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A Telluride-Triggered Nucleophilic Ring Opening of Monoactivated Cyclopropanes[1]

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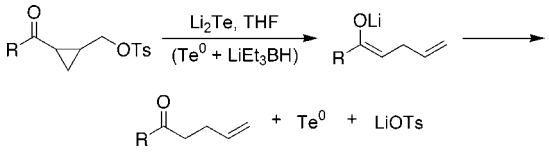
ABSTRACT



Acylcyclopropanemethanol tosylates undergo rapid ring opening at room temperature by the action of lithium telluride to produce the enolate of a homoallylic ketone. The enolate can be protonated to yield the corresponding ketone or treated with benzaldehyde to give the aldol product with good syn or anti diastereoselectivity depending on the conditions.

The synthetically useful nucleophilic ring openings of cyclopropanes activated by substitution with electron-withdrawing groups have been investigated extensively since the discovery by Perkin and Bone.[2,3] While both inter- and intramolecular nucleophilic reactions of diactivated cyclopropanes are common,[3,4] those of monoactivated rings are somewhat rarer, often requiring either a very strong nucleophile,[5−10] electrophilic (Lewis acid) catalysis (carbocations are likely to be involved),[11−14] the involvement of strain or spiroconjugation,[7,15] or a facile, intramolecular process.[14,16] Unactivated cyclopropylmethyllithium species undergo ring opening to allylic alkyllithium intermediates that are trapped by reaction with electrophiles.[17]

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(9) Cuprates: (a) Casey, C. P.; Cesa, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 4236−4244. (b) Frejaville, C.; Jullien, R. *Tetrahedron Lett.* **1971**, *12*, 2039−2041.

(10) Trimethylsilyl anion: Hwu, J. R. *J. Chem. Soc., Chem. Commun.* **1985**, 452−453.

(11) *p*-Toluenesulfonic acid: (a) Lim, Y.-H.; McGee, K. F., Jr.; Sieburth, S. McN. *J. Org. Chem.* **2002**, *67*, 6535−6538. (b) Yates, P.; Helferty, H.; Mahier, P. *Can. J. Chem.* **1983**, *61*, 78−85.

(12) Acetylmethanesulfonate: Demuth, M.; Raghavan, P. R. *Helv. Chim. Acta* **1979**, *62*, 2338−2340.

(13) Trimethylsilyl cation equivalents: (a) Brown, S. P.; Balkrishna, S. B.; Pinnick, H. W. *Tetrahedron Lett.* **1981**, *22*, 4891−4894. (b) Dieter, R. K.; Pounds, S. *J. Org. Chem.* **1982**, *47*, 3174−3177 (also aluminum chloride).

(14) Titanium tetrachloride: Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2003**, *5*, 4281−4284.

(15) (a) Meinwald, J.; Crandall, J. K. *J. Am. Chem. Soc.* **1966**, *88*, 1292−1301. (b) Buss, P.; Prewo, R.; Bieri, J. H.; Rüedi, P. *Helv. Chim. Acta*, **1986**, *69*, 456−466. (c) The ring-opening of 1,1-(bromomethyl)cyclopropane via triphenylphosphine may involve strain induced by the geminal groups: Zefirov, N. S.; Kuznetsova, T. S.; Kozhushkov, S. I.; Potekhin, K. A.; Maleev, A. V.; Struchkov, Yu. T. *J. Org. Chem. USSR* **1988**, *10*, 1874−1877.

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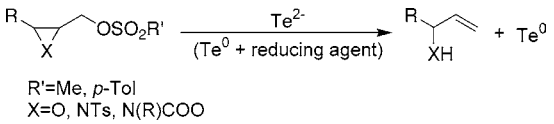
Tellurium-triggered rupture of the three-membered rings of chloromethyloxiranes,[18] mesylates or tosylates of oxiranemethanols,[19] and aziridinemethanols[20] and a related reaction of 5-hydroxymethyl-2-oxazolidinone derivatives[21] provide syntheses of allylic alcohols and amines (Scheme 1). These reactions exemplify the use of nontoxic[22] elemental

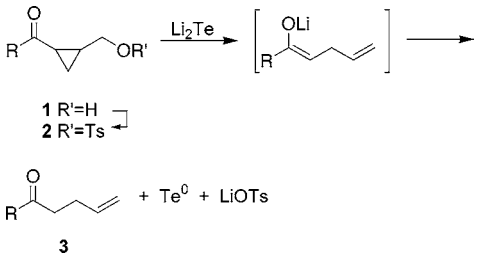
Scheme 1. Allylic Alcohols and Amines by Telluride-Induced Nucleophilic Reduction



tellurium to create the equivalent of a nucleophilic carbanion exocyclic to an oxirane, aziridine, or oxazolidinone ring without the requirement of a silicon or organolithium exocyclic functional group. A bonus is the recovery and reuse of the key tellurium reagent.

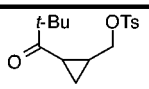
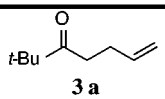
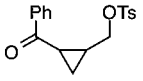
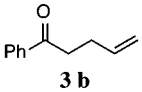
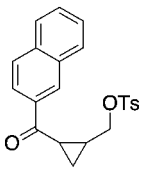
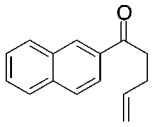
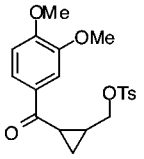
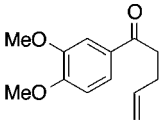
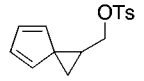
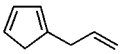
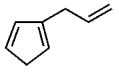
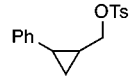
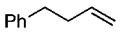
We reasoned that this process, designated "nucleophilic reduction",[19c] could also be applied to cyclopropanemethanol derivatives. In fact, nucleophilic ring-opening of a cyclopropane ring was observed upon treatment of the *p*-toluenesulfonate of 1-[2-(hydroxymethyl)cyclopropyl]-2,2-dimethyl-1-propanone (**2a**) and related compounds with lithium telluride, prepared by reduction of tellurium powder with lithium triethylborohydride,[23] to give the enolates of homoallylic ketones **3a**−**d** (Scheme 2, Table 1).

Scheme 2. Nucleophilic Reduction of **2a**−**d** with Telluride Ion



This telluride-triggered generation of enolates of alkyl or aryl 3-butenyl ketones does not require a strong base (e.g., LDA) or, as with silylmethylcyclopropyl ketones, an electrophile such as titanium tetrachloride.[14] The byproducts are elemental tellurium (reusable) and lithium tosylate. Enolates have been obtained also from α-halocarbonyl compounds and various tellurides;[24] the acylcyclopropanemethanol tosylates **2a**−**d** may be considered as "cyclopropanalogues",[25] similar to vinylogues of α-haloketones in which the carbon−carbon double bond (C_2H_2) of a vinylog is replaced by the cyclopropane ring (C_3H_4).

Table 1. Nucleophilic Reduction of Cyclopropanemethanol Tosylates by Lithium Telluride[a]

entry	substrate	product	yield, %[b]
1	 **2 a**	 **3 a**	90
2	 **2 b**	 **3 b**	78
3	 **2 c**	 **3 c**	97
4	 **2 d**	 **3 d**	75
5	 **2 e**	 **5 a**  **5b**	70[c]
6	 **2 f**	 **6**  **7**	trace[d] 84

[a] All reactions were performed at room temperature on a 0.5 mmol scale with the use of 1.1 equiv of lithium telluride. [b] Isolated yields unless otherwise noted. All yields are based on the alcohols **1a**−**f**. See Supporting Information for details. [c] Yield determined by GC-MS analysis of the crude reaction mixture. [d] As evidenced by the ^{1}H NMR spectrum of the crude reaction mixture.

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(19) (a) Discordia, R. P.; Dittmer, D. C. *J. Org. Chem.* **1990**, *55*, 1414−1415. (b) Discordia, R. P.; Murphy, C. K.; Dittmer, D. C. *Tetrahedron Lett.* **1990**, *31*, 5603−5606. (c) Dittmer, D. C.; Discordia, R. P.; Zhang, Y.; Murphy, C. K.; Kumar, A.; Pepito, A. S.; Wang, Y. *J. Org. Chem.* **1993**, *58*, 718−731. (d) Xu, Q.; Chao, B.; Wang, Y.; Dittmer, D. C. *Tetrahedron* **1997**, *53*, 12131−12146. (e) Kumar, A.; Dittmer, D. C. *Tetrahedron Lett.* **1994**, *35*, 5583−5586. (f) Chao, B.; Dittmer, D. C. *Tetrahedron Lett.* **2000**, *41*, 6001−6004. (g) Kumar, A.; Dittmer, D. C. *J. Org. Chem.* **1994**, *59*, 4760−4764. (h) Pepito, A. S.; Dittmer, D. C. *J. Org. Chem.* **1994**, *59*, 4311−4312.
(20) (a) Pepito, A. S.; Dittmer, D. C. *J. Org. Chem.* **1997**, *62*, 7920−7925. (b) Chao, B.; Dittmer, D. C. *Tetrahedron Lett.* **2001**, *42*, 5789−5791.
(21) Xu, Q.; Dittmer, D. C. *Tetrahedron Lett.* **1999**, *40*, 2255−2258.
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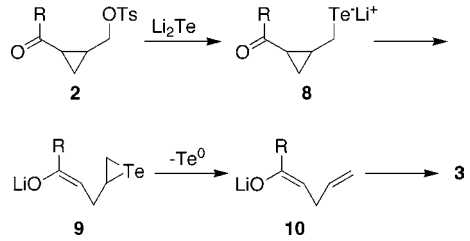
(23) (a) Gladysz, J. A.; Hornby, J. L.; Garbe, J. E. *J. Org. Chem.* **1978**, *43*, 1204−1208. (b) Clive, D. L. Y.; Anderson, P. C.; Moss, N.; Singh, A. *J. Org. Chem.* **1982**, *47*, 1641−1647.

The spirocyclopentadienyl derivative **2e** (Table 1, entry 5) underwent ring opening to give a mixture of 1- and 2-allyl-1,3-cyclopentadienes **5a**,**b**.[26] The 600 MHz ^{1}H NMR spectrum of the mixture allowed sufficient separation of the chemical shifts of the two isomers for determination of the isomer ratio of about 60:40 in favor of 2-allylcyclopentadiene.[26] The facile ring-opening of the spirocyclopentadiene is attributed to the stability of the cyclopentadienyl anion. The reaction of (2-phenylcyclopropyl)methanol tosylate **2f** with telluride ion is different, yielding mainly unstable telluride **7** (84%) with perhaps a trace of the ring-opened product, 3-butenylbenzene **6** (Table 1, entry 6). The formation of a relatively less stable benzyl anion apparently is not favored.

The use of other reducing agents for tellurium gave lower yields of **3a** and often required longer reaction times: sodium borohydride−water−benzene phase transfer catalyst (PTC),[20b] 2 h (17% plus isomers from migration of the double bond); rongalite−NaOH−water−benzene PTC,[19d] 3 h (15−17% plus products of double-bond migration); sodium hydride−DMF,[27] 12 h (20%, complicated by reaction of Na_2Te with DMF[27,28]); sodium naphthalenide−THF,[29] 20 min (44%). We have previously reported that the method of reduction of tellurium could alter the outcome of some tellurium-triggered reactions.[19c] Catalytic amounts (10 mol %) of tellurium with stoichiometric $LiEt_3BH$ may be used, but the reaction is slower (12 h) and the yield of **3a** is lower (50%). The presence of the Lewis acids, lithium ion, and triethylborane (a byproduct in the reduction of tellurium) apparently is helpful since the reaction seems to be somewhat inhibited by the Lewis base, fluoride ion. The reaction of **2a** with lithium telluride in the presence of tetrabutylammonium fluoride was slower and gave a lower yield of **3a** (60% for 15 h vs 90% for 25 min, Table 1, entry 1). This result also may be caused by some depletion of the telluride ion by reaction with the quaternary salt.

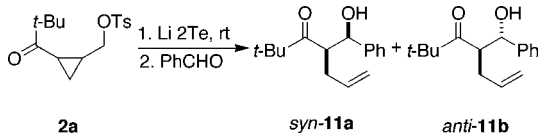
The reaction pathway for the nucleophilic ring opening may be rationalized by initial substitution of the tosylate group by telluride ion to give the monoalkyltelluride ion **8** (which in the case of **2f** leads to telluride **7**). Then, **8** undergoes intramolecular nucleophilic attack on the cyclopropane ring to give the unstable epitelluride intermediate **9**, which readily eliminates elemental tellurium to form enolate **10**, which is protonated during workup (Scheme 3).

Scheme 3. Mechanism for the Telluride-Triggered Nucleophilic Ring Opening of Cyclopropanes



The enolate from **2a** can be trapped by reaction with benzaldehyde to give *syn*- and *anti*-aldol products **11a**[14] and **11b**,[30] respectively, in 75−91% yield. Diastereoselectivity of this aldol reaction varies depending on the temperature and reaction time. The highly diastereoselective formation of the *syn*-aldol **11a** is kinetically controlled and observed at low temperature, whereas the thermodynamically favored *anti*-aldol **11b**, resulting from a slow equilibration through a retroaldol reaction, is formed at higher temperature, also with a high degree of diastereoselectivity (Scheme 4). This behavior closely resembles the aldol reaction of *tert*-butyl *n*-butyl ketone with benzaldehyde reported by Heathcock and Lampe.[31] The aldol products **11a**,**b** also have been obtained by treatment of trimethylsilylmethylcyclopropyl *tert*-butyl ketone and benzaldehyde with titanium tetrachloride at −78 °C (70%, anti/syn = 1:11), with $BF_3{\cdot}Et_2O$ (34%, anti/syn = 1.7:1), and with $SnCl_4$ (40%, anti/syn = 1:2).[14]

Scheme 4. Aldol Reaction of the Enolate Generated from **2a** with Telluride Ion



conditions of enolate trapping	d.r. *syn/anti*	yield, %
-78°C, 1 min.	17 : 1	68
-78°C, 10 min.	12 : 1	91
rt, 24 h	1 : 25	75-81

No reaction is observed under the conditions shown in Scheme 2 if the acylcyclopropanemethanol **1b** is used instead

(24) (a) Bergson, G. *Acta Chem. Scand.* **1957**, *11*, 571−572. (b) Engman, L.; Cava, M. P. *J. Org. Chem.* **1982**, *47*, 3946−3949. (c) Clive, D. L. Y.; Beaulieu, P. L. *J. Org. Chem.* **1982**, *47*, 1124−1126. (d) Osuka, A.; Suzuki, H. *Chem. Lett.* **1983**, 119−120. (e) Engman, L. *Organometallics* **1986**, *5*, 427−437. (f) Suzuki, H.; Inouye, M. *Chem. Lett.* **1986**, 403−406. (g) Huang, Z.; Xia, L.; Huang, X. *Synth. Commun.* **1988**, *18*, 1167−1170. (h) Matsuki, T.; Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2105−2107. (i) Padmanabhan, S.; Ogawa, T.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2114−2116. (j) Li, C. J.; Harpp, D. N. *Tetrahedron Lett.* **1990**, *31*, 6291−6294. (k) Huang, Z.-Z.; Zhou, X.-J. *Synthesis* **1990**, 633−634. (l) Zhou, Z.-L.; Shi, L.-L.; Huang, Y.-Z. *Synth. Commun.* **1991**, *21*, 1027−1037. (m) Vasil'ev, A. A.; Engman, L. *J. Org. Chem.* **1998**, *63*, 3911−3917.

(25) For the use of the term "cyclopropanalogue", see: Duffy, E. P. Ph.D. Thesis, Tufts University, Boston, MA, 1987; *Diss. Abstr. Int. B* **1988**, *48*, 3568.

(26) 5-Allyl-1,3-cyclopentadiene was not detected. In addition, 1- and 5-allylcyclopentadienes are higher in energy than the 2-allylcyclopentadiene by 0.545 and 3.859 kcal mol^{-1}, respectively, according to the ab initio calculations. A 60:40 ratio corresponds to a difference in energy of 0.240 kcal mol^{-1} at 298 K. The calculated energy difference of 0.545 kcal mol^{-1} is expected to afford a 72:28 mixture of isomers. Thermal 1,5-sigmatropic rearrangements in the cyclopentadiene system can interconvert isomers. Our reaction was carried out at room temperature. See Supporting Information.

(27) Suzuki, H.; Manabe, H.; Inouye, M. *Chem. Lett.* **1985**, 1671−1674.

(28) Zingaro, R. A.; Herrera, C.; Meyers, E. A. *J. Organomet. Chem.* **1986**, *306*, C36−C40.

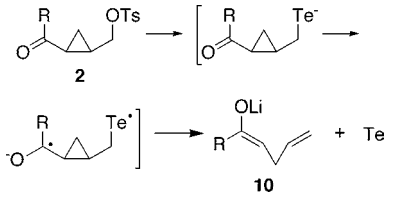
(29) Higa, K. T.; Harris, D. C. *Organometallics* **1989**, *8*, 1674−1678.

(30) Anti-configuration of **11b** was established on the basis of literature analogies and by comparison with the known **11a**:[14] (a) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294−4299. (b) Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 2543−2546.

(31) Heathcock, C. H.; Lampe, J. *J. Org. Chem.* **1983**, *48*, 4330−4337.

of the tosylate **2b**. This observation eliminates the possibility that ring-opening occurs by one-electron transfer from telluride ion to the carbonyl group to form a ketyl, but it does not rule out intramolecular electron transfer (Scheme 5). No significant difference in reactivity between

Scheme 5. Possible One-Electron Transfer Mechanism



cis- and *trans*-cyclopropane isomers in a mixture of both (mainly *cis*-isomer) was observed under the reaction conditions used.

In conclusion, a novel nucleophilic intramolecular cyclopropane ring opening triggered by telluride ion has been observed. The key reagent, elemental tellurium, is recovered and can be reused. In addition, this reaction illustrates a method of enolate generation without the use of strong bases or strong Lewis acids. Further studies on the scope and limitations of this method are currently underway.

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

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