Vinyl Oxocarbenium Ions in Intermolecular [4 + 3] Cycloaddition Reactions

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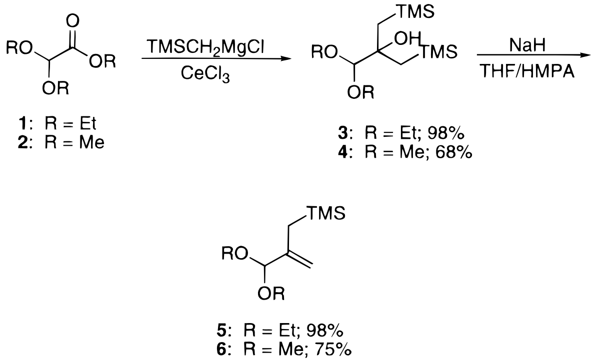
The [4 + 3] cycloaddition reaction of dienes with allylic cations represents an efficient and convergent approach to the synthesis of seven-membered rings.[1] As part of our broad interest in this area,[2] we have begun studies directed toward asymmetric [4 + 3] cycloadditions using chiral allylic cations or their functional equivalents. With the ultimate goal of applying chiral acetal technology in this area, we conducted a study of the application of achiral acetals to [4 + 3] cycloadditions. Our preliminary results are the subject of this report.

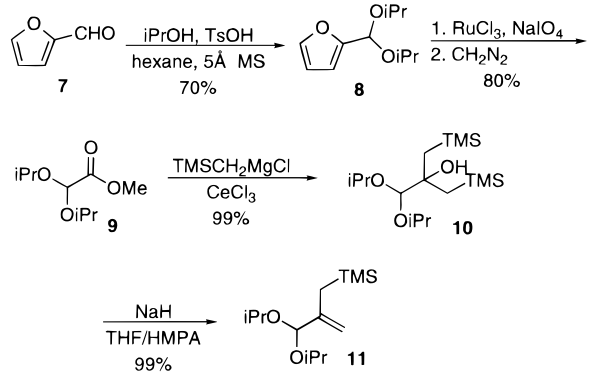
This work represents one of still only a few applications of heteroatom-stabilized allylic cations to the [4 + 3] cycloaddition reaction.[2b,k,3] Of those, the most closely related the work described herein is the seminal report by Albizati and Murray who demonstrated that trialkylsilyl enol ethers derived from pyruvaldehyde dimethyl acetal reacted with dienes in the presence of Lewis acids to afford [4 + 3] cycloaddition products.[3a] We sought to develop a related procedure which utilized a more stable and easily-handled starting material.

Two of the substrates for our study were easily synthesized from commercially available materials. Thus, treatment of either ethyl diethoxyacetate (**1**) or methyl dimethoxyacetate (**2**) with (trimethylsilyl)methylmagnesium chloride/$CeCl_3$ afforded the expected tertiary alcohols **3** and **4** in 98% and 68% yields, respectively.[4] Treatment of the alcohols with sodium hydride in ether/HMPA gave the expected Peterson elimination products **5** and **6** in good to excellent yields (Scheme 1).[5]

Scheme 1



Scheme 2



The diisopropoxy acetal **11** was synthesized in the same fashion, but the starting ester had to be prepared as shown in Scheme 2. Stirring a solution of furfural and isopropyl alcohol in hexane with a catalyic amount of tosic acid and 5 Å molecular sieves gave acetal **8** in 70% yield.[6] Oxidative cleavage of the furan ring with in-situ-generated ruthenium tetraoxide,[7] followed by esterification of the resultant acid, gave an 80% overall yield of methyl diisopropoxyacetate (**9**) from acetal **8**. Ester **9** could be converted to acetal **11** in excellent yield as described above.

We initially examined the Lewis acid-mediated reaction of **5** with 1.5 equiv of furan in dichloromethane at −78 °C to survey the effect of Lewis acid variation on the cycloaddition reaction. The results are shown in Table 1. The best Lewis acids are $TiCl_4$ and $SnCl_4$ (Table 1, entries 1, 15). Mixtures of $TiCl_4$ and $Ti(OiPr)_4$ are also effective in this reaction (Table 1, entries 2−6). The use of various aluminum-based Lewis acids demonstrated that within this family of reagents the reaction improves with increasing Lewis acid strength (Table 1, entries 7−11).[3a] Other Lewis acids give only fair results, though it is interesting and important to note that the reaction can be catalytic in Lewis acid (Table 1, entry 12). In certain reactions, variable amounts of an as yet unidentified side product were formed. While these results clearly suggest a preference for certain Lewis acids over others, temperature and solvent effects may change these apparent preferences, but the requisite studies have yet to be performed.

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(1) For reviews of [4 + 3] cycloadditions, see: (a) Hosomi, A.; Tominaga, Y. [4 + 3] cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 5.1, pp 593−615. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (d) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163−344. (e) For a review of [4 + 3] cycloadditions, see: Harmata, M. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Greenwich, 1997; Vol. 4, in press.

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(3) (a) Murray, D. H.; Albizati, K. F. *Tetrahedron Lett.* **1990**, *31*, 4109. (b) Föhlisch, B.; Krimmer, D.; Gehrlach, E.; Käshammer, D. *Chem. Ber.* **1988**, *121*, 1585. (c) Föhlisch, B.; Flogaus, R.; Oexle, J.; Schädel, A. *Tetrahedron Lett.* **1984**, *25*, 1773. (d) Sasaki, T.; Ishibashi, Y.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 1693. (e) Blackburn, C.; Childs, R. F.; Kennedy, R. A. *Can. J. Chem.* **1983**, *61*, 1981. (g) Hanke, K.; Gotthardt, H. *J. Chem. Soc., Chem. Commun.* **1984**, 1682. (g) Mok, K.-L.; Nye, M. J. *J. Chem. Soc. Chem. Commun.* **1974**, 608. (h) Walters, M. A.; Arcand, H. R. *J. Org. Chem.* **1996**, *61*, 1478. (i) Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23.

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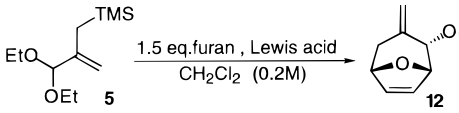
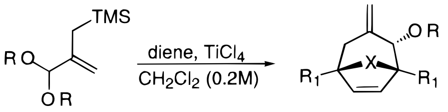
Table 1. Lewis Acid Optimization of the Reaction of 5 with Furan



entry	Lewis acid	equiv	yield (%)[a]
1	$TiCl_4$	1.1	99
2	$TiCl_4$:$Ti(OiPr)_4$, 1:1	2	55 (81)
3	$TiCl_4$:$Ti(OiPr)_4$, 7:5	2	82
4	$TiCl_4$:$Ti(OiPr)_4$, 11:5	2	89
5	$TiCl_4$:$Ti(OiPr)_4$, 13:5	2	84
6	$TiCl_4$:$Ti(OiPr)_4$, 15:5	2	71
7	Et_3Al	1.1	0
8	Et_2AlCl	1.1	29 (40)
9	$EtAlCl_2$	1.1	52
10	$MeAlCl_2$	1.1	61
11	$AlCl_3$	1.1	53
12	TMSOTf	0.1	65
13	TfOH	1.1	60
14	$SbCl_5$	1.1	32
15	$SnCl_4$	1.1	93

[a] Yield after chromatographic purification. Yields in parentheses are based on recovered starting material.

Table 2. [4 + 3] Cycloadditions of Allylic Acetals

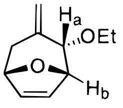


entry	acetal	diene	X	R_1	product	yield (%)[d]
1	**5**	a	O	H	**12**	99
2	**5**	b	CH_2	H	**13**	62
3	**5**	c	O	Me	**14**	47
4	**6**	a	O	H	**15**	62
5	**6**	b	CH_2	H	**16**	43
6	**6**	c	O	Me	**17**	51
7	**11**	a	O	H	**18**	50
8	**11**	b	CH_2	H	**19**	53
9	**11**	c	O	Me	**20**	O

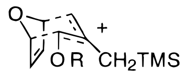
[a] Furan. [b] Cyclopentadiene. [c] 2,5-Dimethylfuran. [d] Yield after chromatographic purification.

With these data in hand we proceeded to examine the ability of acetals **5**, **6**, and **11** to engage in [4 + 3] cycloaddition chemistry. The general procedure consisted of the addition of 1.5 equiv of diene to a 0.2 M solution of acetal in dichloromethane, cooling to −78 °C, and adding 1.1 equiv of $TiCl_4$. The results are presented in Table 2. The yields of the cycloaddition reactions are generally fair to good, the exception being the reaction of **5** with furan which proceeds in essentially quantitative yield (Table 2, entry 4). Only one reaction was truly poor, that of **11** with 2,5-dimethylfuran (Table 2, entry 9). An apparent steric effect precludes the formation of cycloadduct. Only low yields of a product which appeared to be derived from Friedel−Crafts chemistry were obtained.

The reactions exhibit uniformly high simple diastereoselectivity. The assignment of relative configuration is based on the 4.2 Hz coupling constant in the cycloadducts between the hydrogens H_a and H_b shown in adduct **12**. This value is suggestive of the stereochemistry shown,[3a] is generally consistent within the entire group of cycloadducts produced in this study, and is also supported by X-ray data obtained by us on work in a related area.[8] Mechanistically, this implies an endo approach of the diene to the putative oxocarbenium ion intermediate as shown in **21**. However, the exact nature of the reactive species involved in this reaction and mechanistic concertedness of the so-called cycloaddition have not been addressed, and consequently a rigorous interpretation of the data is not yet possible.

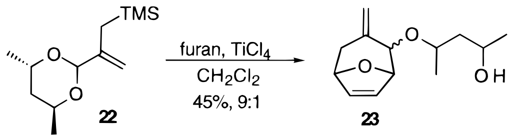


12



21

In summary, we have developed a simple synthesis of (trimethylsilyl)methyl allylic acetals which is likely very general. The application of these acetals in intermolecular [4 + 3] cycloadditions demonstrates their utility and lays the foundation for the study of structurally-related chiral acetals.[9] For example, in a single experiment, reaction of **22** with furan in the presence of $TiCl_4$ gave a 45% yield of cycloadduct **23** with a diastereoselectivity of 9:1. More detailed studies of this reaction and other applications of this new family of bifunctional conjunctive reagents are under study. Results will be reported in due course.[10]



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Supporting Information Available: Experimental details and characterization data for **5**, **6**, and **11** and their precursors. A general cycloaddition experimental procedure, characterization data, and ^1H and ^{13}C NMR data for **12**−**19** (24 pages).

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(8) Jones, D. E.; Kahraman, M.; Barnes, C. L. Unpublished data from these laboratories.

(9) For the application of chiral allylic acetals to the Diels−Alder reaction, see: Sammakia, T.; Berliner, M. A. *J. Org. Chem.* **1994**, *59*, 6890.

(10) All new compounds exhibited satisfactory ^1H and ^{13}C NMR and IR spectral data as well as satisfactory combustion analysis or high resolution exact mass data.