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LETTERS

Chiral Cations in 4+3 Cycloadditions

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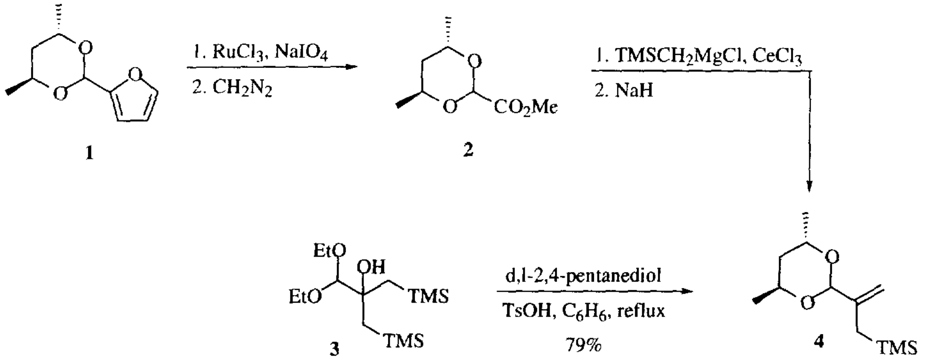
Summary: The reaction of the chiral acetal **4** with furan and cyclopentadiene in the presence of a Lewis acid gives 4+3 cycloadducts in very good yields. Diastereoselectivity in the case of furan is exceptionally high, while that for the reaction with cyclopentadiene is lower. The sense of diastereoselection in the case of furan is opposite to that which would be predicted on the basis of mechanistic models for the origin of stereoselectivity in many reactions of chiral acetals mediated by Lewis acids. © 1999 Elsevier Science Ltd. All rights reserved.

We recently reported that the reaction of racemic **4** with furan in the presence of titanium tetrachloride was highly diastereoselective.[1] A subsequent report by Hoffmann and co-workers on the use of chiral allylic cations in 4+3 cycloadditions prompts us to present a more detailed account of our results in this area.[2]

The preparation of **4** proceeds in a straightforward fashion from either acetal **1** or commercially available ethyl diethoxyacetate (Scheme 1). Oxidative degradation of the furan ring in **1** followed by esterification of the resulting carboxylic acid with diazomethane afforded the ester **2** in 75% yield.[3] Reaction with trimethylsilylmethylmagnesium chloride in the presence of cerium chloride followed by a Peterson elimination reaction gave **4** in 66% yield.[4] Alternatively, the tertiary alcohol **3**, readily prepared from ethyl diethoxyacetate,[1] could be treated with 2,4-pentanediol to afford **4** in high yield via a transacetalization and concomitant acid-mediated Peterson elimination reaction.



Scheme 1

Our initial reactions with **4** and furan were conducted in dichloromethane at -78 °C using titanium tetrachloride as the Lewis acid. Two diastereomers were produced in fair yield in a ratio of 9:1 (equation 1). We initially believed that the origin of the diastereoselectivity in this reaction was the result of a mechanism represented by the structure shown in Figure 1. In this picture, coordination of the Lewis acid to the oxygen bound to the carbon possessing the axial methyl group polarizes the corresponding C-O acetal bond, weakening it. Approach of the nucleophilic diene from the opposite face results in cycloadduct formation, either through a stepwise or concerted mechanism, leading to **5b**. This model serves well for predicting the stereochemical outcome of many reactions of chiral acetals which proceed in the presence of Lewis acids.[5] We assumed that the reaction would be endo selective, but were not certain that this would be the case. Assigning the stereochemistry of these cycloadducts by using NMR was not unambiguous. After several unsuccessful attempts, we were

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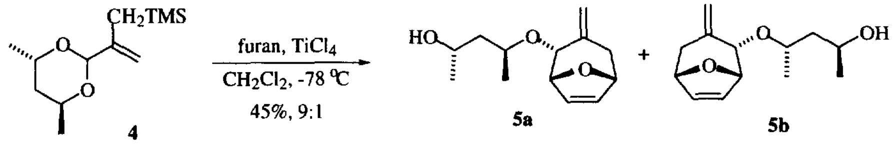


Equation 1

eventually able to prepare a derivative of the major cycloadduct which was crystalline through formation of an ester with adamantane carboxylic acid chloride. A structural determination revealed that our mechanistic hypothesis was incorrect. The major cycloadduct was **5a**.[6] Removal of the auxiliary from both cycloadducts produced the same compound.[7] Thus, they arise from attack on different faces of whatever intermediate is produced from **4** and titanium tetrachloride.

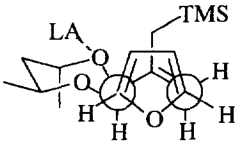


Figure 1

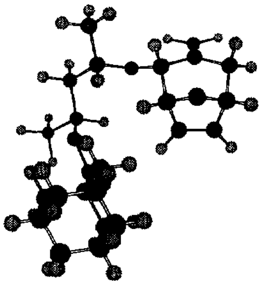
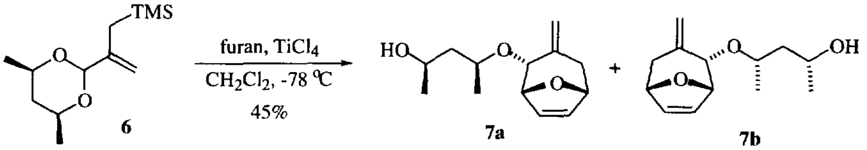


Figure 2. X-ray structure of a derivative of 5a.

As shown in Figure 2, **5a** possessed relative stereochemical relationships which suggested that the diene entered from the same side as the expected Lewis acid coordination site. Such reactions are not without precedent. For example, the DIBAL reduction of acetals derived from 2,4-pentanediol proceeds in a fashion which has been rationalized as proceeding via coordination of the Lewis acidic aluminum to the expected oxygen, followed by acetal opening and intramolecular delivery of hydride.[8] We thought that in our case, it could be possible for the Lewis acid to bind to the furan and deliver it in a similar fashion. Interestingly, the reaction of the meso-acetal **6** with furan in the presence of $TiCl_4$ led to a 5.1:1 mixture of **7a** and **7b** in 45% yield (equation 2). The stereochemistry of the major cycloadduct **7a** was established by crystallography. Again, a mechanism based on an inversion pathway is inconsistent with this result. It appeared interesting to begin to consider that the bidenatate Lewis acid was binding to furan and delivering the diene "intramolecularly" to produce the major cycloadduct. Further studies of Lewis acids, however, suggested that this was not the case.



Equation 2

Table 1 shows the results of a number of cycloaddition experiments. Entry 1 shows that increasing the amount of furan in CH_2Cl_2 results in no cycloaddition. Entries 2-5 demonstrate solvent effects. Capricious results with dichloromethane have led us to use nitroethane with good, consistent results. Entries 6-9 show that lowering the amount of furan used does not have a deleterious effect on the reaction. Excess furan causes problems, presumably due to decomposition associated with reactions of furan mediated by the Lewis acid. Entries 10-12 illustrate that cycloadducts yields decrease with decreasing concentration of the acetal. Entries 13-15 show that the reaction is not catalytic with respect to $TiCl_4$. The remaining entries show that other Lewis acids are effective for the reaction as well. Interestingly, there is some variation in diastereoselectivity as a function of Lewis acid and reaction conditions. Determining the basis for these changes will require additional

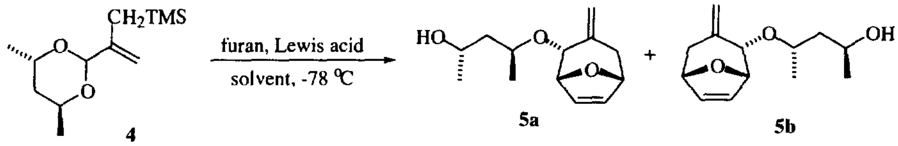


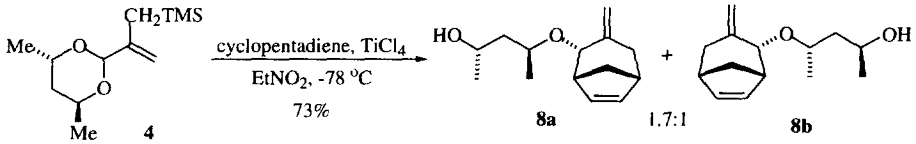
Table 1. The Reaction of 4 with Furan.

Entry	Solvent	Eq. Furan	[M] of 4	Lewis Acid (eq.)	Yield (%)[a]	Ratio 5a:5b[j]
1	CH_2Cl_2	10	0.2	$TiCl_4$ (1.1)	0[b]	-
2	THF	10	0.2	$TiCl_4$ (1.1)	0	-
3	EtOAc	10	0.2	$TiCl_4$ (1.1)	0[c]	-
4	Toluene	10	0.2	$TiCl_4$ (1.1)	0[d]	-
5	$EtNO_2$	10	0.2	$TiCl_4$ (1.1)	71	17.3:1
6	$EtNO_2$	5	0.2	$TiCl_4$ (1.1)	65	15.3:1
7	$EtNO_2$	1	0.2	$TiCl_4$ (1.1)	78	15.8:1
8	$EtNO_2$	25	0.2	$TiCl_4$ (1.1)	9[e]	-
9	$EtNO_2$	50	0.2	$TiCl_4$ (1.1)	5[f]	-
10	$EtNO_2$	10	0.1	$TiCl_4$ (1.1)	59	15.7:1
11	$EtNO_2$	10	0.05	$TiCl_4$ (1.1)	43	17.5:1
12	$EtNO_2$	10	0.01	$TiCl_4$ (1.1)	16[g]	15.4:1
13	$EtNO_2$	10	0.2	$TiCl_4$ (0.5)	26[h]	14.4:1
14	$EtNO_2$	10	0.2	$TiCl_4$ (0.25)	14[i]	25.6:1
15	$EtNO_2$	10	0.2	$TiCl_4$ (0.1)	16	25.9:1
16	$EtNO_2$	10	0.2	$SnCl_4$ (1.1)	59	6.6:1
17	$EtNO_2$	10	0.2	TMSOTf (1.1)	80	8.8:1
18	$EtNO_2$	10	0.2	BF_3/Et_2O (1.1)	77	11.2:1
19	$EtNO_2$	10	0.2	$MeAlCl_2$ (1.1)	70	4.5:1

[a] After chromatographic purification. [b] 42% recovered starting material (RSM). [c] 20% RSM. [d] 85% RSM. [e] 25% RSM. [f] 11% RSM. [g] 60% RSM. [h] 22% RSM. [i] 37% RSM. [j] Determined by HPLC.

study. However, it is important to note that regardless of the specific reaction conditions or the Lewis acid, the major product is always the same.

In the reaction of **4** with cyclopentadiene, two cycloadducts **8a/b** are produced in 73% yield in a ratio of 1.7:1 when titanium tetrachloride is used as the Lewis acid (equation 3). The stereochemical assignments in this case are based on a comparison of the resonances for the methyl groups of both diastereomers in their respective ^1H and ^{13}C NMR spectra with those of **5a** and **5b**. Both **8a** and **8b** lead to a the same compound upon removal of the chiral auxiliary.[7] The drop in diastereoselectivity relative to furan needs to be rationalized and experimentally addressed. Unfortunately, N-acetylpyrolle, 2,5-dimethylfuran, and isoprene have thus far failed to give cycloadducts in anything but poor yields with **4**.



Equation 3

In summary, we have developed a chiral allylic acetal which reacts with furan in the presence of Lewis acid to give 4+3 cycloadducts in good yields with good diastereoselectivities. This work serves as a basis for developing improved systems which react more generally with dienes and should provide part of a foundation for further studies of chiral cations in 4+3 cycloadditions reactions.[1-2, 9] Further results will be reported in due course.[10]

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Reference and Notes

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4. Bunnelle, W.H.; Narayanan, B.A. *Org. Synth.* **1990**, *69*, 89. Data on **4**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (s, 2H), 4.75 (d, 1H, *J* = 1.0 Hz), 4.32 (dq, 1H, *J* = 6.5, 6.8 Hz), 3.98 (ddq, 1H, *J* = 2.5, 6.2, 12.1 Hz,), 1.84 (ddd, 1H, *J* = 6.1, 12.0, 13.1 Hz), 1.62 (ddd, 2H, *J* = 0.8, 14.1, 17.7 Hz), 1.36 (d, 3H, *J* = 7.0 Hz), 1.32 (ddd, 1H, *J* = 1.0, 2.3, 13.3 Hz), 1.20 (d, 3H, *J* = 6.2), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.81, 110.43, 94.93, 68.07, 67.66, 36.75, 21.88, 21.78, 17.19, -1.07; IR (neat) 697 w, 711 w, 771 w, 854 s, 892 m, 924 m, 952 w, 974 w, 1000 s, 1020 m, 1030 w, 1071 s, 1107 m, 1139 s, 1159 s, 1251 s, 1289 w, 1316 m, 1338 w, 1350 w, 1380 m, 1420 w, 1434 w, 1456 w, 1645 w, 2875 m, 2896 m, 2952 m, 2974 s, 3083 w cm^{-1}. Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 63.20; H, 10.69.
5. For data on the mechanism of acetal reactions, see: (a) Mori, I.; Ishihara, K.; Flippin, L.A.; Nozaki, K.; Yamamoto, H.; Bartlett, P.A.; Heathcock, C.H. *J. Org. Chem.* **1990** *55*, 6107. (b) Denmark, S.E.; Almstead, N.G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. (c) Sammakia, T.; Smith, R.S. *J. Am. Chem. Soc.* **1994**, *116*, 7915. (d) Sammakia, T.; Smith, R.S. *J. Am. Chem. Soc.* **1992**, *114*, 10998. (e) Sammakia, T.; Smith, R.S. *J. Org. Chem.***1992**, *57*, 2997.
6. Data on **5a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, 1H *J* = 6.1 Hz), 6.15 (d, 1H, *J* = 6.2 Hz), 5.19 (s(br), 1H), 4.85 (s, 1H), 4.77 (d, 1H, *J* = 4.1 Hz), 4.75 (d, 1H, *J* = 4.1 Hz), 4.13-4.06 (m, 2H), 4.04-3.98 (m, 1H), 2.64 (s(br), 1H), 2.58-2.56 (m, 1H) 2.11 (d, 1H, *J* = 14.5 Hz), 1.68-1.59 (m, 2H), 1.21 (d 6H, *J* = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.63, 133.00, 129.93, 112.58, 79.12, 78.93, 77.25, 72.90, 64.41, 44.94, 35.56, 23.79, 19.61; IR (neat) 3447 m, 2974 s, 2934 m, 1377 w, 1331 w, 1160 m, 1101 s, 1048 m, 982 m, 890 w cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.34; H, 8.88. Data on **5b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17-6.14 (m, 2H), 5.20 (d, 1H, *J* = 1.8 Hz), 4.86 (d, 1H, *J* = 1.7 Hz), 4.74 (d, 1H, *J* = 3.9 Hz), 4.69 (d, 1H, *J* = 4.2 Hz), 4.16-4.11 (m 2H), 3.99-3.91 (m, 1H), 2.58-2.54 (m, 1H), 2.47 (s(br), 1H), 2.10 (d, 1H, *J* = 14.4 Hz), 1.75-1.70 (m, 1H), 1.63-1.57 (m, 1H), 1.29 (d, 3H, *J* = 6.3 Hz), 1.20 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.48, 133.04, 129.82, 112.21, 80.40, 79.19, 78,42, 74.42, 64.27, 45.23, 35.93, 23.95, 20.91; IR (neat) 3456 m, 2979 s, 2940 m, 2908 m, 1431 w, 1385 m, 1339 m, 1163 m, 1098 s, 1030 s, 980 m, 889 m cm^{-1};Anal. Calcd for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1409.
7. The auxiliary was removed by oxidation of the cycloadduct with the Dess-Martin periodinane followed by treatment with potassium carbonate in methanol. Here are the experimental procedures: Oxidation: In a 10 mL round-bottomed flask equipped with a magnetic stirring bar, septum and N_2 balloon, alcohol (e.g., **5a**; 1 eq.) was placed and dissolved in dichloromethane so as to give 0.2 M solution. To this solution DM periodinane (1.05 eq.) was added as solution in dry dichloromethane upon which the mixture turned cloudy. After stirring for 30 min. tlc showed completion of reaction. The reaction mixture was diluted with ether and was added into saturated sodium bicarbonate solution and stirred for 10-15 min. The ether layer was washed with bicarbonate, water and brine and dried over Na_2SO_4. Solvent was removed under reduced pressure and the crude product purified by flash chromatography. Yields: For furan adducts: **5a**-90%, **5b**-83%. For cyclopentadiene adducts: **8a**-81%, **8b**-85%. Elimination: In a 5 mL round-bottomed flask equipped with a magnetic stir bar, N_2 balloon along with a septum was placed the ketone enough dry methanol to give a 0.05 M solution. To this solution, solid K_2CO_3 (10 eq.) was added and the mixture was allowed to stirr at rt for 24 h. The mixture was diluted with ether and rinsed into a separatory funnel and washed with water, brine and dried over Na_2SO_4. Solvent was removed under vacuum and crude product was purified by flash chromatography. Yields: For furan adducts: **5a**-72%, **5b**-74%. For cyclopentadiene adducts: for **8a**-76%, **8b**-93%
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10. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR and IR spectral data as well as satisfactory combustion analysis or high resolution exact mass data.