Synthetic Methods

DOI: 10.1002/ange.201202699

Asymmetric Syntheses of 8-Oxabicyclo[3,2,1]octanes: A Cationic Cascade Cyclization**

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8-Oxabicyclo[3.2.1]octane, or 8-oxatropane, is a common structural motif featured in many classes of polycyclic natural products (Figure 1), some of which show interesting biological activities.[1–4] 8-Oxatropanes are also structural mimics of tropane alkaloids, and consequently there is an increasing interest in their potential pharmaceutical use, particularly against cocaine abuse.[5]

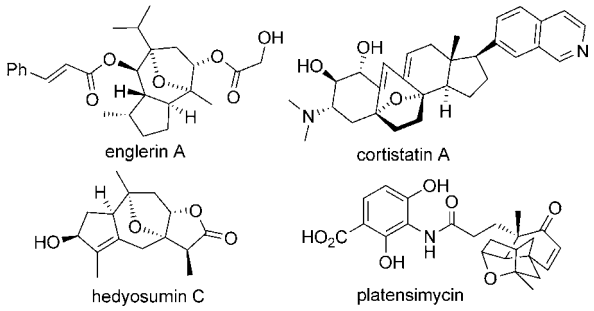
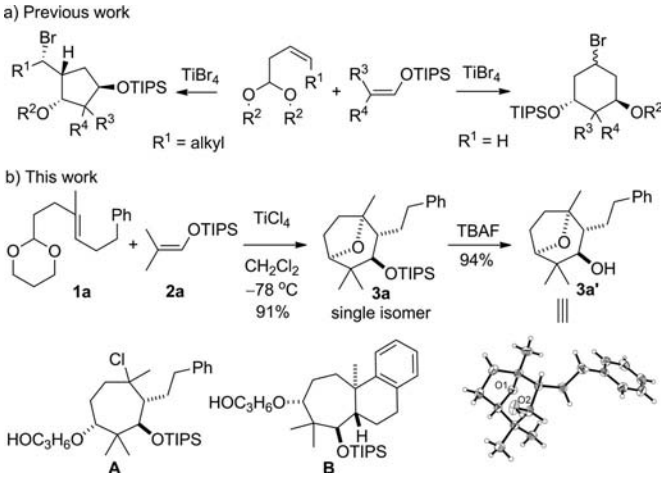


Figure 1. Selected examples of natural products containing the 8-oxatropane core.

Compelled by the interesting biological activities of 8-oxatropanes, many groups have embarked on the search for new methodologies to construct this bicyclic structure. For example, Molander and co-workers have reported a Lewis acid promoted double allylation of 1, 4-dicarbonyl compounds to construct 8-oxatropanes.[6] The same group later reported the syntheses of 8-oxatropanes using a $TiCl_4$-promoted cycloaddition of a bis(trimethylsilyl enol ether) and 1,4-dicarbonyl compounds.[7] Chiu and co-workers found that the cycloaddition reaction also worked well using epoxy enol silanes as the dienophile.[8] Another cycloaddition component, allenamide, which was proposed by Hsung and co-workers has also been applied in this reaction successfully.[9] Recently, Wang and co-workers developed a Lewis acid catalyzed intramolecular cycloaddition of alkynylcyclopropyl ketones with carbonyls to build this skeleton.[10] In addition, many metals such as rhodium(II),[11] platinum(II),[12] gold(I),[13] and tungsten[14] catalyze the 1,3-dipolar cycloaddition of carbonyl ylides and have been shown to be effective in constructing the 8-oxatropane scaffold. Despite the excellent progress made thus far for the synthesis of 8-oxatropanes, practical and asymmetric selective methods are still lacking.[9c,12b,15] Herein, we report an efficient diastereoselective and enantioselective synthesis of 8-oxabicyclo-[3.2.1]octane through a cationic cascade reaction mediated by $TiCl_4$.

Previously, we have reported the syntheses of five- and six-membered ring compounds using the Mukaiyama aldol/Prins cascade reaction (Scheme 1a).[16] We hypothesized that the same cascade reaction design could be also applied for the assembly of seven-membered rings (Scheme 1b). With this notion in mind, we treated a solution of the 1,4-cyclic acetal **1a** and silyl enol ether **2a** with 1.2 equivalents of $TiCl_4$ in the hope of getting either the seven-membered ring compound **A** or **B**. Surprisingly, this reaction afforded the 8-oxatropane **3a** in 91% yield as a single isomer. No trace of side products, such as those produced from a chlorine trapping of *tert*-butyl cation (**A**) or a Friedel–Crafts reaction with the phenyl group (**B**),[17] were observed. The structure of **3a** was ascertained by



Scheme 1. a) Previous work. b) Preliminary study for the work presented herein.[19] TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl.

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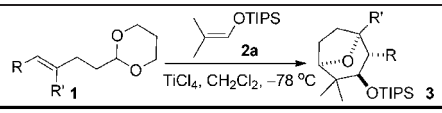
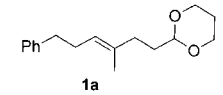
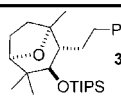
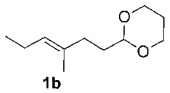
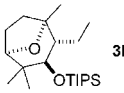
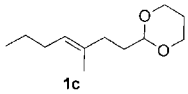
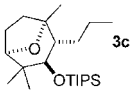
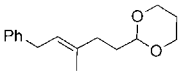
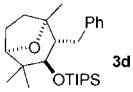
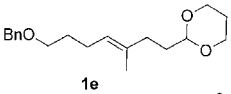
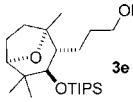
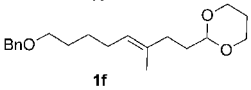
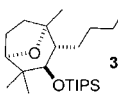
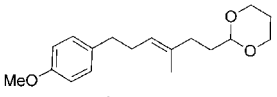
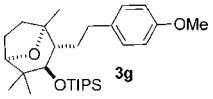
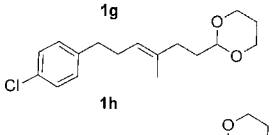
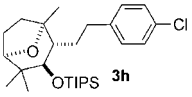
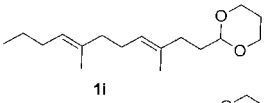
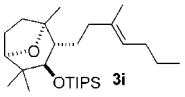
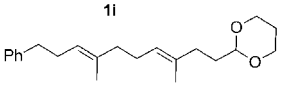
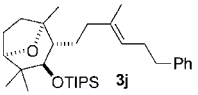
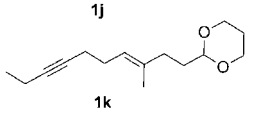
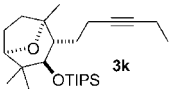
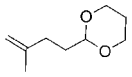
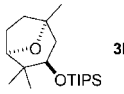
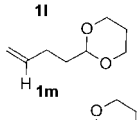
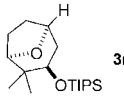
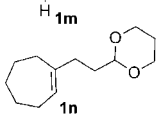
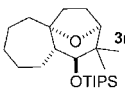
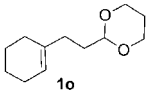
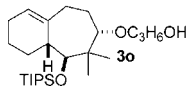
[**] We gratefully acknowledge the Nanyang Technological University, the Singapore Ministry of Education Academic Research Fund Tier 2 (MOE2010- T2-2-067), and Tier 2 MOE2011-T2-1-013 for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201202699.

Table 1: Cascade cyclization between various cyclic acetals and silyl enol ether **2a**.[a]



Entry	Substrate	Product	Yield [%][b]
1	 **1a**	 **3a**	91
2	 **1b**	 **3b**	85
3	 **1c**	 **3c**	90
4	 **1d**	 **3d**	92
5	 **1e**	 **3e**	84
6	 **1f**	 **3f**	89
7	 **1g**	 **3g**	84
8	 **1h**	 **3h**	85
9	 **1i**	 **3i**	66
10	 **1j**	 **3j**	52
11	 **1k**	 **3k**	56
12	 **1l**	 **3l**	74
13	 **1m**	 **3m**	46
14	 **1n**	 **3n**	54
15	 **1o**	 **3o**	57

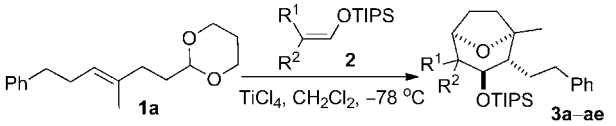
[a] Reaction conditions: $TiCl_4$ solution (0.24 mL, 1.0 M in CH_2Cl_2) was added to a solution of **1** (0.2 mmol), **2** (0.3 mmol), and 4 Å molecular sieve (0.3 g) in anhydrous dichloromethane (2 mL) at −78 °C. [b] Yield of isolated product. Bn = benzyl.

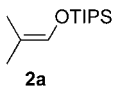
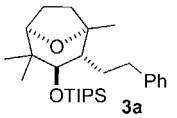
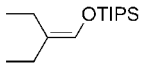
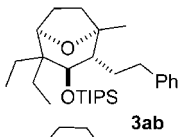
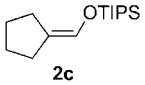
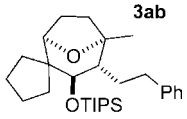
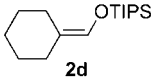
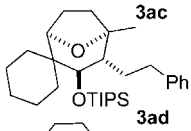
inference from the X-ray crystal data of its alcohol derivative (**3a′**). Other Lewis acids such as, $TiBr_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, and $Sc(OTf)_3$ were also tested, but $TiCl_4$ gave the best results.

With the optimal reaction conditions in hand, fifteen 1,4-cyclic acetal substrates were investigated to explore the reaction scope and the results are summarized in Table 1. Generally, the desired products were obtained in good yields with excellent diastereoselectivities (entries 1–14). The ether group (entries 5 and 6) was well tolerated in the reaction. When an electron-donating group was introduced in the phenyl group (**1g**), the 8-oxabicyclo[3.2.1]octane **3g** was obtained in high yield (entry 7), and there was still no Friedel–Crafts reaction observed for the phenyl unit. It is notable that isolated alkenes (entries 9 and 10) and an isolated alkyne (entry 11) were also tolerated in this reaction, although the yields were slightly compromised. In the case of terminal alkenes, the disubstituted substrate (entry 12) exhibited better reactivity than the monosubstituted substrate (entry 12). For the cycloheptene substrate **1n** (entry 14), the reaction yield was moderate. In contrast, when a similar cyclohexene substrate (**1o**) was tested, the alkene product **3o** was obtained instead of the desired 8-oxatropane (entry 15).

To further expand the scope of this reaction, the reactivity of five different silyl enol ethers were screened (Table 2). Generally, high yields and high diastereoselectivities were obtained when the trisubstituted silyl enol ethers **2a–d** were used (entries 1–4). When the disubstituted silyl enol ether **2e**

Table 2: Cascade cyclization between various silyl enol ethers and cyclic acetal **1a**.[a]



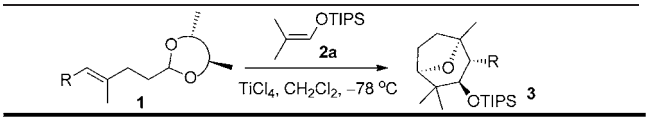
Entry	Substrate	Product	Yield [%][b]	d.r.[c]
1	 **2a**	 **3a**	91	>99:1
2	 **2b**	 **3ab**	85	90:10
3	 **2c**	 **3ac**	87	96:4
4	 **2d**	 **3ad**	91	93:7
5	**2e**	**3ae**	96	59:41

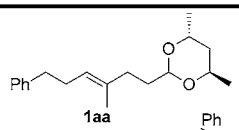
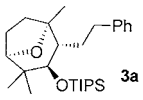
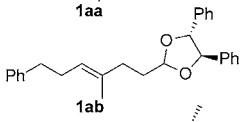
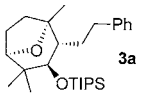
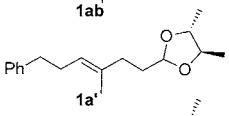
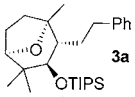
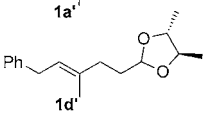
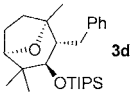
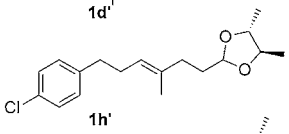
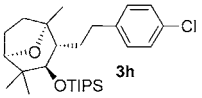
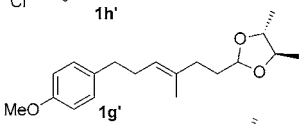
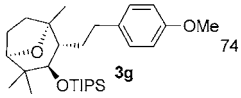
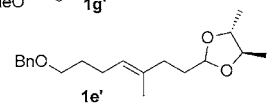
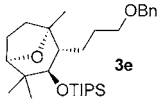
[a] Reaction conditions: see Table 1. [b] Yield of isolated product. [c] The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture.

was used, the yield remained high, but the diastereoselectivity decreased (entry 5).

Encouraged by previous results, we further explored the asymmetric version of this reaction using chiral acetals[18] (Table 3). For chiral acetals (**1a′**, **1aa**, and **1ab**) derived from the same aldehyde, the acetal **1a′** derived from (2*R*,3*R*)-2,3-butanediol gave **3a** with the highest enantioselectivity (entry 3). Accordingly, acetals derived from (2*R*,3*R*)-2,3-butanediol were adopted for further optimization of the reaction. Generally, high *ee* values were obtained independent of the substitution on the olefin substrates (entries 3–7). The absolute stereochemistry of the cyclization products was confirmed by X-ray analysis of a derivative of the enantiomerically enriched product **3h** (entry 5 and see the Supporting Information).[19]

Table 3: Asymmetric cyclization between various chiral cyclic acetals and silyl enol ether **2a**.[a]

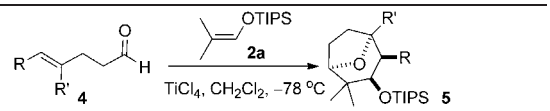


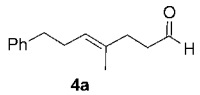
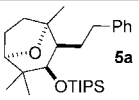
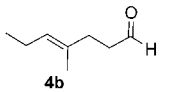
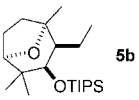
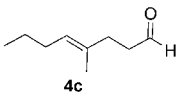
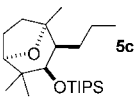
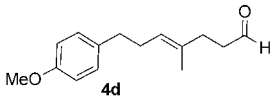
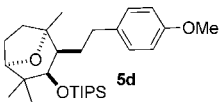
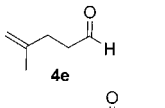
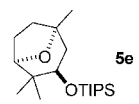
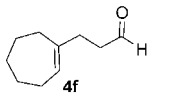
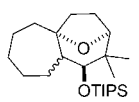
Entry	Substrate	Product	Yield [%][b]	*ee* [%][c]
1	 **1aa**	 **3a**	91	89
2	 **1ab**	 **3a**	66	56
3	 **1a'**	 **3a**	88	97
4	 **1d'**	 **3d**	91	94
5	 **1h'**	 **3h**	80	98
6	 **1g'**	 **3g**	74	95
7	 **1e'**	 **3e**	79	94

[a] Reaction conditions: see Table 1. [b] Yield of isolated product. [c] The *ee* values were determined by chiral HPLC analysis.

From a mechanistic standpoint, we compared the difference in reactivity between acetals and aldehydes (Table 4). Surprisingly, another 8-oxabicyclo[3.2.1]octane diastereomer product, **5a**, was obtained in good yield (51%) with high diastereoselectivity when aldehyde **4a** was used as the substrate (entry 1). The five other substrates, **4b–f**, also gave the bicyclic products in moderate to good yields (entries 2–6). In contrast, the diastereoselectivity of **5f**, which comprises a cycloheptene group, was negligible.

Table 4: Cascade cyclization between various aldehydes and silyl enol ether **2a**.[a]



Entry	Substrate	Product	Yield [%][b]	d.r.[c]
1	 **4a**	 **5a**	51	97:3
2	 **4b**	 **5b**	53	93:7
3	 **4c**	 **5c**	58	93:7
4	 **4d**	 **5d**	56	95:5
5	 **4e**	 **5e**	65	–
6	 **4f**	 **5f**	55	50:50

[a] Reaction conditions: see Table 1. [b] Yield of isolated product. [c] The d.r. values were determined by ^{1}H NMR spectroscopy.

The structures of compounds **5a–d** were ascertained by reference to an X-ray diffraction analysis of compound **5d′** (Figure 2), which was derived from desilylation of **5d**. Interestingly, the 2-alkyl and 3-hydroxy groups in **5d′** were aligned *syn* to each other, and this is in sharp contrast to the 2,3-*anti* stereochemistry observed in products **3a–k** when cyclic acetals were used as substrates (see Scheme 1 and Tables 1–3).

In light of the above results, a reaction mechanism may be proposed to rationalize the impact of the cyclic acetal or aldehyde groups on the stereochemical outcome of the cyclizations. As depicted in Scheme 2, the initial step involves a Mukaiyama aldol reaction between the acetal or aldehyde and the silyl enol ether **C**. Subsequently, the olefin attacks the silylated oxocarbenium via a syn-clinal, closed-chain transi-

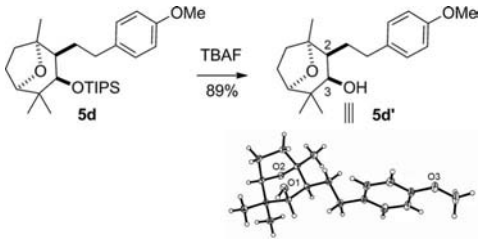
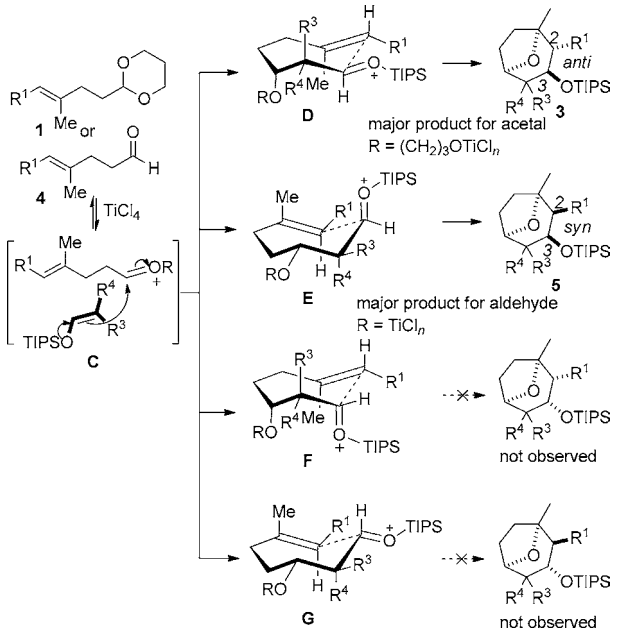


Figure 2. Determination of the relative stereochemistry of **5d′**. Thermal ellipsoids shown at 50% probability.[19]



Scheme 2. Proposed mechanism for cyclic-acetal or aldehyde-initiated cascade cyclization.

tion state with four possible conformations (**D**–**G**). According to our model, the transition-state conformation appears to be critical for defining the relative stereochemistry at the 2- and 3-positions of 8-oxatropane. In the case when an acetal is the substrate, the transition state **D** is favored with the R^1 and OTIPS groups adopting pseudoequatorial positions. As a result, the *anti*-configured product **3** is produced. In comparision, the conformation of transition state **F** was not favored, presumably because of 1,3-diaxial repulsion of the OTIPS/Me and OTIPS/OR groups. In contrast, when an aldehyde is the substrate, the transition state has the conformation **E** with the R^1 and $OTiCl_n$ groups taking pseudo equatorial positions and the OTIPS group occupying a pseudoaxial position, thereby resulting in the formation of the cyclization product **5**. Our data also suggest that the transition state **G** is inactive.

In conclusion, we have developed a novel and practical diastereoselective cationic cascade cyclization reaction for the synthesis of 8-oxabicyclo[3.2.1]octanes, a common structural motif present in many natural products. More importantly, the stereochemical outcome of the 2,3-substituents can be readily controlled through employing either an acetal or an aldehyde as the reaction initiator. In addition, a highly enantioselective reaction can also be achieved by using (2*R*,3*R*)-2,3-butanediol-derived chiral acetals as the substrate. Moreover, the mild reaction conditions and its compatibility with substrates containing multiple electron-rich functional groups, such as olefins, alkynes, and substituted anisole also make the present protocol attractive for organic synthesis. Additional studies on the application of this method to the synthesis of functionalized tropanes are currently in progress and the results will be reported in due course.

Received: April 7, 2012
Revised: May 24, 2012
Published online: July 2, 2012

Keywords: aldol reaction · cyclization · heterocycles · synthetic methods · titanium

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[19] CCDC 873237 (**3a′**), 873239 (**3h**), and 873238 (**5d′**) 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

