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A facile and catalytic method for selective deprotection of *tert*-butyldimethylsilyl ethers with copper(II) bromide

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Abstract—Copper(II) bromide is found to be a simple and efficient catalyst for selective deprotection of *tert*-butyldimethylsilyl ethers of alcohols/phenols at ambient temperature. Various labile functional groups such as ketal, alkene, ketone, OTBDPS, OTHP and allyl and benzyl ethers are found to be compatible under the reaction conditions.

The challenge of synthesizing complex synthetic targets necessitates the continued use of protection/deprotection strategies in synthetic organic chemistry. The ability to efficiently protect, and then deprotect hydroxyl groups has become very important due to the abundance of multiple oxygenated functionalities in various natural product targets.[1] Among different functional groups, the protection of a hydroxyl group as a *tert*-butyldimethylsilyl (TBDMS) ether, a process developed by Corey et al.,[2] has occupied a prominent place in synthetic organic chemistry because it can be installed in high yields and is stable towards basic and mildly acidic conditions. Although tetra-*n*-butylammonium fluoride is the most common reagent for the cleavage of TBDMS ethers,[2] the strong basicity of the fluoride anion makes it inappropriate for base sensitive functionalities. Similarly, acidic reagents such as HCl,[3] H_2SO_4,[4] PPTS,[5] TFA,[6] TsOH,[7] etc., have also been employed for this purpose but which cannot be used in the presence of acid-sensitive functionalities. This has led to the development of several Lewis acids and other reagents including BF_3–OEt_2,[8] BCl_3,[9] $Sc(OTf)_3$,[10] $Ce(OTf)_4$,[11] $InCl_3$,[12] $ZnBr_2$,[13] $Zn(BF_4)_2$,[14] $CeCl_3$–NaI,[15] $BiBr_3$,[16] $BiOClO_4$,[17] Cs_2CO_3,[18] CBr_4–MeOH,[19] I_2[20] and CAN[21] for desilylation. However, many of these methods involve acidic, basic, reducing/oxidizing or high temperature reaction conditions that limit their scope. Thus, there is still a need to develop new reagents in order to remove the TBDMS group selectively, under mild conditions, without affecting other sensitive groups. Recently, we demonstrated that copper(II) bromide ($CuBr_2$) can catalyze the imino Diels–Alder reaction[22] and alkylations of indoles.[23] We investigated the use of this inexpensive reagent in the deprotection of TBDMS ethers (Scheme 1) and report our findings herein.

Initially, the TBDMS ether of cetyl alcohol **1** was subjected to desilylation with 10 mol % of $CuBr_2$ in acetonitrile at room temperature. To our satisfaction, deprotection was observed to yield cetyl alcohol in 50% yield along with unreacted **1** (40%) (Table 1, entry 1). Encouraged by this result, the reaction parameters including solvent, reaction temperature and catalyst concentration were optimized (entries 2–8). Moreover, alumina supported $CuBr_2$, which has been reported earlier as a superior reagent for nuclear bromination of polyalkylbenzenes,[24] was also screened for desilylation (entries 9 and 10). The best result was obtained with 30 mol % of $CuBr_2$ in acetonitrile at room temperature (3 h) to yield cetyl alcohol in 86% yield (entry 2), and therefore the same conditions were used for all subsequent reactions. The exact mechanism of the deprotection with $CuBr_2$ is not clear to us at present.

Although a number of methods are available in the literature for the cleavage of alkyl TBDMS ethers, there

$$\underset{\text{R = alkyl, aryl}}{\text{R-OTBDMS}} \xrightarrow[\text{MeCN, rt}]{CuBr_2\text{ (30 mol\%)}} \underset{\text{67-100\%}}{\text{R-OH}}$$

Scheme 1.

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Table 1. Effect of solvent, reagent and temperature on the $CuBr_2$ catalyzed deprotection of the TBDMS ether of cetyl alcohol **1**

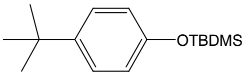
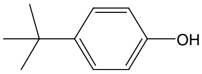
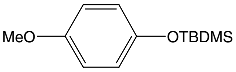
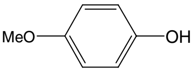
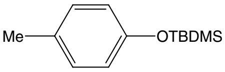
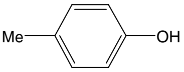
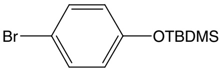
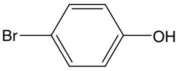
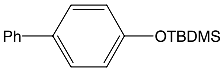
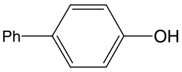
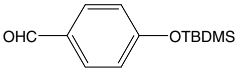
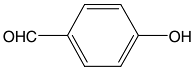
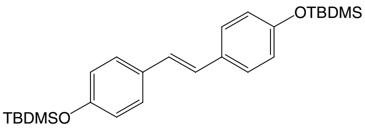
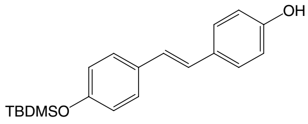
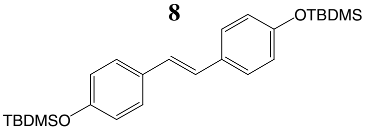
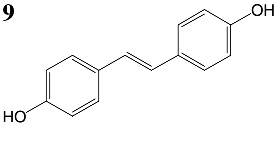
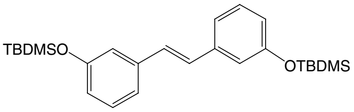
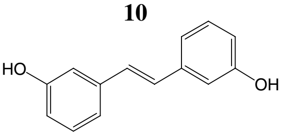
Entry	Solvent	Reagent and conditions[a]	Yield (%)
1	MeCN	$CuBr_2$ (10 mol %), rt	50[b]
2	MeCN	$CuBr_2$ (30 mol %), rt	86
3	MeCN	$CuBr_2$ (30 mol %), Δ	51
4	$CHCl_3$	$CuBr_2$ (30 mol %), rt	35[b]
5	THF	$CuBr_2$ (30 mol %), rt	62
6	EtOAc	$CuBr_2$ (30 mol %), rt	0
7	Dioxane	$CuBr_2$ (30 mol %), rt	31[b]
8	MeOH	$CuBr_2$ (30 mol %), rt	83
9	MeCN	$Al_2O_3/CuBr_2$ (30 mol %), rt	39[b]
10	CCl_4	$Al_2O_3/CuBr_2$ (30 mol %), rt	75

[a] All the reactions were run for 16 h except for entries 2, 3 and 8 where the reactions were complete in 3 h.

[b] 40–54% of **1** was recovered.

are only a few methods reported for the deprotection of phenolic TBDMS ethers.[25] Most of these methods use basic reagents and require elevated temperatures. Consequently, we studied the potential of $CuBr_2$ for the deprotection of phenolic TBDMS ethers. Gratifyingly, a wide range of structurally varied phenolic TBDMS ethers **2**–**7**, possessing both electron-donating or accepting groups on the aromatic ring, underwent easy deprotection to yield the corresponding phenols in good to excellent yields (Table 2, entries 1–6). It was of interest to determine whether mono-deprotection of a symmetric aromatic di-TBDMS ether substrate could be accomplished. Gratifyingly, with 5 mol % of the catalyst, (*E*)-1,2-bis(4-*tert*-butyldimethylsilyloxyphenyl)ethene **8** gave (*E*)-1-(4-*tert*-butyldimethylsilyloxyphenyl)-2-(4-hydroxyphenyl)ethene **9** in 48% yield along with **8** (41%) (entry 7) while double deprotection was observed to afford **10** in quantitative yield with 10 mol % of the catalyst (entry 8). Similarly, (*E*)-1,2-bis(3-*tert*-butyldimethylsilyloxyphenyl)ethene **11** yielded (*E*)-1,2-bis(3-hydroxyphenyl)ethene **12** using 15 mol % of $CuBr_2$ (entry 9). Thus, in contrast to conventional methods for the deprotection of phenolic silyl ethers with basic reagents,[25] the present method allows deprotection of phenolic TBDMS ethers under practically neutral conditions.

Table 2. $CuBr_2$-catalyzed deprotection of aryl-TBDMS ethers in acetonitrile

Entry	Substrate	$CuBr_2$ (mol %)	Time (h)	Product	Yield[a] (%)
1	 **2**	30	0.5		78
2	 **3**	30	3		78
3	 **4**	30	3		68
4	 **5**	30	0.5		73
5	 **6**	30	5		98
6	 **7**	30	4		94
7	 **8**	5	24	 **9**	48[b]
8	 **8**	10	24	 **10**	100
9	 **11**	15	16	 **12**	96

[a] Yields refer to pure isolated product.

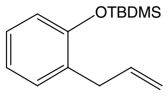
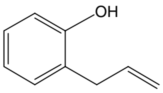
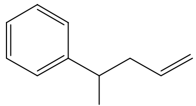
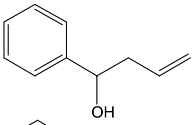
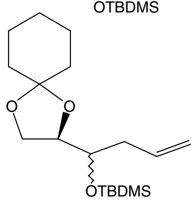
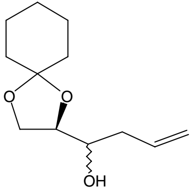
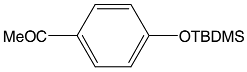
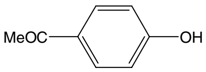
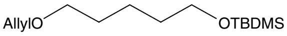
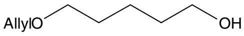
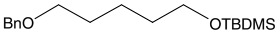
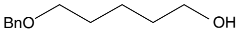
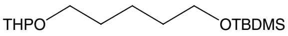
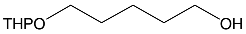
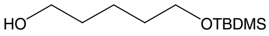
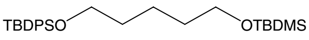
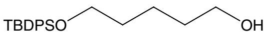
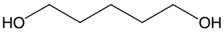
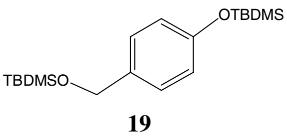
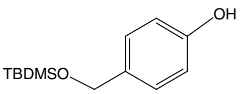
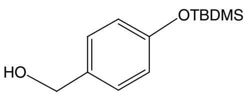
[b] 41% of **8** was recovered.

The utility of this method was further realized in the chemoselective cleavage of TBDMS ethers in the presence of other functionalities. Although, $CuBr_2$ is used for dibromination of alkenes[26] and α-bromination of carbonyl compounds,[27] the TBDMS ethers of 2-allylphenol **13** and homoallylic alcohol **14** underwent smooth deprotection to provide the corresponding alcohols without affecting the double bond (Table 3, entries 1 and 2). Also, for a more complex substrate **15**, having a sensitive ketal and double bond functionalities, the TBDMS ether could be cleaved selectively, in good yield, without affecting the other functionalities (entry 3). Similarly, 4-*tert*-butyldimethyl silyloxyacetophenone **16** underwent easy deprotection to yield 4-hydroxyacetophenone (entry 4) without any evidence of bromination of the acetyl group.

Chemoselective deprotection of a TBDMS ether in the presence of other frequently used protected hydroxyl functions such as allyloxy, benzyloxy and tetrahydropyranyloxy was also achieved with high efficiency (Table 3, entries 5–7). Moreover, selective deprotection of a TBDMS ether in the presence of a TBDPS ether as in 5-(*tert*-butyldiphenylsilyloxy)pentan-1-ol TBDMS ether **17** was achieved to afford 5-(*tert*-butyldiphenylsilyloxy)pentan-1-ol **18** as the major product (60%) along with a small amount (8%) of 1,5-pentanediol using 30 mol % of the catalyst (entry 8).

Finally, selective deprotection of an aryl-TBDMS ether in the presence of an alkyl-TBDMS ether was investigated. Thus, reaction of 4-(*tert*-butyldimethylsilyloxymethyl)phenol TBDMS ether **19** with 30 mol % $CuBr_2$

Table 3. $CuBr_2$ catalyzed chemoselective deprotection of TBDMS ethers

Entry	Substrate	$CuBr_2$ (mol %)	Time (h)	Product	Yield[a] (%)
1	 **13**	30	3		77
2	 **14**	30	5		82
3	 *syn and anti* **15**	30	3	 *syn and anti*	88
4	 **16**	30	24		79
5		30	1.5		88
6		30	2		86
7		30	2	 	54 13
8	 **17**	30	24	 **18** 	60 8
9	 **19**	10	24	 **20**  **21**	59 17

[a] Yields refer to pure isolated product.

yielded 4-(*tert*-butyldimethylsilyloxymethyl)phenol **20** in 59% yield as the major product along with a small amount (17%) of 4-*tert*-butyldimethylsilyloxy benzyl alcohol **21** (the NMR data of which was identical with that obtained from the $NaBH_4$ reduction of 4-*tert*-butyldimethylsilyloxybenzaldehyde) (entry 9). This clearly indicates that deprotection of aryl-TBDMS ethers is faster than that of alkyl-TBDMS ethers with $CuBr_2$.

In conclusion, $CuBr_2$ has been demonstrated to be a convenient deprotecting reagent for TBDMS ethers of alcohols/phenols. The advantages of the method are: (i) the use of a catalytic amount of an inexpensive reagent, (ii) simple experimental procedure, (iii) high chemoselectivity in the presence of ketal, allyl, benzyl, TBDPS and THP ethers and alkene functionalities and (iv) selectivity towards aryl-TBDMS ethers in the presence of aliphatic ones. These facets are very useful in complex multistep synthesis, which requires the sequential protection and deprotection of various functionalities.

Typical experimental procedure: A solution of a TBDMS ether of alcohol/phenol (2.0 mmol) and $CuBr_2$ (0.6 mmol, 0.135 g, 30 mol %) in dry acetonitrile (10 mL) was stirred at room temperature for the appropriate amount of time (Tables 2 and 3). After completion of the reaction, as indicated by TLC, the reaction mixture was concentrated, quenched with water and ethyl acetate (10 mL) and passed through a Celite bed. The Celite was washed with ethyl acetate (2 × 5 mL). The organic layer was washed with water and, brine and then dried (Na_2SO_4). Removal of the solvent followed by preparative thin layer chromatography afforded the respective alcohol/phenol.

All the products were characterized from their spectroscopic data (IR, ^1H, ^{13}C NMR and MS). The data for known compounds are in good agreement with those reported. Spectroscopic and analytical data for selected compounds are provided.[28]

Acknowledgement

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28. Spectral data of selected compounds: *(E)-1,2-Bis(4-tert-butyldimethylsilyloxyphenyl)ethene* **8**: solid. Mp 69–70 °C, IR (KBr): $\nu = 3064, 3028, 2956, 2930, 2886, 2858, 1598, 1489, 1281, 921, 830\ cm^{-1}$. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.26$ (d, 4H, $J = 8.5$ Hz), 6.81 (s, 2H), 6.71 (d, 4H, $J = 8.5$ Hz), 0.89 (s, 18H), 0.11 (s, 12H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 155.0$, 130.8, 127.3, 123.3, 120.3, 25.7, 18.2, 4.4. MS (EI): *m*/*z* 441 ($M + H^+$), 384, 326, 253, 162, 116, 72, 57. Anal Calcd for $C_{26}H_{40}O_2Si_2$: C 70.85, H 9.15. Found: C 70.68, H 9.01. *(E)-1-(4-tert-Butyldimethylsilyloxyphenyl)-2-(4-hydroxyphenyl)ethene* **9**: solid. Mp 82–84 °C; IR (KBr): $\nu = 3604, 3400, 3019, 2957, 2930, 2858, 1607, 1512, 1471, 1463, 1256, 1216, 1169, 911, 838, 758\ cm^{-1}$. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.37$ (d, 4H, $J = 8.0$ Hz), 6.91 (s, 2H), 6.82 (m, 4H), 1.00 (s, 9 H), 0.22 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 154.9$, 154.8, 130.9, 130.5, 127.5, 127.2, 126.1, 120.2, 115.5, 25.6, 18.1, 4.5. MS (EI): *m*/*z* 326 (M^+), 213, 195, 165, 154, 118, 89. Anal. Calcd for $C_{20}H_{26}O_2Si$: C 73.57, H 8.03. Found: C 73.69, H 8.21. *4-(tert-Butyldimethylsilyloxy)-5,6-cyclo-*

hexylidenedioxyhex-1-ene (mixture of *syn* and *anti*-isomers) **15**: liquid; IR (neat): $v = 2934$, 2857, 1254, 1104, 836, 777 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.77$–5.85 (m, 1H), 4.99–5.10 (m, 2H), 3.60–4.04 (m, 4H), 2.09–2.31 (m, 2H), 1.55 (s, 8H), 1.36 (br s, 2H), 0.85 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 134.9$, 134.1, 117.4, 117.1, 109.7, 109.3, 78.3, 77.4, 73.3, 72.3, 66.0, 65.1, 39.3, 37.8, 36.7, 36.2, 34.9, 34.7, 25.8, 25.7, 25.2, 23.99, 23.8, 18.1, 18.0, −3.0, −4.2, −4.4, −4.6, −4.7. MS (EI): *m*/*z* 326 (M^+), 286, 270, 212, 116, 100, 80, 73, 56.