Organic Letters

Letter

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$FeCl_3$-Catalyzed Self-Cleaving Deprotection of Methoxyphenylmethyl-Protected Alcohols

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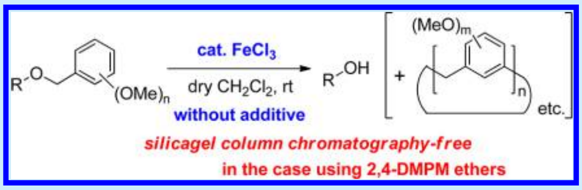
Ⓢ *Supporting Information*

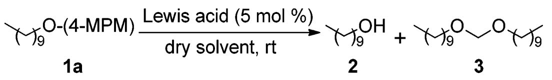
ABSTRACT: 4-Methoxyphenylmethyl ethers are widely utilized as alcohol protecting groups. $FeCl_3$ effectively catalyzes the deprotection of methoxyphenylmethyl-type ethers in a self-cleaving manner to produce oligomeric derivatives and alcohols. Remarkably, the highly pure mother alcohols can be obtained without silica gel column chromatography by using the 2,4-dimethoxyphenylmethyl group as a protective group.



Since the protection of functional groups is frequently required to synthesize important target molecules, the development of efficient deprotection methods with tolerance toward other functional groups is eagerly desired.[1] 4-Methoxyphenylmethyl (4-MPM) ethers are widely utilized as alcohol protecting groups, and their deprotection is generally carried out by the use of stoichiometric oxidants [2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ)[2] and ceric ammonium nitrate (CAN)[3]] or nucleophiles in the presence of catalytic or stoichiometric Lewis acids.[4] $Ph_3C{\cdot}BF_4$[5] and the chlorosulfonyl isocyanate (CSI)−NaOH combination[6] as stoichiometric reagents are also applicable for the deprotection of the 4-MPM ether. Although only a catalytic method that uses $ZrCl_4$ (20 mol %) in CH_3CN has been reported for deprotection, the details including the reaction mechanism were not investigated.[7] A purification process is necessary to remove the residue derived from the deprotected MPM moiety and reagents in all reported cases. Although the Pd/C-catalyzed hydrogenation under atmospheric hydrogen is also a useful deprotection method, simple benzyl (Bn) ethers are preferentially hydrogenated in the presence of the 4-MPM ether.[1] We now demonstrate the efficient iron-catalyzed deprotection of various MPM type ethers in the presence of the Bn ether, and the reaction mechanism has been investigated in detail. Furthermore, an unprecedented green deprotection method has been developed using the 2,4-dimethoxyphenylmethyl (2,4-DMPM) protective group; it does not require SiO_2 flash chromatography purification of the alcohol products.

We have recently revealed that $FeCl_3$ can efficiently activate benzylic C−O bonds toward the subsequent nucleophilic substitution with various nucleophiles accompanied by cleavage of the benzylic C−O bonds.[8] Although $FeCl_3$ (excess amount) is traditionally utilized for the deprotection of Bn ethers,[9] we hypothesized that catalytic $FeCl_3$ in the presence of nucleophiles could also facilitate the deprotection of Bn and MPM ethers. Our pre-examination indicated that only 5 mol % of $FeCl_3$ could achieve the deprotection of the 4-MPM ether in CH_2Cl_2. Therefore, we initially investigated the catalyst efficiency of various Lewis acids using 4-MPM ether (**1a**) derived from 1-decanol as a substrate (Table 1). Although an undesirable byproduct (**3**)[10] was obtained during the deprotection of **1a**, $FeCl_3$ was found to be the most effective catalyst for producing 1-decanol (**2a**) when compared other Lewis acids ($AuCl_3$,[11] TMSOTf, $BF_3{\cdot}Et_2O$) (entries 1 vs 3−5). The formation of the byproduct (**3**) was confirmed in only the deprotection of **1a** for some unknown reason. Such byproducts were never observed during the deprotection of other MPM ether derivatives shown in Figure 1, Scheme 1, eqs 2 and 3, and

Table 1. Lewis Acid and Solvent Efficiency in Deprotection of 4-MPM Ether



entry	Lewis acid	solvent	yield of **1a**/**2**/**3** (%)[a] (time, h)
1	$FeCl_3$	CH_2Cl_2	0/67/32 (1)
2[b]	$FeCl_3$	CH_2Cl_2	0/65/33 (1)
3	$AuCl_3$	CH_2Cl_2	0/55/43 (1)
4	TMSOTf	CH_2Cl_2	0/59/40 (6)
5	$BF_3{\cdot}Et_2O$	CH_2Cl_2	2/58/33 (6)
6	$FeCl_2{\cdot}4H_2O$	CH_2Cl_2	no reaction (6)
7	$Fe(acac)_3$	CH_2Cl_2	no reaction (6)
8	$FeCl_3$	$CHCl_3$	22/59/16 (6)
9	$FeCl_3$	THF	no reaction
10	$FeCl_3$	1,4-dioxane	no reaction
11	$FeCl_3$	toluene	0/48/48 (6)
12	$FeCl_3$	*n*-hexane	74/8/12 (6)

[a] The yields were calculated on the basis of ^1H NMR. [b] 2 equiv of H_2O was added. 4-MPM: 4-methoxyphenylmethyl.

Received: November 19, 2014

DOI: 10.1021/acs.orglett.5b00106

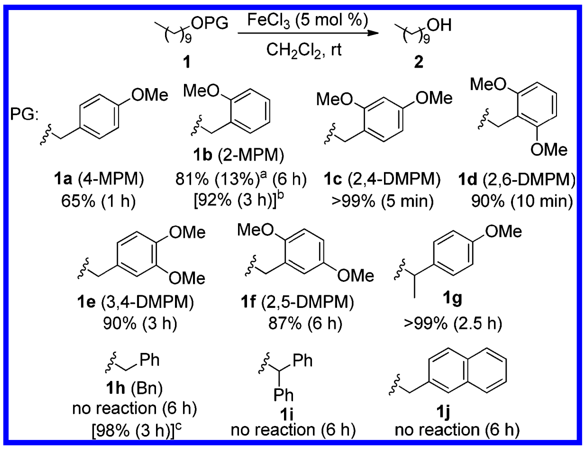
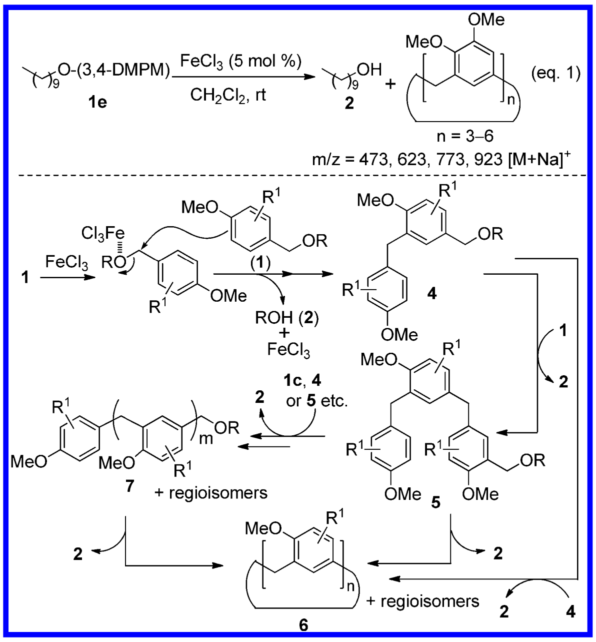


Figure 1. Scope of various benzyl-type ethers. (a) Yield of recovered starting material. (b) 5 mol % of TMSCl was added as an additive. (c) 1.1 equiv of FeCl$_3$ and 1.1 equiv of TMSCl were used. PG: protecting group. MPM: methoxyphenylmethyl. DMPM: dimethoxyphenylmethyl.

Scheme 1. Proposed Reaction Mechanism Based on ESI/MS Analysis of Side Products in FeCl$_3$-Catalyzed Deprotection of 3,4-DMPM Ether (1e)



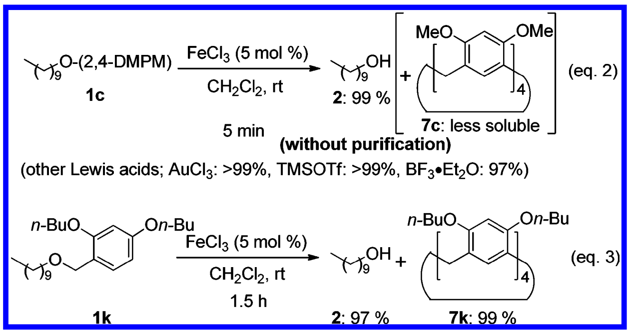
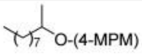
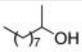
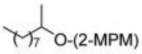
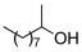
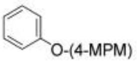
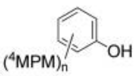
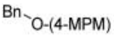
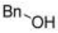
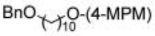
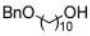
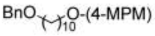
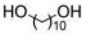
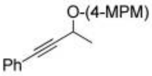
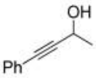
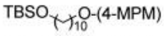
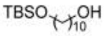
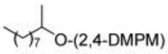
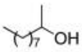
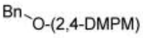
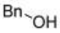
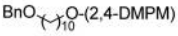
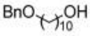
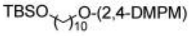
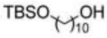
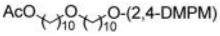
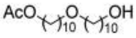
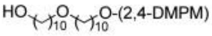
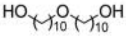
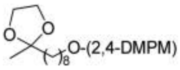
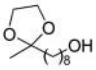
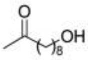
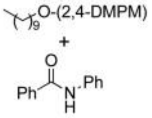
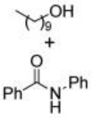
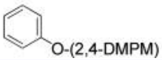
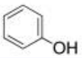


Table 2. Scope and Limitation

$$\text{substrate} \xrightarrow[CH_2Cl_2,\ rt]{FeCl_3\ (5\ mol\ \%)} \text{product}$$

Entry	Substrate	Product	Time	Yield (%)
1			1 h	92
2^a			2 h	98
3			30 min	complex mixture
4			30 min	83
5			1.5 h	95
6^b			2 h	81
7			3 h	54% (39)^c
8			2.5 h	53^d
Without purification using silica-gel column chromatography^e				
9			5 min	99
10			5 min	92
11			5 min	99
12			5 min	quant.
13			5 min	quant.
14			15 min	99
15		 	5 min	69 31
16			5 min	99 97^f
17			5 min	80^g

^{a}5 mol % of TMSCl was added as an additive. ^{b}1.1 equiv of FeCl$_3$ and 1.1 equiv of TMSCl were used. ^{c}Yield of recovered starting material. ^{d}The TBS ether moiety was partially deprotected. ^{e}Highly pure product was obtained without silica gel column chromatography. Spectral data are shown in the Supporting Information. ^{f}The yield was calculated on the bass of ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^{g}The product was purified by silica gel column chromatography due to the contamination of unidentified byproducts. MPM: methoxyphenylmethyl. DMPM: dimethoxyphenylmethyl

Table 2. Other iron catalysts such as $FeCl_2·4H_2O$ and $Fe(acac)_3$ were ineffective (entries 6 and 7). Solvents also strongly influenced the reaction efficiency, the deprotection in $CHCl_3$ requiring a longer reaction time (entries 1 vs 8). The reaction in toluene and *n*-hexane gave low yields of the deprotected alcohol (**2**), while THF and 1,4-dioxane were ineffective and led to no reactions (entries 9–12). The addition of water (2 equiv) did not affect the efficiency of the FeCl$_3$−catalyzed deprotection in CH$_2$Cl$_2$ (entries 1 vs 2), which obviously indicated that water never promoted the present deprotection.

The deprotection efficiency using various MPM- (**1a**−**g**) and Bn-type (**1h**,**i**) ethers was next compared to elucidate the reaction efficiency (Figure 1). The deprotection reactivity of the 2-MPM ether (**1b**) was lower than that of the 4-MPM ether (**1a**) due to the steric hindrance of **1b** around the benzylic position, and the deprotection of **1b** was not complete even after 6 h. Among the dimethoxyphenylmethyl (DMPM)-type ethers, the deprotection of the 2,4-DMPM (**1c**) and 2,6-DMPM (**1d**) ethers bearing two electron-donating methoxy groups at the *meta*-position on each aromatic ring were completed in very short reaction times in comparison to those of the other 3,4-DMPM (**1e**) and 2,5-DMPM (**1f**) ethers. 1-(4′-Methoxyphenyl)ethyl ether (**1g**) possessing a methyl substituent on the benzylic position was less reactive in comparison to **1a**, which also clearly showed that the steric hindrance around the benzylic position strongly influenced the deprotection efficiency. Meanwhile, the Bn (**1h**), diphenylmethyl (**1i**), and 2-naphthyl (**1j**) ethers underwent no deprotection at all in the presence of a catalytic amount of $FeCl_3$ (5 mol %). A catalytic amount of TMSCl (5 mol %)[12] enhanced the Lewis acidity of $FeCl_3$, and the deprotection of **1b** was completed in a shorter time. Furthermore, deprotection of the Bn ether (**1h**) could be accomplished using a stoichiometric amount of $FeCl_3$ and TMSCl (1.1 equiv).[13]

On the basis of the results shown in Figure 1, the present deprotection is effectively facilitated by the use of electron-sufficient (highly nucleophilic) MPM-type ethers (preferably, *m*-dimethoxybenzene derivatives) without steric hindrance. An ESI/MS analysis of the byproducts obtained during the deprotection process of **1e** indicated that the mixture of the cyclic trimer, tetramer, pentamer, and hexamer (*m/z* 478.1934, 623.2623, 773.3293, 923.3951 $[M + Na]^+$) of the 3,4-DMPM moiety were produced together with the deprotected 1-decanol (**2**) (Scheme 1, eq 1).[14,15] Therefore, the present deprotection is presumed to proceed via the iron-catalyzed self-assembling mechanism shown in Scheme 1. First, the benzylic position, activated by coordination of $FeCl_3$ with the benzylic oxygen atom of the substrate (**1**), undergoes intermolecular nucleophilic attack by the electron-rich aromatic ring of the MPM moiety in the other substrate to give the deprotected alcohol (**2**) and the corresponding dimer (**4**) derived from the MPM moieties. Repeated similar reactions then give the oligomers **5** and **6**, in which the benzylic position and the benzene moiety allow the intramolecular annulation to provide the calixarene derivatives (**7**). Therefore, the deprotection of DMPM ethers bearing two methoxy groups at *ortho*- and *para*-positions (**1c** and **1d**) is very smoothly completed as shown in Figure 1 due to dual activation of the nucleophilic (electron rich) position on the aromatic ring by the *ortho*–*para* orientation of two electron-donating methoxy groups.

It is noteworthy that the $FeCl_3$-catalyzed deprotection of the 2,4-DMPM ether (**1c**) produced the resorcinarene derivative (**7c**)[16] as a less-soluble precipitate, and only 1-decanol (**2**) was obtained without any byproducts derived from the 2,4-DMPM protective group after simple filtration and extraction (eq 2).[14] Similarly, 2,4-dibutoxyphenylmethyl ether (**1k**) also effectively underwent the $FeCl_3$-catalyzed deprotection to 1-decanol (**2**) in 97% yield accompanying the formation of the highly lipophilic resorcin[4]arene octabutyl ether (**7k**: *m/z* 959.6376 $[M + Na]^+$) (eq 3),[14] which clearly indicated that the present deprotection could proceed via a self-cleaving mechanism of the DMPM moiety. Additionally, the use of other Lewis acids (e.g., $AuCl_3$, TMSOTf, and $BF_3 \cdot Et_2O$) also could realize the efficient deprotection of **1c** into **2** in excellent yields within 5 min without purification by silica gel column chromatography.[17,18]

The present iron-catalyzed deprotection method was applied to various 4-MPM, 2-MPM, and 2,4-DMPM ethers as substrates (Table 2). The 4-MPM ether derived 2-decanol as a secondary alcohol was also efficiently deprotected by the independent use of only 5 mol % of $FeCl_3$ (entry 1), while the 2-MPM ether underwent the quantitative deprotection using the $FeCl_3$–TMSCl (each 5 mol %) combination (entry 2). Phenyl 4-MPM ether was inapplicable, since the phenol and phenol derivatives were also good nucleophiles and gave a complex mixture (entry 3). As expected from the results in Figure 1, the presence of 5 mol % of $FeCl_3$ as catalyst allowed the chemoselective deprotection of MPM ethers in the presence of Bn ethers within the same molecule (entries 4 and 5), while the deproteciton of both the 4-MPM and Bn ethers could be achieved using a stoichiometric amount of the $FeCl_3$ and TMSCl combined system (entry 6). Additionally, an alkyne and silyl ether tolerated the $FeCl_3$-catalyzed deprotection conditions to give the corresponding alcohols (entries 7 and 8). Furthermore, the silica gel column chromatography-free method could be adapted for the deprotection of various 2,4-DMPM ethers derived from secondary, benzyl, and primary alcohols (entries 9–11). Additionally, the deprotection of 2,4-DMPM ethers bearing a TBS ether, acetoxy group, and hydroxyl group in same molecule could be applied (entries 12–14). Meanwhile, the ketal moiety was partially deprotected to the ketone product probably by the contamination of water resulting from the hygroscopic $FeCl_3$ (entry 15). The present deprotection efficiency was not influenced even by an amide compound in the reaction system (entry 16). Fortunately, the 2,4-DMPM phenyl ether derived from the phenol also underwent the chemoselective deprotection to phenol in high yield due to the highly nucleophilic nature of the 2,4-dimethoxyphenyl group in comparison with that of the phenoxy moiety in the substrate and phenol as the product (entry 17).

In conclusion, we report an efficient, green, and chemoselective deprotection method for MPM-type ethers that uses $FeCl_3$ without any additional nucleophiles. The present deprotection proceeds via a self-cleaving mechanism of the electron-rich MPM protective group itself to give the mother alcohol at room temperature in a short time. Additionally, the deprotection of the 2,4-DMPM ethers produces a less soluble precipitate derived from the 2,4-DMPM protective group which gives highly pure alcohols after simple filtration and extraction without silica gel column chromatography. Therefore, the present unprecedented deprotection method is an environmentally friendly, simple, and industrially applicable process.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Typical procedures and spectroscopic data of products. 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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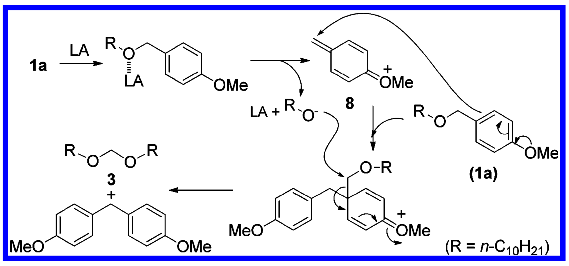
(10) The undesirable byproduct (**3**) could be formed via the *ipso*-substitution of **1a** to the carbocation intermediate (**8**) generated by the $FeCl_3$-catalyzed cleavage of the benzylic C-O bond of another substrate (**1a**). For the related reactions, see: (a) Rathore, R.; Kochi, J. K. *J. Org. Chem.* **1995**, *60*, 7479−7490. (b) Branchi, B.; Bietti, M.; Erocolani, G.; Izquierdo, M. A.; Miranda, M. A.; Stella, L. *J. Org. Chem.* **2004**, *69*, 8874−8885. (c) Lai, Y.-Y.; Lin, N.-T.; Liu, Y.-H.; Wang, Y.; Luh, T.-Y. *Tetrahedron* **2007**, *63*, 6051−6055. (d) Cao, D.; Kou, Y.; Liang, J.; Chen, Z.; Wang, L.; Meier, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 9721−9723



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(11) $AuCl_3$ also effectively catalyzed the cleavage of the benzylic C−O bonds. See: (a) Sawama, Y.; Sawama, Y.; Krause, N. *Org. Lett.* **2009**, *11*, 5034−5037. (b) Sawama, Y.; Kawamoto, K.; Satake, H.; Krause, N.; Kita, Y. *Synlett* **2010**, *14*, 2151−2155.

(12) We have revealed that TMSCl is a good additive to enhance the Lewis acidity of $FeCl_3$. See ref 8.

(13) The independent use of $FeCl_3$ (1 equiv) never induced the deprotection of **1h**. TMSCl may play the role of a nucleophile.

(14) ESI/MS and/or ^{1}H NMR spectra are depicted in the Supporting Information.

(15) No similar synthetic method of calixarenes and resorecinarnes from MPM ethers has been reported in the literature. See: (a) Wanda, S.; Cezary, K. In *Calixarenes and Resorecinarenes*; Wiley-VCH: London, 2009. (b) Recent review: Agrawal, Y. K.; Pancholi, J. P.; Vyas, J. M. *J. Sci. Ind. Res.* **2009**, *68*, 745−768. (c) Ogoshi, T.; Kitajima, K.; Umeda, K.; Hiramitsu, S.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *Tetrahedron* **2009**, *65*, 10644−10649.

(16) A slight amount of **7c** was soluble in CH_2Cl_2 and $CDCl_3$, although **7c** hardly dissolved in Et_2O. Therefore, CH_2Cl_2 used as the solvent was removed in vacuo, and the residue including the deprotected alcohol was redissolved in Et_2O before filtration and extraction to avoid the contamination of **7c**. See the details in the Supporting Information. The ^{1}H NMR of **7c** in $CDCl_3$ could be identified as that of the reported data in ref 15b, and the trimer, pentamer, and hexamer were not observed in the ESI/MS analysis. .

(17) 1 mol% of $FeCl_3$ also effectively catalyzed the deprotection of **1c** to give **2** in quantitative yield for 5 min without purification using silica gel column chromatography.

(18) The $FeCl_3$-catalyzed deprotection of **1c** in the presence of MeOH (2 equiv) under argon atmosphere or the reaction under air smoothly proceeded to give **2** in quantitative yield within 15 or 5 min without purification using silica gel column chromatography, respectively. The present deprotection method does not require strictly pure or dry conditions.