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Catalytic Reactions of Samarium(II) Iodide

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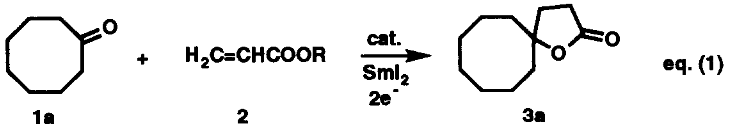
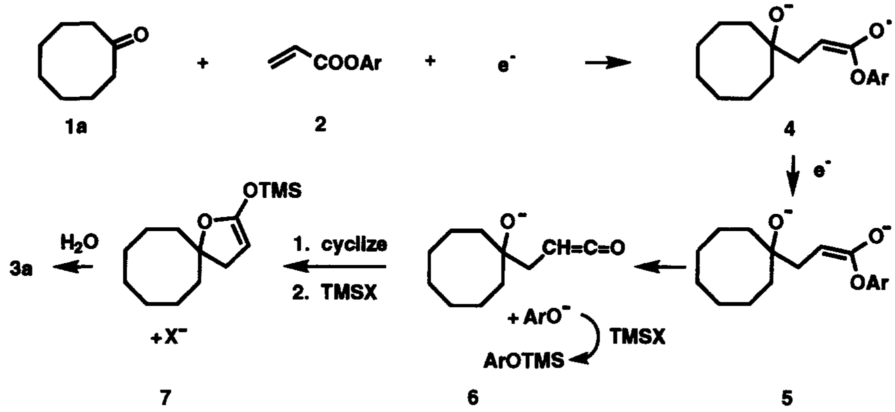
Abstract: *A system for in situ regeneration of SmI_2 from SmI_3 is described which allows the annulation of ketones to γ-lactones, the deoxygenation of oxiranes to olefins and radical π-cyclization to be conducted with 10 mole % SmI_2.* © 1997 Elsevier Science Ltd.

Since its introduction by H. B. Kagan and his group[1] samarium(II) iodide has been extensively investigated as a selective reducing agent in synthetic chemistry.[2] Its use in synthesis has been especially advantageous for ring closure reactions (usually radical initiated), C–C bond formation and stereocontrol (for example stereocontrolled intramolecular pinacol reactions and hydroxyl-directed addition of carbonyl to C=C).[2b] A major drawback of the SmI_2 reagent has been cost since it has been used invariably in stoichiometric amounts. Because of this fact we have studied systems for regenerating Sm(II) from Sm(III) *in situ* so that sub-stoichiometric quantities of SmI_2 could be employed. This paper reports a successful solution of this problem for three of the most interesting applications of SmI_2: (1) annulation of ketones to γ-lactones using acrylate esters, (2) SmI_2 initiated radical cyclization of unsaturated iodides and (3) deoxygenation of oxiranes to form olefins.[2] We have not studied pinacol couplings because several inexpensive and efficient reagents already exist for this application.[3,4] Our initial studies were centered on the cyclooctanone → γ-lactone conversion shown in eq. (1).

Initial experiments on the reduction of SmI_3 to SmI_2 in THF solution revealed that amalgamated Al foil, Mg turnings and Zn powder (20 mesh) were each effective, with the order in terms of reaction rate being Mg > Al > Zn. The replacement of iodine of Sm(III) by chloride or alkoxide ligands greatly complicates regeneration of Sm(II) by these amalgams because of much slower rates of reduction and/or solubility problems. As a result, very poor conversion of cyclooctanone and methyl acrylate to spiro lactone according to eq. (1) results with catalytic amounts of SmI_2 and excess Mg, Al or Zn amalgam even though these metals efficiently reduce SmI_3 to SmI_2. For example, with 10 mole % SmI_2 and excess Mg•Hg in THF at 23 °C under Ar, only 20% conversion of cyclooctanone was observed after 7 days to a mixture of δ-lactone and corresponding γ-hydroxy acid (mainly). In order to convert $SmI_n(OR)_{3-n}$ species to SmI_3, LiI and $Me_3SiOSO_2CF_3$ (TMSOTf) were added to the reaction between cyclooctanone, methyl acrylate, SmI_2 and the metal amalgam. Improved turnover was observed, especially with Zn•Hg, but extensive self reaction of the methyl acrylate occurred, which necessitated the use of a considerable excess of this reactant. Better results were obtained through the use of



Scheme 1



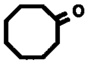
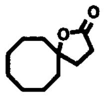
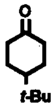
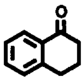
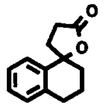
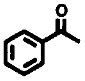
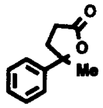
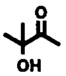
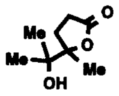
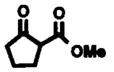
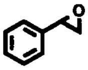
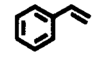
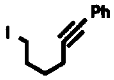
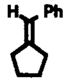
2,4,6-trimethylphenyl acrylate (**2**, mesityl acrylate, MAC), a better Michael acceptor. Optimum yields with 10 mole % of SmI_2 in THF as solvent required the use of 5-6 equiv of LiI, 2 equiv of TMSOTf, 1.4 equiv of MAC and the addition, either by motor-driven syringe or in *ca.* 10 portions, of these reactants and cyclooctanone (the limiting reactant) to Zn•Hg and SmI_2. Under these optimal conditions an 84% yield of spirolactone was obtained with 10 mole % of SmI_2 and a 94% yield was obtained with 20 mole % SmI_2. No turnover of SmI_2 could be effected with Al•Hg as reductant in part because of Al(III)-promoted cleavage of THF with resulting formation of samarium alkoxides. Poor turnover of Sm(II) was also found with Mg•Hg for reasons which are unclear but which probably are connected with the formation of insoluble Sm-containing solids.

The generality of the spirolactonization reaction using SmI_2, Zn•Hg, MAC, LiI, and TMSOTf, as outlined above for **1a** → **3a**, is supported by the results which are summarized in Table I for five diverse ketones with yields ranging between 70 and 85% for 10 mole % SmI_2.

Our working hypothesis for the ketone spiroannulation reaction described by eq. (1) is shown in Scheme 1. Electron transfer from SmI_2, either to the ketone or to MAC (**2**), and C–C coupling generates radical anion **4** which is rapidly reduced to the dianion **5**. Loss of mesityloxy from **5** generates the alkoxy ketene **6** which undergoes ring closure to form the enolate of spiro lactone **3a**. This enolate then reacts with TMSOTf to form the silyl ether **7** which produces **3a** upon aqueous workup. This Scheme is consistent with the known requirement of 2 SmI_2 per ketone for the stoichiometric process. The role of TMSOTf according to Scheme 1 is the conversion of RO^- species to ROTMS. The efficacy of LiI (5-6 equiv) is due to its capacity to convert SmI_2OTf to SmI_3, thus facilitating reduction by Zn•Hg and the likelihood that it reduces the Lewis acidity of Zn(II) by conversion to non Lewis-acidic species such as $Li_2ZnI_2(OTf)_2$. The latter clearly would minimize the formation of alkoxide species by ZnX_2 catalyzed cleavage of THF. In practice it is important to add TMSOTf to the reaction mixture at just the rate required to maintain a light blue color, indicative of the presence of SmI_2. If too much TMSOTf is present in the reaction mixture it causes problems such as reaction with I^- to form TMSI, which cleaves THF.

An interesting diastereoselection was noted with 4-*tert*-butylcyclohexanone as substrate. The major product of the spiro lactonization was the lactone **3b** in which the 3-propionyl group is *cis* to the *tert*-butyl substituent. The predominance of the axial addition product **3b** over the diastereomer was 92 : 8. This

Table 1. Organic reactions mediated by Zn•Hg and 10 mole % of SmI$_2$ in THF.

Substrates	Reaction Cond.	Product	Yield
2 + 	23 °C, 10 h		78-84%
2 + 	23 °C, 8 h		72% (92 : 8 dr)
2 + 	-10 °C, 3 h		70%
2 + 	-10 °C, 3 h		75%
2 + 	0 °C, 6 h		82%
	23 °C, 7 h		75%
	23 °C, 5 h		67%
	80 °C, 32 h 0.2 eq SmI$_2$		82%

stereochemical outcome is a possible indicator that C–C bond formation occurs by reaction of the ketyl radical anion with MAC rather than by reaction of the ketone with the MAC radical anion. The faster rates of spiro lactone formation with aromatic ketones such as acetophenone (Table 1), also argue for the ketyl to MAC addition pathway.

The formation of acrylate radical anions under the reaction conditions clearly is also possible. As indicated in Table 1, treatment of methyl acrylate with Zn•Hg and 10 mole % SmI$_2$, under the conditions described above for spiro lactone synthesis from ketones, afforded a good yield of 2-carbomethoxycyclopentanone. The pathway for this interesting annulation is probably the following: (1) electron transfer from SmI$_2$ to methyl acrylate to form the radical anion, (2) C–C bond formation by Baizer coupling,[5] (3) a second electron transfer, and (4) Dieckmann cyclization.

The catalytic reduction conditions reported herein for Zn•Hg – 10 mole % SmI_2 can also be used to effect the deoxygenation of oxiranes to give the corresponding olefins. Thus, as shown in Table 1, styrene is formed efficiently from the corresponding epoxide (90% yield by gc analysis; 67% isolated yield on a 1 mmole scale).

As indicated by the last entry in Table 1, the radical-induced cyclization of unsaturated iodides can also be conducted under catalytic conditions with 20 mole % of SmI_2 and Zn•Hg in THF. Thus 1-iodo-6-phenyl-5-hexyne is cleanly converted to benzylidenecyclopentane, without the use of TMSOTf since no alkoxide is generated.

Experimental procedures for the preparation of zinc amalgam[6] and the lactone **3a**[7] are provided below. The method for *in situ* regeneration of SmI_2 which is described herein should broaden the use of this valuable reagent, especially on larger scale.[8]

References and Notes:

1. (a) Girard, P.; Kagan, H. B.; Namy, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5. (c) Kagan, H. B. *New. J. Chem.* **1990**, *14*, 453.
2. For recent reviews, see: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (b) Matsuda, F. *J. Synth. Org. Chem. Japan* **1995**, *53*, 65. (c) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure Appl. Chem.* **1988**, *60*, 1725. (d) Molander, G. A.; Harris, C. R. in *Encyclopedia of Reagents for Organic Synthesis*, L. Paquette, ed., J. Wiley, New York, 1995, vol. 6, p. 4428. (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.
3. After the development of the catalytic system reported herein an account appeared describing SmI_2-catalyzed pinacol coupling using Mg metal as co-reductant; see Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666.
4. A process for the preparation of the less expensive $SmBr_2$ has recently been described by Lebrun, A.; Rantze, E.; Namy, J. L.; Kagan, H. B. *New J. Chem.* **1995**, *19*, 699.
5. Baizer, M. M.; Petrovich, J. P. *Progr. Phys. Org. Chem.* **1970**, *7*, 189.
6. Activated zinc powder (20 mesh) was prepared by washing the commercial powder successively with 1*N*HCl, H_2O and CH_3OH, and drying briefly under vacuum; storage was under pure N_2 or Ar. This activated zinc (1 g) was then suspended in 3 mL of dry THF, stirred under Ar with 50 mg of I_2 until colorless and washed with dry THF. The resulting Zn powder was then amalgamated by stirring with 100 mg of $HgCl_2$ in THF at 23 °C for 30 min and washed with dry THF.
7. **1-Oxaspiro[4.7]dodecan-2-one (3a).** A solution of LiI (700 mg, 5.2 mmol), cyclooctanone (**1a**; 126 mg, 1.0 mmol) and mesityl acrylate (**2**; 220 mg, 1.2 mmol) in THF (5 ml) was placed in a 5 ml gas-tight syringe which was mounted on a syringe drive. A small aliquot of the solution (0.5 ml) was added to a mixture of Zn•Hg (1 g, 15 mmol) and SmI_2 (0.1*M*, 1.0 mL, 0.1 mmol) in THF (15 ml) at 23 °C. The rest of the solution was added by drive over 9 h. The reaction mixture changed color gradually from dark blue to light blue [2]. A small portion of TMSOTf (10 µl, 0.06 mmol) was then added neat via a 100 µl gas-tight micro syringe as soon as the color of the reaction mixture faded to light blue. The reaction mixture became dark blue again in less than 2 min. When the color faded to light blue, a second aliquot of TMSOTf (10 µl, 0.06 mmol) to restore the dark blue color. TMSOTf was added in portions as described above until the reaction was judged complete by TLC. The total amount of TMSOTf used was about 550 µl (3.0 mmol), and the total time of reaction was about 9 h. The reaction mixture was concentrated *in vacuo* to remove THF, treated with aqueous bicarbonate and extracted with ether. Removal of ether after drying and chromatography on silica gel (hexanes–EtOAc, 8 : 1) afforded 142 mg (78%) of lactone **3a**. ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (t, J = 8.2 Hz, 2H), 2.02 (m, 2H), 2.01 (t, J = 8.2 Hz, 2H), 1.49-1.74 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 90.3, 35.4, 32.9, 28.8, 27.9, 24.5, 22.0; IR (neat) 927.1, 1167.7, 1191.1, 1260.1, 1769.6, 2856.6, 2923.8 cm^{-1}; MS (CI, M + NH_4^+) *m/z* calcd for $C_{11}H_{22}O_2N$: 200.1651. Found: 200.1645.
8. This research was supported by a NSERC Postdoctoral Fellowship to G.Z.Z. and a grant from the National Science Foundation.

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