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Novel Method for Efficient Aerobic Oxidation of Silyl Ethers to Carbonyl Compounds Catalyzed with *N*-Hydroxyphthalimide (NHPI) and Lipophilic Co(II) Complexes

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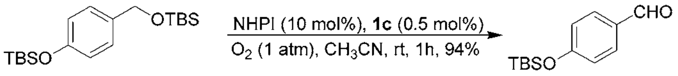
ABSTRACT



In this work, a new method for highly efficient and selective oxidative deprotection of a variety of structurally diverse trimethylsilyl (TMS) and *tert*-butyldimethylsilyl (TBS) ethers using molecular oxygen in the presence of *N*-hydroxyphthalimide (NHPI) and various types of Co(II) complexes is reported. As a result of the relatively neutral reaction medium, acid-sensitive functional groups such as phenolic TBS ethers survived intact under the presented reaction conditions.

The protection of hydroxyl functions as silyl ethers constitutes a very useful tool in synthetic reactions of reasonable complexity.[1] Although the major goal of such a protection is usually to prevent their oxidation, in many cases it is necessary or convenient to achieve the direct transformation of silyl ethers to the corresponding carbonyl compounds.[2] However, in contrast to the oxidation of alcohols, which is easily accomplished under a wide variety of reaction conditions, the oxidation of silyl ethers is often difficult because of the exceedingly low reactivity of the latter. Practically, this transformation can be carried out by either a direct method or in a two-step procedure, deprotection followed by oxidation of the free alcohol. The use of a direct method to establish such a transformation will increase the overall efficiency. However, methods allowing the direct oxidation of silyl ethers to the corresponding carbonyl compounds often require stoichiometric reagents,[2,3] heating,[4] ultraviolet irradiation,[5] highly acidic medium,[6] or prolonged reaction times. Moreover, most of these oxidations bring about a large quantity of noxious byproducts, and the yields of the corresponding carbonyl compounds are not always satisfactory. Some rare examples based on the use of cleaner oxidants such as *t*-BuOOH in the presence of a catalytic amounts of chromium(VI) catalysts were also developed for this purpose.[7] However, these methods also have drawbacks such as the use of molar excess of *t*-BuOOH and prolonged reaction times. Furthermore, the latter methods are not

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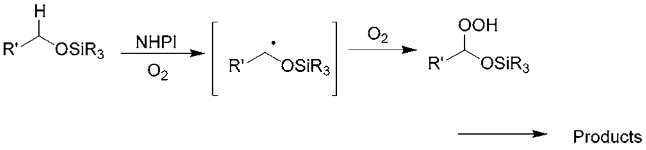
suitable for the oxidative deprotection of TBS ethers at all and afforded the corresponding carbonyl compounds in low yields. From the standpoint of the so-called green and sustainable chemistry, another approach to construct cleaner catalytic systems for oxidation reactions using molecular oxygen (O_2) as final oxidant has been becoming increasingly attractive in recent years.[8] Although there have been many catalytic methods for the aerobic oxidation of alcohols to the corresponding carbonyl compounds,[8−10] despite the importance and attractiveness of this issue, to the best of our knowledge there is no report for the direct aerobic oxidation of silyl ethers to the corresponding carbonyl compounds.

The efficient aerobic oxidation of various types of organic compounds has been carried out using *N*-hydroxyphthalimide (NHPI) as a key radical generator in recent years.[11] It is believed that the phthalimide *N*-oxyl (PINO) radical generated insitu from the reaction of O_2 and NHPI, abstracts the hydrogen atom from the sp^3 (saturated) carbons, forming the corresponding alkyl radicals. Under aerobic conditions, these radicals subsequently react with O_2, which lies predominately in its triplet state to give various types of oxygen-containing compounds such as alcohols, ketones, etc. We hypothesized that PINO radical under aerobic conditions might similarly be able to convert the silyl ethers to the corresponding oxygenated products through the intermediacy of an α-siloxy radical (Scheme 1).

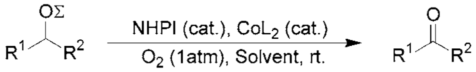
Scheme 1



This led us to become interested in the use of this relatively general reaction pathway for the aerobic oxidation of silyl ethers.

More recently, Ishii and co-workers showed that the use of lipophilic NHPI instead of NHPI itself has an extraordinary effect on both selectivity and total yields of the air oxidation of alkanes.[12] They also found that the use of lipophilic NHPI as catalyst is superior to NHPI from the standpoint of both the turnover number of the catalyst and rate of oxidation of hydrocarbons. However, to our knowledge there is no systematic investigation on the effect of lipophilization of Co(II) ions on the oxidation reaction in the presence of NHPI. In a preceding paper, we have developed a novel method for the selective oxidation of a variety of structurally diverse acetals with molecular oxygen using NHPI combined with $Co(OAc)_2$ under mild reaction conditions.[13] In these investigations, we found that although TBS ethers survived through the oxidation of acetals using a NHPI/$Co(OAc)_2$/O_2 system, the situation is considerably altered in the absence of the acetals. In continuation of this study, we wish herein to disclose our recent finding on the aerobic oxidation of various types of silyl ethers using NHPI as radical generator combined with lipophilic Co(II) complexes (Scheme 2).

Scheme 2



[a] $\Sigma = Me_3Si$, *t*-$BuMe_2Si$; L = CH_3CO_2 (**1a**), $CH_3(CH_2)_4CO_2$ (**1b**), $C_6H_5CO_2$ (**1c**), $CH_3(CH_2)_8CO_2$ (**1d**), $CH_3(CH_2)_{16}CO_2$ (**1e**); solvent = CH_3CN.

The cobalt complexes that we used in our studies were cobalt acetate (**1a**), cobalt hexanoate (**1b**), cobalt benzoate (**1c**), cobalt decanoate (**1d**), and cobalt stearate (**1e**). We first investigated the oxidation of benzyl trimethylsilyl ether (**2**) as a model substrate using O_2 (1 atm) in the presence of NHPI (10 mol %) and different types of the indicated cobalt carboxylate (**1a**−**e**, 0.5 mol %) in CH_3CN at room temper-

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ature. In this study, we found that among the cobalt complexes, **1c** and **1d** exert better effect on total conversion. Table 1 shows the representative results. As can be seen, however, **1c** is better suited as cocatalyst considering both conversion and selectivity.

Table 1. NHPI-Catalyzed Aerobic Oxidation of Benzyl Trimethylsilyl Ether (**1**)[a]

			product distribution (%)[c]		
entry	catalyst[b]	time (min)	benzaldehyde (**3**)	benzoic acid (**4**)	conversion (%)
1		5 h			<5
2	**1a**	30			75
3	**1b**	30			85
4	**1c**	20	99	tr	100
5	**1d**	30	89	11	100
6	**1e**	30			74

[a] Benzyl trimethylsilyl ether (1 mmol)/NHPI/cobalt salts ratios were 1:0.1:0.005 in 5 mL of CH_3CN. [b] The cobalt complexes **1a**−**e** are defined in the text. [c] GC yields.

The oxidation of various types of substituted primary benzylic TMS and TBS ethers with O_2 using a NHPI/**1c** catalytic system at room temperature was selectively achieved, giving the corresponding substituted benzaldehydes in good to excellent yields (Table 2, entries 1−8). These results are similar to those obtained very recently by Minisci's group for the aerobic oxidation of primary benzylic alcohols using NHPI/$Co(OAc)_2$/*m*-chlorobenzoic acid.[14] Under the same reaction conditions, however, primary aliphatic silyl ethers gave the corresponding carboxylic acid in high yields (Table 2, entries 9−12). To show the generality of our new protocol, various types of structurally diverse benzylic and aliphatic secondary silyl ethers including cyclic ones were allowed to react in the presence of a catalytic amount of NHPI (10 mol %) and **1c** (0.5 mol %) under O_2 (1 atm) in CH_3CN at room temperature. As can be seen, the oxidation of both TMS and TBS ethers in all cases furnished the corresponding ketone in excellent yields (Table 2, entries 13−28).

Interestingly, we have also observed that phenolic TBS ethers survived intact under the described reaction conditions (Scheme 3).

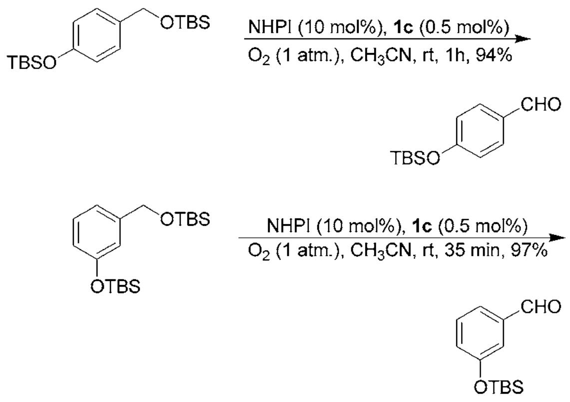
It is also noteworthy that using this method, the oxidation of silyl ethers is much faster than the oxidation of the corresponding alcohols.[9o,14] This observation is presumably because the oxidation of alcohols produces water as a byproduct, which deactivates the Co(II) species via complexation. On the other hand, in our reaction, the silyl ethers are oxidized to the corresponding carbonyl compounds with concomitant formation of either hexamethyldisiloxane or di-*tert*-butyl terramethyl disiloxane (in the case of TBS ethers), which apparently do not affect the catalyst's proficiency.

It is rather difficult to explain exactly the effect of lipophilic carboxylate (benzoate) ligands on overall aerobic oxidation of silyl ethers. However, at this time there are two plausible explanations that seem to be in accord with our evidence. We found that the solubility of cobalt salts in CH_3CN increased significantly with an increase in the carboxylate ligand's size to reach a maximum in **1b** and **1c** and the reaction solution became clear under the operated reaction conditions, whereas in the reactions involving **1a**, **1d**, and **1e** the solutions remained turbid under the same reaction conditions. Although this observation indicates an incomplete

Table 2. Aerobix Oxidative Deprotection of Silyl Ethers Using NHPI Combined with Cobalt Benzoate (**1c**)

entry	R^1	R^2	Σ	time (min/[h])	yield[a,b] (%)
1	Ph	H	TMS	20	92
2	Ph	H	TBS	45	90
3	4-$(NO_2)C_6H_4$	H	TMS	[3]	86
4	4-$(NO_2)C_6H_4$	H	TBS	[5]	91
5	4-$(MeO)C_6H_4$	H	TMS	20	95
6	4-$(MeO)C_6H_4$	H	TBS	30	95
7	4-(*i*-Pr)C_6H_4	H	TMS	20	89
8	4-(*i*-Pr)C_6H_4	H	TBS	40	90
9	$PhCH_2CH_2$	H	TMS	[10]	86[c]
10	$PhCH_2CH_2$	H	TBS	[12]	91[c]
11	$PhCH_2CH_2CH_2$	H	TMS	[12]	90[c]
12	$PhCH_2CH_2CH_2$	H	TMS	[15]	86[c]
13	Ph	CH_3	TMS	60	92
14	Ph	CH_3	TBS	[2]	87
15	Ph	Et	TMS	60	91
16	Ph	Et	TBS	[2]	93
17	4-(Ph)C_6H_4	CH_3	TMS	[3]	85
18	4-(Ph)C_6H_4	CH_3	TBS	[5]	90
19	Ph	Ph	TMS	60	94
20	Ph	Ph	TBS	[2]	95
21	4-*tert*-butylcylcohexyl		TMS	[10]	92
22	4-*tert*-butylcylcohexyl		TBS	[12]	89
23	(−)-bornyl		TMS	[10]	88
24	(−)-bornyl		TMS	[15]	86
25	cycloheptyl		TMS	[10]	89
26	cycloheptyl		TBS	[12]	82
27	Ph	PhCO	TMS	[7]	93
28	Ph	PhCO	TBS	[9]	93

Scheme 3



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solubility of these reagents in the reaction medium, it may not be the whole story of the ligand's effect.

The effect of benzoic acids such as *m*-chlorobenzoic acid (MCBA) on the rate enhancement of the oxidation of alcohols has already been demonstrated by Ishii and co-workers.[9c] They found experimentally that the complex **C** [Co−NHPI], formed in situ from the reaction of **1a** and NHPI, probably decreased the overall rate of reaction. They further showed that addition of MCBA to the catalyst mixture of NHPI/**1a** decomposed the complex **C**, which in turn facilitated the rate of aerobic oxidation of alcohols. Based on this observation, the superior catalytic activity of the NHPI/**1c** system in comparison with NHPI/**1a** is presumably due to the fact that in the former system benzoate ligands (similar to MCBA in Ishii's procedure) strongly prevent the formation of **C** and thus accelerate the overall rate of the aerobic oxidation process (Scheme 4). However, further studies are currently underway to clarify this issue.

Scheme 4

$$Co(OAc)_2 + NHPI \xrightarrow{fast} \mathbf{C}$$

$$Co(Bz)_2 + NHPI \xrightarrow{slow} \mathbf{C}$$

In conclusion, we have developed a remarkably mild and catalytic protocol for the aerobic oxidative deprotection of a relatively wide range of both TMS and TBS ethers. To the best of our knowledge this protocol is the first example of clean oxidative conversion of silyl ethers to the corresponding carbonyl compounds using molecular oxygen. The reaction times are reasonable, and yields are in most cases excellent. Further application of this catalytic system for oxidative deprotection of other types of protecting groups is currently ongoing in our laboratories.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectral data for new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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