Formation of Iodohydrins by Ring Opening of Cyclic Ethers by Samarium(II) Iodide in Benzene-Hexamethylphosphoramide in the Presence of Boron Trifluoride Diethyl Etherate[1]

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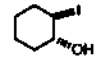
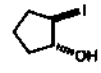
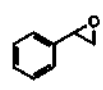
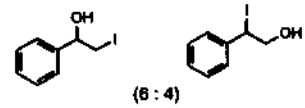
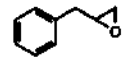
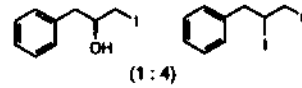
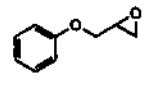
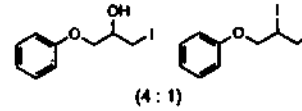
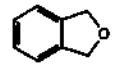
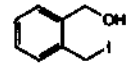
Samarium(II) iodide has been recognized as a powerful one-electron-transfer agent. Since its introduction to synthetic organic chemists through the pioneering research by Kagan and coworkers, numerous useful organic transformations promoted by this reagent have been reported.[2] A variety of additives has been used to make this reagent more effective. Among these are bases, acids including Lewis acids, and cosolvents such as hexamethylphosphoramide (HMPA) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). So far, most of the reported samarium(II) iodide-promoted reactions have been conducted in THF. The superiority of samarium(II) iodide as a powerful one-electron-transfer agent, to some degree, come from its excellent solubility in THF, which allows most of the samarium(II) iodide-promoted organic reactions to be performed in a homogeneous state. Since the additives could affect the reducing power of samarium(II) iodide, the solvent employed could also play a crucial role by modifying the characteristics of samarium(II) iodide and, consequently, thereby affecting the outcome of the reactions promoted by this reagent. Marked differences, for example, were noticed in the samarium(II) iodide-promoted reactions in THP (tetrahydropyran) instead of THF.[3] Acetonitrile has been used as a reaction medium for samarium(II) iodide-promoted reactions.[4] Recently, Tani and coworkers reported that benzene could be employed efficiently in the samarium (II) iodide-promoted reactions. They studied successfully the generation of alkylidenecarbens using samarium(II) iodide in benzene-HMPA.[5]

We have been intrigued with the samarium(II) iodide reactions in solvents other than THF. Benzene would be an interesting choice since it would allow a better reaction environment for employing the relatively strong Lewis acid as additives. Recently, Studer and Curran reported reductive coupling and reductive demethoxylation of aromatic dimethylacetals in the presence of acids.[6] Although acetals are stable toward samarium(II) iodide, upon addition of $BF_3 \cdot OEt_2$ to a solution of aromatic acetals, reductive coupling or demethoxylation of the acetals occurred.

We also tried the same reductive coupling by samarium (II) iodide in THF. However, we observed the formation of a ring-opened product of THF, that is, 4-iodo-1-butanol, as the major product along with the desired coupled product. We decided to investigate the ring-opening of cyclic ethers by samarium(II) iodide in the presence of a Lewis acid since opening of cyclic ethers, in particular, epoxide opening remains a popular method for the halohydrin synthesis. In the presence of a relatively strong Lewis acid such as $BF_3 \cdot OEt_2$, THF is certainly not the solvent of choice. We, therefore, decided to study the reaction of samarium(II) iodide in benzene-HMPA.[5] Addition of HMPA [10% (v/v)] was essential for the successful generation of samarium(II) iodide. Here we report the results of our investigation on the ring opening of cyclic ethers to provide 1,ω-iodohyrins by samarium(II) iodide in benzene-HMPA in the presence of $BF_3 \cdot OEt_2$ (Table 1).

Table 1. Ring opening of cyclic ethers by SmI_2 in benzene-HMPA in the presence of $BF_3 \cdot OEt_2$

Entry	Ethers	Products	Yield (%)
1		 (single isomer)	90
2		 (single isomer)	97
3		 (6 : 4)	87
4		 (1 : 4)	61
5		 (4 : 1)	90
6			62
7			67
8			34

As expected, *trans*-iodohydrin was obtained as a single isomer. We carried out briefly an optimization study on this particular reaction with respect to the amount of samarium (II) iodide and $BF_3 \cdot OEt_2$. The best yield (90%) of the

iodohydrin was obtained in the case of using the starting epoxide (1 equiv), SmI_2 (1.2 equiv), and $BF_3 \cdot OEt_2$ (1.2 equiv). The results of the epoxide ring-opening under these conditions are summarized in Table 1 (entries 1-5). All the epoxides were efficiently opened to provide the corresponding iodohydrins in good to excellent yields. Epoxides from cyclohexene and cyclopentene gave exclusively *trans*-iodohydrins in excellent yields (entries 1 and 2). Styrene oxide provided approximately equal amounts of two regioisomers (6 : 4) of iodohydrins in combined yield of 87% (entry 3). The epoxide from allylbenzene, however, provided the internal iodide as the major product regioselectively (4 : 1) (entry 4). This regioselectivty could be ascribed to the more stable carbenium ion-like transition state formed by complexation of a Lewis acid to the oxygen of the epoxide.[8] Introducing a heteroatom such as an oxygen atom at the carbon next to the epoxide did not give any problem with respect to the yield (entry 5). In this case, the major isomer formed was the one with a hydroxyl group at the internal position (regioselectivity; 4 : 1). This reversal of the regioselectivity also can be easily explained by forming a bidentate-chelated intermediate. Regiochemical control of the ring opening of epoxides under chelating conditions has been reported.[9] Structures of the products from epoxides in Table 1 were confirmed by comparing with the known products prepared by the ring-opening by lithium halides.[10,11]

This ring-opening reaction can be applied to other types of cyclic ethers. Table 1 (entries 6-8) also showed the results of opening of cyclic ethers other than epoxides by samarium(II) iodide in benzene-HMPA in the presence of $BF_3 \cdot OEt_2$. THF was opened to provide 4-iodo-1-butanol (entry 6). In contrast, if the carbon atom adjacent to oxygen bears a methyl group, that is, for 2-methyltetrahydrofuran, only decomposition was observed. Tetrahydropyran (THP) was also transformed to the corresponding iodohydrin without any incident (entry 7). We also observed that 1,3-dihydroisobenzofuran can be opened (entry 8) although the yield was not high. The low yield could be ascribed to the relative instability of the product. All the cases in Table 1 required 1.1-1.5 equiv of samarium(II) iodide except the case of 1,3-dihydroisobenzofuran (4.0 equiv) and all the reactions were completed in 20 min at room temperature.

Although samarium(II) iodide as an efficient electron-donating agent has been well recognized, direct involvement of this reagent in iodination has not been well studied.[12] No apparent change has been noticed upon mixing a samarium(II) iodide-benzene-HMPA solution with $BF_3 \cdot OEt_2$ (without addition of a cyclic ether), which might indicate that the samarium(II) species could be involved as the actual iodinating agent. It has been reported that halohydrins are often the major products from the reaction of Grignard reagents and epoxides. MgX_2, which could be formed by Schlenk equilibrium, has been proposed to be responsible for this halohydrin formation.[13] It would be conceivable that samarium(II) iodide could also act as the iodine atom source similarly in the presence of $BF_3 \cdot OEt_2$.

In conclusion, investigation on the ring opening of cyclic ethers by samarium(II) iodide-benzene-HMPA in the presence of a Lewis acid has shown that this opening reaction is interesting not only because this reagent can be utilized in iodination but also because this reaction possesses synthetic potential for the preparation of iodohydrins.

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References

1. CAUTION: Benzene has been identified as a carcinogen. Hexamethylphosphoramide is a highly toxic and suspected as a carcinogen. All operations with either one should be performed in well-ventilated hood, and gloves should be worn.
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7. Typical procedure: Opening of cyclohexene oxide (entry 1, Table 1). To a solution of SmI_2(1.1 mmol) in benzene (10 mL)-HMPA (1.0 mL) [prepared according to the procedure reported[5]] was added cyclohexene oxide (98 mg, 1.0 mmol) and $BF_3 \cdot OEt_2$ (1.2 mmol, 170 mg) at room temperature under nitrogen. After stirring at 20 min, the mixture was quenched (aq. NH_4Cl), filtered on Celite, and extracted with ether (10 mL × 3).

The extract was washed with saturated NaCl, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane : ethyl acetate=10 : 1) provide the desired iodohydrin as an oil (203 mg, 90%).

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11. Other Lewis acids instead of $BF_3 \cdot OEt_2$ could be used for the opening of cyclic ethers. In fact, we briefly tested this possibility with $SnCl_4$ using styrene oxide. Identical products to those shown in Table 1 were obtained, albeit in lower yields.
12. We have reported an example of iodination during our study on samarium(II) iodide-promoted reactions of epoxyalkanone hydrazones, although in this case the reactive species responsible for iodination might not be identical in nature to the reacting species for the iodination by SmI_2-benzene-HMPA and $BF_3 \cdot OEt_2$ reported here. See Kang, H.-Y.; Hong, W. S.; Lee, S. H.; Choi, K. I.; Koh, H. Y. *Synlett* **1997**, 33-34.
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Synthesis of Iridolactones *via* Stereoselective Favorskii Rearrangement: (+)-Dolicholactone, (+)-Alyxialactone, and (−)-4-*epi*-Alyxialactone

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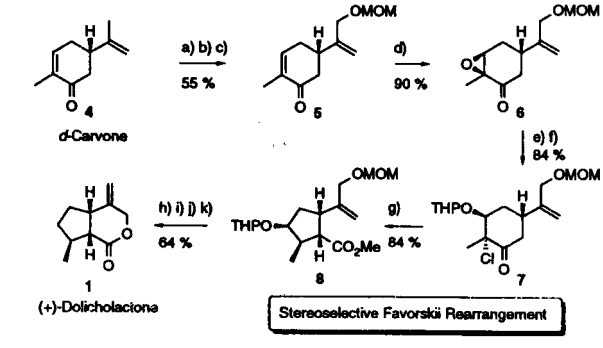
Recently, we reported expedient syntheses of (+)-dihydronepetalactone and (+)-iridomyrmecin from *d*-carvone chlorohydrin. In a key step of the synthesis, a cyclopentanecarboxylate intermediate was obtained *via* stereoselective Favorskii rearrangement.[1] This reaction is remarkable: the presence of a neighboring oxy substituent in the chloroketone substrate dictates the rate and the direction of the rearrangement. Using modified substrates, facile syntheses of a plethora of iridoid lactones[2] are possible, and this report concerns our recent efforts in the synthesis of (+)-dolicholactone (1),[3] (+)-alyxialactone (2),[4] and (−)-4-*epi*-alyxialactone (3).[4] Syntheses of these iridoid lactones have not been reported in literature.

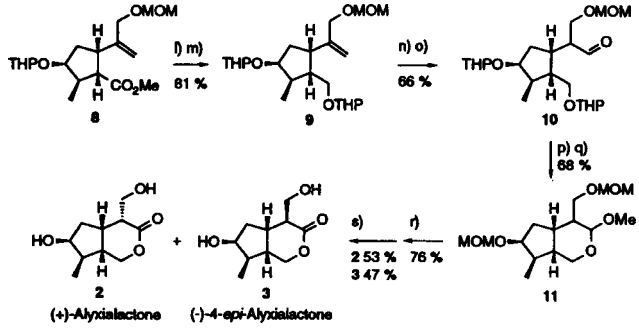
Allylic chlorination of *d*-carvone (**4**), hydroxide substitution, and protection with MOM chloride led to the preparation of the hydroxycarvone derivative **5**. The enone **5** was converted into the epoxyketone **6**, from which the chloroketone derivative **7** was obtained *via* epoxide ring opening by chloride and protection with DHP. The Favorskii rearrangement of **7** proceeded regio- and stereoselectively producing a cyclopentanecarboxylate derivative **8** in good yield (Scheme 1). (+)-Dolicholactone (**1**) was obtained from **8** *via* basic hydrolysis, MOM and THP deprotection, and radical-mediated deoxygenation.

The intermediate **8** was then used for the synthesis of **2** and **3**. It was converted into the triol derivative **9** *via* LAH reduction and DHP protection. Hydroboration with disiamylborane and oxidation of **9** yielded a mixture of epimeric primary alcohols, and they were converted into the corresponding aldehydes **10**. When **10** were treated with *p*-toluenesulfonic acid in methanol at room temperature, both THP protecting groups were removed and a mixture of bi-



a) $Ca(OCl)_2$, Dry ice, DCM-H_2O (10:1); b) K_2CO_3, NaI, H_2O, Reflux
c) MOMCl, DIPEA, cat. DMAP, DCM; d) H_2O_2, 2N NaOH, MeOH, r.t. 1 h
e) 1.5 eq. TMSCl, 1.5 eq. DMSO, MeCN, r.t. 40 min; f) DHP, cat. *p*-TsOH, DCM, r.t. 1 h
g) 1.5 eq. MeONa, MeOH, r.t. 10 min; h) aq. NaOH, Reflux
i) conc. HCl (pH 1), Reflux; j) NaH; CS_2; MeI; k) Bu_3SnH, cat. AIBN, Benzene, Reflux

Scheme 1.



l) LAH, Ether; m) DHP, DCM, cat. *p*-TsOH; n) Disiamylborane, Ether; H_2O_2, aq. NaOH
o) Swern Oxid.; p) cat. *p*-TsOH, MeOH, r.t.; q) MOMCl, DIPEA, cat. DMAP, DCM, 0 °C
r) Jones Reagent, Acetone, 0 °C; s) BCl_3, DCM, 0 °C, 30 min

Scheme 2.