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Iron-Catalyzed Reductive Magnesiation of Oxetanes to Generate (3-Oxidopropyl)magnesium Reagents

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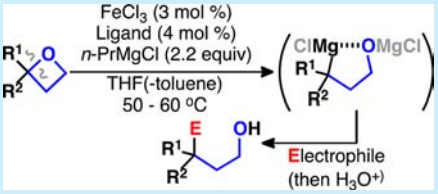
Supporting Information

ABSTRACT: In the presence of $FeCl_n$–(bisphosphine) or $FeCl_n$–(2-iminomethylpyridine) (n = 2 or 3), 2-substituted oxetanes reacted with Grignard reagents undergoing reductive magnesiation at the 2-position to afford substituted 3-oxidopropylmagnesium compounds, which are useful nucleophiles in reactions with a variety of electrophiles.

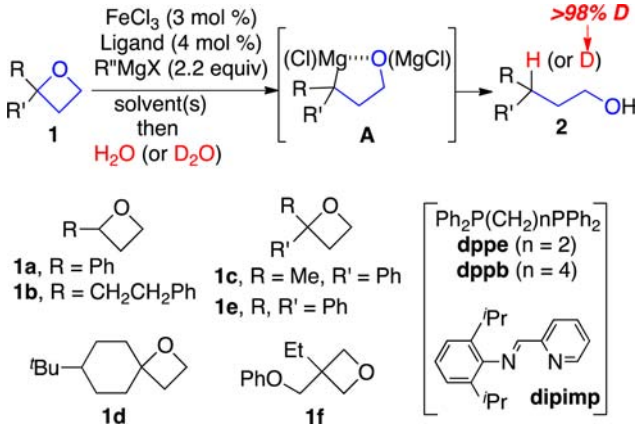


The development of preparative methods for nucleophilic organometallics, such as organomagnesium reagents, is a central issue in the fields of synthetic organic and organometallic chemistry. For instance, the Grignard reagents have been widely used for over a century.[1] Herein, we report the preparation of 3-oxidopropylmagnesium compounds from oxetanes via a novel iron-catalyzed reductive magnesiation reaction. The method is the first to involve the facile generation of substituted 3-oxidepropylmagnesium compounds and features the use of inexpensive and environmentally benign iron catalysts[2−4] and readily accessible oxetane starting materials. The reactivity of 3-oxidepropylmagnesium compounds as nucleophiles toward a variety of electrophiles was also investigated. The substrate 2-substituted oxetanes can readily be prepared by [2 + 2]-cycloaddition of carbonyl compounds with alkenes, the reaction of epoxides or carbonyl compounds with *S*-ylide reagent,[5] or cyclization of 1,3-diols or 3-halo-1-alkanols.[6]

Regarding unsubstituted 3-oxidopropylmagnesium compound, $ClMg(CH_2)_3OMgCl$ (Normant's Grignard reagent) prepared from $Cl(CH_2)_3OH$ and Mg is well-known and has been widely used in organic synthesis.[7] Meanwhile, there have been a few reports for the generation of 3-oxidometal species, such as the lithium, potassium, and sodium reagents, from oxetanes.[8] In 1989, Mudryk and Cohen reported pioneering work on γ-lithioalkoxide generation via the reductive lithiation of oxetanes using lithium 4,4′-di-*tert*-butyl biphenylide.[9] They subsequently developed a regio-switchable metalation procedure by performing the reactions in the absence or presence of a trialkylaluminum Lewis acid. The preparation of 3-oxidopropyl potassium and sodium reagents via reductive metalation with metallic K or K/Na in the presence of 18-crown-6 has also been reported.[10] However, these methods require the use of 2 or more equiv of 4,4′-di-*tert*-butylbiphenyl or crown ether and thus have not often been utilized in organic synthesis.[11]

In this study, the reactions of several oxetanes **1** with Grignard reagents (2.2 equiv) in tetrahydrofuran (THF) in the presence of $FeCl_3$ (3 mol %) and a ligand (4 mol %) were first performed (Scheme 1), and the results obtained following hydrolysis are summarized in Table 1.

Scheme 1. Iron-Catalyzed Reaction of Oxetanes with Grignard Reagents and Hydrolysis



In the absence of any ligand, the $FeCl_3$-catalyzed reaction of 2-aromatic-substituted oxetane **1a** with EtMgBr at 50 °C in THF afforded the ring-opened product 3-phenylpropan-1-ol (**2a**), albeit in moderate yield. In the presence of 1,2-bis(diphenylphosphino)ethane (dppe), the reaction of **1a** with EtMgBr or *n*-PrMgCl smoothly proceeded to provide **2a** quantitatively (Table 1, entries 2 and 3, respectively).[12a] It was noteworthy that quenching with D_2O gave 3-deuterated alcohol **2a** with >98% deuterium incorporation (determined by ^1H and ^{13}C NMR and/or MS analyses) (entry 3). These results suggested that the present ring opening proceeds not through reduction by a metal hydride species (hydrometalation). Other diphosphine ligands, such as 1,4-bis(diphenylphosphino)butane (dppb, entry 4), 1,3-bis(diphenylphosphino)propane, 1,1′-

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Table 1. Reactions of Oxetanes 1 with Grignard Reagents in the Presence of Iron Catalysts (Products Obtained after Hydrolysis)[a]

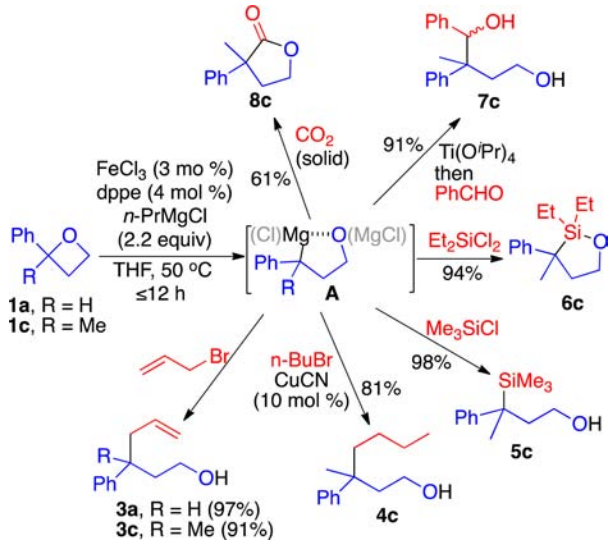
entry	1	ligand	reagents and conditions	yield of 2[b] (%)
1	**1a**		EtMgBr	54 (24 h)
2	**1a**	dppe	EtMgBr	>99 (24 h)
3	**1a**	dppe	*n*-PrMgCl (D_2O)[c]	>99[d]
4	**1a**	dppb	*n*-PrMgCl	>99 (24 h)
5	**1a**	dppe	*n*-PrMgCl ($FeCl_2$)[e]	>99%
6	**1b**	dppe	EtMgBr	0 (24 h)
7	**1b**	dipimp	EtMgBr	7 (24 h)
8	**1b**	dipimp	*n*-PrMgCl	55[f] (24 h)
9	**1b**	dipimp	*n*-PrMgCl (60 °C, D_2O)[c]	82[d] (24 h)
10	**1b**	dipimp	*n*-PrMgCl (60 °C, THF-toluene, D_2O)[c]	>99[d]
11	**1c**	dppe	*n*-PrMgCl (D_2O)[c]	>99[d]
12	**1c**	dipimp	*n*-PrMgCl (D_2O)[c]	>99[d]
13	**1d**	dipimp	*n*-PrMgCl (60 °C, THF-toluene, D_2O)[c]	73[d] (24 h)
14	**1e**	dppe	*n*-PrMgCl	37[g]
15	**1e**	dipimp	*n*-PrMgCl (THF-toluene, D_2O)[c]	91[g]
16	**1f**	dipimp	*n*-PrMgCl (D_2O)[c]	7[h] (72 h)

[a]3 mol % of $FeCl_3$ and 4 mol % of a ligand were used. Unless otherwise indicated, the reaction was performed at 50 °C for 6−12 h. [b]Determined by ^1H NMR analysis of the crude mixture using an internal standard. [c]Quenched by the addition of D_2O rather than H_2O. [d]>98% deuterium incorporation was observed via ^1H NMR and/or MS analyses. [e]$FeCl_2$ was used rather than $FeCl_3$. [f]44% of **1b** remained. [g]40% of 1,1,4,4-tetraphenylhexane-1,6-diol was also obtained. [h]28% conversion. A polymeric compound(s) was produced.

bis(diphenylphosphino)ferrocene, and *n*-Bu_3P (2 equiv to Fe), were equally effective. $FeCl_2$ in place of $FeCl_3$ could be used as a catalyst precursor (entry 5). In contrast to the reaction of 2-aryloxetane **1a**, however, 2-alkyl-substituted oxetane **1b** did not react when $FeCl_3$−dppe was used as the catalyst (entry 6). After ligand screening,[12b] we found that the use of 2-(2,6-diisopropyphenyl)iminomethylpyridine (dipimp) as a ligand was effective and the reaction afforded **2b** in 55% yield (entry 8). In addition, when the reaction was performed at an increased temperature (60 °C) and toluene was used as a cosolvent, **1b** was converted to **2b** in good to excellent yields (entries 9 and 10). Similar to the case with **1a**, D_2O quenching resulted in >98% deuterium incorporation into **2b**. Notably, 2,2-disubstituted oxetanes **1c** and **1d** effectively reacted in the presence of either $FeCl_3$−dppe or $FeCl_3$−dipimp to give the corresponding ring-opened products **2** with nearly complete deuterium incorporation following D_2O quenching (entries 11−13). Meanwhile, $FeCl_3$−dppe converted 2,2-diaryloxetane **1e** to a mixture of **2e** and a ring-opened dimer (1,1,4,4-tetraphenylhexane-1,6-diol) (entry 14). By changing the ligand to dipimp and using toluene as a cosolvent the yield of **2e** was improved (entry 15). On the other hand, oxetane **1f** bearing no substitution at C2 was found to be an inappropriate substrate. These results suggested that the present ring opening proceeds via the reductive metalation of the oxetane substrate at a more substituted position. This reductive metalation may afford organomagnesium compound **A** as the product (Scheme 1). In summary, the reaction of aryl-substituted oxetanes can be performed with an iron−dppe as well as an iron−dipimp catalysts, but the latter is desired for the reactions of alkyl-substituted oxetanes.

Having demonstrated the preparation of the 3-oxidopropylmagnesium compounds, their reactivity was then investigated by treating the various reaction mixtures with different electrophiles. As revealed from the results depicted in Scheme 2, the generated organomagnesium compounds smoothly

Scheme 2. Reactions of the Generated 3-Oxidopropylmagnesium Compounds with Various Electrophiles



reacted with a variety of electrophiles. Reaction mixtures of **1a** and **1c** bearing a 2-phenyl substituent with *n*-PrMgCl and the $FeCl_3$−dppe catalyst were separately treated with allyl bromide to yield allylated products **3a** and **3c**, respectively, in excellent yields. In the presence of CuCN as the catalyst (10 mol %), the organomagnesium compound derived from **1c** reacted with *n*-BuI to afford alkylated product **4c** in 81% yield. Silylation of the same reaction mixture using Me_3SiCl or Et_2SiCl_2 also smoothly proceeded to provide **5c** and **6c**, respectively, in excellent yields. Furthermore, following the addition of $Ti(O^iPr)_4$ to the reaction mixture with **1c**, treatment with PhCHO gave the adduct 7c in good yield as a diastereomeric mixture (54:46). Finally, lactone **8c** was obtained in a synthetically useful yield by treating the reaction mixture prepared from **1c** with CO_2 (solid). In conclusion, the generated organomagnesium compounds **A** from oxetanes **1** are versatile nuclephilic intermediates and could be converted to various organic compounds.

The organomagnesium compounds derived from oxetanes bearing 2-alkyl substituents in the presence of the $FeCl_3$−dipimp catalyst were also useful nucleophiles (Scheme 3); treatment of the reaction mixtures of **1b**, **1g**, and **1h** individually with allyl bromide afforded the corresponding allylated products **3** in good yields. As demonstrated by the formation of **3g** and **3h**, protective groups, including ketals and benzyl ethers, were tolerated.

Next, the reactions of the *syn* and *anti* isomers of 2,3-disubstituted oxetane **1i** were investigated (Scheme 4). Initially, we found that in the presence of the $FeCl_3$−dppe catalyst, the reaction of *anti*-**1i** was rapid and complete within 6 h, while the reaction of *syn*-**1i** proceeded very slowly (41% conversion in 72 h).[13] In contrast, when $FeCl_3$−dipimp was used as the catalyst, both stereoisomers reacted smoothly and subsequent treatment with allyl bromide afforded **3i** in good yield as an *anti*:*syn*

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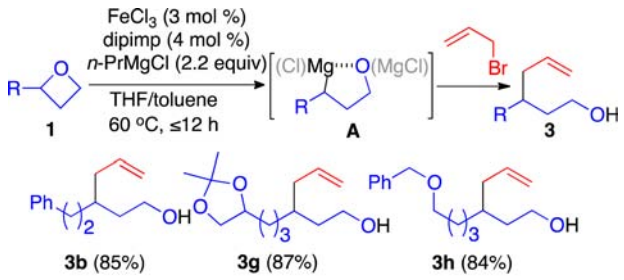
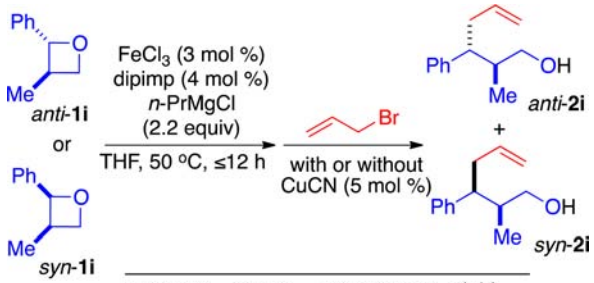
Scheme 3. Iron-Catalyzed Reactions of 2-Alkyl-Substituted Oxetanes and Subsequent Allylation



[dipimp = 2-(2,6-diisopropylphenyl)iminomethylpyridine]

Scheme 4. Iron-Catalyzed Reactions of 2,3-Disubstituted Oxetanes and Subsequent Allylation of the Generated 3-Oxidopropylmagnesium Compounds



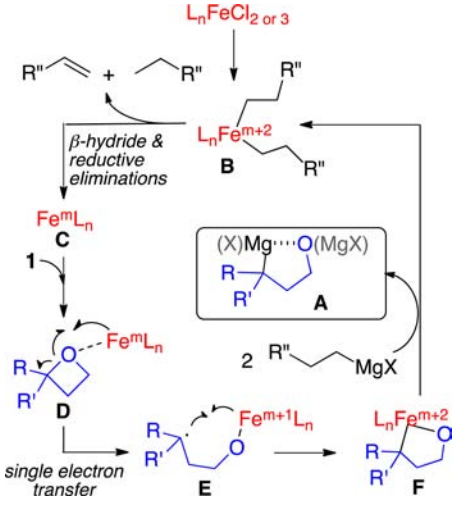
substrate	CuCN	*anti*-**2i**:*syn*-**2i**	yield
anti-**1i**	0	23:77	85%
syn-**1i**	0	23:77	81%
anti-**1i**	0.05	78:22	92%
syn-**1i**	0.05	77:23	85%

[dipimp = 2-(2,6-diisopropylphenyl)iminomethylpyridine]

mixture. Interestingly, regardless of the stereochemistry of the substrate **1i**, the same *anti*:*syn* ratio (23:77) was observed for product **3i**. In addition, treatment of the organomagnesium compounds derived from *anti*- or *syn*-**1i** with allyl bromide in the presence of CuCN as a catalyst (5 mol %) also resulted in the formation of **3i** with a consistent *anti*:*syn* ratio. Notably, however, this ratio was opposite to that obtained when the allylation was performed without the CuCN catalyst. These results indicate that the stereochemistry at the 2-position of oxetanes **1** is lost during the reaction. An explanation for the switch in the diastereoselectivity on the basis of the absence or presence of CuCN must await further study.

Given that $FeCl_2$ and $FeCl_3$ were equally effective as catalyst precursors and the ring opening occurred at the substituted 2-position of the oxetanes, resulting in a loss of stereochemistry, it may be proposed that the reaction mechanism involves a radical process (Scheme 5). A low-valent iron species Fe^mL_n (**C**) (L: ligand) is generated from $FeCl_3$ or $FeCl_2$ via *β*-hydride elimination and reductive elimination of dialkylated complex **B**, generating an alkene and an alkane.[2k,14] Indeed, when $Ph(CH_2)_3MgBr$ was employed as the Grignard reagent in the reaction of **1a** with the $FeCl_3$–dipimp catalyst, $Ph(CH_2)_2CH_3$ (~50%), and a mixture of $PhCH_2CH{=}CH_2$ and $PhCH{=}CHCH_3$ (total ~40%) were obtained as the Grignard-derived side products (yields based on the Grignard reagent). The $PhCH{=}CHCH_3$ may be produced via the isomerization of $PhCH_2CH{=}CH_2$. Then, **2a** was obtained quantitatively, and the homocoupling product $Ph(CH_2)_6Ph$ was not observed.

Scheme 5. Proposed Reaction Mechanism for the Formation of 3-Oxidopropylmagnesium Compounds from 2-Substituted Oxetanes



The generated low-valent iron species **C** may then react with oxetane **1** through coordination and subsequent single-electron transfer to provide *γ*-oxidoradical **E**, which would form cyclic iron complex **F**. Subsequent transmetalation of **F** with 2 equiv of the Grignard reagent would afford (3-oxidopropyl) magnesium compound **A** as the product and simultaneously regenerate complex **B**. Coordination of the oxygen atom in the oxetanes **1** to the iron atom in the structure **D** increases the electron-deficiency of the oxetanes while making the iron complex more electron rich, thus allowing a facile electron transfer.[8,15] While it can be assumed that dppe might be more Lewis basic than dipimp, the higher yields obtained using the iron–dipimp complex than that of the iron–dppe complex can be attribute to the higher Lewis acidity of the former relative to that of the latter. Steric effects of ligands might be also considered; a relatively sterically demanding dppe complex was less reactive than dipimp complex.

In summary, we have developed a facile method for the preparation of substituted 3-oxidopropylmagnesium compounds from 2-substituted oxetanes via a novel iron-catalyzed reductive magnesiation reaction. The method is compatible with protecting groups, including ketals and benzyl ethers. The generated secondary and tertiary organomagnesium compounds react with a variety of electrophiles, such as allyl and alkyl halides, chlorosilanes, carbonyl compounds, and carbon dioxide. Further investigation of the reaction mechanism and application of this method to organic synthesis is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) (a) Use of MeMgI instead of EtMgBr or *n*-PrMgCl resulted in formation of 1-phenylbutan-1-ol (65%) as a main product via nucleophilic ring-opening reaction. (b) Other dinitrogen compounds such as *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and 2,2′-bipyridine were not effective as a ligand. Use of an iron−dipimp as a catalyst has been reported for reductive cyclization of 1,6-enyenes: Lin, A.; Zhang, Z.-W.; Ynag, J. *Org. Lett.* **2014**, *16*, 386.

(13) Investigation for rationalizing the reactivity difference of **1i** is underway. Addition of allyl bromide to the mixture generated from *anti*- or *syn*-**1i** with *n*-PrMgCl in the presence of $FeCl_3$−dppe afforded **2i** in a *anti*:*syn* ratio of 23:77. The results indicate that the ligand has no effect on the allylation step.

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