Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8151–8155

[4+3] Cycloadditions of some allylic dioxolanes

Michael Harmata,* James A. Brackley, III and Charles L. Barnes

Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211, USA

Received 29 June 2006; revised 6 September 2006; accepted 7 September 2006
Available online 29 September 2006

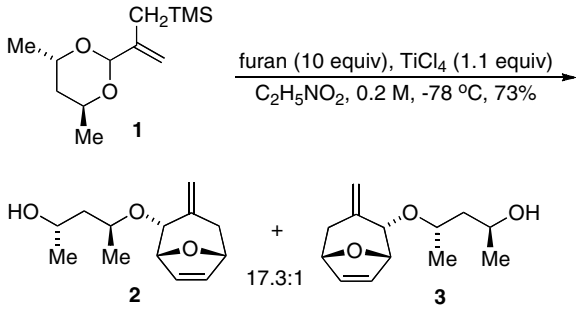
Abstract—Four allylic dioxolanes were prepared and reacted with several dienes in the presence of Lewis acids, affording [4+3] cycloadducts. The reaction could be conducted with catalytic amounts of Lewis acid. The use of a chiral Lewis acid gave a cycloadduct with only a low enantiomeric excess.

The [4+3] cycloaddition reaction of allylic cations and dienes continues to attract a great deal of attention.[1] The process leads directly to seven-membered rings, but can be manipulated to produce both larger and smaller ring systems.[2,3]

Recently, the development of [4+3] cycloaddition chemistry has focused more extensively on the use of heteroatom-stabilized allylic cations as dienophiles.[4] Vinyl thionium,[5] vinyl oxocarbenium,[6] and vinyl iminium ions[7] have all been used as dienophiles in [4+3] cycloaddition reactions. Efforts have been made to develop asymmetric versions of the reaction using both chiral auxiliaries[8,9] and asymmetric catalysis.[10] Both areas are in need of considerable development.[11]

We have been involved in the development of [4+3] cycloaddition chemistry for some time. Several years ago, we studied the [4+3] cycloaddition reaction of allylic dioxanes and other acetals with various dienes.[6,8a,c] We developed reactions that were completely *endo* selective and, when using chiral dioxanes, diastereoselective to the extent of up to a ratio of 17:1. An example is shown in Scheme 1. As part of a continuing program to develop asymmetric [4+3] cycloaddition reactions, we pursued a study of the cycloaddition chemistry of allylic dioxolanes. This letter reports our preliminary results in this area.

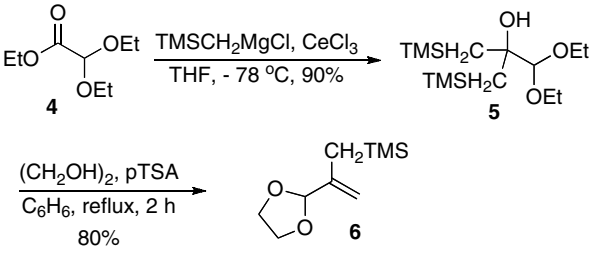
The 'parent' dioxolane was synthesized in accord with our previous work on dioxanes.[8c] The treatment of ethyl



Scheme 1.

diethoxyacetate (**4**) with trimethylsilylmethyl magnesium chloride in the presence of $CeCl_3$ afforded alcohol **5** in a 90% yield. Heating this compound with ethylene glycol and a catalytic amount of tosic acid gave dioxolane **6** in a 80% yield (Scheme 2).

The cycloaddition chemistry of **6** was explored using various amounts of furan as the diene and various Lewis

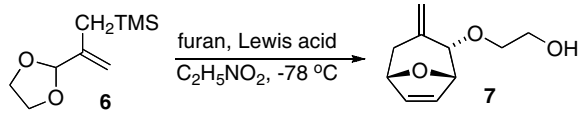


Scheme 2.

* Corresponding author. Tel.: +1 573 882 1097; fax: +1 573 882 2754; e-mail: harmatam@missouri.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.09.036

Table 1. [4+3] Cycloaddition of **6** with furan



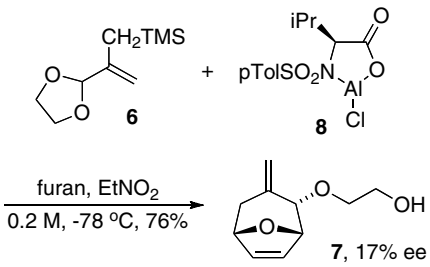
Entry	Furan (equiv)	Lewis acid (equiv)	Yield (%)
1	2.5	$TiCl_4$ (2.1)	20
2	10	$TiCl_4$ (2.1)	33
3	10	$Ti(OiPr)_4$ (2)	0
4	30	$Ti(OiPr)_2Cl_2$ (2)	14
5	10	$SnCl_4$ (2.1)	40
6	10	$AlCl_3$ (2)	43
7	10	Me_2AlCl (1)	70
8	30	Me_2AlCl (1.5)	46
9	10	$MeAlCl_2$ (2)	53
10	10	$EtAlCl_2$ (2)	53
11	10	Et_2AlCl (1.5)	43
12	10	$AlMe_3$ (2)	36
13	10	TMSOTf (1)	56
14	10	$Sc(OTf)_3$ (0.1)	51
15	10	BF_3–OEt_2 (2)	52
16	10	BF_3–OEt_2 (1)	50
17	10	BF_3–OEt_2 (0.5)	54
18	30	BF_3–OEt_2 (0.25)	50
19	30	$ZnBr_2$ (2)	48

acids. The results are summarized in Table 1. Because we obtained excellent results in our studies of allylic dioxanes using nitroethane and found that the cycloaddition reaction of **6** with furan failed using $TiCl_4$ in CH_2Cl_2, all of our studies were conducted using nitroethane as a solvent.

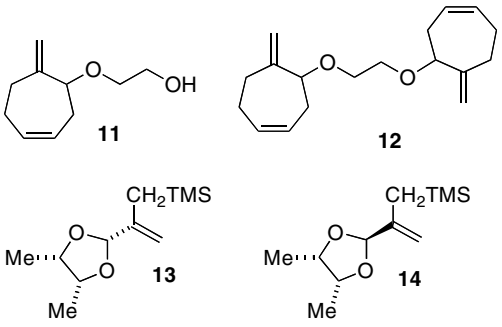
A variety of Lewis acids effected the cycloaddition between **6** and furan. Most notable among the results was the relatively high yield obtained with Me_2AlCl (Table 1, entry 7) and the fact that the reaction could proceed catalytically with scandium(III) triflate and boron trifluoride etherate (Table 1, entries 14, 17–18), though the yields for these processes were only moderate. Simple catalytic [4+3] cycloadditions are relatively rare.[12] Further, simple catalysis implies a potential for asymmetric catalysis. When boron trifluoride etherate was used as the Lewis acid, the yield of **7** was independent of the amount of Lewis acid used and adding additional furan did not appear to dramatically affect the outcome of the reaction (Table 1, entries 15–18).

When chiral Lewis acid **8**[13] (1 equiv) was used to promote the reaction, cycloadduct **7** was obtained in a 76% yield, but with only a 17% enantiomeric excess (Scheme 3).[14] Nevertheless, this establishes the principle that the [4+3] cycloaddition reactions of simple acetals might be subject to asymmetric catalysis.

Other dienes were explored with **6** and the results are summarized in Table 2.[15] Most interesting was the result obtained for the cycloaddition with butadiene. The product was 'dimer' **12**, rather than the simple cycloadduct **11**. The formation of **12** may involve an acetal exchange of **11** with **6** followed by cycloaddition or the simple etherification of the two molecules of **11** mediated by Lewis acid.[16]



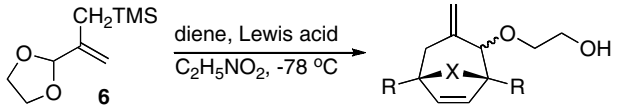
Scheme 3.



We next examined acetals **13** and **14**. These were prepared in standard fashion in a 89% yield (**13**:**14**, 2:1) and separated using MPLC. Stereochemical assignments were made on the basis on NOESY data. Cycloaddition experiments using both compounds are summarized in Table 3. Several conclusions can be drawn from the data. In general, **13** afforded better yields of cycloadducts than **14** (Table 2, entries 1–2). This may be due to a greater accessibility of the oxygen atoms in the former relative to the latter. However, the diastereoselectivity was better with **14** than with **13** (Table 2, entries 4 and 5). The stereochemistry of the major isomer of the cycloadduct for the reaction with furan was assigned by X-ray crystallography as **15a**.[17] As in our dioxane studies, this product is not the one expected by the invertive ring opening of the dioxolane. Attempts to induce enantioselectivity in the process using **8** were not successful. Although rigorous determinations of enantiomeric excesses were not made, chiral chromatography suggested that the ratio of enantiomers was close to 1:1. It appears that both cycloadducts from cyclopentadiene are *endo*, based on NMR data in comparison to our previous work and we assigned the major isomer as **16a** based on these criteria.

We also examined the cycloaddition chemistry of the chiral acetal **17**, prepared using (2*R*,3*R*)-2,3-butanediol and **5** (98% yield). A summary of the reactions performed with this acetal and furan and cyclopentadiene

Table 2. Selected [4+3] cycloadditions of **6**

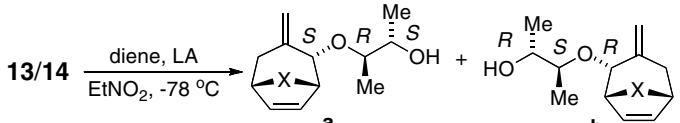


9: X=O, R=Me
10: X=CH_2, R=H

Entry	Diene (equiv)	Lewis acid (equiv)	[M]	Product	Yield (%)
1	2,5-DMF (1.5)	$Sc(OTf)_3$ (0.1)	0.2	**9**	15[a]
2	2,5-DMF (1.5)	$Sc(OTf)_3$ (0.1)	0.05	**9**	20[a]
3	2,5-DMF (10)	$Sc(OTf)_3$ (0.1)	0.05	**9**	45[a]
4	C_5H_6 (20)	**8** (0.62)	0.15	**10**	63[b,c]
5	C_5H_6 (20)	Et_2AlCl (1.1)	0.2	**10**	31[b]
6	1,3-Butadiene (excess)	$Sc(OTf)_3$ (0.1)	0.05	**12**	45

[a] *Endo* only.
[b] *Endo*:*exo*, 5:1.
[c] Enantiomer ratio not determined.

Table 3. [4+3] Cycloadditions of **13** and **14**



15: X=O
16: X=CH_2

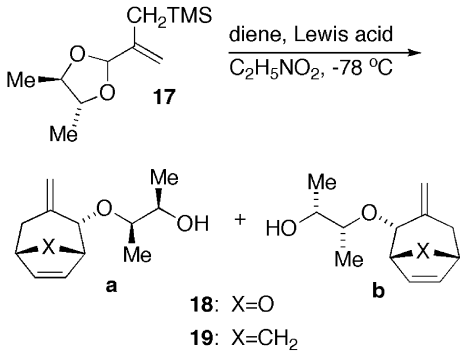
Entry	Acetal	Diene (equiv)	Lewis acid (equiv)	[M]	Product yield (%)
1	**13**	Furan (20)	Et_2AlCl (1.2)	0.18	**15** (59)[a]
2	**14**	Furan (20)	Et_2AlCl (1.2)	0.1	**15** (30)[b]
3	**13**	Furan (20)	**8** (1.1)	0.2	**15** (40)[c]
4	**13**	Furan (20)	$Sc(OTf)_3$ (0.1)	0.05	**15** (89)[d]
5	**14**	Furan (20)	$Sc(OTf)_3$ (0.1)	0.05	**15** (73)[e]
6	**13**	C_5H_6 (20)	**8** (1)	0.16	**16** (88)[f]

a:**b** ratios based on ^1H NMR:
[a] 5.8:1.
[b] 24:1 (after chromatography).
[c] 6.2:1.
[d] 5.5:1.
[e] 7.3:1.
[f] 3.8:1.

is given in Table 4. It is worth noting that as little as 1.5 equiv of diene were suitable for a successful cycloaddition. Interestingly, there seemed to be little correlation between concentration and yield. Diastereoselectivity was reasonable and could probably be improved by using a chiral acetal with more steric bulk in the diol portion of the acetal. The structure of the major diastereomer from the reaction of **17** with furan (**18a**) was determined by X-ray analysis.[17] Interestingly, the formation of this product can be rationalized on the basis of the invertive ring opening of the dioxolane, a phenomenon we have not observed previously. We assume the minor product is the result of a lack of complete facial selectivity. More mechanistic studies are needed in order to find the basis for the differences in behaviour between dioxanes and dioxolanes in this reaction.

In summary, we have shown that allylic dioxolanes are viable dienophiles in [4+3] cycloadditions. The reactions can be catalytic in Lewis acid. Chiral acetals give diastereomeric cycloadducts in ratios as high as 8:1. A single example of a chiral Lewis acid effecting a [4+3] cycloaddition between an achiral allylic acetal and furan proceeded with a low enantioselectivity, but suggests that a catalytic, asymmetric process may be developed using this approach. Further studies along these lines are under current consideration. The results will be reported in due course.[18,19]

Table 4. [4+3] Cycloadditions of **17**



Entry	Diene (equiv)	Lewis acid (equiv)	[M]	Product yield (%)	dr (**a**:**b**)[a]
1	Furan (20)	$Sc(OTf)_3$ (0.1)	0.12	**18** (42)	5.5:1
2	Furan (20)	Et_2AlCl (1.1)	0.2	**18** (40)	10.8:1[b]
3	Furan (1.5)	Et_2AlCl (1.1)	0.2	**18** (34)	—
4	Furan (1.5)	$Sc(OTf)_3$ (0.1)	0.18	**18** (62)	7.4:1[b]
5	Furan (10)	Et_2AlCl (1.1)	0.05	**18** (62)	5.9:1
6	Furan (10)	$Sc(OTf)_3$ (0.1)	0.05	**18** (65)	6:1
7	Furan (20)	**8** (1)	0.2	**18** (30)	8.3:1
8	C_5H_6 (1.5)	$Sc(OTf)_3$ (0.1)	0.2	**19** (52)	5.3:1

[a] Based on NMR of crude material.
[b] After chromatography.

Acknowledgments

This work was supported by the National Science Foundation and by the Petroleum Research Fund, sponsored by the American Chemical Society, to whom we are very grateful.

References and notes

1. (a) Harmata, M. *Adv. Cycloaddit.* **1997**, *4*, 41–86; (b) Rigby, J. H.; Pigge, F. C. *Org. React. (N.Y.)* **1997**, *51*, 351–478; (c) Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217–232; (d) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595–605.
2. (a) West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795–6803; (b) Harmata, M.; Elahmad, S.; Barnes, C. L. *J. Org. Chem.* **1994**, *59*, 1241–1242; (c) Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2000**, *2*, 2913–2915; (d) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747–2750.
3. (a) Harmata, M.; Shao, L. *Synthesis* **1999**, 1534–1540; (b) Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2001**, *3*, 2533–2535; (c) Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59–61; (d) Harmata, M.; Wacharasindhu, S. *Org. Lett.* **2005**, *7*, 2563–2565.
4. Harmata, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 523–535.
5. (a) Harmata, M.; Fletcher, V. R.; Claassen, R. J., II. *J. Am. Chem. Soc.* **1991**, *113*, 9861–9862; (b) Harmata, M.; Jones, D. E. *Tetrahedron Lett.* **1996**, *37*, 783–786; (c) Harmata, M.; Kahraman, M. *Tetrahedron Lett.* **1998**, *39*, 3421–3424; (d) Ou, L.; Hu, Y.; Song, G.; Bai, D. *Tetrahedron* **1999**, *55*, 13999–14004; (e) Harmata, M.; Kahraman, M.; Adenu, G.; Barnes, C. L. *Heterocycles* **2004**, *62*, 583–618.
6. Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371–2395.
7. (a) Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23–26; (b) Walters, M. A.; Arcand, H. R. *J. Org. Chem.* **1996**, *61*, 1478–1486.
8. (a) Harmata, M.; Jones, D. E. *J. Org. Chem.* **1997**, *62*, 4885; (b) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1266–1268; (c) Harmata, M.; Jones, D. E.; Kahraman, M.; Sharma, U.; Barnes, C. L. *Tetrahedron Lett.* **1999**, *40*, 1831–1834; (d) Beck, H.; Stark, C. B. W.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 883–886; (e) Stark, C. B. W.; Pierau, S.; Wartchow, R.; Hoffmann, H. M. R. *Chem. Eur. J.* **2000**, *6*, 684–691; (f) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934–1949.
9. (a) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174–7175; (b) Xiong, H.; Hsung, R. P.; Shen, L.; Hahn, J. M. *Tetrahedron Lett.* **2002**, *43*, 4449–4453; (c) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694–12695; (d) Rameshkumar, C.; Hsung, R. P. *Angew. Chem., Int. Ed* **2004**, *43*, 615–618.
10. (a) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058–2059; (b) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50–51.
11. Huang, J.; Hsung, R. P. *Chemtracts* **2005**, *18*, 207–214.
12. (a) Harmata, M.; Sharma, U. *Org. Lett.* **2000**, *2*, 2703–2705; (b) Prie, G.; Prevost, N.; Twin, H.; Fernandes, S. A.; Hayes, J. F.; Shipman, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6517–6519.
13. Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197–198.
14. The assignment of enantiomeric excess was made by the method of Anderson and Shapiro: Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304–1305. The hydroxyethyl group of **7** was removed and the resulting

allylic alcohol was derivatized with 2-chloro-4(*R*),5(*R*)-dimethyl-2-oxo-1,3,2-dioxaphospholane. The integration of a ^{31}P NMR then gave the relative ratio of enantiomers.
15. 2-Methylfuran, pyrrole and *N*-Boc-pyrrole all failed to afford cycloadducts with **6**.
16. Compound **12** appears to be a single species by NMR, but it is likely that it is actually a mixture of diastereomers and the NMR signals for the diastereomers are isochronous.
17. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 612843 (**15a**) and 612844 (**18a**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail; deposit@ccdc.cam.ac.uk].
18. General procedure for the synthesis of allylic acetals: A round-bottomed flask equipped with a stir bar was charged with **5** followed by the addition of (1.2–3 equiv) diol and 5 mol % PTSA. Benzene was added to form an ~0.083 M solution. The system was refluxed into a Dean–Stark trap under positive N_2 pressure. The reaction progress was monitored by TLC (10% Et_2O/hexanes) Upon the completion of the reaction, approximately 80% of the solvent was distilled off. The reaction was quenched with 5–10 mL of 6% $NaHCO_3$ and filtered through a pad of $NaHCO_3$. The organic layer was diluted with 20 mL of Et_2O, washed with 10 mL of H_2O (1×) then with 10 mL of brine (1×). After drying over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. The product was purified by flash chromatography. Data for **6**: ^1H NMR (250 MHz, $CDCl_3$) δ 5.12 (s, 2H), 4.86–4.85 (m, 1H), 4.00–3.98 (m, 2H), 3.96–3.90 (m, 2H), 1.58 (s, 2H), 0.04 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 143.7, 112.4, 105.6, 65.0, 20.2, −1.2. IR: (cm^{-1}) 2956(s), 2891(s), 1731(m), 1689(m), 1644(m), 1612(m), 1475(w), 1427(m), 1249(s), 967(m), 943(m), 902(m), 851(s). Anal. Calcd for $C_9H_{13}O_2Si$: C, 58.02; H, 9.74. Found: C, 58.06; H, 9.61.
19. General procedure for the [4+3] cycloaddition of dioxolanes: A round-bottomed flask equipped with a magnetic stir bar and rubber septum was flame-dried and cooled under positive N_2 pressure. To the cooled flask was added 1 equiv dioxolane followed by freshly distilled and cooled $C_2H_5NO_2$, to form a 0.05 M solution. The system was then purged with N_2 for approximately one min. Ten equivalents of diene were added via syringe and the system was stirred while cooling to −78 °C. $Sc(OTf)_3$ (10 mol %) was added quickly into the reaction pot followed by purging with N_2 for 1 min. The reaction mixture was stirred at −78 °C for 15 min to 2.5 h. The reaction progress was monitored by TLC. Upon the completion of the reaction, the reaction flask was removed from the cooling bath and the mixture was diluted with 25 mL of ethyl ether and 25 mL H_2O with vigorous stirring. The nitroethane was then extracted from the organic layer with three 10 mL portions 2.5 M NaOH. The combined aqueous layers were washed with three 2 mL portions of ethyl ether. The combined organic layers were washed with 10 mL of water (1×), 10 mL of 1 N HCI (1×) and 10 mL of brine (1×). The organic layer was then dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash chromatography. Data for **7**: ^1H NMR (250 MHz, $CDC1_3$) δ 6.18 (s, 2H), 5.22–5.19 (m, 1H), 4.90–4.89 (m, 1H), 4.81 (d, $J = 4.2$ Hz, 1H), 4.77 (d, $J = 4.0$ Hz, 1H), 4.09–4.08 (m, 1H), 3.85–3.71 (m, 4H), 2.63–2.54 (m, 1H), 2.12 (d, $J = 14.4$ Hz, 1H), 1.85 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCI_3$) δ 142.1, 133.1, 129.7, 112.1, 79.6, 79.2, 78.8, 71.8, 62.1, 35.7; IR (cm^{-1}) 3426(s), 2951(s), 1652(m), 1429(m), 1405(m), 1341(m), 1321(m), 1126(s), 1056(s), 979(m), 954(m), 902(m), 885(m). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.39; H, 7.75. Found: C, 65.76; H, 7.62.