An Oxidative Prins Cyclization Methodology

Chuanfeng Chen and Patrick S. Mariano*

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

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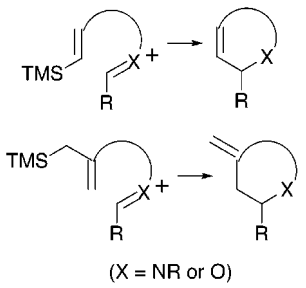
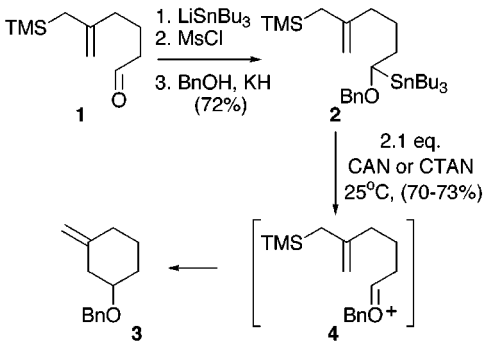
The closely related Mannich[1] and Prins[2] cyclization reactions are the cornerstones of versatile methods for the synthesis of nitrogen and oxygen heterocycles. These processes are initiated by the formation of respective iminium and oxonium ions. When these intermediates are tethered to alkenes, intramolecular additions occur to generate cyclic carbocations from which products arise by a number of different termination processes. Ingenious strategies have been developed to control both ring-size preferences and the resultant ring functionality in these reactions. Perhaps the most interesting are those that utilize tethered vinylsilanes and allylsilanes. Mannich[1] and Prins[3] cyclizations of substrates of this type occur with high levels of regiocontrol, because of β-silyl carbocation stabilization, to produce heterocyclic products with either endocyclic or exocyclic unsaturation (Scheme 1).

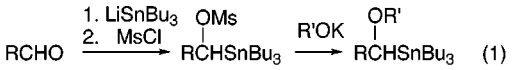
Scheme 1



Scheme 2



Likewise, a number of direct and efficient procedures have been developed for promoting formation of the iminium and oxonium ion intermediates in the respective Mannich and Prins cyclization processes. For the Prins process, some common methods include carbonyl complexation with Brϕnsted and Lewis acids and Lewis acid promoted acetal cleavage. An example of the latter approach is found in TMSOTf-catalyzed siloxyacetal condensations (so-called silyl-modified Sakurai reactions), which serve as highly efficient methods for cyclic ether synthesis.[3e−g] Another approach, introduced by Yoshida,[4] takes advantage of an anodic SET-destannylation sequence to produce the key oxonium ion intermediate. Although certainly less direct than siloxyacetal condensation, the oxidative methodology has some potentially attractive features. First, this method is compatible with a number of simple procedures that have been developed to synthesize the α-stannyl ether substrates (e.g., alkoxide substitution of α-stannyl mesylates, eq 1).[5,6]



Second, redox considerations[7] suggest that α-stannyl ethers will be readily transformed to oxonium ions by metal-based oxidizing agents [e.g., Ce(IV)], thus avoiding the need for the electrochemical protocol. Finally, this method might find application to cyclizations of complex substrates that possess Lewis acid sensitive groups or otherwise difficult-to-differentiate carbonyl or acetal centers (see below).

As an initial test of these proposals, the allylsilane-tethered α-stannyl ether **2** was prepared from the aldehyde **1**[8a] (Scheme 2) and subjected to Ce(IV) oxidations. Treatment of **2** with 2.1 molar equiv of either $Ce(NH_4)_2(NO_3)_6$ (CAN) in anhydrous MeCN or $Ce(NBu_4)_2(NO_3)_6$ (CTAN)[8b] in 5:2 MeCN−CH_2Cl_2, both containing 4-Å molecular sieves, at 25 °C for 3−12 h, followed by aqueous workup and silica gel chromatography, leads in each case to clean production of the benzyloxymethylenecyclohexane **3** (70−73%). These results demonstrate

(1) Overman, L. E.; Ricca, D. J. *Comprehensive Organic Synthesis*; Heathcock, C., Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 1007.

(2) Snider, B. B. *Comprehensive Organic Synthesis*; Heathcock, C., Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 527. For some recent studies, see: Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679. Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271.

(3) For allylsilane terminations, see: (a) Fleming, I.; Pearce, A.; Snowden, R. L. *J. Chem. Soc., Chem. Commun.* **1976**, 182. (b) Castaneda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695. (c) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496. (d) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibya, S. *Heterocycles* **1987**, *26*, 2805. (e) Mekhalfia, A.; Marko, I. E.; Adams, H. *Tetrahedron Lett.* **1991**, *32*, 4783. (f) Mekhalfia, A.; Marko, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779. (g) Sano, T.; Oriyama, T. *Synlett* **1997**, 716. For vinylsilane terminations, see: Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516. Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386. Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426. Berger, D.; Overman, L. E. *Synlett* **1992**, 811.

(4) Yoshida, J.; Ishichi, Y.; Isoe, S. *J. Am. Chem. Soc.* **1992**, *114*, 7594. Yoshida, J.; Takada, K.; Ishichi, Y.; Isoe, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2361.

(5) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. Linderman, R. J.; Chen, S. *Tetrahedron Lett.* **1995**, *36*, 7799. Linderman, R. J.; Chen, S. *Tetrahedron Lett.* **1996**, *37*, 3819. Duchene, A.; Boissiere, S.; Parrain, J.-L.; Quintard, J.-P. *J. Organomet. Chem.* **1990**, *387*, 153.

(6) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron* **1994**, *50*, 5927.

(7) (a) Oxidation potentials of α-stannyl ethers are in the range of 1.1−1.2 V (ref 7b), and the reduction potential of Ce(IV) is ca. 1.7 V (ref 7c). (b) Yoshida, J.; Ishichi, Y.; Nishiwaki, K.; Shiozawa, S.; Isoe, S. *Tetrahedron Lett.* **1992**, *33*, 2599. (c) Nair, V.; Matthew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, *26*, 127.

(8) (a) Prepared by Swern oxidation of the known alcohol: Lee, T. V.; Channon, J. A.; Cregg, C.; Porter, J. R.; Roden, F. S.; Yeoh, H. T. L. *Tetrahedron* **1989**, *45*, 5877. (b) Prepared by using the procedure described in Dehmlow, E. V.; Makrandi, J. K. *J. Chem. Res., Synop.* **1986**, 32.

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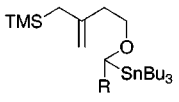
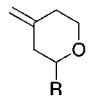
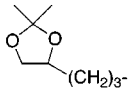
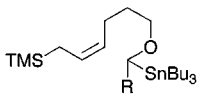
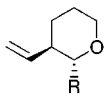
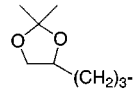
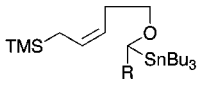
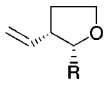
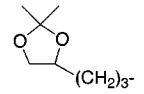
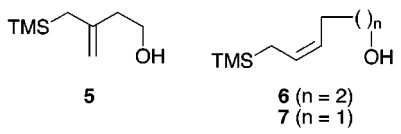
Table 1. $Ce(NBu_4)_4(NO_3)_6$ Promoted Oxidative Prins Cyclizations of α-Stannyl Ethers

α–Stannyl Ether		Prins Cyclization Product[a]	Yield (%)[b]
			
13	(R = iBu)	**24**	88
14	(R = cyclohexyl)	**25**	83
15	(R = 	**26**	91
			
16	(R = iBu)	**27**	85
17	(R = cyclohexyl)	**28**	74
18	(R = Bn)	**29**	74
19	(R = 	**30**	70
			
20	(R = iBu)	**31**	68
21	(R = Bn)	**32**	83
22	(R = 	**33**	96
23	(R = $(MeO)_2CH(CH_2)_2$)	**34** (R = $OHC(CH_2)_2$)	81

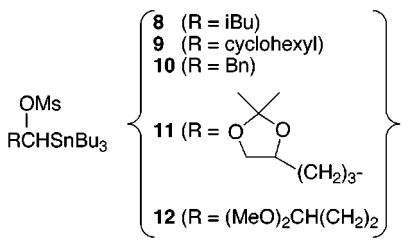
[a] All reactions were conducted at 25°C in anhydrous 5:2 MeCN–CH_2Cl_2 containing 4-Å molecular sieves and 2.1 equiv of CTAN. [b] Following aqueous workup and silica gel chromatographic purification.

that the oxonium ion intermediate **4** is cleanly formed under Ce(IV) oxidation conditions and that, like its Lewis acid–acetal derived counterpart,[3a] it undergoes facile cationic cyclization.

The generality of the oxidative Prins cyclization methodology was further probed using the allylsilane-tethered α-stannyl ethers **13**–**23** (Table), each prepared by addition of a trimethylsilylmethylalkenol-derived alkoxide (**5**–**7**)[9] to the corresponding α-stannyl mesylate (**8**–**12**).

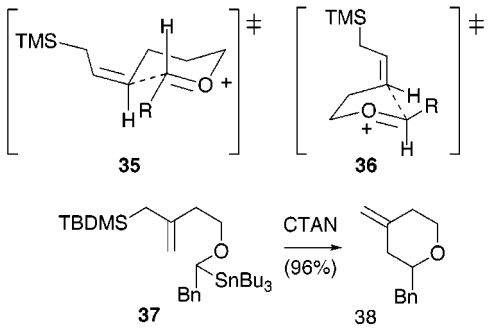


5 **6** (n = 2), **7** (n = 1)



Reactions were carried out by treating the stannyl ether substrates with 2.1 equiv of CTAN under the conditions described above. In all cases, cyclization occurs efficiently to produce the respective tetrahydropyran or tetrahydrofuran products. We have found that the procedure employing CTAN is preferable in the cases studied thus far because of the better solubility of this reagent (vs CAN) and the substrates in CH_2Cl_2-containing solvent systems.

As expected,[10] oxidative cyclizations of the linear allylsilane substrates **16**–**19** provide the *trans*-vinyl-R products predominantly as a consequence of minimized steric interactions in the trans-forming transition state **35**. Stereochemical assignments are based on the large diaxial coupling (J = 8–10 Hz) observed between H-2 (ca. 4 ppm) and H-3 (ca. 2 ppm) in the ^{1}H NMR spectra of **27**–**30**. Oxidative Prins cyclizations of the stannyl ethers **20**–**23** also occur efficiently to afford, in each case, the expected[11] *cis*-tetrahydrofuran as the major product. In these substrates, cyclization via transition state **36** is preferred. The allylic-TBDMS α-stannyl ether **37** is also a substrate for this reaction, efficiently (93%) producing the pyran derivative **38** under the oxidative conditions.



These results, exemplified by cyclizations of the acetal-containing stannyl ethers **15**, **19**, **22**, and **23**,[12] show that oxidative Prins cyclizations can be performed on substrates that contain a Lewis acid sensitive functionality. Thus, whereas the typical Lewis acid catalyzed siloxyacetal condensation and other procedures are superior for promoting Prins cylizations in general, their application to acetal-containing, multiply functionalized substrates may be problematic. It is in these cases where the alternative, albeit less direct, oxidative Prins method might be employed advantageously.

(9) (a) **5**: Ochiao, M.; Fujita, E.; Arimoto, M.; Yamaguchi, H. *Chem. Pharm. Bull.* **1983**, *31*, 86. (b) **6** and **7**: Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckhamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014.

(10) (a) Similar arguments have been advanced to explain the stereochemistry of seven-membered ring-forming Prins cyclizations (ref 3b) and sequential Prins-Pinacol reactions (ref 10b). (b) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354.

(11) (a) The stereochemistry of **31**, for example, is assigned as cis on the basis of the observed 5.5 Hz coupling constant for the H-2 and H-3 protons and comparisons to the reported (ref 3g) 7.0 Hz coupling in closely related *cis*-2-phenyl-3-vinyltetrahydrofuran. In addition, the strong preference for *cis*-tetrahydrofuran formation in 5-exo-Prins cyclizations has been noted ealier by Oriyama (ref 3g) and Hoffmann (ref 11b). (b) Hoffmann, R. W.; Giesen, V.; Fuest, M. *Liebigs Ann. Chem.* **1993**, 629.

(12) (a) The dioxolane moiety is retained in these processes despite the report that CAN in MeCN at 70 °C effectively deprotects cyclic acetals and ketals (ref 12b). Clearly the use of only 2.1 equiv of CTAN at 25 °C is required when another oxidatively active functionality is present. (b) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Marko, I. E. *Tetrahedron Lett.* **1999**, *40*, 1799. (c) The anomalous removal of the sensitive dimethylacetal in conversion of **23** to **34** likely occurs during either workup or chromatographic purification rather than under the oxidative Prins cyclization conditions.

Experimental Section

Typical Procedures for Preparation and Prins Cyclization of Allylsilane-Tethered α-Stannyl Ethers. To a suspension of KH (35%, 0.2 g, 1.75 mmol) in ether (20 mL) was added a solution of *trans*-1-trimethylsilylhex-2-en-6-ol (172 mg, 1 mmol) and 18-crown-6 (13 mg, 0.05 mmol) in ether (2 mL) at 0 °C. The mixture was stirred at 25 °C for 40 min before a solution of the α-stannyl mesylate (476 mg, 1.05 mmol) in 5 mL of CH_2Cl_2 was added. After being stirred at 25 °C for 2 h, the mixture was diluted with water, washed with brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The residue was subjected to silica gel chromatography (50:1 hexanes−ether) to give 403 mg (76%) of the tethered α-stannyl ether **16** as an oil. ^{1}H NMR ($CDCl_3$): −0.02 (s, 9H), 0.84−0.89 (m, 23H), 1.26−1.34 (m, 6H), 1.44−1.60 (m, 9H), 1.73−1.78 (m, 1H), 1.88−1.92 (m, 1H), 2.01−2.03 (m, 2H), 3.28 (dt, J = 6.6, 15.3 Hz, 1H), 3.33 (dt, J = 6.6, 15.3 Hz, 1H), 3.89 (dd, J = 10.5, 5.0 Hz, 1H), 5.23 (m, 1H), 5.38 (ddt, J = 19.5, 8.7, 2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): −1.9, 9.1, 13.6, 18.3, 21.7, 23.4, 23.8, 25.7, 27.4, 29.2, 30.2, 44.3, 70.7, 75.1, 125.7, 126.9. HRMS (*m*/*z*): calcd for $C_{26}H_{56}OSiSn$ (M^+), 531.3195; found, 531.3215.

A CH_2Cl_2 solution (2 mL) of the tethered stannyl ether **16** (53 mg, 0.1 mmol) was added to a stirred, −23 °C acetonitrile (5 mL) solution of CTAN (0.21 g, 0.21 mmol), which included suspended 4-Å molecular sieves (0.1 g). After being warmed from −23 to 25 °C and being stirred for 12 h, the mixture was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated in vacuo, giving a residue that was subjected to silica gel chromatography (50:1 hexanes−ether) to yield 14 mg (85%) of the tetrahydropyran **27** as an oil. ^{1}H NMR ($CDCl_3$): 0.82 (d, J = 6.55 Hz, 3H), 0.86 (d, J = 6.75 Hz, 3H), 1.29−1.32 (m, 2H), 1.39 (ddd, J = 16.2, 12.3, 4.3 Hz, 1H), 1.53−1.56 (m, 1H), 1.63 (tt, J = 13.0, 4.3 Hz, 1H), 1.75−1.83 (m, 2H), 1.90 (tdd, J = 9.50, 8.7, 3.9 Hz, 1H), 3.05 (ddd, J = 6.9, 9.4, 5.5 Hz, 1H), 3.36 (td, J = 11.8, 2.3 Hz, 1H), 3.94 (dt, J = 2.3, 11.3 Hz, 1H), 4.96 (dd, J = 10.3, 1.8 Hz, 1H), 5.01 (d, J = 17.3 Hz, 1H), 5.54 (ddd, J = 17.3, 10.3, 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): 24.1, 23.8, 24.0, 25.8, 30.6, 43.1, 47.0, 68.1, 78.9, 115.2, 140.2. HRMS (*m*/*z*): calcd for $C_{11}H_{20}O$ (M^+), 168.1514; found, 168.1500.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and high resolution mass spectral data for all previously unknown starting materials and oxidative cyclization products reported in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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