Cycloaddition

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# Efficient Construction of Oxa- and Aza-[*n*.2.1] Skeletons: Lewis Acid Catalyzed Intramolecular [3+2] Cycloaddition of Cyclopropane 1,1-Diesters with Carbonyls and Imines**

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Highly efficient construction of cyclic skeletons is one of the most important themes in organic synthesis. The structurally diverse and interesting family of bridged oxa- and aza-[*n*.2.1] ($n = 2,3,4$) skeletons are well-represented and widely distributed in nature; they can be found in natural products such as platensimycin,[1] quinocarcin,[2] bruguierol,[3] and pyrido[3,4-b]homotropane (PHT; Figure 1),[4] and exhibit broad-ranging

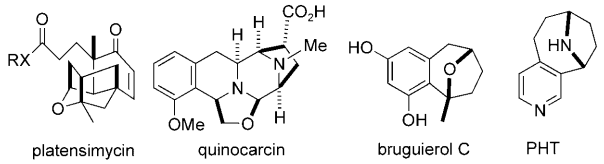
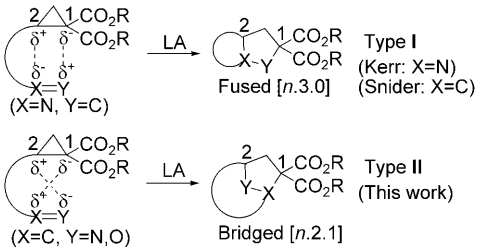



***Figure 1.*** Several representative natural products.

biological activity. The complex architectures provide the impetus for the development of new synthetic methodologies. Additionally, such skeletons are also useful building blocks in organic synthesis.[5] Therefore, it is not surprising that much attention has been paid to developing creative strategies for the construction of such bridged skeletons.

Undoubtedly cycloadditions are one of the most efficient and direct transformations for the construction of cyclic skeletons. Although there are many strategically novel methods developed for the diverse [*n*.2.1] skeletons,[6] the development of a more general and efficient strategy to afford such oxa- and aza-[*n*.2.1] bicyclic skeletons remains important, and continues to attract interest from the organic synthesis community.

A cyclopropane is a versatile building block for cyclic skeletons,[7] and the easily accessible cyclopropane 1,1-diester has been used in various Lewis acid (LA) promoted [3+*n*] cycloadditions.[8–12] The ease of running the reaction and the regio- and stereoselectivity make intramolecular cycloadditions[6c,13] an efficient strategy for construction of complex cyclic skeletons. The representative examples for Lewis acid catalyzed intermolecular [3+2] cycloadditions of cyclopropane 1,1-diester are presented by the work of Johnson and co-workers,[9a–e] and Carson and Kerr.[10d] Compared to the Lewis acid catalyzed intermolecular [3+2] cycloadditions of cyclopropane 1,1-diester, the intramolecular variant is less prevalent despite showing potential in the synthesis of natural products.[14,15] The intramolecular [3+2] cycloaddition can be classified into two categories: formation of 1) a fused bicyclic [*n*.3.0] skeleton (type **I**) and 2) a bridged bicylic [*n*.2.1] skeleton (type **II**; Scheme 1).




***Scheme 1.*** Two types of intramolecular [3+2] cycloadditions of cyclopropane 1,1-diesters.

Snider and co-workers reported a preliminary result on a type **I** intramolecular [3+2] cycloaddition of a cyclopropane 1,1-diester with a C=C bond.[15a] Recently, Kerr and co-workers reported a type **I** intramolecular [3+2] cycloaddition of a cyclopropane 1,1-diester with a C=N bond by which aza-[3.3.0] and aza-[4.3.0] skeletons were constructed; these reactions were successfully applied to the total synthesis of FR901483 and allosecurinine.[15b–e] Herein we report our recent results on the construction of the bridged oxa- and aza-[*n*.2.1] ($n = 2, 3, 4$) skeletons through the type **II** intramolecular [3+2] cycloaddition of cyclopropane 1,1-diester.

We selected **1a** (see Table 1 for structures) as the model substrate to explore the optimized reaction conditions for an intramolecular [3+2] cycloaddition to give **2a**, and the results are summarized in the Supporting Information. The best result (93% yield) was obtained using $Sc(OTf)_3$ as the catalyst in 1,2-dichloroethane. The structure of **2a** was unambiguously confirmed by X-ray crystal structure analysis[16] (Figure 2).

Several substrates (**1b**–**1p**) having different substituents were subjected to the intramolecular [3+2] cycloaddition (Table 1). The corresponding [3.2.1] (Table 1, entries 1–8),

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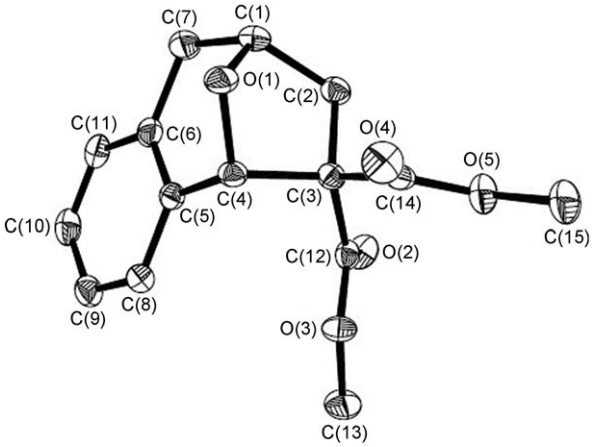



***Figure 2.*** ORTEP drawing for the product **2a**. The thermal ellipsoids drawn at the 30% probability level.

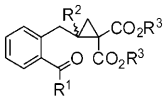
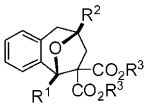
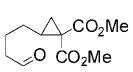
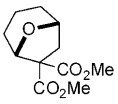
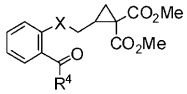
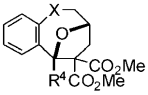
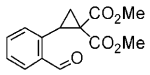
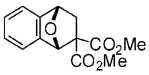
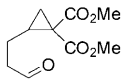
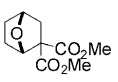
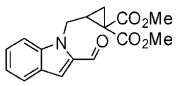
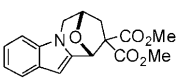
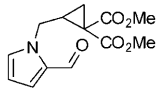
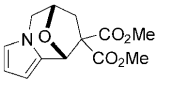
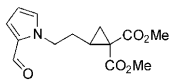
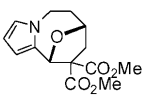
[4.2.1] (Table 1, entries 9–12), and [2.2.1] (Table 1, entries 13 and 14) skeletons were successfully formed. In some cases $Sc(OTf)_3$ showed poor catalytic efficiency, therefore either a dilute solution of $Yb(OTf)_3$ (Table 1, entries 4, 13, and 14) or $SnCl_4$ (Table 1, entries 9–12) was used instead. As in the case of aldehydes, the reactions of ketones also proceeded nicely (Table 1, entries 3–5). The aliphatic substrates **1g** (Table 1, entry 8) and **1m** (Table 1, entry 14) led to lower product yields, probably because of their conformational flexibility, which resulted in intermolecular oligo- or polymerization. Reaction of substrate **1e**, having a quaternary carbon center in the cyclopropane ring, also took place smoothly and afforded adduct **2e** in an excellent yield (Table 1, entry 6).

Compared to its intermolecular variants, in which an aldehyde and a cyclopropane bearing a cation-stabilizing substituent (donor-acceptor cyclopropane) were employed,[9a–e] the scope of the cyclopropane and carbonyl substitutions has been extended to this intramolecular [3+2] cycloaddition.

Since many natural products such as pyrrolo[1,2-*a*]azepine and pyrrolo[1,2-*a*]azocine, contain seven- and eight-membered heterocyclic skeletons, several heteroatom-containing substrates were made and successfully reacted to deliver the desired products (Table 1, entries 10–12 and 15–17). To test whether the type **II** intramolecular [3+2] cycloaddition strategy was efficient for construction of chiral bridged [*n*.2.1] skeletons, (+)-**1a** was reacted under the optimized reaction conditions and the cycloadduct (−)-**2a** was successfully obtained with 97% *ee* in 91% yield (Table 1, entry 2).

After the successful construction of oxabicyclo[*n*.2.1] skeletons, we tried to build their aza analogues (Table 2). We chose the reaction of **1a** and aniline **3a** for screening the reaction conditions. The challenge for this kind of reaction was the formation of its oxa-analogue **2a**. In 1,2-dichloroethane, the desired azabicyclo[3.2.1]octane product **4a** was always accompanied by various amounts of **2a**. When the reaction (**1a**/**3a** = 1:1.5) was carried out in toluene and in the presence of 4 Å molecular sieves, the formation of **2a** was completely suppressed and **4a** was obtained successfully (Table 2, entry 1). Under the optimized reaction conditions, the reactions of **1a** with amines **3** were carried out. It was found that both aryl amines **3a**–**3d** (Table 2, entries 1–4) and

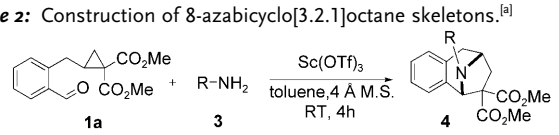
***Table 1:*** Lewis acid catalyzed intramolecular [3+2] cycloaddition of cyclopropanes **1**.[a]

| Entry | Cyclopropane **1** | Product **2** | Yield [%][b] |
|---|---|---|---|
| |  |  | |
| 1 | **1a** $R^1$ = H, $R^2$ = H, $R^3$ = Me | **2a** | 90 |
| 2 | (+)-**1a**, 90% *ee* | **(−)-2a** | 91, 97% *ee* |
| 3 | **1b** $R^1$ = Me, $R^2$ = H, $R^3$ = Me | **2b** | 90 |
| 4 | **1c** $R^1$ = vinyl, $R^2$ = H, $R^3$ = Me | **2c** | 74[c] |
| 5 | **1d** $R^1$ = phenylethynyl, $R^2$ = H, $R^3$ = Me | **2d** | 91 |
| 6 | **1e** $R^1$ = H, $R^2$ = Me, $R^3$ = Me | **2e** | 92 |
| 7 | **1f** $R^1$ = H, $R^2$ = H, $R^3$ = Et | **2f** | 96 |
| |  |  | |
| 8 | **1g** | **2g** | 47 |
| |  |  | |
| 9 | **1h** X = $CH_2$, $R^4$ = H | **2h** | 68[d] |
| 10 | **1i** X = O, $R^4$ = H | **2i** | 75[d] |
| 11 | **1j** X = O, $R^4$ = Me | **2j** | 35[d] |
| 12 | **1k** X = S, $R^4$ = H | **2k** | 85[d] |
| |  |  | |
| 13 | **1l** | **2l** | 85[c] |
| |  |  | |
| 14 | **1m** | **2m** | 27[c] |
| |  |  | |
| 15 | **1n** | **2n** | 87 |
| |  |  | |
| 16 | **1o** | **2o** | 90 |
| |  |  | |
| 17 | **1p** | **2p** | 42[d] |

[a] Reaction conditions: 0.29 mmol scale, 20 mol% of $Sc(OTf)_3$, 4.0 mL of DCE, RT, 2 h, Ar. [b] Yields of isolated products. [c] 32 mL of DCE and 10 mol% of $Yb(OTf)_3$ were used, 35°C, 1 day. [d] 4.0 mL of DCE and 20 mol% of $SnCl_4$ were used, 60°C, 2 h. DCE = 1,2-dichloroethane.

***Table 2:*** Construction of 8-azabicyclo[3.2.1]octane skeletons.[a]



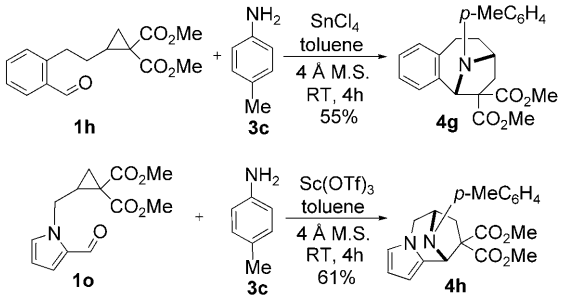

1a 3 4

| Entry | Amine **3** | Product **4** | Yield [%][b] |
|---|---|---|---|
| 1 | **3a**: R = 4-$BrC_6H_4$ | **4a** | 80 |
| 2 | **3b**: R = 4-$MeOC_6H_4$ | **4b** | 82 |
| 3 | **3c**: R = 4-$MeC_6H_4$ | **4c** | 75 |
| 4 | **3d**: R = Ph | **4d** | 84 |
| 5 | **3e**: R = Bn | **4e** | 79 |
| 6 | **3f**: R = *t*Bu | **4f** | 81[c] |

[a] Reaction conditions: a mixture of **1a** (0.29 mmol) and **3** (0.44 mmol) in toluene (4.0 mL) was stirred in the presence of 4 Å molecular sieves at RT for 2 h under Ar. Then 10 mol% of $Sc(OTf)_3$ was added, and the mixture was stirred for an additional 2 h. [b] Yields of isolated products. [c] **3f** (1.45 mmol, 5 equiv) was used. Bn = benzyl.

alkyl amines **3e** and **3f** (Table 2, entries 5 and 6) could react with aldehyde **1a** successfully to give the corresponding cycloadducts **4a**–**4f** in good yields.

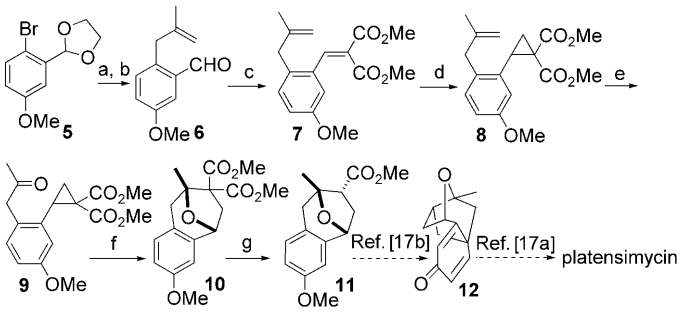
By using similar reaction conditions ($SnCl_4$), we investigated the cycloaddition of **1h** with **3c** and found that the corresponding 9-azabicyclo[4.2.1]nonane **4g** was obtained in moderate yield (Scheme 2). Additionally, reaction of **1o** and **3c** successfully afforded the diaza[3.2.1]octane product **4h** in 61% yield (Scheme 2). However, the reaction of aldehyde **1l** with aniline **3c** was complex and no aza[2.2.1]heptane cycloadduct was isolated.




***Scheme 2.*** Examples for azabicyclo[4.2.1] and azabicyclo[3.2.1] skeletons.

To demonstrate the potential of this strategy, construction of the compact core of platensimycin[1] was targeted (Scheme 3). Cyclopropane 1,1-diester **9** was prepared from **5**. Intramolecular [3+2] cylcoaddition of **9** was successfully accomplished and cycloadduct **10** was obtained in 87% yield. Delightfully, the subsequent dealkoxycarbonylation of **10** almost exclusively gave the desired *endo*-isomer **11**, which could be additionally converted into intermediate **12** (Nicolaou et al.)[17a] by using the method reported by Njardarson and co-workers.[17b]

In summary, we have developed the first type **II** intramolecular [3+2] cycloaddition of cyclopropane 1,1-diesters with aldehydes, ketones, and imines. This type of reaction can be promoted by Lewis acids efficiently, and provides a general and efficient strategy for construction of bridged oxa- and aza-[*n*.2.1] (*n* = 2,3,4) skeletons. As an example for demonstrating its potential, this strategy was used to access the compact core of platensimycin. Additional investigation on this strategy, including synthesis of several closely related natural products, is being carried out in our laboratory.




***Scheme 3.*** Formal synthesis of platensimycin: a) *t*BuLi, diethyl ether, methallyl chloride; b) 1 M HCl, THF, 56% over two steps; c) $CH_2(CO_2Me)_2$, piperidine, reflux, 84%; d) $Me_3SOI$, NaH, DMSO, 90%; e) $OsO_4$, $NaIO_4$, $THF/H_2O$ = 2:1, 91%; f) $Sc(OTf)_3$ (20 mol%), DCE, 87%; g) LiCl, wet DMSO, 160°C, 79%. DMSO = dimethylsulfoxide.

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