Cerium(III) Triflate versus Cerium(III) Chloride: Anion Dependence of Lewis Acid Behavior in the Deprotection of PMB Ethers

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Cerium(III) triflate deprotects *p*-methoxybenzyl ethers of simple alcohols better than the cerium(III) chloride/sodium iodide system. It can be used in 1% M instead of equimolecular amounts, giving better yields. Aromatic alcohols rearrange, but the addition of a scavenger overcomes this drawback. Unfortunately, unsaturated alcohols are deprotected with decomposition, probably due to side electrophilic additions to double bonds. A comparison between the mechanisms of cerium triflate and cerium chloride is reported.

Introduction

Lanthanide(III) salts have become reagents of choice for many Lewis acid catalyzed processes providing high levels of activity often combined with water tolerance.[1] In this context, there have been a number of reports detailing the use of $CeCl_3$ as a mild but effective Lewis acid, particularly in conjunction with sodium iodide.[2]

More recently, cerium(III) triflate has been introduced in order to catalytically promote some reactions, whereas cerium chloride was used in stoichiometric amounts.[3–5] $Ce(OTf)_3$ is a very cheap, easy-to-handle catalyst and easily prepared from $CeCl_3{\cdot}7H_2O$ and now commercially available. It can be easily recovered from the reaction mixture and it is water-tolerant, that is, it can be used as a Lewis acid catalyst in water containing organic solvents, thus providing certain solutions for the environmental problems associated with the use of harmful, heavy transition metals. Finally, it has been demonstrated to be easily recovered from waste-reaction water without loss of activity.[3] The aim of this paper is to provide a comparison of the reactivity between the two cerium(III) salts.

Results and Discussion

Cleavage of *p*-methoxybenzyl (PMB) ethers were chosen for this work, since this reaction was already widely discussed with the $CeCl_3$/NaI system.[6] Conversely from cerium chloride, cerium triflate is known to function better in nitromethane than in acetonitrile. Therefore, nitromethane was the solvent of choice for our investigation.[7] We found that catalytic amounts (1%) of cerium(III) triflate are able to remove PMB protecting groups from aliphatic alcohols in much shorter reaction times than the $CeCl_3$/NaI system and in almost quantitative yields (Table 1, Entry 1). For example, octanol is completely deprotected in 30 min, while decanol is reported to be cleaved in 90% yield in ca. 1 d.

On the other hand, any attempt to obtain alcohols carrying double or triple bonds were unsuccessful, and complex mixtures of products were always obtained.

Aromatic alcohols can be cleaved only in the presence of either a scavenger such as 1,3-dimethoxybenzene (Entries 11, 12) or strong electron-withdrawing substituents on the aromatic ring (Entry 13). However, comparable yields in much shorter reaction times are obtained in these cases, too. Finally glycidol (Entry 14) is completely deprotected to produce glycerol, whereas no deprotection was registered using the $CeCl_3$/NaI system.

Moreover, this method may be proposed to selectively deprotect PMB ethers in the presence of other protecting groups, such as Bn (benzyl), TBDPS (*tert*-butyldiphenylsilyl) and Tr (trityl), which remain substantially unaffected,

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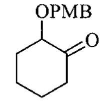
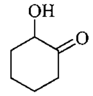
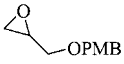
Table 1. *p*-Methoxybenzyl cleavage from various ROPMB compounds in nitromethane at reflux with 1% mol of $Ce(OTf)_3$

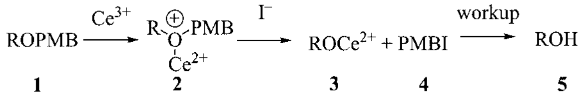
Entry	Starting material	Product	Time [h]	Yield [%]
1	nC$_8$H$_{17}$OPMB[a]	nC$_8$H$_{17}$OH	0.5	> 99
2	iC$_5$H$_{11}$OPMB[b]	iC$_5$H$_{11}$OH	0.5	78
3	cC$_6$H$_{11}$OPMB	cC$_6$H$_{11}$OH	0.5	73
4	tC$_5$H$_{11}$OPMB[c]	tC$_5$H$_{11}$OH	5	> 99
5	MenthylOPMB[c]	Menthol	1	75
6	BuOPMB	BuOH	0.5	85
7	*s*BuOPMB	*s*BuOH	0.5	75
8	nC$_5$H$_{11}$OPMB	nC$_5$H$_{11}$OH	0.5	87
9			0.5	96
10	PhCH$_2$OPMB	PhCH$_2$OH	1	83
11	C$_6$H$_5$OPMB	C$_6$H$_5$OH	0.5	30[d]
12	C$_6$H$_5$OPMB	C$_6$H$_5$OH	0.5	> 99[e] [f]
13	pNO$_2$C$_6$H$_4$OPMB	pNO$_2$C$_6$H$_4$OH	0.5	80[g]
14		Glycerol	1	90
15	THPO(CH$_2$)$_5$OPMB[c]	THPO(CH$_2$)$_5$OH	0.5	61[h]
16	TBDPSO(CH$_2$)$_5$OPMB[i]	TBDPSO(CH$_2$)$_5$OH	16	75
17	BnO(CH$_2$)$_5$OPMB	BnO(CH$_2$)$_5$OH	0.5	76
18	TrO(CH$_2$)$_5$OPMB[c]	TrO(CH$_2$)$_5$OH	0.25	75

[a] 30% $Ce(OTf)_3$. [b] 10% $Ce(OTf)_3$. [c] At 60 °C. [d] 65% of [(4-methoxyphenyl)methyl]phenol. [e] Addition of 1 equiv. of 1,3-dimethoxybenzene as a scavenger. [f] With $CeCl_3$/NaI/MeCN system, phenol was obtained in 86% yield after 48 h of reflux (see ref.[6]). [g] With $CeCl_3$/NaI/MeCN system, 4-nitrophenol was obtained in 89% yield after 21 h of reflux (see ref.[6]). [h] 39% of diol. [i] At room temperature.

if the reaction temperature is lowered (Entries 16–18). At 60 °C, THP is only partially removed (Entry 15). At 100 °C, the diol was almost quantitatively recovered with either THP/PMB or Tr/PMB double protection.

Comparison of our results with cerium(III) chloride reveal some clear differences. The most relevant ones are: (i) the employed amounts of cerium salt (1.5 equiv. vs. 1% mol) and (ii) the reaction times (many vs. a few hours).

The different behaviors of the two salts, which are very similar at first sight, prompted us to investigate the mechanism of the two reactions more closely. The mechanism of the $CeCl_3$/NaI system, which was recently discussed,[2] involves coordination of the cerium cation to the oxygen atom, followed by the intervention of the iodide anion as a nucleophile to cleave the ethers, originating in a cerium alkoxide (Scheme 1). However, it is worth noting that in all the reports on deprotection promoted by $CeCl_3$, quantities of cerium salt ranging from 1 to 2 equiv. (typically 1.5) are employed and cleavage occurs or worse still does not at all with less than 1 equiv. In that cited paper,[2] for the first time, it was reported that cerium chloride is consumed during the reaction course, notwithstanding, it exerts its first coordinating role in a heterogeneous phase.



$$\mathrm{ROPMB} \xrightarrow{\mathrm{Ce^{3+}}} \mathrm{R}\overset{\oplus}{\underset{\mathrm{Ce^{2+}}}{\mathrm{O}}}\mathrm{PMB} \xrightarrow{\mathrm{I^-}} \mathrm{ROCe^{2+}} + \mathrm{PMBI} \xrightarrow{\text{workup}} \mathrm{ROH}$$

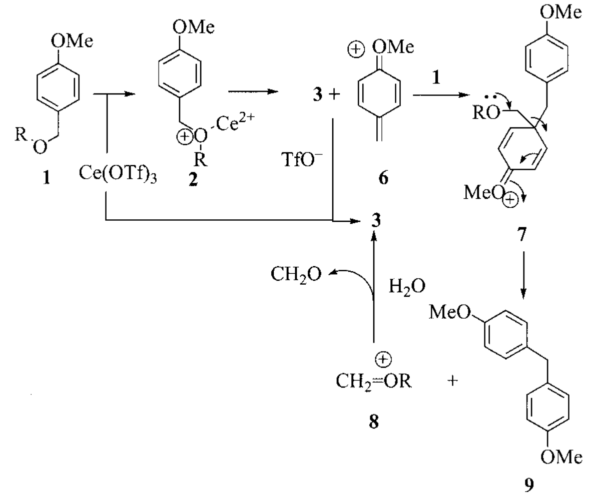
1 2 3 4 5

Scheme 1. Accepted mechanism for cerium chloride mediated cleavage of ethers

In fact, the alkoxide is unable to support the catalytic loops and, conversely from what many authors have reported,[8] adventitious water is incapable of forming alcohol from cerium alkoxide, so it survives until reaction workup. Besides, we have already seen cerium alkoxides as unreactive species, for example, when we compared the addition of organocerium reagents to allyl alcohols with addition to unsaturated aldehydes.[9]

On the other hand, all the reactions involving cerium(III) triflate occur with catalytic amounts of cerium salt (typically 1–5%, rarely 30%), thus implying that cerium is regenerated during the reaction course. Then, the triflate anion displaces the alkoxide anion from cerium and finally water protonates it to an alcohol. But, why can the iodide anion present in the $CeCl_3$/NaI system not work like the triflate anion? Obviously, it is captured before by the leaving carbonium ion. Moreover, intervention of iodide in this reaction step seems to be destructive. In fact, when a ratio greater than 1:1 ($CeCl_3$/NaI) was used, appreciable increase in reactivity was never observed.[2] In the present reaction, addition of NaI completely inhibits the cleavage and similar observations were found in the deprotection of acetals.[4]

It is known that metal centers of metal triflates are more cationic than those of metal chlorides,[10] and thus, we expect that cerium(III) triflate is more Lewis-acidic than cerium(III) chloride, resulting in stronger coordination of the cerium ion to the ether. The most labile R–O bond of the ether should be broken more easily than with $CeCl_3$. We suppose, therefore, the formation of the true *p*-methoxybenzyl cation **6**. Conversely from acetals,[4] in the present reaction, water is unnecessary, so we propose that **6** can work as an electrophile in an $^{s}E_{Ar}$-like reaction (Scheme 2).



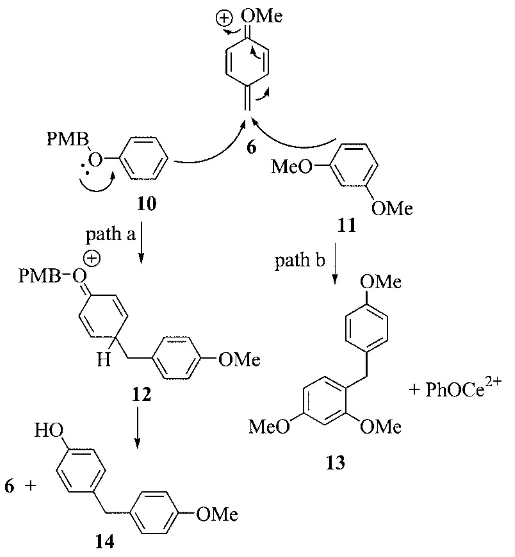
Scheme 2. Proposed mechanism for cerium(III) triflate catalysed PMB ethers deprotection

This hypothesis is supported by the following experimental evidence:

(a) The isolation of bis(4-methoxyphenyl)methane (**9**) as a by-product.

(b) The higher reaction rate with decreasing catalyst amounts. In a fashion of an electrophilic substitution reaction, free **6** should attack **1**. Higher amounts of catalysts increase the amount of **6** with detriment of both free ether and reaction rate. In fact, higher amounts of catalyst lower the reaction rate: for example, the reaction is completed in 11 h, 4 h, 30 min with 30%, 10% and 1% of catalyst, respectively. $CeCl_3$ completely coordinates the PMB ether, converting quantitatively **1** into **2**. If **6** should be formed in this reaction too, as supposed by Marcantoni et al.,[6] the SE_{Ar}-like mechanism is not available due to the absence of free **1**. An external nucleophile is necessary to trap **6** and iodine was demonstrated as the best option.[6]

(c) The behavior of *p*-methoxybenzyl phenyl ether (**10**). Under classical reaction conditions, we recover 65% of 4-[(4-methoxyphenyl)methyl]phenol (**14**) as a rearranged product. In our opinion (Scheme 3, path a) the 4-position of the phenol-activated aromatic ring can easily compete with the 1-position of the 4-methoxy-substituted aromatic ring to trap **6**, giving the oxonium ion **12**, which in turn can undergo cleavage to produce **6** and **14**. Introduction of a compound highly reactive in SE_{Ar} reactions such as 1,3-dimethoxybenzene allows formation of phenol and 1,3-dimethoxy-4-[(4-methoxyphenyl)methyl]benzene (**13**) (Scheme 3, path b). Electron-withdrawing substituents on the phenol aromatic ring block this pathway and normal cleavage occurs (Table 1, Entry 15).



Scheme 3. Deprotection of phenyl PMB ether

(d) **6** can add to double bonds of unsaturated ethers, allowing the formation of polymeric chains, which leads to the complex reaction mixture obtained with these substrates.

(e) Some activation of the aromatic ring is necessary for the occurrence of the reaction. In fact, cleavage of benzyl *p*-methoxybenzyl ether exclusively leads to benzyl alcohol and **6**.

(f) In a similar fashion of the mechanism depicted in Scheme 2, deprotection of glycidol must be possible, since there is no nucleophile available which is able to open the oxirane ring. In fact GC-MS analysis of the crude mixture shows the complete deprotection with retention of the ring and the expected formation of **9**. Unfortunately, the oxirane ring does not survive the workup of the reaction mixture and glycerol was the only separated reaction product.

(g) The fate of formaldehyde remains a unanswered question in our mechanism.

In order to obtain further information on the proposed mechanism we performed the deprotection of 1-butoxy-1-(4-methoxyphenyl)ethane (**15**), with the hope of detecting acetaldehyde. Unfortunately, together with butanol (recovered in 76% yield, similar to Entry 8, Table 1), neither acetaldehyde nor the expected 1,1-bis(4-methoxyphenyl)ethane were detected. The reaction course follows a different pathway since 4-vinylstyrene arising from β-elimination was the only detectable product, except in traces arising from the cleaved protecting group. This evidence, however, does not invalidate but reinforce the supposed mechanism, because simple PMB ethers do not have β-hydrogen atoms promoting elimination, and the presence of a double bond leads, once more, to a complex reaction mixture. Moreover, it is reasonable that intramolecular elimination is faster than the intermolecular SE_{Ar}-like reaction.

Iodide should be useless in this hypothesized mechanism, since β-elimination prevents formation of a carbenium ion in the reaction with cerium(III) chloride. Actually, a reaction carried out with only 1.5 equiv. of $CeCl_3$, leads to butanol (67%) and 1,3-bis(4-methoxyphenyl)-1-butene (57%) (**16**), whose formation is easily rationalized on the basis of the proposed mechanism.

Conclusion

Cerium triflate is able to deprotect aliphatic and aromatic PMB ethers better than the $CeCl_3$/NaI system. In fact, catalytic instead of more than stoichiometric amounts of the salt can be employed. Conversely from the $CeCl_3$/NaI system, glycidol can be deprotected. Other protecting groups, except the THP group, on diols can be tolerated as in the $CeCl_3$/NaI system. Activated aromatic PMB ethers can be cleaved by the aid of a scavenger, which can compete with intermolecular rearrangement. Only unsaturated ethers lead to intractable reaction mixtures, through pathways which are not completely understood yet.

The present work sheds new light on the mechanism of cerium salts. The accepted cerium chloride cleavage mechanism and the above-introduced cerium triflate cleavage one are, therefore, not as different as they appear: the strength of the nucleophile and the weakness of the C−O bond in the cerium-coordinated ether **2** are the driving force of the reaction. Triflate is a stronger Lewis acid with respect to chloride, therefore, in the second step, the intervention of strong nucleophiles is unnecessary.[6] Moreover, when the shape of the molecule allows fast elimination, an external noncoordinated nucleophile is also not needed by cerium chloride. Triflate anions, conversely from chloride and iodide anions, can shift the cerium center from the alkoxide, so it can be catalytically used, since it is not consumed during the reaction course. Finally, it can be easily recovered from the reaction mixture.[4]

Experimental Section

General Remarks: Deprotection runs were monitored by a GC-MS Hewlett−Packard workstation, formed by a GC-HP 6890 (30-m HPS capillary column, 1 mL/min He as carrier gas) and by an HP 5973 mass detector. ^{1}H NMR spectra were recorded with a Bruker WM 300 spectrometer, in $CDCl_3$ solutions with TMS as the internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. Commercial products (Aldrich or Fluka) were used without further purifications. PMB ethers[11] and cerium(III) triflate[12] were prepared by conventional methods. 1-Butoxy-1-(4-methoxyphenyl)ethane (**15**) was prepared in two classical steps: LAH reduction of 4-methoxyacetophenone and substitution on 1-bromobutane with sodium 1-(4-methoxyphenyl)ethoxide. Deprotected diols were prepared from monoprotected PMB alcohols by standard procedures for introduction of THP Bn, TBDPS and Tr groups.[13] All isolated compounds gave satisfactory microanalyses.

General Procedure: Nitromethane (3 mL), cerium(III) triflate (3 mg, 5.1 μmol) and the protected alcohol (0.51 mmol) were mixed into a round-bottom flask equipped with a magnetic stirrer and heater. The reaction mixture was heated at reflux or at 60 °C and monitored by GC-MS. When the starting material had disappeared (Table 1), a saturated aqueous solution of $NaHCO_3$ was added and the mixture extracted twice with diethyl ether. The alcohols were identified by comparison with authentic samples. GC yields were determined by the standard addition method, but some reaction mixtures (menthol, octanol, cyclohexanol, phenol) were separated by preparative TLC [hexane/ethyl acetate (7:3) as eluent] with comparable yields and in high purity (> 97%) by NMR spectroscopy. Data of by-products obtained from these runs:

Bis(4-methoxyphenyl)methane (9): Average yield 77%. ^{1}H NMR = 3.76 (s, 6 H, CH_3O), 3.85 (s, 2 H, CH_2), 6.68−7.20 (A_2B_2, 8 H, Ar) ppm. MS: *m*/*z* (%) = 228 (100) [M]$^+$, 197 (71), 121 (28). $C_{15}H_{16}O_2$ (228.3): calcd. C 78.95, H 7.02; found C 79.00, H 7.00.

4-[(4-Methoxyphenyl)methyl]phenol (14): Yield 72 mg (0.34 mmol, 65%). ^{1}H NMR = 3.82 (s, 3 H, CH_3O), 3.84 (s, 2 H, CH_2), 6.65−7.15 ($2A_2B_2$, 9 H, Ar + OH) ppm. MS: *m*/*z* (%) = 214 (100) [M]$^+$, 183 (38), 121 (28), 108 (41). $C_{14}H_{14}O_2$ (214.3): calcd. C 78.50, H 6.55; found C 79.40, H 6.60.

$THPO(CH_2)_5OH$,[14] $TBDPSO(CH_2)_5OH$,[15] $BnO(CH_2)_5OH$,[16] $TrO(CH_2)_5OH$,[17] and 2-PMBO-cyclohexanone[18] were identified by comparison with literature data.

Deprotection of Phenyl PMB Ether (10) in the Presence of 1,3-Dimethoxybenzene (11): Nitromethane (3 mL), cerium(III) triflate (3 mg, 5 μmol), **10** (100 mg, 0.47 mmol) and **11** (65 mg, 0.47 mmol) were mixed into a round-bottom flask equipped with a magnetic stirrer and heater. The reaction mixture was heated at reflux for 30 min. A saturated aqueous solution of $NaHCO_3$ was added and the mixture extracted twice with diethyl ether. The GC yield (> 99%) was determined by the standard addition method, and isolated yields (98%) by preparative TLC [hexane/ethyl acetate (7:3) as eluent]. Data of the by-product isolated by preparative TLC:

1,3-Dimethoxy-4-(4-methoxybenzyl)benzene (13): Yield 115 mg (0.45 mmol, 95% yield). ^{1}H NMR = 3.76 (s, 3 H, CH_3O), 3.77 (s, 3 H, CH_3O), 3.78 (s, 3 H, CH_3O), 3.83 (s, 1 H, CH_2), 6.48−7.20 (m, 7 H, Ar) ppm. MS: *m*/*z* = 258 (100) [M$^+$], 227 (50), 121 (33). $C_{16}H_{18}O_3$ (258.3): calcd. C 74.42, H 6.98; found C 74.40, H 7.00.

Deprotection of 1-Butoxy-1-(4-methoxyphenyl)ethane (15)

a) With Cerium Triflate: Nitromethane (3 mL), cerium(III) triflate (3 mg, 5 μmol) and **15** (100 mg, 0.5 mmol) were mixed into a round-bottom flask equipped with a magnetic stirrer and heater. The reaction mixture was heated at 60 °C for 1 h. A saturated aqueous solution of $NaHCO_3$ was then added and the mixture extracted twice with diethyl ether. Butanol (76%) was determined by the standard addition method. The GC-MS profile revealed only high amounts of butanol. Only trace amounts of 4-vinylanisole were detected (*m*/*z* = 134, match 98% with Nist98 spectral library).

b) With Cerium Chloride: $CeCl_3 \cdot 7H_2O$ (280 mg, 0.75 mmol) was added to a solution of **15** (100 mg, 0.5 mmol) in acetonitrile (5 mL) and the resulting mixture was stirred at reflux temperature for 1 h (no starting material remained as monitored by GC-MS) The reaction mixture was diluted with Et_2O and treated with HCl (0.5 N, 5 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O. Butanol (67%) was determined by the standard addition method. 1,3-Bis(4-methoxyphenyl)-1-butene (**16**) was separated by preparative TLC [hexane/ethyl acetate (7:3) as eluent]. Yield 76 mg (0.283 mmol, 57%): ^{1}H NMR: δ = 1.42 (d, *J* = 7.1 Hz, 3 H, CH_3), 3.77−3.80 (m, 1 H, CH), 3.79 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 6.21 (dd, *J* = 6.4 and 16.0 Hz, 1 H, CH=), 6.33 (d, *J* = 16.0 Hz, 1 H, CH=), 6.70−7.30 (m, 8 H, Ar) ppm. MS: *m*/*z* (%) = 268 (62) [M$^+$], 253 (100), 145 (57), 121 (22). $C_{18}H_{20}O_2$ (268.4): calcd. C 80.60, H 7.46; found C 80.70, H 7.40.

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[7] In refluxing acetonitrile *p*-methoxybenzyl cleavage from octanol proceeds sluggishly (only 10% was removed after 13 h). In nonpolar solvents such as THF or DCM, the reaction does not work at all.

[8] Many proposed mechanisms reported in ref.[2] invoke catalysis of cerium chloride in the reaction of carbon−oxygen cleavage by intervention of water in the last mechanistic step.

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