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Tetrahydropyran Ring-Opening Reactions Promoted by SmI_2

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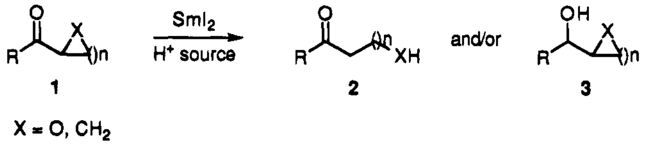
Many reductive transformations promoted by samarium diiodide (SmI_2) are used in ring-forming reactions; however, ring-opening reactions remain a far less studied area.[1-3] Ketones and other carbonyl functions react readily with SmI_2 to form metal-associated ketyls possessing both free radical and anionic character.[1] However, ring scission by the ejection of tethered atoms adjacent to carbonyl functions via SmI_2-generated ketyls is currently limited to small rings (**1**, $n = 1$) as shown in Scheme 1.[1-3] Several noteworthy synthetic efforts have been achieved using epoxides, vinyl epoxides, and cyclopropanes with the ring opening driven by strain energy release to afford general structure **2** ($n = 1$) rather than the direct reduction product **3** ($n = 1$).[1-3]

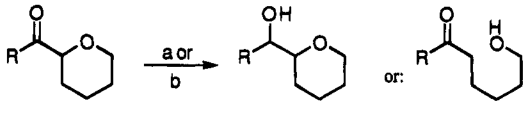
Scheme 1



A similar ring-opening reaction of larger rings has not been reported, in part because there are no benefits to the release of ring strain energy in those cases. Consequently, nonstrained rings such as those which are six-membered (**1**, X = O, $n = 4$) are readily reduced by most methods to alcohol **3** (X = O, $n = 4$), leaving the ring intact (vide infra). In this paper, we report that nonstrained tetrahydropyrans bearing an α-ketone (**1**, X = O, $n = 4$) are cleaved with SmI_2, forming an intermediate samarium(III) enolate. Since the enolate can be readily quenched *in situ* with several electrophiles, the process can be considered a regiocontrolled approach to carbon-carbon bonds by an S_N2 displacement.

We began by treating tetrahydropyran **4a**, prepared by standard transformations,[4] with HMPA and SmI_2 (3 equiv) at 0 °C, as shown in Table 1.[5] The cyclic ether readily underwent carbon-oxygen bond cleavage to produce acyclic alcohol **6a** in 70% yield after workup. A variety of other examples shown in Table 1 demonstrate a range of possible precursors for this reaction which all lack the ring strain of previous substrates.[1-3,6] No proton source, such as an alcohol, was used during the course of these reactions which is often important in similar reactions of epoxides and acyclic α-keto deoxygenations.[1,2] The related reaction of **4a** with nBu_3SnH forms an analogous *O*-stannyl ketyl, which does not result in ring cleavage, but instead gives exclusively alcohol **5a** by direct reduction of the ketone.[7,8]

Table 1

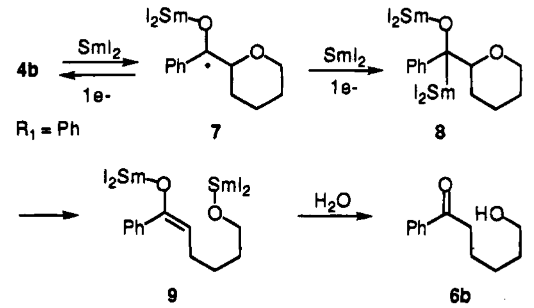


tetrahydropyran	condns	products (% yield)	
4a, R = nBu	b	**5a** (0)	**6a** (70)
4a, R = nBu	a	**5a** (92)	**6a** (0)
4b, R = Ph	b		**6b** (98)
4c, R = cHex	b		**6c** (81)
4d, R = CH_2Ph	b		**6d** (72)
4e, R = CH_2cHex	b		**6e** (45)

[a] $nBuSn_3H$, AIBN, PhH, 80 °C. [b] HMPA, SmI_2, THF.

A possible mechanistic rationale which accounts for the ring-cleavage reaction of SmI_2 with the substituted tetrahydropyran **4b** is shown in Scheme 2. The first equivalent of SmI_2 reversibly reduces the ketone to the samarium ketyl **7**.[11f] A second equivalent of SmI_2 reduces **7** to disamarium species **8** which then rapidly undergoes β-elimination to **9**.[9] Water workup affords the observed product **6b**, in 98% yield. It is interesting to note that when 1 equiv of SmI_2 is added to **4b**, little to no ring-

Scheme 2



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(3) Motherwell, W. B; *Aldrichim. Acta* **1992**, *25*, 71. (b) Batey, R. B.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, 6211. For other deoxygenations with SmI_2, see: (c) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, 2945. (d) Inanaga, J. *Rev. Heteroatom Chem.* **1990**, *3*, 75. (e) Hanessian, S.; Girard, C.; Chirara, J. L. *Tetrahedron Lett.* **1992**, 573. (f) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, 4437. (g) Inanaga, J.; Katsuki, J.; Yamaguchi, M. *Chem. Lett.* **1991**, 1025.

(4) Enholm, E. J.; Schreier, J. A. *J. Heterocycl. Chem.* **1995**, 0000.

(5) Typical procedure: An α-keto tetrahydropyran (1 equiv) in THF was added slowly by syringe to a degassed solution of samarium diiodide (2.5 equiv, 0.1 M) and HMPA (5 equiv) in THF and stirred for 15 min. The reaction was then quenched with water and stirred for 10 min. Dilute HCl (1.0 N) was added, and the reaction was stirred for 30 min. The resulting mixture was extracted with ethyl acetate and the organic layers were washed with water several times to remove HMPA. The organic layer was then washed with $NaHCO_3$ (aqueous saturated) and NaCl (aqueous saturated) and dried over Na_2SO_4. After evaporation of the solvents, the product was purified by flash column chromatography.

(6) An example of an α-keto tetrahydrofuran opening is known, but this ring is clearly under strain: Pratt, D. V.; Hopkins, P. B. *Tetrahedron Lett.* **1987**, 3065.

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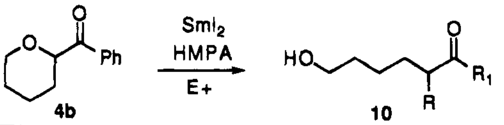
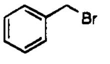
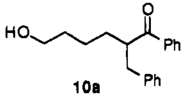
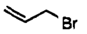
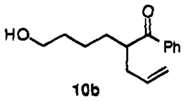
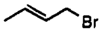
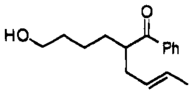
Table 2



4b 10

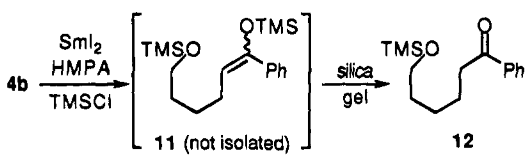
E+	Product	Yield
	 10a	86%
	 10b	70%
	 10c (3 : 1; E : Z)	65%

opening reaction occurs (<4%).[10] Thus, ketyl species **7** can form, but is not readily able to eject the oxygen by itself. When the second equivalent of SmI$_2$ is added, **6b** begins to form almost immediately. The reaction appears to be driven by the second equivalent of SmI$_2$. The related *O*-stannyl ketyl of **7** does not have the ability to reduce a radical to an anion; conversely, this readily occurs in many reductions with SmI$_2$.[1-3] The *O*-stannyl ketyl simply reacts by a radical chain mechanism with a hydrogen atom from a second molecule of nBu$_3$SnH to produce **5a**, leaving the ring still intact.[8]

The additional bond-forming capabilities of the disamarium intermediate **9** presented a potentially useful extension of this reaction. The use of the samarium(III) enolate in two-electron (2e$^-$) reactions was initially envisioned as having potential for the introduction of external electrophiles (E$^+$) by S$_N$2 displacement.[11,12] Enolate quenching experiments were next designed and implemented with the goals of better understanding the mechanistic aspects of the reaction taking advantage of disamarium intermediate **9** for the formation of new carbon–carbon bonds.

The phenyl ketone **4b** was selected for several quenching experiments with the hope that the added conjugation would provide stability to the ketyl, enolate, and disamarium intermediates. Activated alkyl halides including allyl bromide, crotyl bromide, and benzyl bromide were readily quenched by the Sm(III) enolate at carbon as shown in Table 2.[3,14] Cyclohexanone also underwent an aldol-type reaction, but in modest (35%) yield, probably due to enolate anion exchange with the disamarium intermediate **9** or by retro-aldol reaction.[13] Note that

Scheme 3



regiocontrol in enolate formation can be indirectly achieved with some ketone precursors, because the enolate can only form on the tetrahydropyran side. The addition of HMPA (5 equiv) to the reaction mixture was essential because it stabilized the disamarium intermediate; in its absence, no addition products were observed. The enolate quenching reaction sequence overall resulted in the formation of a new carbon–carbon bond at the expense of a carbon–oxygen bond.

Its interesting to note that there are several nucleophilic sites on the Sm(III) enolate **9** where an electrophile can react. Even in the presence of several equivalents of electrophile, only carbon–alkylated products were observed (Table 2). To complement this reactivity, electrophiles which can be trapped at other nucleophilic sites might broaden the scope of the reaction. Quenching **4b** after SmI$_2$ treatment with excess chlorotrimethylsilane produced TMS enol ether **11**, which was a single geometric isomer according to ^{1}H NMR analysis of the crude mixture. The TMS enol ether was subsequently cleaved during purification by flash silica gel chromatography, producing the (trimethylsilyl)oxy derivative **12** (54%). In addition to the regiochemical differences in deprotection at these sites, the wide range of reactions available to TMS enol ethers demonstrates a contrast in reactivity for each function and could prove useful in future applications.[15] In conclusion, this study shows that strain-release is not required for the scission of α-keto cyclic ethers by samarium ketyls. Samarium(III) enolates, which could be trapped with activated alkyl halides and chlorotrimethylsilane, were produced by the reductive opening of tetrahydropyran ethers. The reaction sequence represents a new approach to the rapidly-developing manifold of one- and two-electron transformations in synthesis.[11]

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Supplementary Material Available: Spectral data for compounds **6a–e**, **10a–c**, and **12** (5 pages).

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[9] Dilithium species similar to **8** have been proposed; for a review, see: House, H. O. In *Modern Synthetic Methods*; W. A. Benjamin, Inc.: Philippines, 1972; Chapter 3 and references therein.

[10] Careful treatment of **4b** with SmI$_2$ (1 equiv) in HMPA at 23 °C for 1 h gave a 90% isolated yield of recovered **4b**, a 6% yield of the secondary alcohol from direct ketone reduction, and <4% yield of ring-opened product **6b**.

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[13] Typical procedure: An α-keto tetrahydropyran (1 equiv) in THF was added slowly by syringe to a degassed solution of samarium diiodide (2.5 equiv, 0.1 M) and HMPA (5 equiv) in THF and stirred for 20 min. An electrophile (4 equiv) was added, and the reaction mixture was stirred for 2–12 h with monitoring by TLC. The reaction was then quenched with water, and the mixture was stirred for 10 min. Dilute HCl (1.0 N) was added, and the reaction mixture was stirred for 30 min. The resulting mixture was extracted with ethyl acetate, and the organic layers were washed with water several times to remove HMPA. The organic layer was then washed with NaHCO$_3$ (aqueous saturated) and NaCl (aqueous saturated) and dried over Na$_2$SO$_4$. After evaporation of the solvents, the product was purified by flash column chromatography.

[14] Other examples of carbonyl additions to samarium enolates include: (a) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036 and references therein. (b) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317. (c) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

[15] (a) Rasmussen, J. K. *Synthesis* **1977**, 91. (b) Brownbridge, P. *Synthesis*, **1983**, 1, 85.