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Intramolecular Radical Cyclization of 2-Haloethanal Allyl Acetal and Allyl 2-Halophenyl Ether with a Grignard Reagent in the Presence of Iron(II) Chloride

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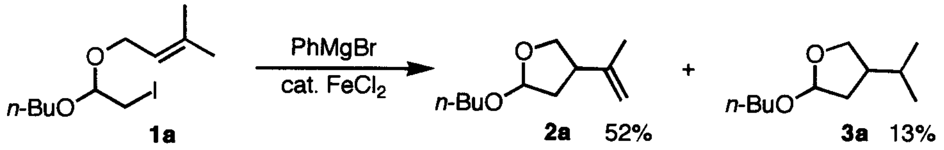
Abstract: Treatment of 2-iodoethanal alkenyl acetals, generated by iodoetherization from butyl vinyl ether and allylic alcohols, with phenylmagnesium bromide in the presence of a catalytic amount of $FeCl_2$ provided tetrahydrofuran derivatives in good yields. Allyl 2-halophenyl ethers also afforded dihydrobenzofuran derivatives upon treatment with phenylmagnesium bromide under $FeCl_2$ catalysis.

Carbon-carbon bond formation *via* radical reactions is one of the most important synthetic steps in the construction of organic molecules.[1] Recently, we have found that intramolecular radical cyclization of allyl 2-iodophenyl ether and 2-iodoethanal allyl acetal has been carried out by means of tributylmanganate (n-Bu_3MnLi or n-$Bu_3MnMgBr$).[2] We report here that the same-type cyclization reaction proceeded upon treatment of 2-haloethanal allyl acetal and allyl 2-halophenyl ether with Grignard reagents in the presence of an Fe(II) salt catalyst.

To a solution of iron(II) chloride (6.3 mg, 0.05 mmol) in THF (5 mL) was added phenylmagnesium bromide (1.0 M THF solution, 1.2 mL, 1.2 mmol) at 0 °C. After being stirred for 3 min, a THF solution of 2-iodoethanal prenyl acetal **1a** (1.0 mmol) was added to the resulting brown-black solution. The mixture was stirred for 1 h at the same temperature and poured into water (20 mL). Extraction with hexane (20 mL x 3) followed by silica gel column chromatography afforded a tetrahydrofuran derivative **2a** having an isopropenyl group (0.11 g) in 52% yield along with an isopropyl-substituted product **3a** (13%) (Scheme 1).

Scheme 1



Other representative results are summarized in Table 1. The starting materials, 2-haloethanal acetals **1**, were easily prepared by the reaction of allylic or propargylic alcohols with enol ethers in the presence of *N*-halosuccinimide in dichloromethane.[3] Several comments are worth noting. (1) 2-Bromoethanal acetals **1b**, **1f**, and **1g** were equally effective precursors as 2-iodoethanal acetals **1a**, **1d**, **1e**, and **1h** for radical cyclization. Moreover, 2-chloroethanal acetal **1c** gave **2a** in 16% yield upon treatment with PhMgBr under an $FeCl_2$

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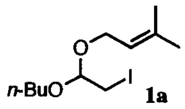
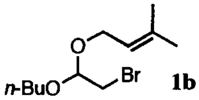
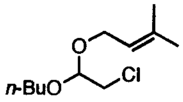
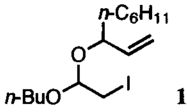
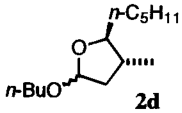
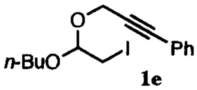
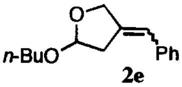
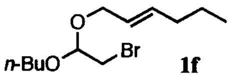
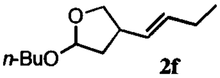
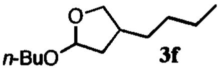
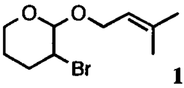
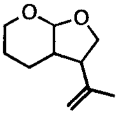
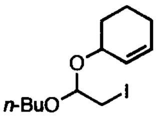
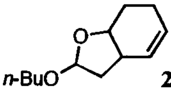
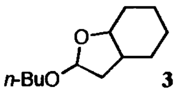
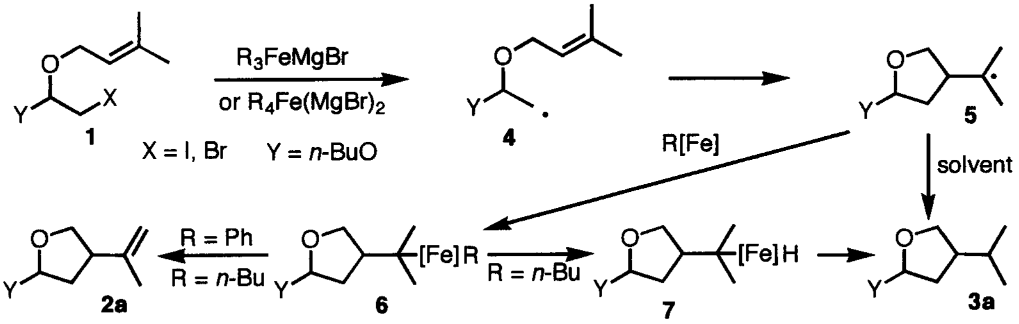
Table 1. Iron(II) Chloride-Catalyzed Radical Cyclization Reaction of Haloacetal

Entry	Substrate	RMgBr	Product (Yield)
1	 **1a**	*n*-BuMgBr	**2a** : 42% **3a** : 46%
2	 **1b**	PhMgBr	**2a** : 77% **3a** : <1%
3		*n*-BuMgBr	**2a** : 40% **3a** : 43%
4	 **1c**	PhMgBr	**2a** : 16% **3a** : <1%
5		*n*-BuMgBr	**2a** : 1% **3a** : 5%
6	 **1d**	PhMgBr	 **2d** **2d** : 83%
7		*n*-BuMgBr	**2d** : 56%
8	 **1e**	PhMgBr	 **2e** **2e** : 29%
9		*n*-BuMgBr	**2e** : 54%
10	 **1f**	PhMgBr	 **2f** **2f** : 68% **3f** : <1%
11		*n*-BuMgBr	 **3f** **2f** : 23% **3f** : 18%
12	 **1g**	PhMgBr	 **2g** **2g** : 71%
13		*n*-BuMgBr	**2g** : 58%
14	 **1h**	PhMgBr	 **2h** **2h** : 36% **2h** : 1%
15		*n*-BuMgBr	 **3h** **2h** : 26% **3h** : 22%

catalyst. These results were in sharp contrast to those obtained with tributylmanganate.[2] The treatment of 2-bromoethanal prenyl acetal **1b** with tributylmanganate provided **2a** in only 41% yield and no trace of **2a** was detected in the reaction of 2-chloroethanal acetal **1c** with tributylmanganate. (2) The distribution of the products (**2** and **3**) heavily depended on the nature of the Grignard reagent employed. The use of PhMgBr decreased the formation of saturated product **3** compared to the use of *n*-BuMgBr.[4] This tendency was more clearly seen in the reaction of 2-bromoethanal allyl acetals as substrates. For instance, whereas treatment of 2-bromoethanol acetal **1b** or **1f** with PhMgBr gave alkenyl-substituted tetrahydrofuran derivative **2a** or **2f** almost exclusively (Entries 2 and 10), the reaction with *n*-BuMgBr provided a mixture of **2a** and **3a** or **2f** and **3f** (Entries 3 and 11). Thus, the combined use of 2-bromoethanal acetals with phenylmagnesium bromide is recommended for the selective formation of alkenyl-substituted tetrahydrofuran derivative **2**. (3) The carbon-carbon triple bond was also effective to trap a radical intermediate intramolecularly (Entries 8 and 9). (4) (*E*)-Alkene **2f** was produced selectively (*E*/*Z* = >95/5) in the cyclization of 2-alkenyl ethers (Entry 10). (5) Treatment of **1d** with PhMgBr in the presence of a catalytic amount of $FeCl_2$ gave **2d** as a mixture of two stereoisomers which could be converted into a single isomeric *trans* lactone by oxidation.[5] (6) Not only primary alkyl halides but also secondary bromide **1g** proved to cyclize effectively to give the desired products (Entries 12 and 13).

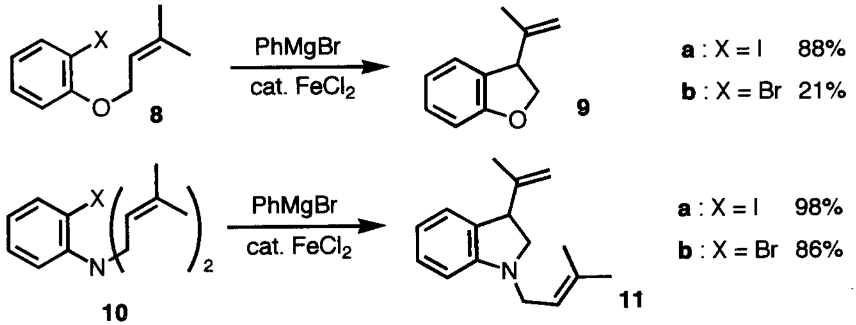
The cyclization reaction with a stoichiomeric iron reagent was studied to clarify the reaction mechanism. Whereas treatment of **1a** with tributylironate[6,7] gave cyclized product **2a** in only 12% yield along with recovered starting material (70%), the use of higher ate complex $n\text{-}Bu_4Fe(MgBr)_2$[6] gave a mixture of **2a** and **3a** in 77% combined yield (**2a**/**3a** = 35/65). Moreover, the reaction of **1a** with $Ph_3FeMgBr$ or $Ph_4Fe(MgBr)_2$ gave a mixture of **2a** and **3a** in 82% or 55% combined yield (**2a**/**3a** = 60/40 or 56/44), respectively. Upon quenching these reaction mixtures with D_2O, it was observed that there was no deuterium incorporated in the product **3a**.[8] Based on these facts, we are tempted to assume the following reaction mechanism (Scheme 2).[9] Single-electron transfer from the iron ate complex to haloacetal **1** would give an alkyl radical **4** under departure of the halogen atom. 5-Exo mode cyclization affords a carbon radical **5**. Part of the radical abstracts hydrogen from the solvent to give **3a**. The rest recombines with an alkyl iron species to give **6**. Dehydrometallation of **6** would provide the alkenyl product **2a**.[10] In the case of the reaction with *n*-BuMgBr (R = *n*-Bu), dehydroironation from the butyl iron moiety of **6** followed by reductive elimination would provide us with another route to saturated product **3a**. In the catalytic reaction, the Fe(0) species, generated in the course of the formation of products **2a** and **3a**, might play a critical role and react with **1** to give the radical **4** and Fe(I). The cyclization of **4** into **5** followed by recombination with Fe(I) giving **6** could complete the catalytic cycle.

Scheme 2



We next turned our attention to the radical cyclization of aryl iodide and aryl bromide bearing an alkenyl group. Treatment of 2-iodophenyl prenyl ether **8a** with PhMgBr in the presence of a catalytic amount of FeCl$_2$ provided benzofuran derivative **9** as a single product in 88% yield.[11] Saturated benzofuran derivative, 3-isopropyl-2,3-dihydrobenzofurane could not be detected in the reaction mixture. *N*,*N*-Diprenyl-2-iodoaniline **10a** gave *N*-prenyl-3-isopropenyl-2,3-dihydroindole **11** in 98% yield. Whereas the reaction of bromide **10b** gave **11** in 86% yield under the same reaction conditions, the use of 2-bromophenyl derivative **8b** in place of an iodo compound afforded **9** in only 21% yield in addition to the recovered starting material **8b** (25%).

Scheme 3



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Reference and Note

1 a) Giese, B. "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds," ed by Baldwin, J. E. Pergamon Press, Oxford (1986). b) Giese, B. *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 969–980. c) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.*, **1990**, *112*, 6738–6740. d) Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc.*, **1991**, *113*, 1791–1799. Curran, D. P. in "Comprehensive Organic Synthesis," ed by Trost, B. M.; Fleming, I. Pergamon Press, Oxford (1991), Vol. 4, Chap. 4.2, p. 779–831.

2 Nakao, J.; Inoue, R.; Shinokubo, H. Oshima, K. *J. Org. Chem.*, **1997**, *62*, 1910–1911. Inoue, R.; Nakao, J.; Shinokubo, H. Oshima, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2039-2049.

3 Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.*, **1986**, *108*, 6384–6385.

4 The reaction of **1a** with *i*-PrMgBr provided a mixture of **2a** and **3a** in almost the same ratio as that with *n*-BuMgBr.

5 Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.*, **1978**, 419–420. Morikawa, T.; Nishiwaki, T.; Iitake, Y.; Kobayashi, Y. *Tetrahedron Lett.*, **1987**, *28*, 671–674.

6 For a recent review on alkyl iron ate complex, see: Kauffmann, T. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 386–403.

7 Cross-coupling reactions between halides and Me$_3$FeLi have been reported. Corey, E. J.; Posner, G. H. *Tetrahedron Lett.* **1970**, 315–318.

8 Quenching the FeCl$_2$-catalyzed reactions with D$_2$O could not afford any deuterated product, either.

9 Recently, nickel or cobalt-catalyzed radical cyclization reaction has been reported. Vaupel, A.; Knochel, P. *Tetrahedron Lett.*, **1994**, *35*, 8349–8352; Bamhaoud, T.; Prandi, J. *J. Chem. Soc. Chem. Commun.*, **1996**, 1229–1230.

10 The ease of recombination providing **6** might be attributed to the stability of radical **5**. A tertial radical derived from **1a** could be stable enough to recombine with R[Fe] species. In contrast, a primary radical generated from **1b** abstracts hydrogen more easily.

11 Cyclization of allyl 2-iodophenyl ether into a benzofuran derivative mediated by organozincate was also reported. Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.*, **1996**, *118*, 8733–8734.