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tert-Butyl Ethers: Renaissance of an Alcohol Protecting Group. Facile Cleavage with Cerium(III) Chloride/Sodium Iodide

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Abstract: The *tert*-butoxy derivative is one of the most underused alcohol protecting groups. After having developed an easy and useful protocol for its introduction, we offer here a simple procedure for its removal by treatment with anhydrous $CeCl_3$ and NaI in CH_3CN. The procedure led to the successful cleavage of aliphatic and aromatic *tert*-butyl ethers and was compatible with various other functionalities and protecting groups present in the molecule.

Keywords: alcohols, *tert*-butyl ethers; cerium(III) chloride/sodium iodide system; deprotection; protecting groups

Introduction

The development of new protection and deprotection methodologies is still an important challenge in the synthesis of polyfunctionalized chemical structures.

Among the alcohol protecting groups, the *tert*-butoxy derivative is one of the most underused,[1] although stable under strongly basic conditions.[2] Its scarce employment in organic synthesis is probably due to the harsh conditions required for its formation and its cleavage.[1,2]

We recently developed a new method to obtain *tert*-butyl ethers *via* an unusual reaction of alcohols with Boc_2O in the presence of $MgClO_4$.[3] The protocol was very efficiently applied to a large variety of alkyl and aryl substrates.

However, a protecting group can only be considered valuable when, together with a valid method for its introduction, a mild deprotection procedure is available. From a close analysis of the literature methods for ether dealkylation,[1,2,4] we did not find any general procedures for the cleavage of *tert*-butyl ethers.

The known methods suffer from drastic conditions or show restricted applications. For example, strong acids, such as HI, HBr and HCl, which easily remove the *tert*-butoxy group, cannot save the majority of other functional groups present in the substrate.[5] In an analogous manner, the CF_3COOH,[5] Me_3SiI[6] and *t*-$BuMe_2SiOTf$[7] based methods also cleave, under the same reaction conditions, other ether functionalities. The $ZnBr_2$-promoted method[8] requires a large amount (5 equivs.) of catalyst to cleave unfunctionalized *tert*-butyl ethers. The $TiCl_4$-promoted method is related to a few specific substrates.[9] Finally, the $FeCl_3$-Ac_2O protocol[10] is a two-stage reaction; in fact, firstly *tert*-butyl ethers are converted into acetates, which in turn can be easily hydrolyzed to alcohols in a separate step. Although this methodology works under mild conditions, it is not compatible with other ester functions present in the molecular skeleton, since, of course, they are hydrolyzed in the second step of the reaction. In conclusion, a general, mild and chemoselective deprotection methodology is still lacking.

In our previous communication[3] on the formation of *tert*-butyl ethers, we reported some preliminary results on their deprotection accomplished with the $CeCl_3 \cdot 7\,H_2O$/NaI system. It is known that this system, in fact, is able to cleave the carbon-oxygen bond of ethers (R′−O−R) provided that the R framework bonded to oxygen is able to stabilize an incipient positive charge.[11] This should be the case with the *tert*-butyl ether[12] and, in fact, in our preliminary investigation[3] we succeeded in the deprotection of three *tert*-butyl ethers by using the hydrated $CeCl_3$/NaI system.

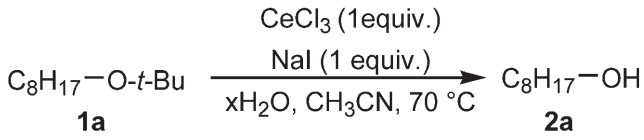
Herein we report a complete study on the cerium(III) chloride/NaI-promoted deprotection of *tert*-butyl ethers which involves evaluating of the effects of water and temperature on the reaction. Moreover, scope and limitations of the protocol will be presented by examining the compatibility of the system with various functionalities and with other protecting groups present in the molecule skeleton.

Results and Discussion

Effect of Water

Preliminary experiments carried out by treating various *tert*-butyl ethers with $CeCl_3 \cdot 7\,H_2O$/NaI in CH_3CN showed that the reaction was quite slow. It seemed appropriate to investigate if the amount of water present in the reaction mixture could vary the reaction rate.[13] Therefore, we carried out a systematic study on the influence of the amount of water on the reaction rate, by drying $CeCl_3$[14] before use and then adding water in known amounts to the reaction mixture.

The cleavage of *tert*-butyl octyl ether (**1a**) to 1-octanol (**2a**) was chosen as the standard reaction (Scheme 1). We carried out the reactions by treating **1a** (1 mmol) with anhydrous $CeCl_3$ (1 equiv.), NaI (1 equiv.) at 70 °C in anhydrous CH_3CN (60 equivs.) in the presence of increasing amounts of added water. As shown in the Figure 1, the reaction goes to completion in less than 4 hours when at the most 1 equiv. of H_2O was added. The reaction rate decreases when 3 equivs. of water are present, however, the reaction is almost completed after 5 h. By increasing the amount of H_2O, the conversion at 5 h decreases. In conclusion, an amount of water not exceeding the 4–5% does not dramatically influence the rate of the deprotection. Otherwise, a trial carried out with HPLC grade CH_3CN as solvent (<2% water reported) gave the same results as the reaction carried out with 1 equiv. of water, confirming the trend of our previous findings.



Scheme 1. Model reaction of *tert*-butyl octyl ether (**1a**) to afford 1-octanol (**2a**).

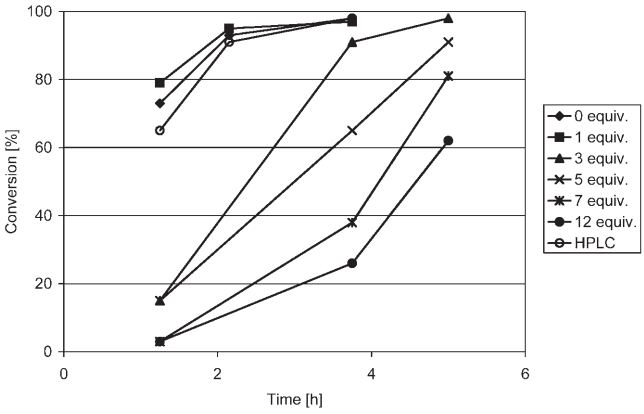


Figure 1. Rate of the cleavage of *tert*-butyl octyl ether (**1a**) with $CeCl_3$ (1 equiv.), NaI (1 equiv.) in CH_3CN at 70 °C in the presence of variable amounts of H_2O.

Effect of Temperature and NaI

In order to find the best reaction conditions, the effect of the amount of the promoters and the effect of the temperature were also examined.

The cleavage of **1a** proceeds only when both $CeCl_3$ and NaI are added. The reaction is sluggish with less than 1 equiv. of $CeCl_3$, probably because it remains in some way bonded to the product. Analogously, the rate of the conversion decreases with less than 1 equiv. of NaI. Thus, a 1:1:1 ratio between $CeCl_3$, NaI and the substrate was chosen as the best reaction conditions.

Moreover, the effect of the temperature was examined. In Figure 2 the conversion percentages of the deprotection of **1a** carried out at various temperatures are reported. At 70 °C the reaction is completed in less than 4 h, while on lowering the temperature to 40 or 50 °C a pronounced drop of the conversion after 5 h was observed.

Scope and Limitations

The optimized reaction conditions were employed to set up a general procedure for the cleavage of various *tert*-butyl ethers, and the overall results are reported in the Table 1.

At first, aliphatic *tert*-butyl ethers where considered. The reaction works well in all cases, with primary and secondary *tert*-butyl ethers (Table 1, entries 1–8). Various functional groups, such as a nitro group, a ketone and a double bond are well tolerated, (Table 1, entries 4–6); the configurations of double bonds and chiral centers are not altered (Table 1, entries 3, 6 and 8). The presence of a free hydroxy group does not influence the substrate reactivity, in fact the 6-*tert*-butoxyhexan-1-ol

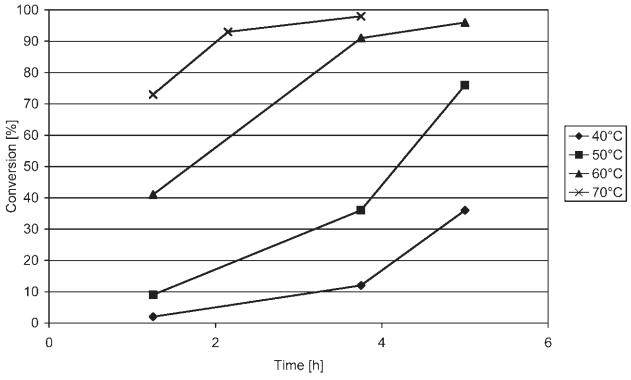
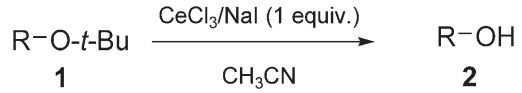
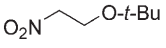
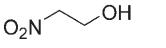
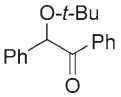
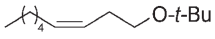
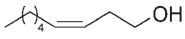
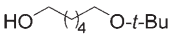
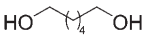
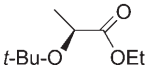
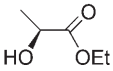
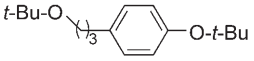
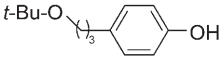


Figure 2. Rate of the cleavage of *tert*-butyl octyl ether (**1a**) with $CeCl_3$ (1 equiv.), NaI (1 equiv.) in CH_3CN at various temperatures.

Table 1. Cleavage of *tert*-butyl ethers **1** to the corresponding alcohol **2** with $CeCl_3$ (1 equiv.), NaI (1 equiv.) in anhydrous CH_3CN at various temperatures.



Entry	Starting material		*T* [°C]	Time [h]	Product		Yields [%]
1	C_8H_{17}-O-*t*-Bu	**1a**	70	3.5	$C_8H_{17}OH$	**2a**	>99
2		**1b**	70	3.5	2-octanol	**2b**	>99
3	(−)-menthyl-O-*t*-Bu	**1c**	70	2	(−)-menthol	**2c**	>99
4		**1d**	70	32		**2d**	97
5		**1e**	70	3	benzoin	**2e**	>99
6		**1f**	70	77		**2f**	98
7		**1g**	70	3		**2g**	98
8		**1h**	70	14		**2h**	95[a]
9	Ph-O-*t*-Bu	**1i**	40	3	Ph-OH	**2i**	>99
10	α-naphthyl-O-*t*-Bu	**1j**	40	3	α-naphthol	**2j**	>99
11	β-naphthyl-O-*t*-Bu	**1k**	40	3	β-naphthol	**2k**	>99
12	*p*-Me-C_6H_4-O-*t*-Bu	**1l**	40	3	*p*-Me-C_6H_4-OH	**2l**	>99
13	*p*-MeO-C_6H_4-O-*t*-Bu	**1m**	40	2	*p*-MeO-C_6H_4-OH	**2m**	>99
14	*o*-CN-C_6H_4-O-*t*-Bu	**1n**	40	6	*o*-CN-C_6H_4-OH	**2n**	>99
15	*p*-CHO-C_6H_4-O-*t*-Bu	**1o**	40	6	*p*-CHO-C_6H_4-OH	**2o**	>99
16	*p*-NO_2-C_6H_4-O-*t*-Bu	**1p**	40	5	*p*-NO_2-C_6H_4-OH	**2p**	>99
17	*p*-F-C_6H_4-O-*t*-Bu	**1q**	40	3.5	*p*-F-C_6H_4-OH	**2q**	>99
18	*m*-Cl-C_6H_4-O-*t*-Bu	**1r**	40	3.5	*m*-Cl-C_6H_4-OH	**2r**	>99
19		**1s**	40	24		**2s**	92

[a] Reaction carried out by using $CeCl_3 \cdot 7\,H_2O$ (1 equiv.) and NaI (1 equiv.).

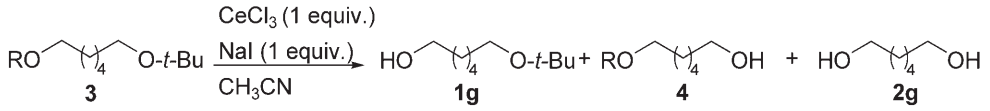
(**1g**) can be converted in the corresponding diol **2g** in 3 h, a time comparable to that of *tert*-butyl octyl ether (**1a**).

Even the ester group is compatible with the reaction conditions. However, with compound **1h** we obtained excellent yields in the deprotection only using hydrated $CeCl_3$, (Table 1, entry 8). Employing the standard methodology with dried $CeCl_3$, we were not able to isolate any desired product at the end of the reaction. Nevertheless, as will be reported later on in the text, the ester group can tolerate anhydrous $CeCl_3$ when an acetoxy group is present together with the *tert*-butyl ether which has to be cleaved. At the moment, we cannot rationally explain these results. The only speculative hypothesis is that the forming hydroxy group in the α-position to the ester in compound **2h** could in some way induce an anomalous reactivity. Unfortunately, at the moment we do not have any better and convincing evidence.

Aromatic *tert*-butyl ethers were then investigated. Preliminary experiments on *tert*-butyl phenyl ether (**1i**) showed that the reaction is very fast, so that lower temperatures can be used: 40 °C are sufficient for reaction to go to completion in acceptable times, (Table 1, entry 9).

The procedure can be successfully applied to other aromatic substrates, such as α- and β-*tert*-butyl naphthyl ethers (**1j** and **1k**) and 1-*tert*-butoxy-4-methylbenzene (**1l**) (Table 1, entries 10–12). On the other hand, various substituents on the aromatic ring are well tolerated. A methyl ether, an aldehydic, a cyano and a nitro group, as well as a halo substituent, remain unaffected (Table 1, entries 13–18). Moreover, the nature of the substituent influences the rate of deprotection: the presence of an electron-donating substituent, such as a methoxy group in the *para*-position (Table 1, entry 13), accelerates the

Table 2. Selective deprotection of *tert*-butyl ethers **3** with $CeCl_3$ (1 equiv.), NaI (1 equiv.) in anhydrous CH_3CN at various temperatures.



Entry	Starting material	R	T [°C]	Time [h]	Yields [%] **1g/4/2g/3**
1	**3a**	Ac-	70	4	**1g/4a/2g/3a** = 0/>99/0/0
2	**3b**	$PhCH_2$-	70	4	**1g/4b/2g/3b** = 0/>99/0/0
3	**3c**	$(i\text{-}Pr)_3Si$- (TIPS)	40	35	**1g/4c/2g/3c** = 98/0/0/0
4	**3d**	$CH_3O\text{-}C_6H_4\text{-}CH_2$- (PMB)	50	96	**1g/4d/2g/3d** = 57/0/0/42
5	**3e**	THP-	50	96	**1g/4e/2g/3e** = 26/19/45/8

reaction, while an electron-withdrawing one slows it down (Table 1, entries 14–16).

Moreover, the difference in reactivity between aromatic and aliphatic *tert*-butyl ethers suggests the possibility of carrying out selective deprotections. In fact, when a diether such as **1 s** is treated with $CeCl_3$/NaI in CH_3CN at 40 °C only the aromatic *tert*-butyl ether undergoes cleavage and the mono-ether **2 s** is obtained in excellent yields after 24 h (Table 1, entry 19).

Finally, in order to evaluate the scope and limitations of the proposed protocol, we carried out the reaction on various differently protected 1,6-diols **3**. As shown by the results reported in Table 2, the *tert*-butyl ether can be selectively cleaved in the presence of both an ester (an acetoxy group) and a benzyl ether (Table 2, entries 1 and 2).

In recent years, we proposed the use of the $CeCl_3 \cdot 7\ H_2O$/NaI system at reflux in CH_3CN to deprotect trialkylsilyl[15] and *p*-methoxybenzyl[16] ethers. Herein, we were able to selectively cleave the more resistant among silyl ethers, the $i\text{-}Pr_3SiO$ group, in the presence of the *tert*-butoxy group by carrying out the reaction at 40 °C for a long time (35 h).

On the other hand, a selective deprotection of the *p*-methoxybenzyl group in the presence of the *tert*-butoxy group cannot be completely achieved since the reaction is very slow: in fact, after 96 h at 50 °C only a 57% yield of the product **1g** was obtained, together with the starting material.

In contrast, a complete lack of selectivity was observed in the case of 2-(6-*tert*-butoxyhexyloxy)-tetrahydro-2*H*-pyran (**3e**): neither the *tert*-butoxy group nor the THP group could be selectively cleaved to any extent, so a mixture of all the possible products was recovered after 4 days at 50 °C.

In the light of these results and taking into account our previous findings, we can arrange various alcohol protecting groups in order of their reactivity towards the action of the $CeCl_3$/NaI system: $PhCH_2 \approx$ ester $\ll t\text{-Bu} \approx$ THP < PMB $\ll$ TIPS < TBDMS, the benzyl ethers and ester derivatives being unreactive towards this system and the silyl ethers being the most labile.

Concerning the reaction mechanism, our experience suggests that $CeCl_3$ is able to promote the cleavage of a carbon-oxygen bond in an ether when a framework able to stabilize an incipient positive charge is present. This is the case, owing to its well-known high oxophilicity, Ce(III) can coordinate the ethereal oxygen, thus weakening the carbon-oxygen bond of the *t*-butyl framework, which can undergo a nucleophilic attack by the iodide anion.[12] Even though substitution on a tertiary carbon can be difficult, this is the only possible explanation for the observed reactivity. In fact, in the absence of NaI the deprotection does not occur at all. Moreover, the cleavage *via* a *tert*-butyl carbocation can be excluded since in the case of aryl *tert*-butyl ethers we never observed the formation of by-products containing a *tert*-butyl moiety as the substituent on the aromatic ring.

Conclusion

We have developed a simple and general method for the cleavage of *tert*-butyl ethers. Treatment of a *tert*-butyl ether with anhydrous $CeCl_3$ and NaI in CH_3CN at the appropriate temperature provides the corresponding alcohol. The procedure can be successfully applied to a large variety of aliphatic and aromatic substrates, various functional groups as well as some other alcohol protecting groups are compatible with the reaction conditions. In fact, ketones, carbon-carbon double bonds, aldehydes, nitro and cyano groups as well as other ether functionalities (alkyl and benzyl derivatives) are completely tolerated.

The discovery of this deprotection procedure follows our publication of a very efficient protocol for the synthesis of *tert*-butyl ethers from aromatic and aliphatic alcohols. Therefore two simple and efficient procedures for the introduction and the removal of the *tert*-butyl group for protecting and deprotecting a hydroxy function are now available, so that this ether derivative can become a routinely used alcohol protecting group.

Experimental Section

General Remarks

The ^1H and ^{13}C NMR spectra were recorded at 400 or 300 MHz and 100 or 75 MHz, respectively. The chemical shifts (δ) are given in ppm relative to the signals of the solvent ($CHCl_3$) or TMS. Coupling constants are given in Hz. Carbon types were determined by DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad signal). The purification of the reaction products was carried out by flash chromatography on silica gel (230–400 mesh).

Materials

Commercial grade reagents and solvents were used without further purification. All reagents were purchased from Aldrich and used as received.

Preparation of the Starting Materials: Synthesis of *tert*-Butyl Ethers 1 and 3

tert-Butyl ethers **1a–c**, **1e–k**, **1m** and **1p–s** were prepared from the corresponding alcohols according to the previously reported procedure.[4] 2-Methyl-2-(2-nitroethoxy)-propane (**1d**), 1-*tert*-butoxy-4-methylbenzene (**1l**), 2-*tert*-butoxybenzonitrile (**1n**) and 4-*tert*-butoxybenzaldehyde (**1o**) are commercial products.

1-*tert*-Butoxyoctane[4] (**1a**) 2-*tert*-butoxy-octane[4] (**1b**), (1*S*,2*R*,4*R*)-2-*tert*-butoxy-1-isopropyl-4-methylcyclohexane[4] (**1c**) 2-*tert*-butoxy-1,2-diphenylethanone[4] (**1e**), 1-*tert*-butoxy-non-3-ene[4] (**1f**), (*S*)-ethyl 2-*tert*-butoxypropanoate[17] (**1h**), 1-*tert*-butoxybenzene[4] (**1i**), 1-*tert*-butoxynaphthalene[4] (**1j**), 2-*tert*-butoxynaphthalene[4] (**1k**), 1-*tert*-butoxy-4-methoxybenzene[18] (**1m**) 1-*tert*-butoxy-4-nitrobenzene[19] (**1p**), 1-*tert*-butoxy-4-fluorobenzene[4] (**1q**), 1-*tert*-butoxy-3-chlorobenzene[4] (**1r**) are completely characterized known compounds. ^1H and ^{13}C NMR data for not described previously compounds are given below.

6-*tert*-Butoxyhexan-1-ol (1g): ^1H NMR: δ = 1.15 (s, 9H), 1.30–1.35 (m, 4H), 1.45–1.55 (m, 5H), 3.30 (t, $J_{H,H}$ = 6.8 Hz, 2H), 3.59 (t, $J_{H,H}$ = 6.6 Hz, 2H); ^{13}C NMR: δ = 25.6 (CH_2), 26.0 (CH_2), 27.5 (CH_3), 30.5 (CH_2), 32.6 (CH_2), 61.4 (CH_2), 62.7 (CH_2), 72.4 (C).

1-*tert*-Butoxy-4-(3-*tert*-butoxypropyl)-benzene (1s): ^1H NMR: δ = 1.18 (s, 9H), 1.55 (s, 9H), 1.75–1.90 (m, 2H), 2.67 (t, $J_{H,H}$ = 7.8 Hz, 2H), 3.35 (t, $J_{H,H}$ = 6.5 Hz, 2H), 7.05–7.10 (m, 2H), 7.15–7.20 (m, 2H); ^{13}C NMR: δ = 27.5 (CH_3), 27.7 (CH_3), 31.8 (CH_2), 32.0 (CH_2), 60.5 (CH_2), 72.5 (C), 83.3 (C), 120.9 (CH), 129.2 (CH), 139.7 (C), 149.0 (C).

tert-Butyl ethers **3a–e** were prepared from 1,6-hexanediol (**2g**) which was firstly monoprotected to products **4a–e** and then the *tert*-butyl group was introduced according to the previously reported procedure.[4]

Acetic Acid 6-*tert*-Butoxyhexyl Ester (3a): 1,6-Hexanediol was protected as the mono-acetate following a known procedure.[20] The isolated mono-ester was treated with Boc_2O in the presence of $Mg(ClO_4)_2$ to give **3a**. ^1H NMR: δ = 1.18 (s, 9H), 1.35–1.40 (m, 4H), 1.50–1.55 (m, 2H), 1.60–1.65 (m, 2H), 2.04 (s, 3H), 3.33 (t, $J_{H,H}$ = 6.4 Hz, 2H), 4.05 (t, $J_{H,H}$ = 6.6 Hz, 2H); ^{13}C NMR: δ = 20.9 (CH_3), 25.7 (CH_2), 25.9 (CH_2), 27.5 (CH_3), 28.5 (CH_2), 30.5 (CH_2), 61.3 (CH_2), 64.5 (CH_2), 72.3 (C), 171.1(C).

(6-*tert*-Butoxyhexyloxymethyl)-benzene (3b): 1,6-Hexanediol was protected as the mono-benzyl ether following a known procedure.[21] The isolated mono-ether was treated with Boc_2O in the presence of $Mg(ClO_4)_2$ to give **3b**. ^1H NMR: δ = 1.18 (s, 9H), 1.30–1.40 (m, 4H), 1.50–1.55 (m, 2H), 1.60–1.65 (m, 2H), 3.32 (t, $J_{H,H}$ = 6.8 Hz, 2H), 3.47 (t, $J_{H,H}$ = 6.6 Hz, 2H), 4.50 (s, 2H), 7.25–7.35 (m, 5H); ^{13}C NMR: δ = 26.1 (CH_2), 26.1 (CH_2), 27.6 (CH_3), 29.7 (CH_2), 30.6 (CH_2), 61.5 (CH_2), 70.4 (CH_2), 72.4 (C), 72.8 (CH_2), 127.4 (CH), 127.6 (CH), 128.3 (CH), 138.7 (C).

(6-*tert*-Butoxyhexyloxy)-triisopropylsilane (3c): 1,6-Hexanediol was protected as the mono-silyl ether[22] following a known procedure. The isolated mono-ether was treated with Boc_2O in the presence of $Mg(ClO_4)_2$ to give **3c**. ^1H NMR: δ = 1.05–1.10 (m, 21H), 1.18 (s, 9H), 1.35–1.40 (m, 4H), 1.50–1.60 (m, 4H), 3.33 (t, $J_{H,H}$ = 6.8 Hz, 2H), 3.67 (t, $J_{H,H}$ = 6.6 Hz, 2H); ^{13}C NMR: δ = 12.0 (CH), 18.0 (CH_3), 25.8 (CH_2), 26.1 (CH_2), 27.6 (CH_3), 30.7 (CH_2), 33.0 (CH_2), 61.6 (CH_2), 63.4 (CH_2), 72.3 (C).

1-[(6-*tert*-Butoxyhexyloxy)methyl]-4-methoxybenzene (3d): 1,6-Hexanediol was mono-protected as the *p*-methoxybenzyl ether following a known procedure.[23] The isolated mono-ether was treated with Boc_2O in the presence of $Mg(ClO_4)_2$ to give **3d**. ^1H NMR: δ = 1.18 (s, 9H), 1.35–1.40 (m, 4H), 1.45–1.55 (m, 2H), 1.55–1.65 (m, 2H), 3.32 (t, $J_{H,H}$ = 6.8 Hz, 2H), 3.43 (t, $J_{H,H}$ = 6.6 Hz, 2H), 3.80 (s, 3H), 4.43 (s, 2H), 6.85–6.90 (m, 2H), 7.25–7.30 (m, 2H); ^{13}C NMR: δ = 26.1 (CH_2), 27.5 (CH_3), 29.7 (CH_2), 30.6 (CH_2), 55.2 (CH_3), 61.5 (CH_2), 70.1 (CH_2), 71.4 (C), 72.4 (CH_2), 72.5 (CH_2), 113.7 (CH), 129.2 (CH), 130.8 (C), 159.1 (C).

2-(6-*tert*-Butoxyhexyloxy)-tetrahydro-2*H*-pyran (3e): 1,6-Hexanediol was mono-protected as the THP ether following a known procedure.[24] The isolated mono-ether was treated with Boc_2O in the presence of $Mg(ClO_4)_2$ to give **3e**. ^1H NMR: δ = 1.18 (s, 9H), 1.35–1.45 (m, 4H), 1.50–1.65 (m, 8H), 1.70–1.85 (m, 2H), 3.26 (t, $J_{H,H}$ = 6.6 Hz, 2H), 3.35–3.40 (m, 1H), 3.45–3.55 (m, 1H), 3.70–3.75 (m, 1H), 3.85–3.90 (m, 1H), 4.55–4.60 (m, 1H); ^{13}C NMR: δ = 19.6 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 26.1 (CH_2), 27.5 (CH_3), 29.7 (CH_2), 30.6 (CH_2), 30.7 (CH_2), 61.5 (CH_2), 62.2 (CH_2), 67.5 (CH_2), 72.3 (C), 98.8 (CH).

Cleavage of *tert*-Butyl Ethers 1 to Alcohols 2

In a two-necked flask equipped with a magnetic stirring bar, $CeCl_3 \cdot 7\,H_2O$ (1.0 mmol) was heated at 130 °C under vacuum.[14] After 1 h the stirring was turned on and the heating was continued for 1 additional hour. After switching off the heating and the vacuum pump argon was introduced in the flask. After cooling, the *tert*-butyl ether **1** (1.0 mmol), NaI (1.0 mmol) and 2 mL of anhydrous CH_3CN were added to the dried cerium(III) chloride. The mixture was then heated at the desired temperature until the TLC analysis revealed the disappearance of the starting material. The crude reaction mixture was diluted with water and extracted with Et_2O. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. The alcohols

2 were purified by flash chromatography on silica gel with a mixture of petroleum ether/$Et_2O = 1:1$.

Alcohols **2a**–**r** are commercial products.

4-(3-*tert*-Butoxypropyl)-phenol (2s): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.20$ (s, 9H), 1.80–1.85 (m, 2H), 2.60 (t, $J_{H,H} = 7.8$ Hz, 2H), 3.37 (t, $J_{H,H} = 6.6$ Hz, 2H), 5.48 (br, 1H), 6.70–6.75 (m, 2H), 7.00–7.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 27.6$ (CH_3), 31.5 (CH_2), 32.2 (CH_2), 60.8 (CH_2), 72.9 (C), 115.1 (CH), 129.4 (CH), 134.1 (C), 153.7 (C).

Selectivity in the Deprotection of Compounds 3

In a two-necked flask equipped with a magnetic stirring bar, $CeCl_3 \cdot 7\,H_2O$ (1.0 mmol) was heated at 130 °C under vacuum.[14] After 1 h the stirring was turned on and the heating was continued for 1 additional hour. After switching off the heating and the vacuum pump, argon was introduced in the flask. After cooling, the *tert*-butyl ether **3** (1.0 mmol), NaI (1.0 mmol) and 2 mL of anhydrous CH_3CN were added to the dried cerium(III) chloride. The mixture was then heated at the desired temperature until the TLC and GM-MS analysis revealed the disappearance of the starting material or after 96 h if the reaction is very slow. The crude reaction mixture was diluted with Et_2O and filtered. The filtered salts were washed several times with Et_2O; the collected organic fractions were combined and the solvent was removed by rotary evaporation. The products were purified by flash chromatography on silica gel with the appropriate mixture of petroleum ether and Et_2O.

Acetic acid 6-hydroxyhexyl ester (**4a**)[25] and 6-(tetrahydro-2*H*-pyran-2-yloxy)hexan-1-ol (**4e**)[26] are known products. 6-Benzyloxyhexan-1-ol (**4b**) is a commercial product.

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