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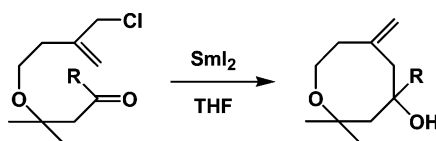
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ABSTRACT



A general, efficient, and experimentally simple method for generating medium rings utilizing the SmI_2 -mediated Barbier-type coupling has been developed. Various eight- and nine-membered carbocycles and heterocycles are assembled with high efficiency via this protocol. Amazingly, the process does not require high-dilution conditions and almost quantitative yields of the frequently inaccessible medium-sized rings are obtained.

Compounds having medium-ring frameworks have historically attracted much attention because of their potential biological activity and the synthetic challenge posed by the required formation of the ring itself. While various types of annulation methods for the construction of the medium rings have evolved, the development of a general and efficient method for preparing medium-sized carbocycles and heterocycles by simple cyclization of acyclic precursors via the carbon–carbon bond formation reaction has not proven to be as easy.¹

Samarium(II) iodide (SmI_2) has become an exceedingly useful reagent for promoting reductive coupling reactions over the past decade.^{2,3} The SmI_2 -mediated intramolecular Reformatsky reactions, ketone–olefin reductive couplings, Barbier-type couplings, and pinacol couplings have been adapted, which allows construction of medium-ring molecules.⁴ Recently, we reported the extremely convenient cyclization of eight- and nine-membered rings using the intramolecular Barbier-type coupling between the aldehydes and allyl chlorides induced by SmI_2 .^{5,6} For example, the treatment of aldehydes **1a** and **1b** with SmI_2 in the presence

of HMPA affected the simultaneous ring closure affording the cyclooctanols **2a** and **2b** in 99 and 98% yields, respectively (Scheme 1). The addition of HMPA was essential for the reductive cyclization.^{7,8} Subsequent studies on the Barbier-type cyclizations revealed that the ketones are also good

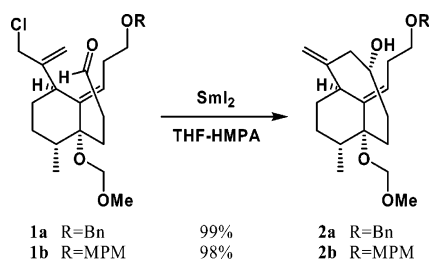
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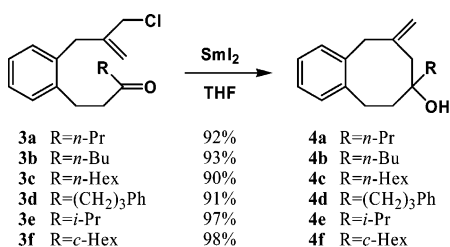
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Scheme 1



substrates for the medium-sized ring-closing reaction. Particularly, the couplings efficiently proceeded between the ketones and the allyl chlorides in the absence of HMPA.⁹ From a synthetic point of view, this is highly advantageous because HMPA is a potent carcinogen. Herein, we describe a new version of the medium-ring closure reaction through the intramolecular Barbier-type coupling induced by SmI₂. Important mechanistic information on the nature of the SmI₂-promoted annulation reactions is also reported.

Scheme 2



Scheme 2 summarizes the cyclizations of the eight-membered carbocycles. A typical example is the Barbier-type cyclization of the *n*-propyl ketone **3a**. When **3a** was reacted with SmI₂ at ambient temperature in THF, the

(5) For a review on Barbier-type couplings mediated by SmI₂, see: Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, 99, 745.

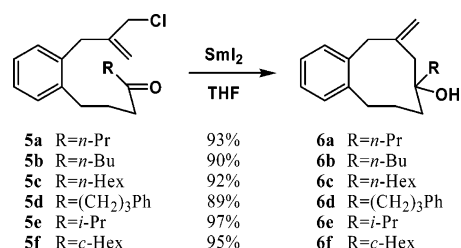
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(8) The role of HMPA in reactions of SmI₂ is quite understood. See: (a) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, 34, 1717. (b) Hou, Z.; Wakatsuki, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1205. (c) Hou, Z.; Zhang, Y.; Wakatsuki, Y. *Bull. Chem. Soc. Jpn.* **1997**, 70, 149. (d) Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, 38, 1137. (e) Shotwell, J. B.; Sealy, J. M.; Flowers, R. A., II. *J. Org. Chem.* **1999**, 64, 5251. (f) Shabangi, M.; Kuhlman, M. L.; Flowers, R. A., II. *Org. Lett.* **1999**, 1, 2133. (g) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2000**, 122, 7718. (h) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2002**, 124, 6895.

(9) In contrast, when the cyclization reaction of aldehydes and allyl chlorides was carried out in the absence of HMPA, only the intermolecular pinacol coupling product was isolated rather than the cyclization product. Therefore, the single-electron transfer from SmI₂ occurred at the aldehyde group to generate the ketyl-radical intermediate. See: Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, 30, 1063.

Scheme 3



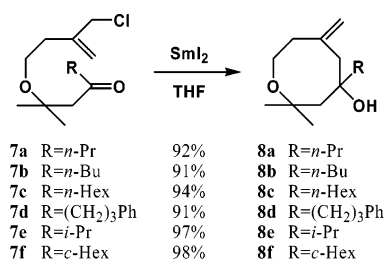
intramolecular coupling smoothly took place between the ketone and the allyl chloride to give the benzene-ring-fused cyclooctanol **4a** in 92% yield. By carrying out the cyclization reactions of the *n*-butyl ketone **3b**, *n*-hexyl ketone **3c**, and 3-phenylpropyl ketone **3d** under the same conditions, excellent yields of the cyclooctanols **4b–d** were obtained. Interestingly, despite utilizing the sterically hindered isopropyl ketone **3e** and cyclohexyl ketone **3f** for the cyclizations, the cyclooctanols **4e** and **4f** were generated in yields (97 and 98%, respectively) higher than those of the cyclooctanols **4a–d** (90–93%) derived from the less-hindered ketones **3a–d**.¹⁰ The excellent yields of **4a–f** (90–98%) are remarkable in view of the difficulties normally encountered during the cyclization of eight-membered rings. It is particularly noteworthy that the eight-membered rings were constructed under non-high-dilution conditions.

As shown in Scheme 3, the nine-membered carbocycles are also readily accessed by the same medium-ring cyclization mediated by SmI₂. For the nine-membered ring-closing reactions of the *n*-propyl ketone **5a**, *n*-butyl ketone **5b**, *n*-hexyl ketone **5c**, and 3-phenylpropyl ketone **5d**, the Barbier-type couplings occurred cleanly and the benzene-ring-fused cyclononanols **6a–d** were constructed in excellent yields. In a manner similar to the cyclizations of the eight-membered carbocycles, the cyclononanols **6e** and **6f** were cyclized from the sterically hindered isopropyl ketone **5e** and cyclohexyl ketone **5f** in yields (97 and 95%, respectively) higher than those of **6a–d** (89–93%).¹⁰

The annulation method using SmI₂ was successfully applied to the elaboration of the medium heterocycles (Scheme 4). The eight-membered ring ethers **8a–d** were also produced in excellent yields by performing the coupling cyclizations of the *n*-propyl ketone **7a**, *n*-butyl ketone **7b**, *n*-hexyl ketone **7c**, and 3-phenylpropyl ketone **7d** under the same conditions mentioned above. The sterically hindered isopropyl ketone **7e** and cyclohexyl ketone **7f** also provided the eight-membered ethers **8e** and **8f** in yields (97 and 98%, respectively) higher than those of **8a–d** (91–93%).¹⁰ Again, the ready formation of the medium-ring ethers was accomplished without resorting to high dilution.

(10) Obviously, the yield of the cyclized product increased by increasing the ketone substituent size. The experimental results may be explained by assuming that the bulky alkyl group completely suppresses the single-electron transfer from SmI₂ to the ketone group and the intermolecular pinacol reaction.⁹ Then, the single-electron transfer predominantly occurs at the allyl chloride group to form the π -allyl samarium intermediate, and the intramolecular organo-samarium addition reaction exclusively proceeds.

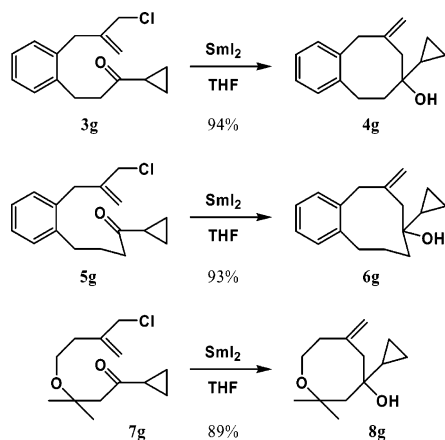
Scheme 4



The cyclization reactions are operationally quite simple. Particularly impressive is the fact that these medium-sized carbocycles and heterocycles were obtained in almost quantitative yields under non-high-dilution conditions. The optimum reaction conditions for the coupling cyclizations involved the rapid addition of a 0.1 M solution of SmI₂ in THF (2.5 equiv) to a 2.0 M solution of the starting material in THF. The reactions were completed within several hours after the SmI₂ was added.^{11,12}

The mechanism of the Barbier-type couplings promoted by SmI₂ has been the object of much study and speculation.¹³ On the basis of these mechanistic studies, the question of whether the crucial carbon–carbon bond formation step in the medium-ring cyclization was the result of the ketyl-radical addition or the organo-samarium addition was left open. Thus, we conducted a study to indicate whether the ketyl radical or organo-samarium species was involved in the reaction. Recognizing the propensity of cyclopropyl carbonyl ketals to undergo facile ring opening, the cyclopropyl ketones **3g**, **5g**, and **7g** were synthesized as test substrates.¹⁴ As shown in Scheme 5, **3g**, **5g**, and **7g**

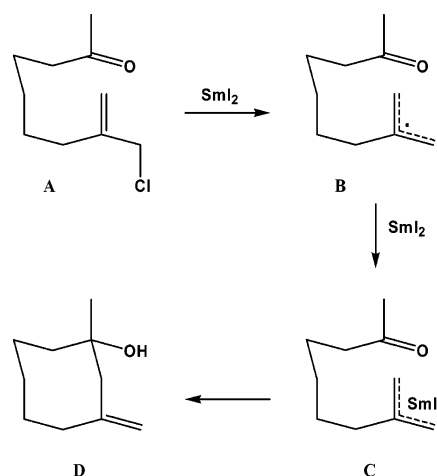
Scheme 5



underwent efficient cyclizations to give the expected medium-ring alcohols **4g**, **6g**, and **8g** without any formation of the fragmentation products.

Therefore, it seems feasible that the medium-ring formation reactions take place through the organo-samarium addition pathway as illustrated in Scheme 6. The allyl

Scheme 6



chloride group of the starting material **A** is initially reduced through the single-electron transfer from SmI₂, and the π -allyl radical **B** is generated. The radical **B** is then reduced to π -allyl samarium **C**. The intramolecular 1,2-addition of the organo-samarium species to the ketone group provided the cyclization product **D**.^{9,10}

In summary, we have developed a general, efficient, and experimentally simple method for generating medium (eight- and nine-membered) rings utilizing the intramolecular reductive couplings promoted by SmI₂. The quantitative formation of a medium ring without the need for high-dilution conditions is particularly noteworthy, because eight- and nine-membered rings are the most difficult to construct using any conventional ring-closure method. Apparently, this annulation method is one of the most convenient entries into medium-sized rings. Moreover, the exceptional synthetic versatility of the cyclization products is also noteworthy. This protocol should be widely applicable to the synthesis of a wide range of medium carbocycles and heterocycles.

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Supporting Information Available: Experimental procedures and spectroscopic data for all cyclization products **4a–g**, **6a–g**, and **8a–g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) See Supporting Information for experimental details concerning the medium-ring closure reaction using SmI₂.

(12) Reductive coupling cyclization also took place under high-dilution conditions, which involved the slow, dropwise addition of a 0.005 M solution of the starting material in THF to a 0.1 M solution of SmI₂ in THF.

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