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Synthesis of carbocycles by enone-selective reduction using organoiodotin hydride

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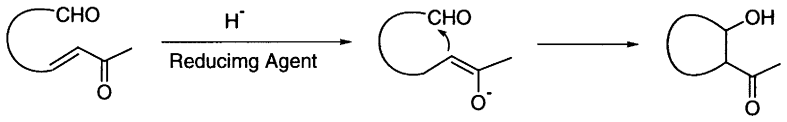
Abstract

By using di-*n*-butyliodotin hydride (*n*-Bu_2SnIH), carbocycles were prepared from substrates bearing both enone and formyl moieties, where the enone-selective reduction was followed by a diastereoselective intramolecular aldol reaction.

Keywords: organoiodotin hydride; enone-selective reduction; 1,4-reduction; intramolecular aldol reaction.

Chemoselective reduction of bifunctional substrates provides cyclic compounds when the initially reduced functionality affords a nucleophilic intermediate to react with the remaining electrophile. The preparation of carbocycles is important to enable access to naturally occurring compounds. Intramolecular aldol reactions which are useful and various methods for generating carbanions have been developed.[1] On the other hand, the direct formation of an enolate nucleophile by the reduction of enone in the presence of a formyl group has not been focused on so far (Scheme 1).[2] This is because of the easy access to the reduction of aldehydes other than enones when conventionally used reducing agents are employed.[3]



Scheme 1.

Recently, we have found that an iodo-substituted tin hydride such as *n*-Bu_2SnIH[4] causes selective reduction of enones even in the presence of aldehydes.[5] We thus focused our work on a novel type of cyclization starting from substrates bearing enone and formyl groups.

We initially tried the reaction of aromatic bifunctional substrate **1** by an equimolar amount of *n*-Bu_2SnIH at room temperature for 5 h. After protonolysis of the reaction mixture, β-hydroxy cyclic ketone **2** was obtained selectively (Scheme 2). Use of chlorotin hydride (*n*-Bu_2SnClH) resulted in a

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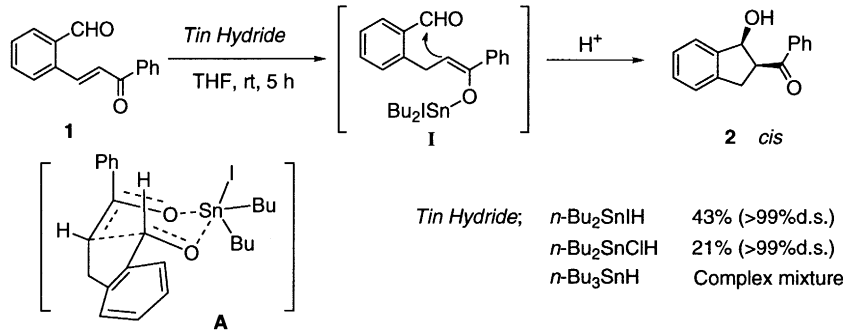
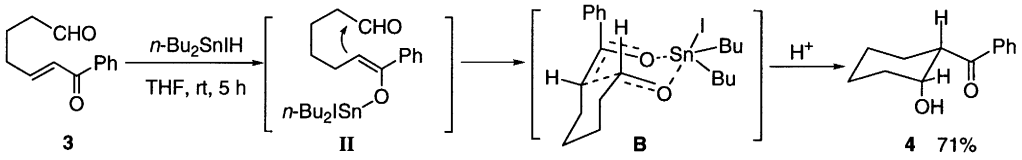
lower yield than when using *n*-Bu_2SnIH. Tri-*n*-butyltin hydride did not give the product and the reaction resulted in a complex mixture.



Scheme 2.

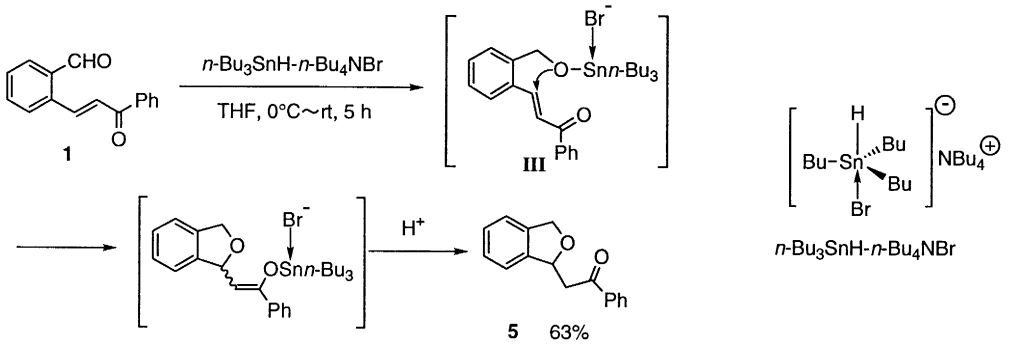
The result promoted by *n*-Bu_2SnIH indicates that a 1,4-reduction of an enone group predominates over the reduction of a formyl group. The resulting tin enolate(I) immediately attacks the remained formyl group.[6,7] No product derived from the reduction of the formyl groups or the non-cyclized one was detected. Namely, the formyl group does not have to be protected at all. Moreover, the latter aldol reaction proceeds with *cis*-selectivity. It seems that the high stereoselectivity arises from the selective formation of (*Z*)-enolates(I) by the 1,4-reduction of the enone moieties of **1**.[8] The subsequent aldol reaction proceeds through a six-membered cyclic transition state **A** to form an *erythro* aldol intermediate.[9] The tin center of I bears adequate ligand accessibility because of the electron-withdrawing halogen substituent. Unfortunately, a further increase of the yield of **2** was not successful. This would be because of the ring strain of the intermediate **A**. So we next used a linear type substrate **3** (Scheme 3). As expected, *cis*-substituted cyclohexane derivative **4** was obtained in a higher yield than in the case of **2**. The enone-selective reduction generated (*Z*)-tin enolate(II) which subsequently afforded **4** through the transition state **B** with less ring strain than the transition state **A**.



Scheme 3.

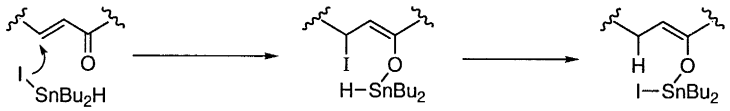
We have already reported that *n*-Bu_3SnH, when an equimolar *n*-Bu_4NBr is added, forms itself into a pentacoordinate tin, and acts as an effective reducing agent for aldehydes and ketones.[10] In contrast to the reaction when using *n*-Bu_2SnIH, a non-halogen-substituted tin, *n*-Bu_3SnH-Bu_4NBr, gave cyclic ether **5** selectively (Scheme 4).

Selective reduction of the formyl group of **1** takes place, and the resulting Sn–O bond in III acts as a nucleophile to attack the remaining enone in a fashion of 1,4-addition.[11] The difference in chemoselectivity of *n*-Bu_2SnIH from that of *n*-Bu_3SnH-*n*-Bu_4NCl arises from the halogen substituent on the tin center. In the pentacoordinate tin complex, *n*-Bu_3SnH-*n*-Bu_4NBr, the Sn–H bond which occupies the apical position acts as a hydride donor to cause the direct attack toward the formyl group. In contrast, the ability of hydride donation in *n*-Bu_2SnIH would be low; in addition, it seems that the tin–iodine bond has high nucleophilicity.[12] Hence, we consider that 1,4-addition of the enone by the Sn–I bond takes place prior to addition by the Sn–H bond, which is a key reaction to determine the enone-selectivity (Scheme 5).[13]



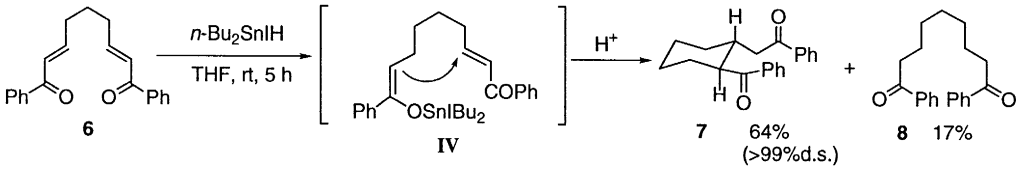
Scheme 4.

The reaction does not proceed in a radical manner — no decrease of the yield of **2** under the conditions in Scheme 2 was observed in the presence of a radical inhibitor such as *p*-dinitorobenzene.



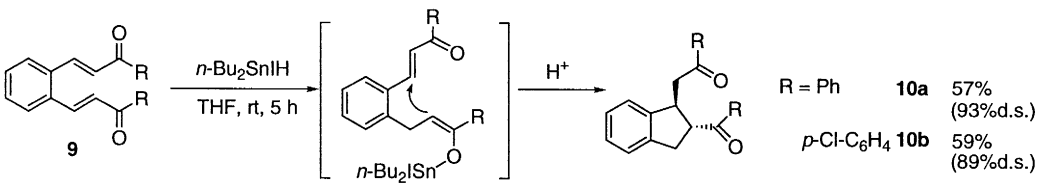
Scheme 5.

Synthesis of carbocycle was also possible when dienone **6** was used as the starting substrate. Treatment with 1 equiv. of *n*-Bu_2SnIH gave cyclic diketone **7** as a major product with high *trans*-selectivity (Scheme 6). 1,4-Reduction of one of the enones takes place and the generated tin enolate(IV) induces a Michael addition toward the other unreacted enone. In this case, the reaction was accompanied with saturated ketone **8** derived from the 1,4-reduction of both enones.



Scheme 6.

ortho-Substituted aromatic dienone **9** also afforded cyclic products **10** in moderate yields under the same conditions (Scheme 7).[14] The reaction proceeded with high diastereoselectivities, and no product formed by the reduction of both enones was detected.



Scheme 7.

In this way, iodo-substituted tin hydride (*n*-Bu_2SnIH) afforded a novel type of cyclization by enone-selective reduction in the reduction of a bifunctional substrate. Various carbocycles could be prepared in a one-pot procedure.

Acknowledgements

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6. Representative procedure: To a solution of *n*-Bu_2SnH_2 (0.5 mmol) in 1 mL of THF was added *n*-Bu_2SnI_2 (0.5 mmol). The mixture was stirred at room temperature for 10 min. IR spectra showed the change from 1800 cm^{-1} to 1857 cm^{-1}, which indicates the formation of *n*-Bu_2SnIH. To the solution was added **1** (1 mmol) and the mixture was stirred at rt until the Sn–H absorption disappeared (5 h). After quenching with MeOH (5 mL), volatiles were removed under reduced pressure. The residue was subjected to column chromatography (Fuji-gel FL100DX) eluting with hexane:EtOAc (9:1) to give product **2**. Further purification was performed by kugelrohr distillation or preparative TLC eluting with hexane:Et_2O (9:1). ^{1}H NMR ($CDCl_3$) δ 3.04 (br, 1H, O*H*), 3.15 (dd, 1H, *J*=8.3 and 16.1 Hz, CH), 3.60 (dd, 1H, *J*=7.8 and 16.1 Hz, CH), 4.31–4.39 (m, 1H, C*H*COPh), 5.51 (d, 1H, *J*=5.8 Hz, C*H*OH), 7.24–8.05 (m, 9H, Ph).
7. Substrates **1** or **3** were prepared by the reaction of the corresponding dialdehyde with 1 equiv. of a Wittig reagent.
8. The formation of (*Z*)-enolate by the reaction of a simple enone with Bu_2SnIH has been confirmed.[5]
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11. ^{1}H NMR data for **5** was as follows: ($CDCl_3$) δ 3.34 (dd, 1H, *J*=4.9 and 16.6 Hz, C*H*COPh), 3.54 (dd, 1H, *J*=7.3 and 16.6 Hz, C*H*COPh), 5.08 (dd, 1H, *J*=1.0 and 12.2 Hz, OC*H*), 5.15 (dd, 1H, *J*=2.4 and 12.2 Hz, OC*H*), 5.87–5.93 (m, 1H, OC*H*CH_2), 7.19–8.02 (m, 9H, Ph).
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14. ^{1}H NMR for **10a**: ($CDCl_3$) δ 3.09 (dd, 1H, *J*=7.3 and 16.1 Hz), 3.25 (dd, 1H, *J*=7.8 and 16.6 Hz), 3.43 (dd, 1H, *J*=9.3 and 16.1 Hz), 3.50 (dd, 1H, *J*=5.9 and 16.6 Hz), 4.09–4.17 (m, 1H), 4.40–4.47 (m, 1H), 7.16–7.98 (m, 14H).