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Cyclopropanation of Protected Chiral, Acyclic Allylic Alcohols: Expedient Access to the *anti*-Cyclopropylcarbinol Derivatives

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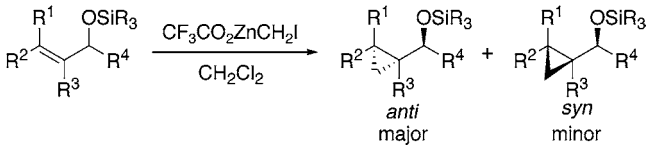
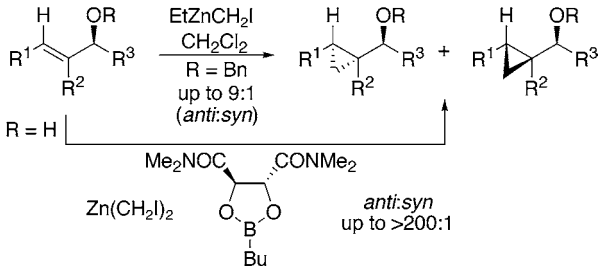
ABSTRACT



The diastereoselective cyclopropanation of silyl-protected chiral allylic alcohols using Shi's carbenoid (TFA−Et_2Zn−CH_2I_2) gave access to the *anti*-cyclopropylcarbinyl silyl ethers with excellent diastereocontrol. The level of stereocontrol was shown to depend on the sizes of the protective group and the allylic substituent.

The directed cyclopropanation of chiral, acyclic allylic alcohols is a well-documented process,[1] and many reagents and reaction conditions are known to lead to cyclopropylcarbinols. The presence of a proximal basic group plays a predominant role in assisting the delivery of the carbenoid. For example, acyclic chiral allylic alcohols can be converted effectively to the syn isomer under the appropriate reaction conditions.[2,3] However, few methods are known for the synthesis of the related acyclic *anti*-cyclopropylcarbinol derivatives.[4] During our investigation of the relative directing abilities of oxygenated groups in the cyclopropanation of chiral allylic compounds, we observed that the reaction of *O*-benzyl-protected (*E*)-allylic secondary alcohols with Furukawa's reagent[5] gave access to the *anti*-cyclopropylcarbinyl ethers with modest levels of diastereoselection (Scheme 1).[4c]

Scheme 1



The anti selectivities were greatly improved if one of the two antipodes of a chiral dioxaborolane ligand was added. Herein, we report that the cyclopropanation of acyclic allylic silyl ethers with the appropriate zinc carbenoid reagent results in a new simple and direct way to access *anti*-cyclopropyl-

(1) For a comprehensive review of substrate-directable reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(2) (a) Ratier, M.; Castaing, M.; Godet, J.-Y.; Pereyre, M. *J. Chem. Res., Miniprint* **1978**, 2309. (b) Schöllkopf, U.; Tiller, T.; Bardenhagen, J. *Tetrahedron* **1988**, *44*, 5293. (c) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942. (d) Molander, G A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525. (e) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1992**, *57*, 798. (f) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1995**, *60*, 2474. (g) Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966. (h) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12160.

(3) For a recent review on Simmons−Smith cyclopropanation, see: Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1.

(4) (a) Delanghe, P. H. M.; Lautens, M. *Tetrahedron Lett.* **1994**, *35*, 9513. (b) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1995**, *60*, 2474. (c) Charette, A. B.; Lebel, H.; Gagnon, A. *Tetrahedron* **1999**, *55*, 8845.

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carbinol derivatives. We also show that the level of diastereocontrol is highly dependent on the nature of the protective groups.

We envisioned that the introduction of a bulky protective group may actually prevent preassociation of the zinc reagent with the substrate and thus lead to the formation of the anti diastereomer through a transition structure that minimizes steric interactions between the reagent and the substituents (Figure 1, **A** is favored over **B**). The ground-state conformation in which the silyloxy group is synclinal to the alkene has been proposed by Gung to be the most stable for small R^4 substituents.[6] Nonassisted attack of the carbenoid on this favored conformer (which should also be the most reactive on the basis of stereoelectronic arguments) should lead to the anti isomer. This approach contrasts with the cyclopropanation of unprotected allylic alcohols in which minimization of the A-1,3 strain is the main controlling element for good diastereocontrol (Figure 1, **D** is favored over **C**). One potential problem with this approach is the lack of reactivity of the classical zinc carbenoid reagents, which sometimes are not sufficiently reactive to cyclopropanate alkenes that do not contain basic proximal groups. However, several improved versions of the reagent have recently been reported and should prove to be sufficiently reactive to provide the cyclopropane product in good yields with this class of substrates.

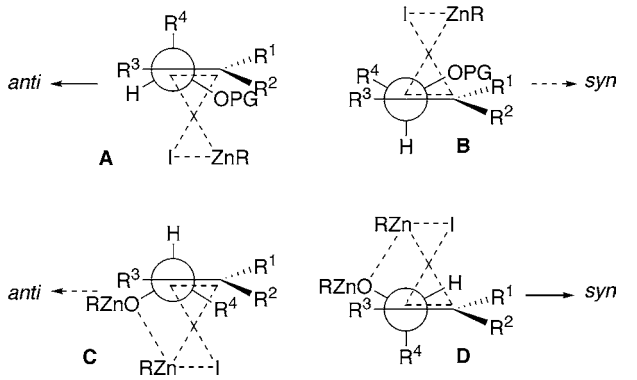
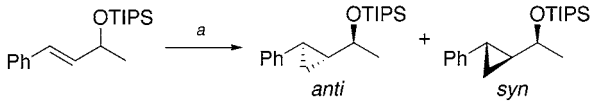


Figure 1. Postulated transition structures for directed vs nondirected cyclopropanation reactions.

The reaction was initially performed by reacting the chiral racemic triisopropylsilyl ether derived from (*E*)-4-phenylbut-3-en-2-ol to different zinc carbenoids (Table 1). As expected, the classical Simmons−Smith reagent[7] gave only poor conversion, though the selectivity was in favor of the desired anti diastereomer (entry 1). The selectivities increased with Furukawa-type carbenoids (entries 2−5), and synthetically

Table 1. Effect of the Nature of the Reagent



entry	reagent	conversion (%)[b]	anti:syn[c]
1	$IZnCH_2I$[d]	8	84:16
2	$EtZnCH_2I$	48	92:8
3	$Zn(CH_2I)_2$[e]	44	90:10
4	$EtZnCH_2Cl$	92	94:6
5	$Zn(CH_2Cl)_2$[e]	88	97:3
6	2,4,6,-$Cl_3C_6H_2OZnCH_2I$	60	89:11
7	2,4,6,-$F_3C_6H_2OZnCH_2I$	52	93:7
8	$CF_3CO_2ZnCH_2I$	>99	>99:1

[a] Reaction conditions: substrate is added to 2.0 equiv of preformed reagent, CH_2Cl_2, 0 °C to room temperature. [b] Determined by ^1H NMR using an internal standard. [c] Determined by GC analysis of the corresponding acetate derivatives. [d] Formed by treating 2.0 equiv of I_2 with 2.0 equiv of Et_2Zn and 2.0 equiv of CH_2I_2. [e] 1.0 equiv of reagent was used.

useful conversions and diastereoselectivities were observed with the Denmark's procedure (entries 4−5).[8] The aryloxide-derived carbenoids[9] gave lower conversions, probably due to the bulkiness of the reagent making the approach to the alkene more difficult (entries 6−7). A highly activated reagent prepared from trifluoroacetic acid[10] (Shi's reagent) gave the best conversion and diastereoselectivity, making it the optimal carbenoid for the following studies.

The next step was to study the effect of the protective group on the selectivity of the reaction (Table 2). We compared the level of diastereoselection as a function of the size of the silyl ether protective group. Gratifyingly, all but two substrates gave the anti diastereomer as a major product with an excellent ratio (anti:syn ratio superior to 94:6) when treated with Shi's reagent. It is also apparent that the diastereoselectivities usually increased by increasing the steric bulk of the silyl ether, the triisopropylsilyl being the optimal protective group for maximizing the anti:syn ratio.[11] As expected, the nature of the allylic substituent (R^4) also influences the ratio considerably (entries 6−9). While the small methyl and ethyl allylic substituents allowed excellent diastereoselectivities, the level was lower in the case of isopropyl (entries 2 and 7 vs 8). Conversely, the presence of a methyl substituent at the R^3 position did not seem to affect the level of diastereoselection, yielding the corresponding trisubstituted cyclopropylcarbinyl silyl ethers in good yields and excellent diastereomeric ratios (entries 10−11).

It is well established that (*Z*)-allylic secondary alcohols give high levels of syn selectivity when treated under the

(5) (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, 3353; (b) *Tetrahedron* **1968**, *24*, 53.

(6) (a) Gung, B. W.; Melnick, J. P.; Wolf, M. A.; King, A. *J. Org. Chem.* **1995**, *60*, 1947. (b) Khan, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650.

(7) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, H. M. *Org, React.* **1973**, *20*, 1.

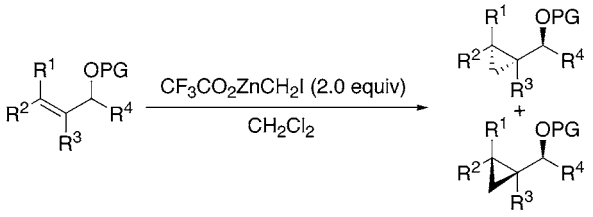
(8) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.

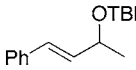
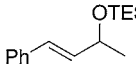
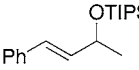
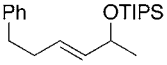
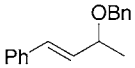
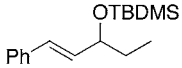
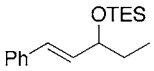
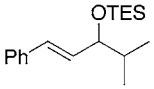
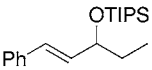
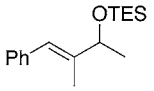
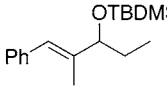
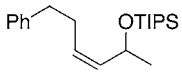
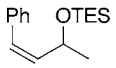
(9) Charette, A. B.; Francoeur, S.; Martel, J.; Wilb, N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4539.

(10) (a) Yang. Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621. (b) Charette, A. B.; Beauchemin, A.; Francoeur, S. *J. Am. Chem. Soc.* **2001**, *123*, 8139.

(11) Reaction of a bulkier allylic *tert*-butyldiphenylsilyl ether led mostly to decomposition of the starting material, which in this case probably occurs faster than the cyclopropanation under these Lewis-acidic conditions.

Table 2. Cyclopropanation of Acyclic Allylic Silyl Ethers



entry	substrate	t (h)	T (°C)	yield (%)[a]	*anti* : *syn*[b]
1		0.5	0	86	98 : 2
2		0.5	0	87	> 99 : 1
3		0.5	0	88	> 99 : 1
4		1.0	0	84	96 : 4
5		2.0	–20	80	94 : 6
6		3.0	–20	85	97 : 3
7		1.0	0	87	97 : 3
8		7.0	–20	78	70 : 30
9		4.5	–20	88	98 : 2
10		4.0	–20	88	> 99 : 1
11		4.5	–20	88	99 : 1
12		2.0	0	52	97 : 3
13		6.0	0	89	25 : 75

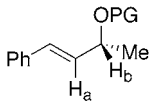
[a] Isolated yield of both diastereomers. [b] Determined by GC analysis of the corresponding acetate derivatives.

[a] Isolated yield of both diastereomers. [b] Determined by GC analysis of the corresponding acetate derivatives.

Simmons−Smith conditions, due to the strong preference for an hydroxy-directed process on the A-1,3 minimized conformer in the transition structure (**D** in Figure 1).[2,4b] Therefore, we were pleased to observe that the cyclopropanation of a (*Z*)-allylic silyl ether gave the anti product as the major diastereomer (entry 12). However, the introduction of a more sterically demanding R^1 substituent led to an inversion of the selectivity, which shows the importance of the conformation adopted by the substrate when reacting with the zinc carbenoid (entry 13).

In general, the reaction times were short, especially when the cyclopropanations were performed at 0 °C. We observed in some cases that the reactions were cleaner when performed at −20 °C (entries 5, 6, and 8−11) although longer reaction times were required.

The π-facial selectivity can be accounted for by the models presented in Figure 1 by considering the most stable ground state conformations. Further evidence for this is provided by looking at the coupling constants between the allylic proton and the vicinal alkene proton of various starting materials (Figure 2). The observed values are in agreement



PG	$J_{a\text{-}b}$ (Hz)	*anti* : *syn*
TBDMS	5.63	98:2 (0 °C)
TIPS	5.91	>99:1 (0 °C)
TES	5.93	>99:1 (0 °C)
Bn	7.72	94:6 (–20 °C)

Figure 2.

with Gung's conclusions[6a] indicating that a smaller value is consistent with an increase in the population of conformer in which the C−O bond is eclipsed with the C═C bond.

In summary, we have developed a simple methodology for accessing the cyclopropylcarbinyl silyl ethers of anti relative stereochemistry with good yields and good to excellent diatereoselectivities.[12] The diastereoselectivities depend on the substitution pattern of the olefinic substrates, but synthetically useful levels are attained in most cases. Further studies are underway to determine the effect of other types of substituent on the allylic ethers in order to expand the scope of the Simmons−Smith cyclopropanation and will be reported in due course.

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

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(12) The sense of induction appears to be highly dependent upon the nature of the alkene substituent. It has been observed that the cyclopropanation of a β-chloro allylic ethers under the conditions reported here led preferentially to the syn diastereoisomer: Evans, D. A.; Burch, J. D. *Org. Lett.* **2001**, *3*, 503.