Carbocycles

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Formation of Seven-Membered Carbocycles by the Use of Cyclopropyl Silyl Ethers as Homoenols**

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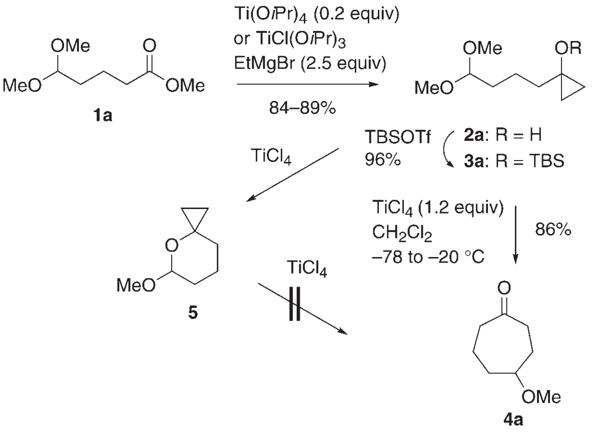
The presence of heteroatom substituents on cyclopropanes enhances their reactivity toward electrophiles. Ring-opening reactions of cyclopropanols and siloxy derivatives have been extensively investigated.[1] An interesting variation involves the addition of other functionalities (e.g., vinyl or ethynyl) to cyclopropanols, which offers unique composite groups for the formation of C−C bonds.[2,3] The use of a cyclopropanol, which could be viewed as a "homoenol" or "homoenolate" equivalent, in the nucleophilic addition to a carbonyl compound or an acetal, has been limited primarily to 1-alkoxy-1-siloxycyclopropanes.[4] Little was known about the cognate homologous aldol or Mukaiyama reaction of parent cyclopropanols or siloxycyclopropanes.[5,6] We report herein an expedient entry to seven-membered carbocycles by the Kulinkovich cyclopropanation of acetal-tethered esters and a subsequent Lewis acid mediated ring expansion of the resulting cyclopropyl silyl ethers.

In an initial experiment, cyclopropanol **2a** was first prepared in 84–89 % yield by the Kulinkovich cyclopropanation[7,8] of commercially available methyl 5,5-dimethoxyvalerate (**1**) with ethylmagnesium bromide (Scheme 1). Following silylation (96 %), treatment of the resulting siloxycyclo-



Scheme 1. Annulation of seven-membered carbocycles. TBS = *tert*-butyldimethylsilyl, OTf = trifluoromethanesulfonate.

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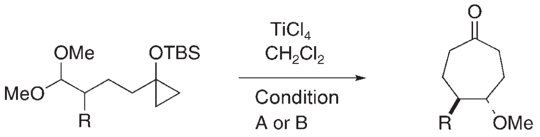
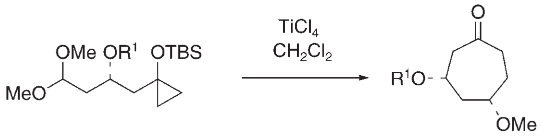
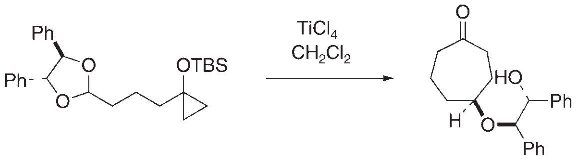
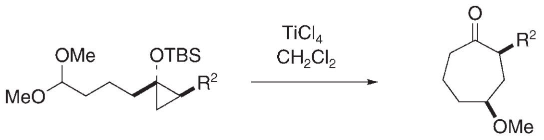
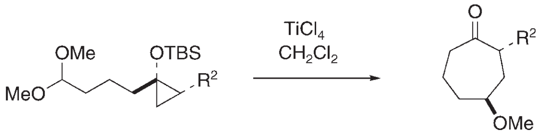
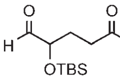
propane **3a** with $TiCl_4$ afforded 4-methoxycycloheptanone (**4a**) in 86% yield. The yield (63%) was lower when the corresponding trimethylsilyl (TMS) ether was employed. The use of a silyl ether proved to be necessary: cyclopropanol **2a** was quickly converted into **5** and its hemiacetal at −78°C upon exposure to $TiCl_4$, but **5** gave only trace amounts of **4a** under several different conditions. This observation is in contrast to the interesting synthesis developed by Minbiole and co-workers of oxepanes from the respective endocyclic acetals.[6] These results suggest that the siloxycyclopropane is indeed the actual nucleophile that adds to the oxocarbenium ion intermediate.

Diastereoselectivity by a resident stereocenter was next examined with **3b–e** under two different conditions (Table 1). Both yields and stereoselectivity were improved by maintaining the reaction mixture at low temperature (−78°C; condition B). Unfortunately, 1,2- and 1,3-diastereoselectivity was surprisingly low (entries 1–4).[9] Enantioselective synthesis was achieved, albeit in modest selectivity, by means of a nonracemic C_2-symmetric acetal (entry 5). The stereochemistry of the major product **4f** was secured by X-ray analysis.[10] (*R*,*R*)-(+)-Hydrobenzoin was chosen as a chiral auxiliary primarily because of its commercial availability and ease of removal. At present, the origin for the observed 1,3-diastereofacial selectivity is unclear.[11]

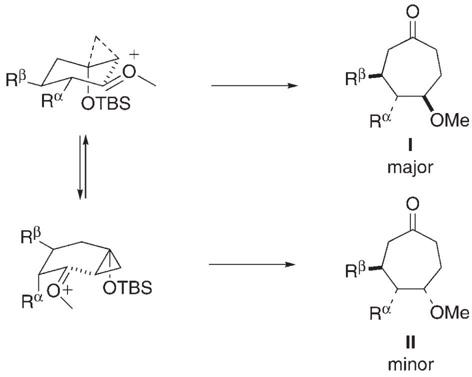
Regioselectivity was also examined: it is the less-substituted C–C bond of the three-membered ring that reacts with the oxocarbenium ion (entries 6–8).[12] It is interesting to note that the major products **4h** and **4i**, obtained from **3h**[13a] and **3i**,[13b] are diastereomeric (Table 1).

Table 1: Diastereo- and regioselectivity of seven-membered-ring formation.

Entry	Substrate	Conditions[a]	Major product	Yield [%]	Diastereoselectivity
					
1	**3b**: R=Me	A	**4b**	77	1:0.9
		B	**4b**	91	1.7:1
2	**3c**: R=OTBS	A	**4c**	45	1:0.9
			+**6**[b]	22	
					
3	**3d**: R^1=TBS	A	**4d**	58	1.3:1
		B	**4d**	65	1.5:1
4	**3e**: R^1=TIPS	A	**4e**	67	2:1
					
5	**3f**	A	**4f**	72	3:1
		B	**4f**	84	3.5:1
					
6	**3g**: R^2=Me	A	**4g**	82	2.5:1
7	**3h**: R^2=$(CH_2)_2$OTIPS	A	**4h**	76	2.5:1
					
8	**3i**: R^2=$(CH_2)_2$OTIPS	A	**4i**	68	3:1

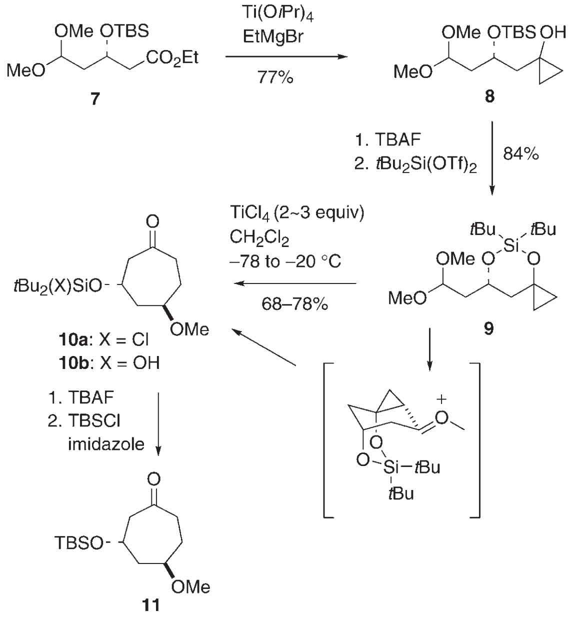
[a] Condition A: $TiCl_4$ (1.2 equiv), −78→−20°C; condition B: $TiCl_4$ (2.0 equiv), −78°C. [b]  **6**

The surprisingly modest diastereoselectivity in the cyclization might be attributed to competing stereochemical pathways that involve chair, boat, and/or twist-boat (not shown) conformations (Scheme 2).[14] Assuming that a chairlike transition state is of lower energy, the configuration of the major isomers **I** is tentatively assigned as shown in Table 1. The minor isomers **II** could arise from a boatlike transition state; for example, when $R^{\alpha} = H$ (e.g., **3d** and **3e**), the indicated boat conformation might become competing. At present, one cannot discount the involvement of a gauche conformation of the oxocarbenium ion in a chairlike transition state in the formation of the minor isomers. Elucidation of important factors that influence diastereocontrol might be possible by judicious placement of multiple substituents but must await further investigations.



Scheme 2. Stereochemical rationale.

Toward eventual applications in natural product synthesis, such as the stereoselective syntheses of skipped polyols, we developed an effective strategy for diastereoselective cyclization by relying on di-*tert*-butylsilylene as a conformational lock (Scheme 3). Subsequent to the Kulinkovich cyclopropanation of **7**,[9] the resulting cyclopropanol **8** was converted into silylene **9** by standard methods. The key cyclization proceeded cleanly by the action of $TiCl_4$ to deliver **10** as a single diastereomer, but as an inconsequential mixture of **10a** and **10b**. The stereochemistry of **10** was tentatively assigned by consideration of the most plausible transition state. As additional support, **10** was converted into **11**, which proved to be identical to the minor isomer from the cyclization of **3d** (Table 1, entry 3). Together with diastereoselective hydroxycyclopropanation of secondary homoallylic alcohols,[13b] this diastereoselective approach should be useful in a rapid increase in molecular complexity by the coupling of two large segments.



Scheme 3. Diastereoselective cyclization by using di-*tert*-butylsiylene. TBAF = tetrabutylammonium fluoride.

In conclusion, a concise synthesis of multifunctionalized seven-membered carbocycles has been achieved by sequential application of the Kulinkovich cyclopropanation of acetal-tethered esters and the Lewis acid mediated addition of the resulting cyclopropyl silyl ethers to the oxonium ion intermediates. Particularly noteworthy is the effective use of a *tert*-butylsilylene group for diastereoselective cyclization. Mechanistic studies and applications in natural product synthesis will be reported in due course.

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