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# Iron-Catalyzed Regio- and Stereoselective Ring Opening of [2.2.1]- and [3.2.1]Oxabicyclic Alkenes with a Grignard Reagent

**Masaharu Nakamura,*,†,‡ Keiko Matsuo,‡ Toshihiro Inoue,‡ and Eiichi Nakamura*,‡**

*Department of Chemistry, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

*nakamura@chem.s.u-tokyo.ac.jp*

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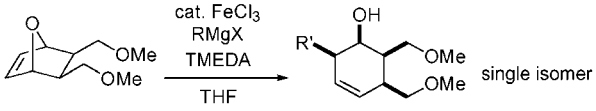
## ABSTRACT




R = aryl, alkenyl, or 1° and 2° alkyl ; R' = aryl, alkenyl, or H

**Arylative and alkenylative ring-opening reactions of a [2.2.1]- or [3.2.1]oxabicyclic alkene with a Grignard reagent take place in the presence of a catalytic amount of iron(III) chloride and a stoichiometric amount of TMEDA to produce a highly substituted 3-cyclohexen-1-ol or 3-cyclohepten-1-ol in good yield with high regio- and stereoselectivity.**

Being environmentally benign, economical, and nontoxic, organoiron complexes are attracting increasing attention as catalysts for chemical synthesis.[1] Among recent advances, catalytic carbon−carbon bond formation reactions are particularly noteworthy,[2] and the first application of an organoiron catalyst for catalytic asymmetric synthesis was reported recently from this laboratory.[3]

In a series of recent publications, Lautens et al. have demonstrated the utility of regio- and stereoselective ring-opening reactions of the oxabicyclic alkenes for the synthesis of cycloalkenols.[4] This transformation is best achieved in the presence of a nickel,[4a−c] palladium,[4d] rhodium,[4e−g,5] or zirconium[6] catalyst by using organometallic reagents such as an organoaluminum,[6] organozinc,[3,4d] or organoboron[5] reagent as well as neutral nitrogen or oxygen nucleophiles.[4] The utility of the Grignard reagent, the most readily available carbon nucleophile, has thus far been rather limited in terms of the structural variety of the Grignard reagent, the selectivity, and the reproducibility of the reaction.[4b,7] We report in this letter an iron-catalyzed ring-opening reaction

† PRESTO, Japan Science and Technology Corporation (JST).
‡ The University of Tokyo.

(1) Davies, S. G. *Organotransition Metal Chemistry—Application to Organic Synthesis*; Pergamon Press: Oxford, 1982. Peason, A. J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, p 939.

(2) A number of examples of iron-catalyzed coupling reactions have been reported as efficient C−C bond formation reactions. (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487−1489. (b) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351−360. (c) Takacs, M. J.; Myoung, Y.-C.; Anderson, L. G. *J. Org. Chem.* **1994**, *59*, 6928−6942. (d) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 513−514. (e) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017−6028. (f) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed.* **1996**, *35*, 1700−1701. (g) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199−1205. (h) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901−1903. (k) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856−13863 and references therein.

(3) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978−979.

(4) (a) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532−533. (b) Lautens, M.; Ma, S. *J. Org. Chem.* **1996**, *61*, 7246−7247. (c) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 11090−11091. (d) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804−1805. (e) Lautens, M.; Fagnou, K.; Tayler, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259−270. (f) Lautens, M.; Fagnou, K.; *J. Am. Chem. Soc.* **2001**, *123*, 7170−7171. (g) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311−1314. (h) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58.

(5) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390−391.

(6) Millward, D. B.; Sammis, G.; Waymouth, R. M. *J. Org. Chem.* **2000**, *65*, 3902−3909.

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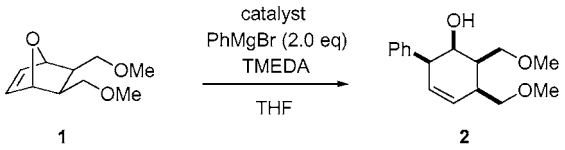
of an oxabicyclic alkene with a Grignard reagent that proceeds in a highly regio- and stereoselective manner.

The iron-catalyzed ring-opening reaction of 4,5-bis-(methoxymethyl)-7-oxabicyclo[2.2.1]hept-2-ene (**1**) is performed by way of example, and optimization studies are summarized in Table 1. When **1** was treated with phenyl-

**Table 1.** Effect of TMEDA on the Iron-Catalyzed Ring-Opening Reaction of **1**[a]




**1** **2**

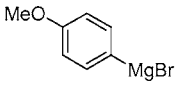
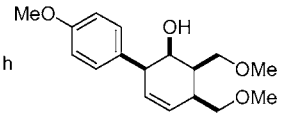
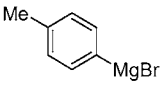
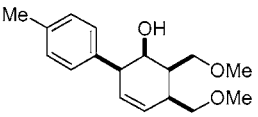
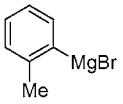
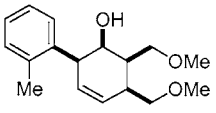
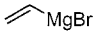
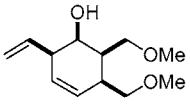
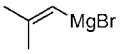
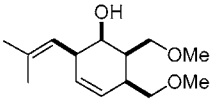
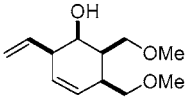
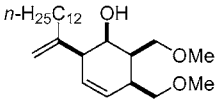
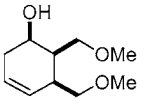
| entry | catalyst | TMEDA | temp | time | yield[b] |
|---|---|---|---|---|---|
| 1 | $FeCl_3$ (5 mol%) | none | 25 °C | 8 h | 65% |
| 2 | $FeCl_3$ (5 mol%) | 3.0 equiv | 25 °C | 3 h | 74% |
| 3 | none | 3.0 equiv | 25 °C | 10 h | 0% |

[a] Reaction was performed by the addition of a THF solution of $FeCl_3$ (5 mol %) to a mixture of the oxabicyclic alkene **1** and phenylmagnesium bromide (2.0 equiv) in THF in the presence or absence of TMEDA (3.0 equiv). [b] Isolated yield.

magnesium bromide in the presence of iron(III) chloride (5 mol %) at 25 °C for 8 h, a phenyl-substituted cyclohexenol **2** was obtained as a sole product in 65% yield (Table 1, entry 1).[3] Addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 3 equiv) to the reaction mixture facilitates the ring-opening reaction to complete the reaction at 25 °C for 3 h, and the yield of the desired product **2** increased to 74% yield (Table 1, entry 2). The reaction took place in such a manner that the phenyl group attacks the carbon−carbon double bond from the *exo*-face of the substrate to give all-cis-substituted cyclohexenol product **2** after subsequent $\beta$-eliminative ring opening of the oxygen bridge. The $^1$H NMR and the GC analysis of the crude product did not show any trace of other isomers, indicating that the reaction is completely regio- and stereoselective. In the absence of the iron catalyst, the reaction does not take place even after 10 h and gives back all of the starting material (Table 1, entry 3).

The results of the ring-opening reaction of **1** with a variety of Grignard reagents are shown in Table 2. The reaction of **1** with (*o*-methoxyphenyl)magnesium bromide or *p*-tolylmagnesium bromide gave a single regio- and stereoisomer **3** or **4** in about 70% yield (Table 2, entries 1 and 2).[8] The

**Table 2.** Iron-Catalyzed Ring-Opening Reactions of **1**[a]

| entry | RMgX | temp. | time | product (yield)[b] |
|---|---|---|---|---|
| 1 |  | 25 °C | 3 h |  **3** (69%) |
| 2 |  | 25 °C | 5 h |  **4** (72%) |
| 3 |  | 65 °C | 1 h |  **5** (75%) |
| 4 |  | 65 °C | 13 h |  **6** (41%)[c] |
| 5 |  | 65 °C | 5 h |  **7** (40%)[d] |
| 6 | EtMgBr | 25 °C | 1 h |  **6** (24%)[e] |
| 7 | $n$-$C_{14}H_{29}MgBr$ | 25 °C | 1 h |  **8** (54%) |
| 8 | *i*-PrMgBr | 25 °C | 1 h |  **9** (92%) |

[a] Reaction was performed with $FeCl_3$ (5 mol %), RMgX (2.0 equiv), and TMEDA (3.0 equiv) in THF. [b] Isolated yield. [c] Oxabicyclic alkene **1** and 1,6-bis(dimethoxymethyl)cyclohex-2,4-diene were obtained in 20 and 5% yields, respectively. [d] In entry 5, oxabicyclic alkene **1** and 1,6-bis(methoxymethyl)cyclohex-2,4-diene were obtained in 14 and 28% yields, respectively. [e] 1,6-Bis(methoxymethyl)cyclohex-2,4-diene, 5,6-bis(methoxymethyl)-7-oxabicylo[2.2.1]heptane, and (1*R**,5*S**,6*S**)-2,3-bis(methoxymethyl)cyclohex-4-en-1-ol **9** were obtained in 18, 25, and 13% yields, respectively.

reaction took place with equal facility for *o*-tolylmagnesium bromide, which bears an α-substituent of some steric hindrance, to give the cyclohexenol **5** in 75% yield (Table 2, entry 3).

(7) Nickel-catalyzed ring opening of oxabicyclo[2.2.1]- and -[3.2.1]-alkenes with a phenyl Grignard reagent gives a mixture of regio- and stereoisomers through *exo* or *endo* attack of the nucleophile. The regioselectivity of the C−C bond formation depends highly on the solvent and the catalyst. Thus, only a methyl Grignard reagent gives the corresponding ring-opening product with high regioselectivity.[4b]

(8) Representative experimental procedure for the synthesis of (1*R**,2*S**,5*S**,6*S**)-5,6-bis(methoxymethyl)-2-(*p*-methoxyphenyl)-cyclohex-3-en-1-ol (**3**): To a solution of (*p*-methoxyphenyl)magnesium bromide (1.0 M in THF, 0.6 mL) and TMEDA (0.90 mmol, 135.9 $\mu$L) in THF (0.75 mL) was added the oxabicyclic alkene **1** (0.30 mmol, 55.3 mg) at 0 °C. To the reaction mixture was added $FeCl_3$ (0.1 N in THF, 0.015 mmol, 150 $\mu$L) at 0 °C. The resulting dark brown solution was stirred at 25 °C for 3 h. The reaction mixture was quenched with saturated $NH_4Cl$ (0.2 mL), filtered through a pad of Florisil, and then concentrated in vacuo. Purification with silica gel chromatography gave the cyclohexenol **3** (61.3 mg, 74% yield). Spectral and physical properties of **3** were identical to those in the literature.[4]

Vinylmagnesium bromide and 2-methyl-1-propenylmagnesium bromide also smoothly reacted with **1** under the same catalytic conditions (Table 2, entries 4 and 5). It was surprising that ethylmagnesium bromide gave the vinylated product **6** as a sole organic group transfer product (Table 2, entry 6). This is likely due to $\beta$-hydride elimination of an ethyl iron intermediate[9] prior to the C−C bond-forming step. More surprising was the reaction of *n*-$C_{14}H_{29}MgBr$, which afforded the product of 2-tetradecenyl-group transfer product **8** as shown in entry 7. The structure of the incoming group again suggested intervention of $\beta$-hydride elimination, but now with the formation of a 2-metallo-1-alkenyl species.

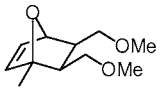
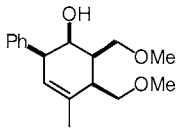
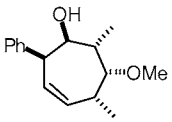
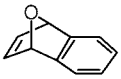
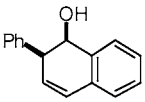
When a secondary alkyl Grignard reagent was allowed to react with **1**, hydride reduction took place in good yield. Thus, the reaction of **1** with 2-propylmagnesium bromide proceeded with high regio- and stereoselectivity to give the compound **9** in 92% yield (Table 2, entry 8).

Other oxabicyclic alkenes took part in the ring-opening reaction under the iron catalysis (Table 3). In the reaction of bridgehead-substituted substrate **10**, the reaction took place in such a manner that the phenyl group is delivered to the olefinic terminus distant from the methyl group to give exclusively the product **11** in 80% yield (Table 3, entry 1). Arylative ring opening of an oxabicyclo[3.2.1]octene **12** with phenylmagnesium bromide gave the corresponding cycloheptenol **13** in 67% yield as a single diastereomer (Table 3, entry 2). The reaction of **14** provided benzocyclohexenol **15** in 54% yield. Although the formation of naphthalene was accompanied by the ring-opening reaction (28% yield), the regio- and diastereoselectivity are sufficiently high to give a single stereoisomer in good yield (Table 3, entry 3).

In summary, we found that an iron catalyst prepared in situ by the reaction of iron(III) chloride and a Grignard reagent in the presence of TMEDA is effective for the arylative, alkenylative, and reductive ring opening of a [2.2.1] or [3.2.1] oxabicyclic alkene with a Grignard reagent, which took place with high regio- and stereoselectivity. We have so far been unable to discuss the detailed reaction mechanism, especially the C−O bond cleavage step, which may take place via two likely mechanistic possibilities, carbometalation/$\beta$-oxygen elimination[4h] or oxidative addition/$\pi$-allylmetal formation.[4b] Likewise, no concrete reasoning for the formation of some alkenylated products can be provided at the present time. Studies on the reaction mechanism and toward application for asymmetric synthesis therefore continue.

(9) Kochi, J. K. *Organometallic Mechanism and Catalysis;* Academic Press: New York, 1978; Chapter 14.

**Table 3.** Reaction of Various Oxabicyclic Alkenes with Phenylmagnesium Bromide[a]

| entry | substrate | temp. | time | product (yield)[b] |
|---|---|---|---|---|
| 1 |  **10** | 25 °C | 3 h |  **11** (80%) |
| 2 |  **12** | 65 °C | 9 h |  **13** (67%)[c] |
| 3 |  **14** | 25 °C | 2 h[d] |  **15** (54%)[e] |

[a] Reaction was performed with $FeCl_3$ (5 mol %), PhMgBr (2.0 equiv), and TMEDA (3.0 equiv) in THF. [b] Isolated yield. [c] Starting alkene **12** was obtained in 9% yield. [d] Reaction was performed at 0 °C for 1 h and at 25 °C for 2 h. [e] Naphthalene was obtained in 28% yield as a side product.

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**Supporting Information Available:** Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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