Diastereocontrol of [4 + 3] Cyclic Oxyallyl Cycloadditions by Alkoxy Substituents

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The exceptional reactivity of oxyallyl has been of considerable interest to theoretical and synthetic chemists. In particular, the [4 + 3] cycloaddition to 1,3-dienes has been shown to provide a versatile method for formation of seven-membered rings containing well-defined facial differentiation useful for further elaboration. The two key features of the oxyallyl cycloaddition are the propensities to (a) favor a "compact" (i.e., endo-like) transition state over the alternate "extended" (exo-like) one and (b) prefer the "ortho" orientation of certain (e.g., C1-substituted) unsymmetrical dienes and oxyallyls, leading to highly predictable stereo- and regiochemical preferences.[1,2] However, an enantioselective process remains as an important problem to be addressed so as to enhance the synthetic utility of the oxyallyl [4 + 3] cycloaddition reactions. Lautens and co-workers recently reported an elegant "chelate-controlled" diastereoselective [4 + 3] cycloaddition reaction by a related use of a chiral furyl alcohol and a zinc cation, whereas the "non-chelated" cycloadduct was obtained from the corresponding furyl ether.[3] Hoffmann and Harmata groups independently developed an asymmetric process by means of a chiral acetal.[4−6] Herein we report highly diastereoselective [4 + 3] cycloadditions of *cyclic* oxyallyls containing alkoxy substituents.

Our approach was stimulated by unique directing effects of an allylic alkoxy group in several diastereoselective transformations of the adjacent carbon−carbon double bond.[7] Such conformational discrimination induced by an allylic alkoxy substituent is expected to develop more fully in oxyallyl cations, compared to nonpolar olefins (Scheme 1).

Scheme 1

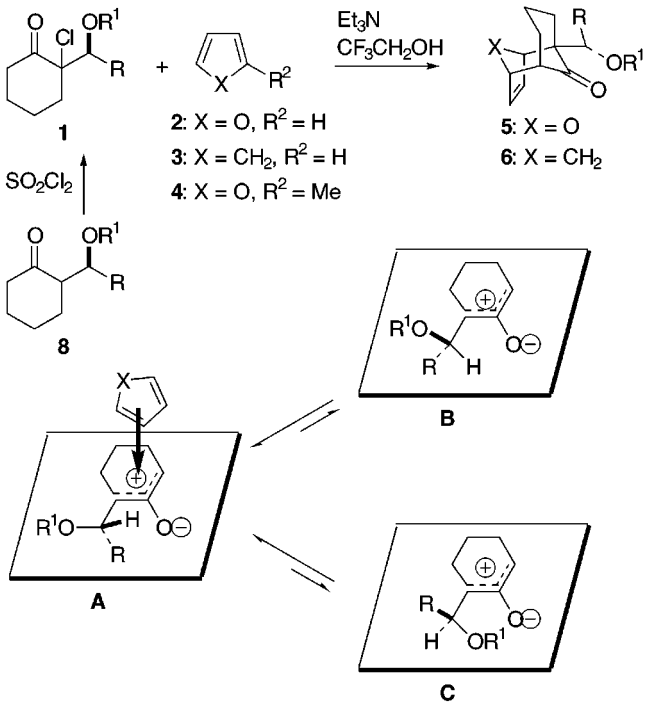

Table 1[a]

entry	α-haloketones	dienes	cycloadducts	yields
1	**1a**: R = Et, R^1 = TBS	**2**	**5a**: R = Et, R^1 = TBS, X = O	(77%)
2	**1b**: R = Et, R^1 = TIPS	**2**	**5b**: R = Et, R^1 = TIPS, X = O	(63%)
3	**1c**: R = Et, R^1 = Et	**2**	**5c**: R = Et, R^1 = Et, X = O	(42%)
4	**1a**	**3**	**6a**: R = Et, R^1 = TBS, X = CH_2	(57%)
5	**1b**	**3**	**6b**: R = Et, R^1 = TIPS, X = CH_2	(<10%)[b]
6	**1d**: R = Me, R^1 = TBS	**2**	**5d**: R = Me, R^1 = TBS, X = O	(81%)
7	**1d**	**3**	**6d**: R = Me, R^1 = TBS, X = CH_2	(57%)
8	**1e**: R = Ph, R^1 = TBS	**2**	**5e**: R = Ph, R^1 = TBS, X = O	(48%)
9	**1e**	**3**	**6e**: R = Ph, R^1 = TBS, X = CH_2	(52%)

a. For experimental details, see Supporting Information. *b.* The reaction proved to be very sluggish, where the starting chloroketone **1b** was recovered in excellent yield.

In our initial investigations, we chose Föhlisch's dehydrohalogenation procedure for a convenient generation of oxyallyls from α-haloketones in light of the ease of operation.[8] Moreoever, our studies focused on use of cyclic oxyallyls, i.e., oxyallyls embedded in a ring, because of their geometrically constrained conformation and also the demonstrated synthetic utility of the resulting cycloadducts in the preparation of medium-sized rings.[2,9] On the basis of steric and electro-

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(2) Intramolecular [4 + 3] cycloadditions have also been developed to take advantage of additional conformational constraint: (a) Harmata, M. *Tetrahedron* **1997**, *53*, 6235. (b) Harmata, M. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 4, pp 41−86. (c) West, F. G. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 4, pp 1−40.

(3) Lautens, M.; Aspiotis, R.; Colucci, J. *J. Am. Chem. Soc.* **1996**, *118*, 10930.

(4) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1266.

(5) Harmata, M.; Jones, D. E.; Kahraman, M.; Sharma, U.; Barnes, C. L. *Tetrahedron Lett.* **1999**, *40*, 1831.

(6) For related reactions, see: (a) Kende, A. S.; Huang, H. *Tetrahedron Lett.* **1997**, *38*, 3353. (b) Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326.

(7) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761 and references therein.

(8) For [4 + 3] cycloadditions involving cyclic oxyallyls, see: (a) Föhlisch, B.; Gehrlach, E.; Herter, R. *Angew. Chem., Int., Ed. Engl.* **1982**, *21*, 137. (b) Föhlisch, B.; Joachimi, R. *Chem. Ber.* **1987**, *120*, 1951. (c) Föhlisch, B.; Joachimi, R.; Reiner, S. *J. Chem. Res., Synop.* **1993**, 253.

(9) (a) Oh, J.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1992**, *57*, 6664. (b) Oh, J.; Cha, J. K. *Synlett* **1994**, 967. (c) Kim, H.; Ziani-Cherif, C.; Oh, J.; Cha, J. K. *J. Org. Chem.* **1995**, *60*, 792. (d) Cha, J. K.; Oh, J. *Current Org. Chem.* **1998**, *2*, 217.

(10) (a) Cf. Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 162. (b) While inconsequential, α-halo ketones **1** were obtained as single diastereomers, whose stereochemistry is thought to have the α-chloro configuration, assuming the intermediacy of the enol tautomer.

(11) The observed selectivities given in Table 1 are kinetic in origin, since pure individual cycloadducts and their epimers remain unchanged when resubjected to the identical reaction conditions.

(12) The stereochemistry of **5b** and **5c** was not independently determined, but tentatively assigned by analogy.

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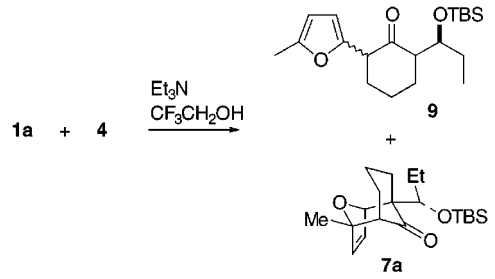
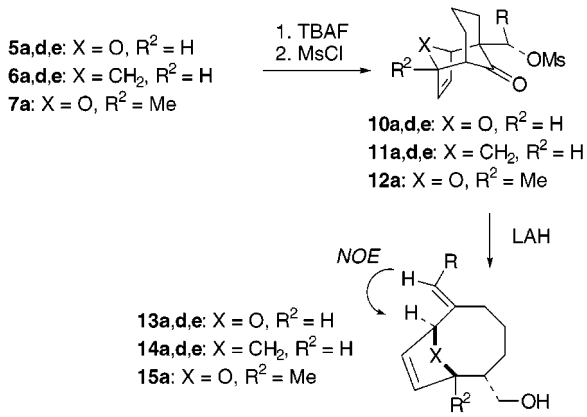
Scheme 2



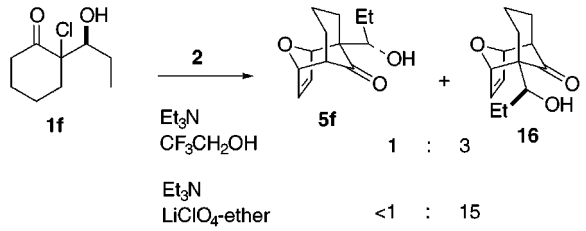
Scheme 3



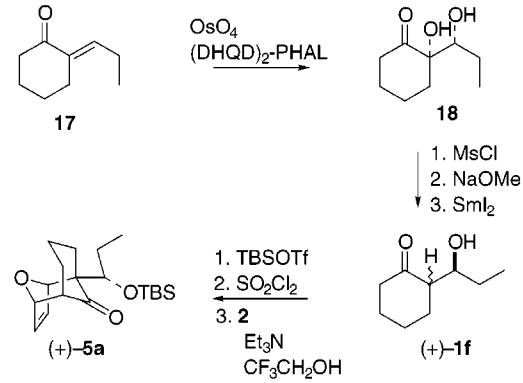
static considerations, conformation **A** would be anticipated to be most favorable. Approach of a diene (**2**, **3**, or **4**) from the less-hindered face (opposite to the bulkier R group), coupled with inherent preference for the "compact" orientation, would result in the diastereoselective formation of cycloadducts **5** and **6**. This method lends itself to an enantioselective synthesis of the cycloadducts by means of the enantiomerically enriched secondary alcohol function present in **1**.

The requisite substrates for the [4 + 3] cycloaddition reactions were prepared by chlorination (SO_2Cl_2) of ketones **8**,[10] which, in turn, were prepared conveniently by aldol condensation of cyclohexanone with an appropriate aldehyde and subsequent silylation. As can be seen from Table 1, the adjacent alkoxy group was found to uniformly exert an exceptional degree of diastereocontrol in cycloadditions with both furan (**2**) and cyclopentadiene (**3**). No other stereoisomers were observed within the limits of ^{1}H and ^{13}C NMR spectroscopy.[11] Protecting groups (entries 1−3) in the secondary alcohol appear to have little effect on diastereofacial selectivity. The directing effect by the alkoxy group also seems to be general regardless of the size of the R group (e.g., see entries 1, 6, and 8). The [4 + 3] cycloaddition of **1a** and 2-methylfuran (**4**) took place more slowly than that of **1a** and **2** to afford **7a** (25%) and **9** (32%), along with recovered starting material (40%) (Scheme 2); this atypical regiochemistry might be attributed to steric crowding imposed by the methyl group of **4** in the transition state as depicted in conformation **A**.

Scheme 4



Scheme 5



The stereochemical assignment of the [4 + 3] cycloadducts **5**, **6**, and **7a** was made by their conversion to **13**, **14**, and **15a**, respectively, involving reductive cleavage ($LiAlH_4$) of β-keto mesylates **10**, **11**, and **12a** (Scheme 3) in 67−80% overall yields.[12] The geometry of the newly generated double bond was then firmly established to be as shown in structures **13**−**15** by difference NOE measurements.

The directing effect of the free hydroxyl group was next examined (Scheme 4). Cycloaddition of furan and **1f** (R= Et, R^1= H), which was readily prepared by desilylation (aqueous HF, CH_3CN) of **1a**, gave a 1:3 mixture of **5f** (R= Et, R^1 = H) and **16** in 48% yield. By use of 5 M $LiClO_4$−ether in place of trifluoroethanol,[13] greater than 15:1 diastereofacial selectivity in favor of **16** was obtained in 60−65% yield. The observed stereochemical outcome can be rationalized by involvement of internal hydrogen bonding, which favors the conformation generalized as type **C** (R^3= H) leading to the formation of the major product **16**.

To obtain enantiomerically enriched cycloadducts, *E*-olefin **17** was subjected to the Sharpless asymmetric dihydroxylation (Scheme 5);[14] the resulting diol (+)-**18** was then converted to (+)-**1f**, in 60% overall yield, by way of SmI_2 of the corresponding epoxide.[15] Silylation, chlorination, and cycloaddition under identical conditions afforded the cycloadduct (+)-**5a**, whose enantiomeric excess was measured to be >90% by the NMR studies of the desilylated alcohol with a chiral shift reagent.

In summary, we have developed highly diastereoselective [4 + 3] cycloadditions of cyclic oxyallyls by the influence of an adjacent alkoxy group. The complementary diastereofacial selectivity can also be obtained by means of the free hydroxy substituent. This new method is easily amenable to an enantioselective preparation of the synthetically useful cycloadducts which contain the well-defined diastereofacial bias.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For use of the $LiClO_4$/Et_3N reagent in [4 + 3] oxyallyl cycloadditions, see: (a) Herter, R.; Föhlisch, B. *Synthesis* **1982**, 976. (b) Föhlisch, B.; Herter, R. *Chem. Ber.* **1984**, *117*, 2580. For dramatic rate acceleration of Diels−Alder reactions in 5 M $LiClO_4$−ether, see: (c) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4596.

(14) (a) For a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Use of $(DHQD)_2$-PHAL gave the diol, α_D = +74°, while a comparable enantiomeric excess (α_D = −71°) was obtained by $(DHQ)_2$-PHAL.

(15) A more efficient approach could be developed by an enantioselective aldol condensation. See: (a) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (b) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *Tetrahedron* **1998**, *54*, 10389. (c) Yanagisawa, A.; Matsumoto, Y.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 892.