Cycloaddition

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Lewis Acid Catalyzed Intramolecular [3+2] Cross-Cycloaddition of Donor–Acceptor Cyclopropanes with Carbonyls: A General Strategy for the Construction of Acetal[*n*.2.1] Skeletons**

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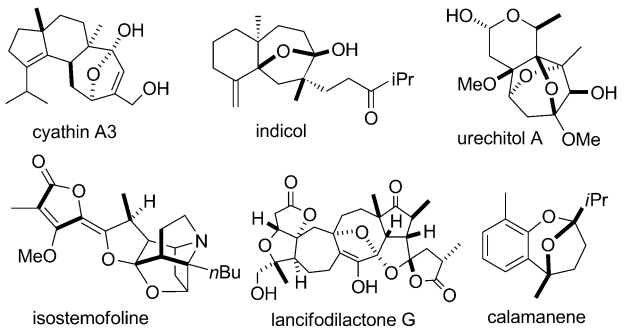
Dedicated to Professor Zhengming Li on the occasion of his 80th birthday

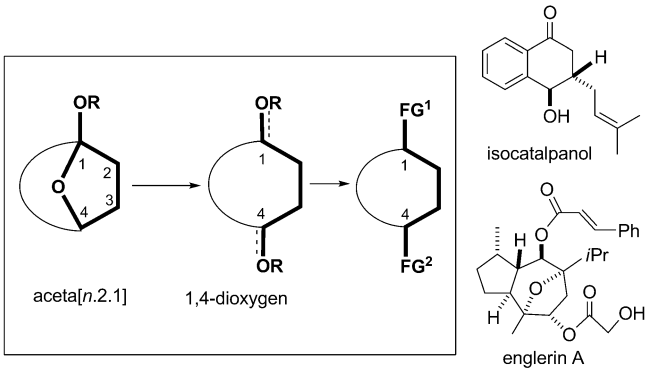
The structurally diverse, complex, and interesting family of bridged oxa[*n*.2.1] skeletons ($n = 2$–4) with an additional bridgehead oxygen (acetal[*n*.2.1] skeletons) is widely distributed in nature and exhibits a broad range of important biological activities (Scheme 1). One of the prominent structural features of such core skeletons is an embedded



Scheme 1. Several representative natural products.

1,4-dioxygen acetal moiety, which can be conveniently transformed into the important class of 1,4-difunctionalized six- to eight-membered rings (Scheme 2).[1,2,3e,h,4e] Thus, it is not surprising that great attention has been paid to the development of creative strategies for the efficient construction of such bridged skeletons.

Cycloadditions and domino reactions involve the simultaneous formation of more than two covalent bonds in one step, and therefore they are the most efficient and direct transformations for the synthesis of cyclic skeletons. Although various cycloaddition and domino strategies have been



Scheme 2. Strategy to 1,4-difunctionalized six- to eight-membered rings.

developed for the construction of such bridged skeletons, including the Diels–Alder reaction, 1,3-dipolar cycloaddition of carbonyl ylides, transition-metal-catalyzed cyclization, and radical cyclization,[3,4] the development of general, efficient, and conceptually new strategies to afford such structurally diverse skeletons still remains important and challenging.

Cyclopropanol-derived monodonor–monoacceptor cyclopropanes (D-A CP),[5] form an important subclass of the donor–acceptor cyclopropane family,[6] and are versatile building blocks in organic synthesis. D-A CP can be employed for the construction of five-membered rings by Lewis acid (LA) promoted [3+2] cycloadditions. Despite the importance of the tetrahydrofuran skeleton, it is surprising that in comparison to examples using C=C, alkynes, and nitriles,[7–9] [3+2] cycloadditions of D-A CP with carbonyls seemed to be less successful.[10,11] Reissig et al reported the reaction of siloxyl D-A CP with carbonyls under the catalysis of a stoichiometic amount of $TiCl_4$, and an Aldol adduct was obtained instead of the [3+2] cycloaddition product.[10] Pagenkopf and Yu reported a similar result from the reaction of a glucal-derived alkoxyl D-A CP with an aldehyde.[5a,11] Inspired by our recently reported type II intramolecular [3+2] cross-cycloaddition ([3+2] IMCC) of cyclopropane 1,1-diester,[12] we expected this strategy could be applied to D-A CP (Scheme 3). We now report our recent results for the construction of the acetal[*n*.2.1] skeletons by the [3+2] IMCC of D-A CP. To the best of our knowledge, this is the first catalytic cycloaddition with carbon–heteroatom multiple bonds, and the first intramolecular cycloadditon of D-A CP.

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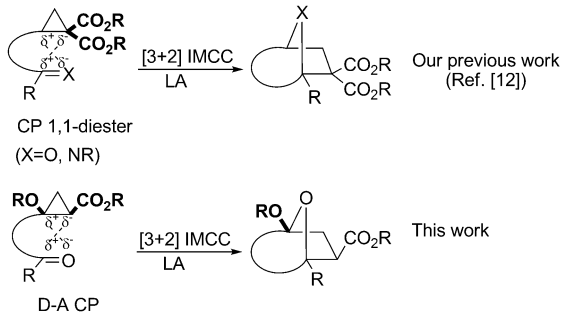
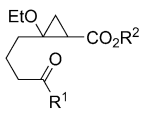
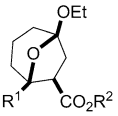
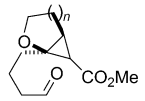
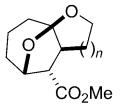
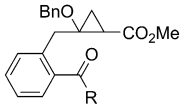
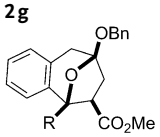
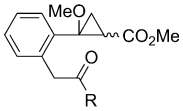
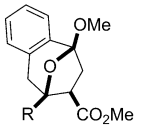
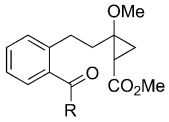
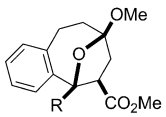


Scheme 3. LA-catalyzed type II [3+2] IMCC of D-A CP.

In an initial exploration of the [3+2] IMCC a single diastereoisomer of **1a** was used as the substrate (see the Supporting Information for the optimization of the reaction conditions). To our delight, reactions promoted by 1.2 equivalent of $TiCl_4$ and trimethylsilyl trifluoromethanesulfonate (TMSOTf), as Lewis acids, in $MeNO_2$, as the solvent, were both successful, and the reaction using TMSOTf gave a better yield and diastereoselectivity with *exo*-**2a** as the major isomer. This result implied that the properties of the LA, especially the steric bulk, might have a great influence on the stereochemistry. The investigation was then focused on changing the silyl group. Reactions promoted by triethylsilyl trifluoromethanesulfonate (TESOTf) and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) both gave excellent diastereoselectivities, as well as better yields. $EtNO_2$ was also proven to be a suitable solvent. Surprisingly, we found that a catalytic amount of TESOTf also gave similar results with regard to the yield and diastereoselectivity. This is the first catalytic example reported for reactions of this type of D-A CP with carbon–heteroatom multiple bonds.

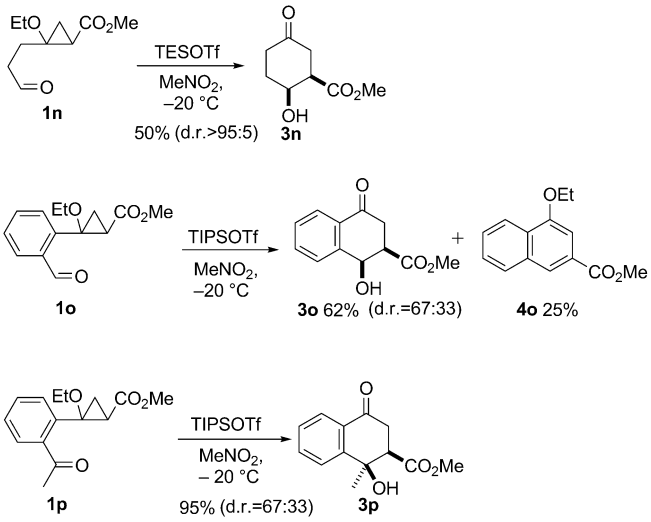
With the optimized reaction conditions established, we began to examine the generality of this method (Table 1). Substrates **1** were used either in a single diastereoisomeric form (in most cases) or as a mixture of the two inseparable isomers. As shown in Table 1, the construction of the 8-oxabicyclo[3.2.1]octane and 9-oxabicyclo[4.2.1]nonane skeletons were successfully carried out. In most cases, the *exo* cycloadducts **2** were obtained as the major diastereoisomers and in moderate to good yields. Exceptionally, substrates **1f** and **1g** with fused rings gave *endo* cycloadducts **2f** and **2g** with excellent diastereoselectivity (see the Supporting Information). The structures of *exo*-**2k** and *exo*-**2m**[13] were unambiguously confirmed by X-ray crystal structure analysis. The following experiments confirmed that the reaction results were not influenced by the relative stereochemistry of substrates **1**: each of the two isomers of **1a** gave the same result with regard to yield and diastereoselectivity and **1h** behaved the same. For substrates **1j** and **1k**, a mixture of the two inseparable isomers was used in the [3+2] IMCC, and cycloadducts **2j** and **2k** were afforded in good yields and with the *exo* isomer as the major isomer. It should be noted a diverse range of substrates could be used, thus demonstrating the generality of the method; aromatic and aliphatic aldehydes/ketones, and substrates with fused rings or long alkyl chains all successfully underwent the [3+2] IMCC.

Table 1: Construction of 8-oxa[3.2.1] and 9-oxa[4.2.1] skeletons.[a]

Cyclopropane **1**	Product **2**	Yield [%][b]	*exo*/*endo*[c]
			
1a R^1 = H, R^2 = Me	**2a**	78 (72)[d]	84:16
1b R^1 = Me, R^2 = Me	**2b**	80	> 95:5
1c R^1 = vinyl, R^2 = Me	**2c**	94	90:10
1d R^1 = phenylethynyl, R^2 = Me	**2d**	73	> 95:5
1e R^1 = H, R^2 = Et	**2e**	56	69:31
			
1f *n* = 1	**2f**	50	< 5:95
1g *n* = 2	**2g**	28	< 5:95
			
1h R = H	**2h**	78 (71)[d]	40:60
1i R = Me	**2i**	79	52:48
			
1j[e] R = H	**2j**	78	77:23
1k[e] R = Me	**2k**	85	86:14
			
1l R = H	**2l**	59	> 95:5
1m R = Me	**2m**	77	89:11

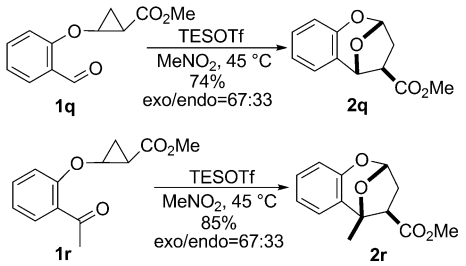
[a] Reaction conditions: one diastereomer was used, 0.4 mmol scale, 20 mol% of TESOTf, 10.0 mL of $MeNO_2$, −20 °C, 2 h, Ar. [b] Yields of the isolated products. [c] The *exo*/*endo* ratios were determined by the yields of the isolated products or by NMR analysis. [d] The yield when the other diastereomer was used [e] The mixture of two diastereomers was used. Bn = benzyl.

When we used the [3+2] IMCC to build 7-oxabicyclo-[2.2.1]heptane skeletons, ring-opening products **3** were obtained, probably as a result of the hydrolysis of the presumed [3+2] IMCC cycloadducts **2** (Scheme 4). Compound **3n** was obtained from the aliphatic substrate **1n** in 50% yield and with excellent diastereoselectivity (> 95:5). Under TESOTf catalysis an aromatized naphthalene derivative **4o** was obtained together with the ring-opening product **3o**. TIPSOTf gave a better yield of **3o** (62%) with moderate diastereoselectivity (*exo*/*endo* = 67:33). The reaction of ketone **1p** gave exclusively the ring-opening product **3p** in 95% yield and with a moderate diastereoselectivity (*exo*/*endo* = 67:33). This supplies an effective method for the construction of skeletons with a 1,4-dioxygen-substituted cyclohexane.



Scheme 4. Construction of skeletons with a 1,4-dioxygen-substituted cyclohexane.

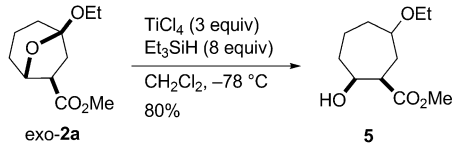
Following the successful construction of oxabicyclo[*n*.2.1] skeletons with an "external acetal" moiety, we then turned our attention to the construction of a 2,8-dioxabicyclo-[3.2.1]octane skeleton with an "internal acetal" moiety, which is a core skeleton that exists in natural products (Scheme 5). However, under the above reaction conditions [3+2] IMCC of aldehyde **1q** did not happen and **1q** was



Scheme 5. Construction of 2,8-dioxabicyclic[3.2.1] skeletons.

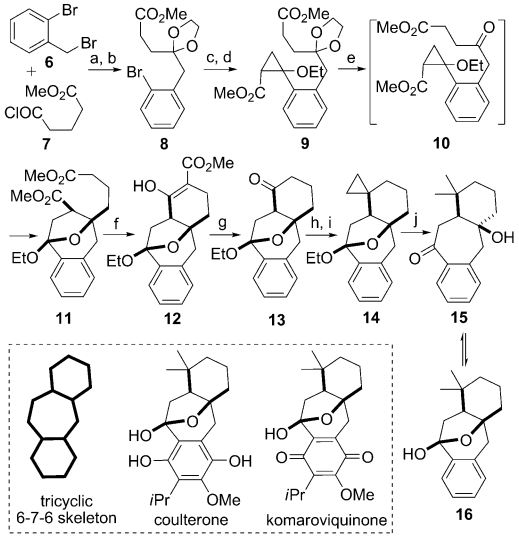
recovered completely. To our delight, when the reaction mixture was heated to 45 °C for 2 h, cycloadduct **2q** was furnished in a good yield (74 %) and with a moderate diastereoselectivity (*exo*/*endo* = 67:33). For ketone **1r**, under the same reaction conditions, cycloadduct **2r** was also obtained in a good yield (85 %) and with the same diastereoselectivity as that for aldehyde **1q**.

Cycloheptane is a core skeleton that widely exists in biologically important natural and unnatural products. A convenient transformation of the acetal moiety of the constructed acetal[3.2.1] skeleton might provide a method for the synthesis of these structures. We selected *exo*-**2a** as an example to test this method. *Exo*-**2a** was used in a LA-promoted reductive ring-opening process.[2g] Thus, after being treated with 3 equivalents of $TiCl_4$ and 8 equivalents of Et_3SiH at −78 °C in dichloromethane, ring-opening product **5** was successfully obtained in good yield (Scheme 6).



Scheme 6. $TiCl_4$-promoted reductive ring-opening reaction.

Terpenes containing a 6-7-6 tricyclic core skeleton are a large family of natural products, a typical example of which is the icetexane diterpenoids, for example, coulterone and komaroviquinone.[14] To further demonstrate the potential of this strategy, a modular approach to the synthesis of this family of compounds was accomplished (Scheme 7). D-A CP **9** was prepared from **6** and **7**. Surprisingly, deprotection of



Scheme 7. Synthesis of the core skeleton of komaroviquinone: a) Mg, CuI,THF/Et_2O, 76 %; b) $(CH_2OH)_2$, PTSA, toluene, reflux, 81 %; c) $[PdCl_2(PPh_3)_2]$, tributyl(1-ethoxyvinyl)stannane, toluene, reflux; d) N_2CHCO_2Me, $[Rh_2(OAc)_4]$, Et_2O, 59 % over two steps; e) $[PdCl_2(MeCN)_2]$ (5 mol %), acetone, 81 %, *exo*/*endo* = 91:9; f) *t*BuOK, toluene, 69 %; g) LiCl, wet DMSO, 160 °C, 81 %; h) PPh_3MeBr, *t*BuOK, THF, 98 %; i) $ZnEt_2$, CH_2I_2, toluene, 60 °C, 46 % (63 %, brsm); j) H_2, PtO_2, 1 M HBr/MeOH/EtOAc, run twice, 34 %. See the Supporting Information for reaction details. DMSO = dimethyl sulfoxide. PTSA = *p*-toluenesulfonic acid. THF = tetrahydrofuran.

acetal **9**, to give the ketone, catalyzed by $[PdCl_2(MeCN)_2]$ in acetone led directly to the [3+2] IMCC cycloadduct **11** in 81 % yield with a excellent diastereoselectivity (*exo*/*endo* = 91:9). The $[PdCl_2(MeCN)_2]$ probably acted as a LA to promote the [3+2] IMCC of the possible ketone intermediate **10**.[15] A Dieckmann condensation of the major cycloadduct *exo*-**11**, which was the diastereoisomer with the desired stereochemistry, afforded β-ketoester **12** in 69 % yield. The structure of **12** was confirmed by X-ray crystal structure analysis.[13] β-Ketoester **12** was then converted into ketone **13** by dealkoxycarbonylation. Olefination of ketone **13** followed by a Simmons–Smith cyclopropanation furnished **14**. Finally, hydrogenation and hydrolysis of **14** occurred simultaneously

to afford ketone **15**, which existed in equilibrium with the hemiacetal form **16**, as revealed by the ^{1}H and ^{13}C NMR spectra.

In summary, we have successfully developed the first intramolecular cycloadditon of D-A CP. This is also the first catalytic [3+2] cycloaddition of D-A CP with carbon–heteroatom multiple bonds. This [3+2] IMCC provides a general and efficient strategy for the construction of structurally diverse acetal[*n*.2.1] skeletons and 1,4-dioxygen-substituted cyclic skeletons. Features of this strategy include the mild reaction conditions, large range of substrates (a variety of substituted cyclopropanes and carbonyls), and, in most cases, moderate to excellent diastereoselectivities. The conversion of an acetal[3.2.1] skeleton into a functionalized cycloheptane was carried out by the reductive ring opening of the acetal. A modular synthesis of icetexane diterpenoids was also accomplished, and during this synthesis a novel domino Pd-catalyzed deprotection/[3+2] IMCC reaction was discovered. Further investigation will focus on the application of the [3+2] IMCC strategy to the synthesis of natural products containing acetal[*n*.2.1] and six- to eight-membered cyclic skeletons.

Experimental Section

General procedure for the [3+2] IMCC of D-A CP **1**: Under an argon atmosphere, D-A CP **1** (0.3 mmol) was dissolved in 4.5 mL of $MeNO_2$ and cooled to −20 °C, and to this mixture was added slowly TESOTf (0.06 mmol, 3 mL, 0.02 M in $MeNO_2$). The solution was stirred at −20 °C for 2 h, quenched with a vigorously stirred solution of saturated aqueous $NaHCO_3$ (30 mL), and extracted with diethyl ether (3 × 45 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1:50 to 1:30) to afford adduct **2** as a mixture of diastereoisomers.

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