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Generation of radical species by one electron oxidation with metallic compounds for the construction of carbon skeletons

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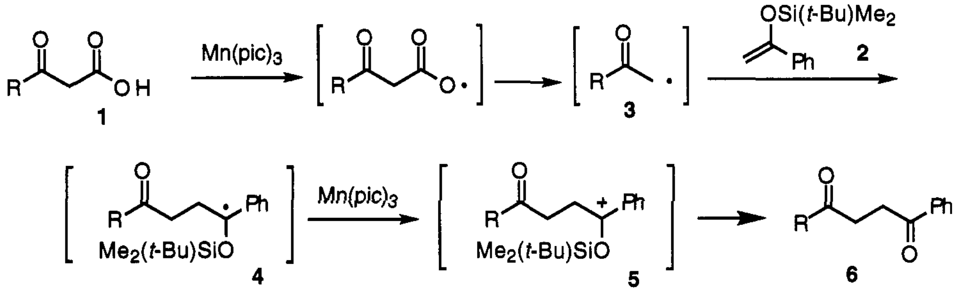
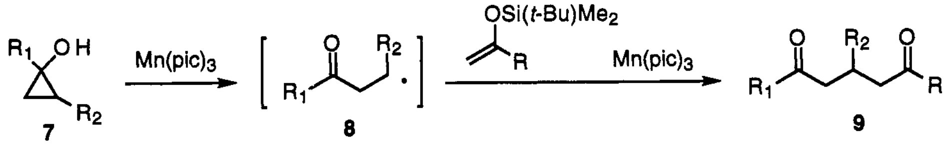
Abstract: By oxidation of β-keto acids, cyclopropanols, and acyl chromate complexes with tris(2-pyridinecarboxylato)manganese(III) (Mn(pic)$_3$), α-keto, β-keto, and alkyl radicals are generated respectively, which react with olefinic compounds to afford intermolecular addition products in good yield. The cation radicals can be generated from α-stannylalkyl sulfides, (1-stannylalkyl)amino compounds, and α-stannyl carboxylic esters by oxidation with ammonium hexanitratocerate(IV) (CAN). These cation radicals of the stannyl compounds readily cleave into carbocations or carbon radicals, which are utilized as reactive intermediates for the carbon-carbon bond formation.

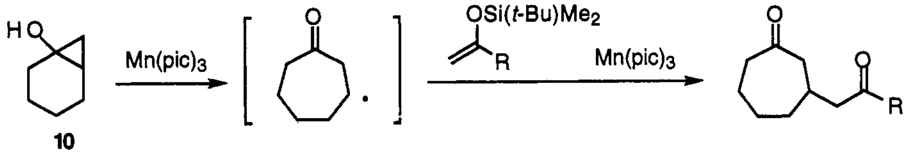
Radical reactions, when applied to organic synthesis, frequently lead to complex mixtures of products which still remain hard to be controlled. This makes it difficult to use radical intermediates for intermolecular bond forming reactions (ref.1). In order to carry out intermolecular radical reactions efficiently, we have tried to generate radical intermediates by the use of metallic oxidants with the expectation that both the radical species and the radical acceptors would interact with the metallic species employed (ref. 2).

To find a suitable metallic oxidant for the generation of radicals leading to their intermolecular addition to olefins, we examined the oxidation of α-keto acids with various metallic oxidants in the presence of a silyl vinyl ether as an acceptor of the resulting radicals. These studies revealed that Mn(III) 2-pyridinecarboxylate (Mn(pic)$_3$) can be employed as an oxidant to promote the intermolecular radical addition reaction efficiently. When Mn(pic)$_3$ was added to a mixture of a β-keto acid **1** and a silyl vinyl ether **2**, an addition product **6** of the resulting α-keto radical and the vinyl ether **2** was obtained in good yield even in the presence of a slightly excess amount of the vinyl ether **2** (ref. 3). In this reaction, Mn(pic)$_3$ oxidizes the keto acid **1**, generating a β–keto carboxyl radical, which cleaves into an α-keto radical **3**. This α-keto radical **3** then reacts with the vinyl ether **2**, to give a radical addition intermediate **4**. Mn(pic)$_3$ works effectively to terminate the radical reaction by oxidizing this radical intermediate **4** to a carbocation **5**, leading to the 1,4-diketone **6** .

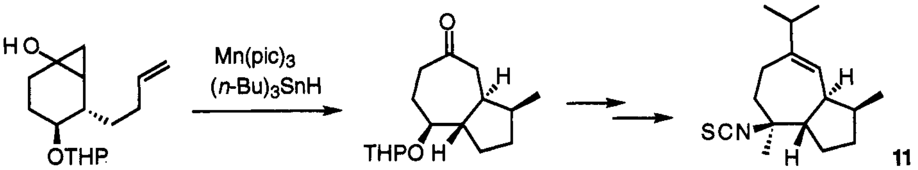


Mn(pic)$_3$ could be further utilized to the generation of β-keto radicals from cyclopropanols and their addition reaction to olefins. Notably, the 1, 2-bond is cleaved selectively in the oxidation of 1, 2-disubstituted cyclopropanols **7**, giving α-substituted β-keto radicals **8**, which react with olefins to form 1,5-dicarbonyl compounds **9** (ref. 4). From [n.1.0] bicycloalkanols such as **10**, 1,5-diketones are formed with ring-expansion (ref. 5).

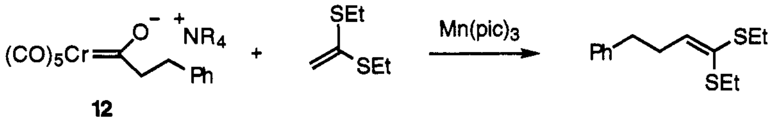




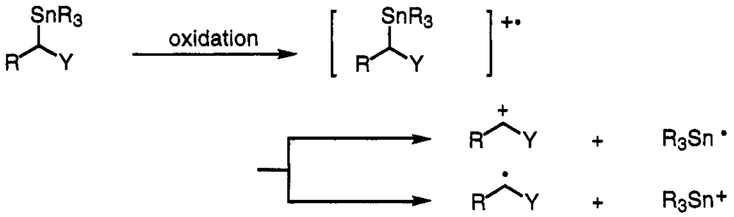
A marine sesquiterpene having a hydroazulene structure, 10-isothiocyanatoguaia-6-ene (**11**) was synthesized stereoselectively by applying this method to an addition reaction of the ring-expanded radical to an intramolecular olefinic moiety (ref. 6).



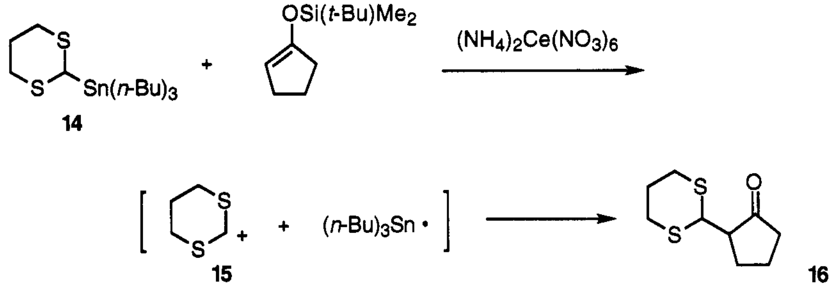
Oxidation of carbanions seems, in principle, to be a most convenient way to generate alkyl radicals. However, synthetic application of this process is rather troublesome because extensive self-coupling reactions may occur. Acyl chromate complexes **12** were found to eliminate alkyl radicals on one electron oxidation with Mn(pic)3, and these added to various olefins without forming self-coupling products (ref. 7).



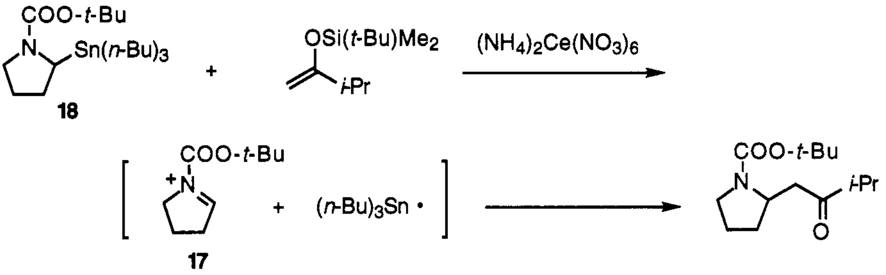
Utilization of radical cations has also been examined for the development of C-C bond forming reactions. Although heteroatom containing compounds are readily oxidized, these cation radicals have not been widely employed as synthetic intermediates for C-C bond formation because the cation radical center is localized mainly on the heteroatom. To generate useful reactive intermediates from organo-heteroatom compounds, we intended to use stannyl derivatives. It was supposed that the C-Sn bond in the cation radicals of the stannyl compounds would readily dissociate due to its low bond energy, resulting in the formation of carbocations or carbon radicals with elimination of the stannyl radical or cation, respectively.



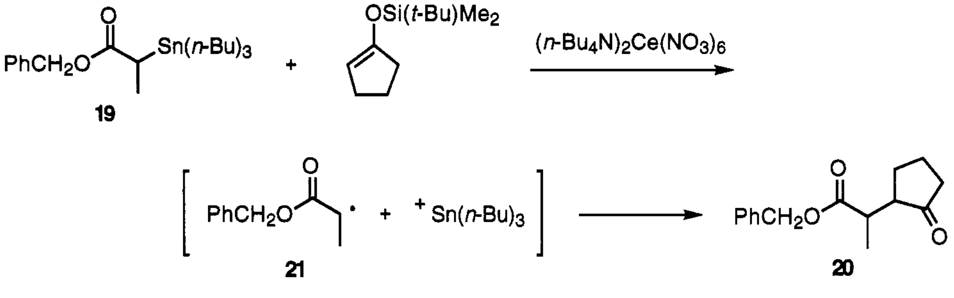
In fact, 2-stannyl-1,3-dithiane **14** was cleaved to a dithianyl cation **15** by oxidation with ammonium hexanitratocerate (CAN), and the reaction of **15** with carbon nucleophiles such as silyl vinyl ethers afforded the corresponding adducts **16** (ref. 8).



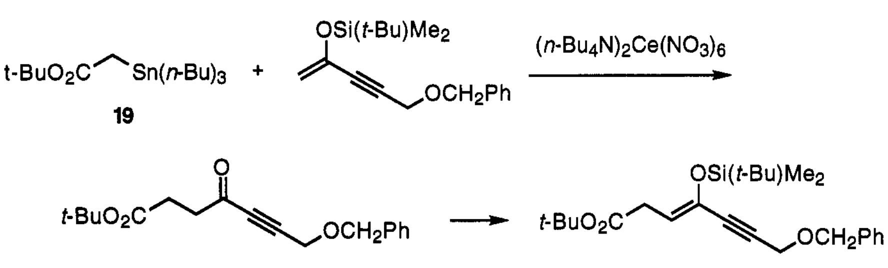
Acyliminium ions **17**, useful synthetic intermediates for the preparation of various amino compounds, can be generated under mild reaction conditions from N-(1-stannylalkyl) amides or carbamates **18** by oxidation with CAN. Various substituents can be introduced at the α-position of the amino group by the reaction of the iminium ions with carbon nucleophiles (refs. 9 and 10).

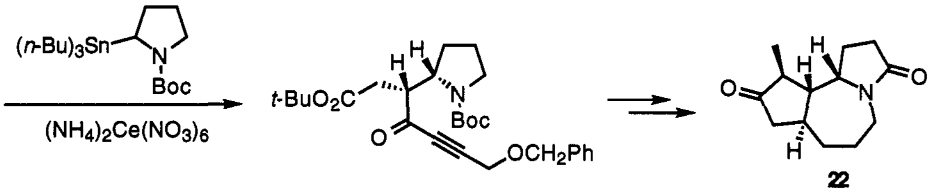


The cross-coupling reaction between the α positions of two carbonyl compounds, which is one of the most straightforward methods for the preparation of 1,4-dicarbonyl compounds, was found to proceed selectively using α-stannyl carboxylates. When a mixture of an α-stannyl carboxylate **19** and a silyl vinyl ether was treated with tetrabutylammonium hexanitratocerate (CBAN), a cross coupling product **20** was isolated without the formation of self-coupling products (ref. 11). In this reaction, an α-carbonyl radical **21** is first generated from the α-stannyl carboxylate via the C-Sn bond dissociation of the cation radical of **19** and is then trapped with a silyl vinyl ether, affording an unsymmetrical 1,4-dicarbonyl compounds selectively.



These synthetic methods for generation of carbocations and radical species from stannyl compounds were applied to the synthesis of a tricyclic *stemona* alkaloid, stemonamide (**22**) (ref. 12). The carbon skeleton of stemonamide was constructed efficiently by applying these reactions as shown in the following scheme.





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