclopropane 1,1-Diester



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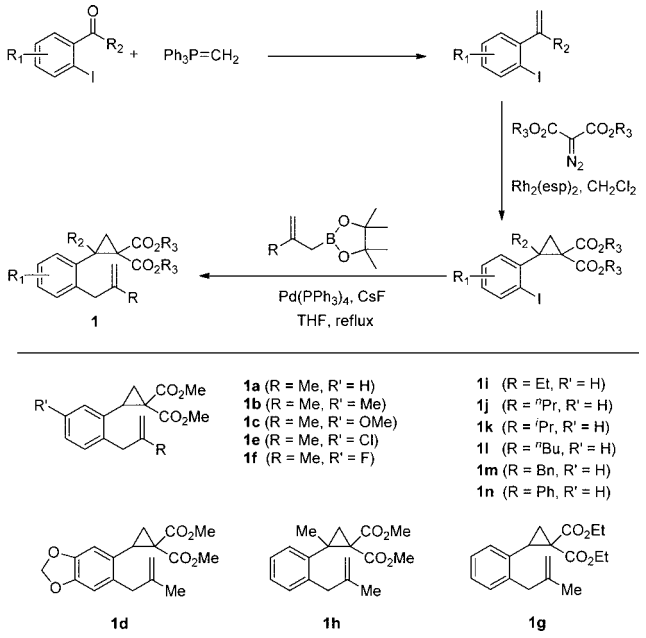
Scheme 2. Synthesis of Substrates 1



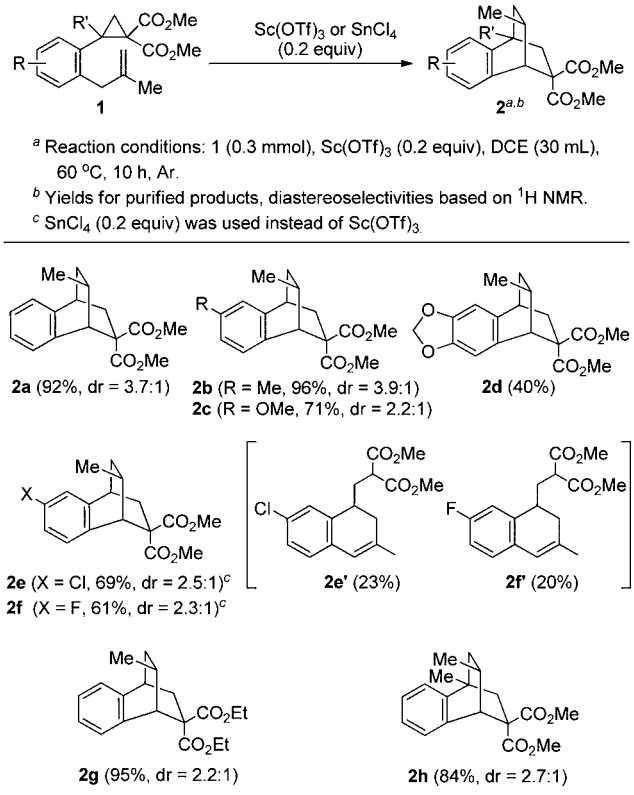
have been reported, most of the three-atom moieties contain heteroatoms to afford heterocycles.[4] There are quite limited examples with three-carbon moieties to afford cyclohexane skeletons.[4ag−aj] Herein, we report our results on a new type of formal [3 + 3] cycloaddition.

Substrates **1** could be easily prepared from substituted *o*-iodobenzaldehydes via Wittig olefination/cyclopropanation/Suzuki−Miyaura cross-coupling process (Scheme 2).[3b,5,6]

Substrate **1a** was selected for the subsequent cycloaddition study. We found that while most of the common Lewis acids could not catalyze the reaction to afford [3 + 3]IMCC cycloadducts, $Sc(OTf)_3$ and $SnCl_4$ proved to be effective. Under catalysis of $Sc(OTf)_3$ (0.2 equiv) in 1,2-dichloroethane (DCE), bridged product **2a** was obtained in an excellent yield (92%) as a pair of diastereoisomers (dr = 3.7:1) (Scheme 3). Several other substrates **1** with various substituents on the benzene ring were also proven to be successful (Scheme 3). Substrates with electron-donating groups (**1b−d**) afforded the corresponding cycloadducts **2b−d**. It was surprising that unlike other examples [3 + 3]IMCC of substrate, **1d** gave a single diastereoisomer (**2d**) exclusively. [3 + 3]IMCC of substrates with electron-withdrawing groups (**1e** and **1f**) did not work under the above conditions but successfully proceeded under catalysis by $SnCl_4$ (0.2 equiv). With unsuccessful second annulations, the byproducts **2e′** and **2f′** were produced. The substrate **1h**, having a quaternary carbon center in the cyclopropane ring also worked well to afford the cycloadduct **2h**.

Under catalysis by $Sc(OTf)_3$ (0.2 equiv), [3 + 3]IMCC of several other substrates **1** with various alkyl substituents on the vinyl group was also successful in affording the corresponding cycloadducts **2i−m** (Scheme 4). It should be noted that when the reaction of **1i** was carried out at a higher temperature (83 °C), instead of the [3 + 3]IMCC cycloadduct **2i**, **2i′** was produced with an unsuccessful second annulation. This was similar to the formation of **2e′** and **2f′**. When the substituent on the vinyl group was phenyl (**2n**), the reaction proceeded as a [3 + 2]IMCC pathway that was similar to our previously reported diene examples.[3b] An explanation for this is that, unlike the alkyl-substituted alkenes, the phenyl-substituted one gave a more

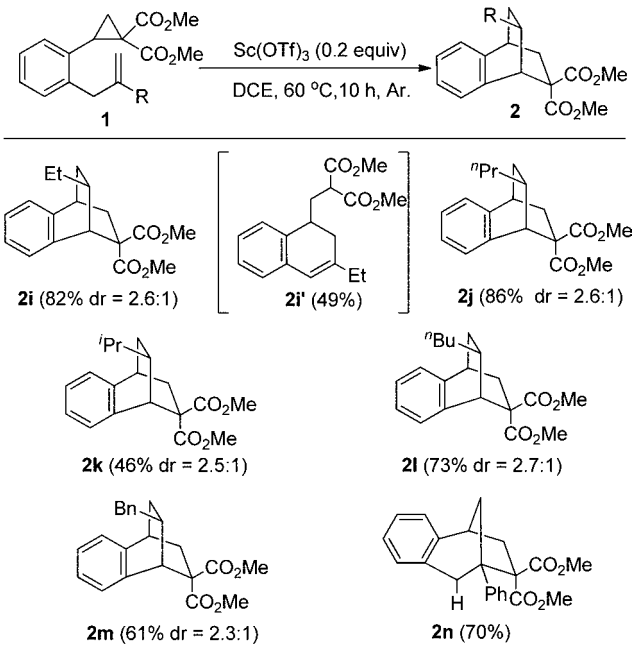
Scheme 3. $Sc(OTf)_3$-catalyzed [3 + 3] IMCC of 1a−h



[a] Reaction conditions: 1 (0.3 mmol), $Sc(OTf)_3$ (0.2 equiv), DCE (30 mL), 60 °C, 10 h, Ar.
[b] Yields for purified products, diastereoselectivities based on ^1H NMR.
[c] $SnCl_4$ (0.2 equiv) was used instead of $Sc(OTf)_3$.

2a (92%, dr = 3.7:1) **2b** (R = Me, 96%, dr = 3.9:1) **2c** (R = OMe, 71%, dr = 2.2:1) **2d** (40%)
2e (X = Cl, 69%, dr = 2.5:1)[c] **2e'** (23%) **2f'** (20%)
2f (X = F, 61%, dr = 2.3:1)[c]
2g (95%, dr = 2.2:1) **2h** (84%, dr = 2.7:1)

Scheme 4. $Sc(OTf)_3$-catalyzed [3 + 3] IMCC of 1i−m



stable benzyl cation after the first annulation process. All of these results indicate that, besides the steric effect of the R group, the stability of carbocations (before and after the 1,2-H shift) as well as the different ring strains of the two bridged rings (bicyclo[2.2.2]octane and bicyclo[3.2.1]octane) might also be involved in the pathway selection.

It should be noted that the [3 + 3]IMCC reaction could also be easily carried out on gram scale (Scheme 5). This might exhibit its potential in natural products synthesis as well as in

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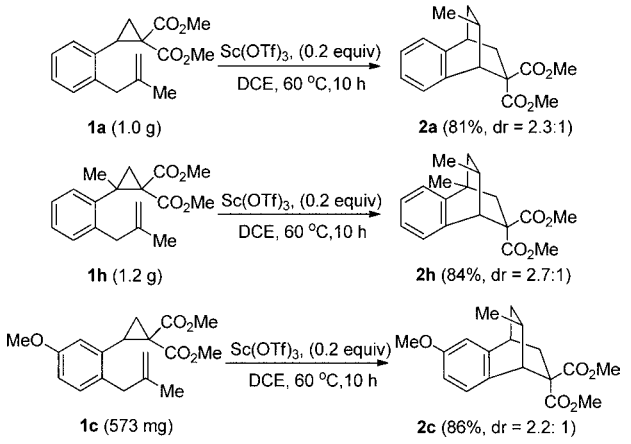
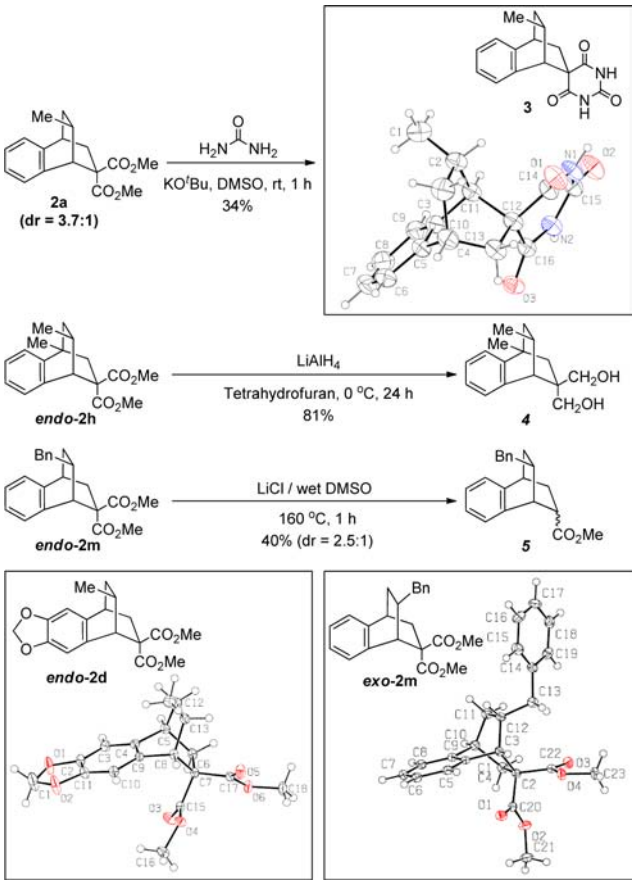
Scheme 5. [3 + 3]IMCC reaction in gram scale



construction of structurally diverse libraries for further chemical biology study and lead discovery.

The two diastereoisomers of the cycloadducts **2** could be separated via preparative HPLC. We found that most of the major diastereoisomers were colorless oils, and the minor ones were white solids. Three postmodifications were carried out on the bridged products (Scheme 6). **2a** was converted to its barbituric acid derivative **3**. The ester groups of *endo*-**2h** were reduced by $LiAlH_4$. Krapcho decarboxylation[7] was carried out on *endo*-**2m** to afford **5**. The structures of *endo*-isomer of **3**, *endo*-**2d**, and the minor isomer (*exo*-**2m**) of **2m** were unambiguously

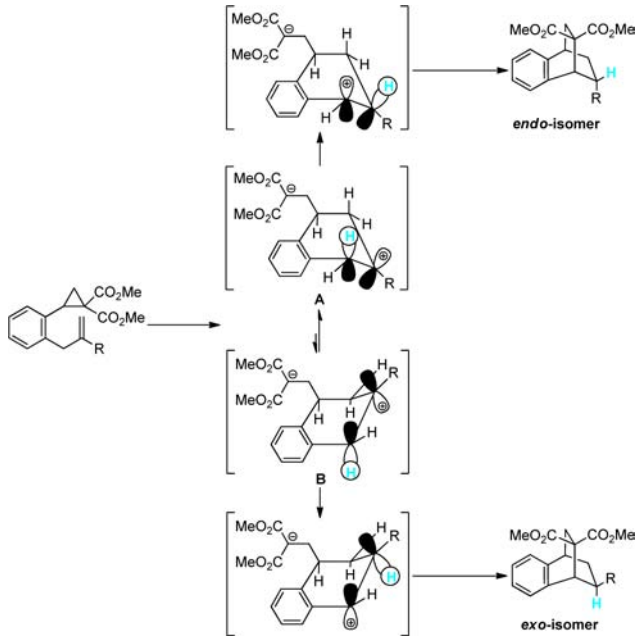
Scheme 6. Post-modifications of three products and single crystals of *endo*-isomer of 3, *endo*-2d, and *exo*-2m



confirmed by NMR spectroscopy, HRMS, and X-ray crystal structure analysis (Scheme 6).[8]

The interpretation of the diastereoselectivity can be understood as follows: after the first ring closure, there are two possible conformations (A and B) of the obtained zwitterion (Scheme 7).

Scheme 7. Interpretation of the Diastereoselectivity



Conformation A was considered to be the more preferred one due to the steric hindrance. In conformation A, the rearranged H of the benzyl CH_2 is the one on the sp^3-obital roughly parallel to the cationic sp^2-obital. This results the diastereoselectivity which prefers the endo isomer.

In summary, we have successfully developed a novel type of Lewis acid catalyzed [3 + 3]IMCC of cyclopropane 1,1-diesters in which the 1,2-shift of allylic H is involved. This is a new type of [3 + 3] cycloaddition of donor−acceptor cyclopropanes with a three-carbon moiety to afford a cyclohexane skeleton. This supplies an efficient and conceptually new strategy for construction of bridged benzobicyclo[2.2.2]octane skeletons. This [3 + 3]IMCC could be run up to gram scale from easily prepared starting materials. This [3 + 3]IMCC, together with our previously reported [3 + 2]IMCC strategy,[3b] can afford either the bicyclo[2.2.2]octane or bicyclo[3.2.1]octane skeletons from similar starting materials by regulating the substituents on the vinyl group. Further investigation of this [3 + 3]IMCC strategy, including its potential application to total synthesis of polycyclic terpenoids and alkaloids as well as construction of structurally diverse libraries, is being carried out in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01927.

X-ray data for compound **3** (CIF)
X-ray data for compound **2d** (CIF)
Detailed experimental procedures, characterization data, and crystallographic data (PDF)
X-ray data for compound **2m** (CIF)

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Notes

The authors declare no competing financial interest.

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(8) CCDC 1052869 (**3**), 1057266 (*endo*-**2d**), and 1052868 (*exo*-**2m**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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