Samarium Diiodide: A Mild and Selective Reagent in Organic Synthesis

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Samarium diiodide (SmI_2) is emanating as a mild and selective reagent for wide ranging transformations [1]. This compound was first reported in the literature in 1930 but attracted attention as a reagent in organic synthesis not before 1980 when a convenient preparation of SmI_2 along with its application to organic functional group transformations was described by Kagan [2]. SmI_2 is a powerful one electron reducing agent that can be conveniently and easily prepared in THF as an approximately 0.1M solution from samarium metal through its oxidation by any one of the following methods [2–4]. Samarium diiodide can also be used as a commercial product (Aldrich).
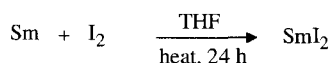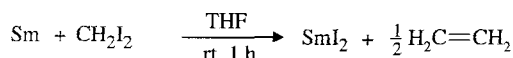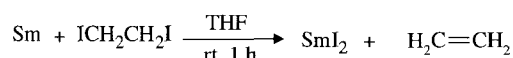

Samarium diiodide serves as a reagent of choice for a variety of synthetically important reactions such as pinacolic couplings, Barbier-type, aldol-type, Reformatsky-type, Sm based Simmons-Smith reactions, radical reactions, ketyl-olefin couplings, and nucleophilic acyl substitutions [1].

The reductive cleavage of the α-heterosubstituted carbonyl compounds constitutes one of the most widely used processes mediated by SmI_2. The heterosubstituents which can be readily cleaved include halides, oxygen- and sulfur containing α-substituents (e.g. -OH, -OR, -OSiR$_3$, -OC(O)R, -OSO$_2$Ar, -SAr). The carbonyl compounds comprise of ketones (e.g., 3-bromo-camphor [5]) as well as esters.
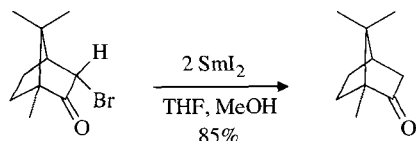

When the α-heteroatom is a part of a ring, then the cleavage provides a useful entry into the corresponding ring opened products. Small ring compounds such as epoxides [6] and aziridines [7], respectively, undergo reductive cleavage to furnish β-substituted ketones or esters.
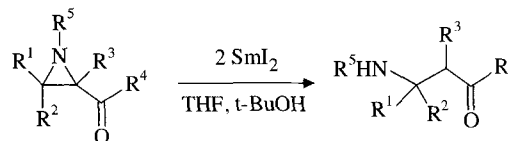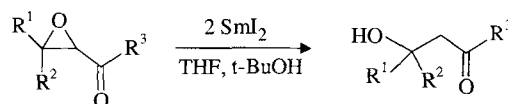
Samarium diiodide readily transfers an electron to aldehydes and ketones generating ketyl radical anions which can then participate in pinacolic coupling and related processes. For successful pinacolic coupling, any proton source must be excluded from the reaction mixture. A proton source, if present, may lead to selective 1,2-reduction to the corre- sponding alcohols. Both aldehydes as well as ketones are cleanly coupled in excellent yield in nearly every instance [8]. Aromatic substrates (e.g. benzaldehyde or acetophenone) couple very fast relative to aliphatic ones [8a]. A number of functional groups including amines, nitriles, and nitro groups are tolerated. In a recent report [9], advanced taxane intermediates have been prepared in good yield employing a stereoselective pinacol coupling mediated by SmI_2 as the key step.

ketoesters [13] and amides [14] containing an unactivated alkene moiety.
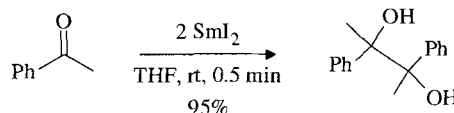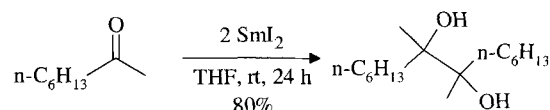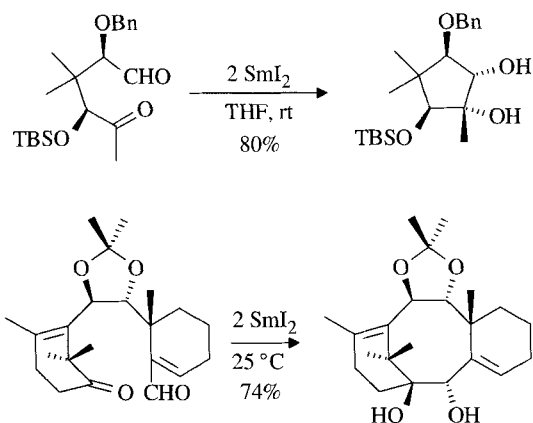
Ketyl radical anions formed by SmI_2-mediated one-electron reduction of aldehydes and ketones can also participate in ketyl–olefin coupling reactions with a variety of radical acceptors such as alkenes, alkynes, and even allenes. Hexamethylphosphoric triamide (HMPA) is generally used as an additive for these reactions and is believed to be responsible for the remarkable persistence of ketyls [10] under the strongly reductive reaction conditions and thereby providing a chance to these longer-lived intermediates to be trapped by various radical acceptors. In the absence of HMPA, longer reaction times are required and in few cases results in predominant 1,2-reduction product [10]. Both inter- and intramolecular couplings are possible. Intermolecular reactions are more or less limited to electron-poor olefins that are good acceptors for nucleophilic radicals.
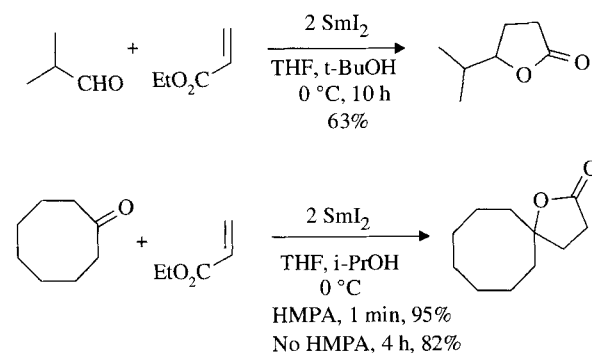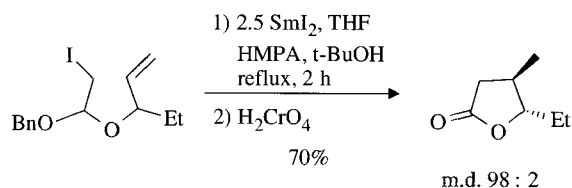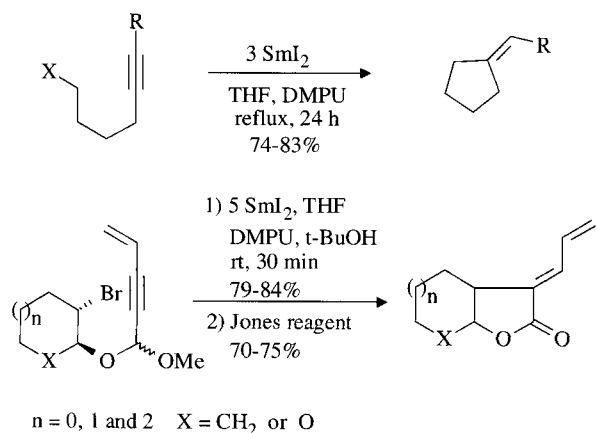
However, intramolecular ketyl–olefin coupling reactions are highly efficient and can accommodate substrates lacking activating substituents on the olefin moiety. A diverse range of ring systems can be generated using this method. For example, five-, six-, and seven-membered rings [11] have been prepared from the corresponding α,β-unsaturated ketoesters.

Unactivated olefinic ketones also undergo SmI_2-promoted 5-*exo* and 6-*exo* reductive cyclization [12] providing various cyclopentyl and cyclohexyl systems. Interestingly no products derived from 7-*exo* cyclization have been observed for n = 3. Instead, cyclooctanols were produced in modest yield through 8-*endo* cyclization process [10]. However, electron withdrawing substituents or π-conjugating substituents on the olefin dramatically increased the yield of cyclized product. Chelation phenomenon was effectively implemented to exert excellent stereochemical control in intramolecular reactions of β-
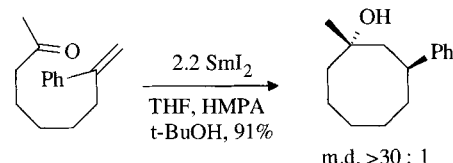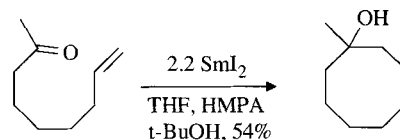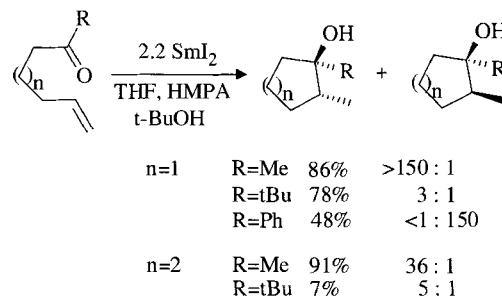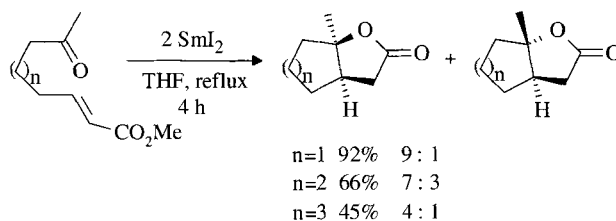
Samarium diiodide effectively promotes radical processes from alkyl, aryl and alkenyl halides as well as many other precursors (e.g. α-heterosubstituted sulfones, cyclopropyl ketones). Frequently the use of samarium diiodide offers distinct advantages over other reagents [15] as a complementary method. One limitation in these reactions is the possibility of further reduction of the radical to the corresponding anion. This implies that the radical must possess sufficient living time to undergo the desired reaction. Indeed several classes of radical cyclization reactions have been successfully performed. *Exo*-methylene-cyclopentanes are produced in good yield from cyclization of 6-halohex-1-ynes [16]. Preparation of γ-lactones has been accomplished [15a] *via* radical cyclization promoted by SmI_2 followed by oxidation. Similarly, a diastereoselective SmI_2-promoted synthesis of lactones that proceeds *via* an initial cyclization has been reported [15b]. It was observed that an oxygen atom within the chain cyclizes onto alkenes extremely more rapidly than their all-carbon analogues. Among other functional groups, hydrazones have been found to be exceedingly efficient acceptors for alkyl radicals generated by SmI_2 [17].

$3 \, SmI_2$

THF, DMPU
reflux, 24 h
74-83%

1) 5 SmI_2, THF
   DMPU, t-BuOH
   rt, 30 min
   79-84%
2) Jones reagent
   70-75%

n = 0, 1 and 2   X = CH_2 or O

1) 2.5 SmI_2, THF
   HMPA, t-BuOH
   reflux, 2 h
2) H_2CrO_4

70%

m.d. 98 : 2

SmI_2-promoted Reformatsky-type reaction offers a useful alternative to the normal Zn-promoted ones. It is particularly useful in reactions with hindered ketones [18]. Again intramolecular versions of this reaction gained more popularity and were successfully employed for the construction of medium and large ring compounds [19]. In a recent report [20], the dramatic influence of HMPA as an additive on the course of SmI_2-induced reactions of α-halo-esters was observed and succinic acid derivatives were produced. On the other hand, the same substrate reacted with SmI_2 in the absence of HMPA to provide β-ketoesters [21].

SmI_2
0 °C, <1 min
71%

2 SmI_2
THF, -78 °C
HMPA

2 SmI_2
THF, -78 °C
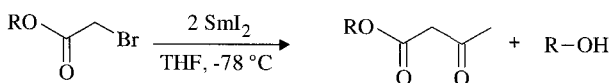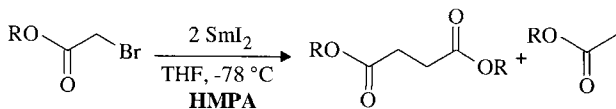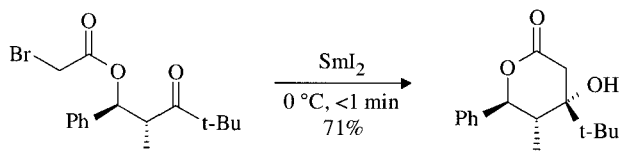
Reductive cleavage of N–O bonds in hydroxylamines and hydroxamic acid derivatives [22] can be performed using SmI_2. Chemoselective reduction of O–alkylhydroxylamines to amines was successful achieved in densely functionalized compounds using this procedure [22a].

SmI_2
THF, -78 °C
90 min, 93%
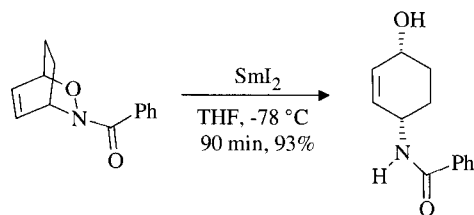
A continuous growth and the increasing number of applications [23] of this fascinating reagent to a diverse class of organic substrates is due to the versatility and tuneable character of SmI_2.

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Note added in proof. Since the above was written a number of further applications of SMI_2-mediated pincolization of diketones have appeared. For example see: H. M. R. Hoffmann, I. Münnich, O. Nowitzki, H. Stucke, D. J. Williams, Tetrahedron **52** (19916) 11783; O. Nowitzki, I. Münnich, H, Stucke, H. M. R. Hoffmann, Tetrahedron **52** (1996) 11799