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$Cu(OTf)_2$-catalyzed Et_3SiH-reductive etherification of various carbonyl compounds with trimethylsilyl ethers

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Abstract—A triethylsilane-reductive etherification of the trimethylsilyl ethers with a variety of carbonyl compounds in good yields at room temperature employing 0.5 mol% $Cu(OTf)_2$ as an extremely efficient catalyst is described here.

Etherification is one of the oldest known and most frequently used functional group transformations.[1] It is usually accomplished by Williamson's method involving coupling of an alkoxy anion with an alkyl halide.[2] However, base-labile functionalities in the reactants and competing eliminations in case of the secondary and tertiary halides restrict its application to a wide range of substrates. Alternatively, silane-reductive etherification of various acetals,[3,4] ketals[4] or carbonyl compounds[5] with appropriate addends can be conducted under a variety of acidic conditions. TMSOTf-catalyzed coupling of the TMS-ethers with different carbonyl compounds to the corresponding ethers employing triethylsilane as a reducing agent has also been reported.[6] While this method continues to enjoy wide applications[7] in the synthesis, its biggest disadvantage lies in the handling and storage of moisture-labile TMSOTf.

Metal trifluoromethanesulfonates [$M(OTf)_n$] are water-stable, reusable and valuable Lewis acid catalysts for various types of reactions.[8] Some rare earth $M(OTf)_n$ have been shown to catalyze the benzyl-type etherification by direct condensation of alcohols[9] or via *p*-methoxybenzyl (PMB) trichloroacetimidate.[10] The presence of a 4-hydroxy or 4-methoxy group on the phenyl ring is, however, a prerequisite for effective coupling. Since these $M(OTf)_n$ have not been reported in the reductive etherification of alkyl TMS-ethers with carbonyl compounds, this fact prompted us to exploit their catalytic properties still further.

To tackle this problem, we began with a systematic study to find out (1) which $M(OTf)_n$ is effective and cheaply available, (2) the minimum amount of $M(OTf)_n$ required for this catalytic purpose, (3) which silane is the best reducing agent, and (4) the effects of solvents as well as temperature. *n*-Octyl trimethylsilyl ether **1** and benzaldehyde were selected for model study and the results are summarized in Table 1. In entry 1, reaction of **1** with equimolar amounts of benzaldehyde and triethylsilane in dichloromethane using 10 mol% of $Cu(OTf)_2$ rapidly furnished the corresponding benzyl ether **2** at room temperature in 85% isolated yield. A two to ten-fold decrease of the catalytic amount caused a slight increase in reaction time and a marginal drop in yields (entries 2 and 3). The best results were realized when 0.5 mol% of the catalyst was used, as indicated in entry 4, and compound **2** was obtained in very high yield (90%). This turned out to be the minimum catalytic concentration required for optimum activity and decreasing its amount still further actually led to an adverse effect on the outcome of the reaction (entry 5). Lowering down the reaction temperature to 0°C did not increase the yield (entry 6), and the reaction also took a longer time for completion.

Subsequently, a set of experiments was performed to search for the best suitable reductant and solvent under the optimum amount of $Cu(OTf)_2$. Employment of Me_2EtSiH (entry 7) and $(i\text{-}Pr)_3SiH$ (entry 8) in dichloromethane afforded the expected product **2** in 76 and 87% yields, respectively. This reflected that the steric hindrance of silane agent was not an influencing factor. Reactions using polar solvents like acetonitrile (entry 9), propionitrile (entry 10) or nitromethane

Keywords: etherification; reduction; $Cu(OTf)_2$.
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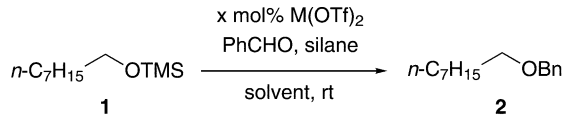
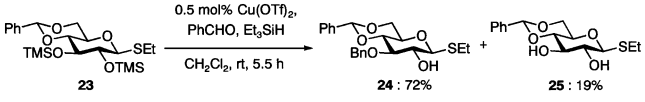
Table 1. $M(OTf)_n$-catalyzed silane-reductive benzylation of trimethylsilyl *n*-octyl ether **1** with benzaldehyde at room temperature



1 2

entry	x	$M(OTf)_n$	solvent	silane	t (h)	yield (%)
1	10	$Cu(OTf)_2$	CH_2Cl_2	Et_3SiH	0.5	85
2	5	$Cu(OTf)_2$	CH_2Cl_2	Et_3SiH	0.75	83
3	1	$Cu(OTf)_2$	CH_2Cl_2	Et_3SiH	1	80
4	0.5	$Cu(OTf)_2$	CH_2Cl_2	Et_3SiH	2.5	90
5	0.1	$Cu(OTf)_2$	CH_2Cl_2	Et_3SiH	7	77
6	0.5	$Cu(OTf)_2$	CH_2Cl_2	Et_3SiH	4	82[a]
7	0.5	$Cu(OTf)_2$	CH_2Cl_2	Me_2EtSiH	2.5	76
8	0.5	$Cu(OTf)_2$	CH_2Cl_2	$(i\text{-}Pr)_3SiH$	2.5	87
9	0.5	$Cu(OTf)_2$	CH_3CN	Et_3SiH	2.5	87
10	0.5	$Cu(OTf)_2$	EtCN	Et_3SiH	2.5	86
11	0.5	$Cu(OTf)_2$	CH_3NO_2	Et_3SiH	3	82
12	0.5	$Cu(OTf)_2$	$PhCH_3$	Et_3SiH	20	0
13	0.5	$Cu(OTf)_2$	THF	Et_3SiH	20	0
14	0.5	$La(OTf)_3$	CH_2Cl_2	Et_3SiH	20	0
15	0.5	$Sm(OTf)_3$	CH_2Cl_2	Et_3SiH	5	52
16	0.5	$Yb(OTf)_3$	CH_2Cl_2	Et_3SiH	4.5	58
17	0.5	$Sc(OTf)_3$	CH_2Cl_2	Et_3SiH	2.5	64
18	0.5	$VO(OTf)_2$	CH_2Cl_2	Et_3SiH	5.5	55
19	0.5	$In(OTf)_3$	CH_2Cl_2	Et_3SiH	4	21
20	0.5	$Zn(OTf)_2$	CH_2Cl_2	Et_3SiH	5.5	26

[a]The reaction was carried out at 0 °C.



(entry 11) worked equally well to deliver ether **2**, with a slight decrease in yields, while toluene and THF gave disappointing results (entries 12 and 13).

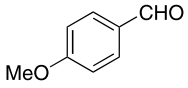
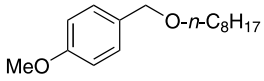
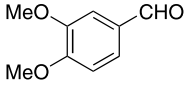
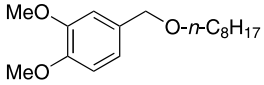
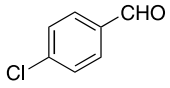
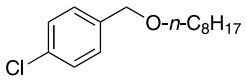
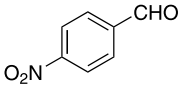
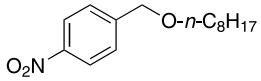
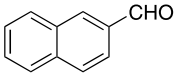
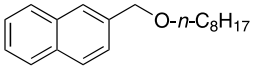
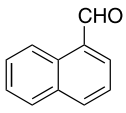
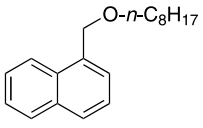
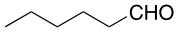
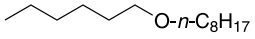
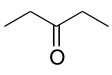
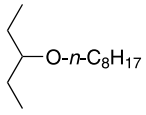
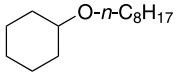
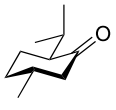
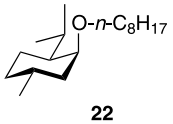
With the above information in hand, we then screened other $M(OTf)_n$ as catalysts for benzylation reaction (entries 14–20). All of the $M(OTf)_n$ studied so far, except $La(OTf)_3$, produced the desired benzyl ether **2**; the best results were still those obtained with $Cu(OTf)_2$ (entry 4). $Yb(OTf)_3$, $Sc(OTf)_3$ $Sm(OTf)_3$ and $VO(OTf)_2$ displayed moderate to good reactivity, while lower yields were encountered with $In(OTf)_3$ and $Zn(OTf)_2$.

In order to study the scope and limitations of this methodology, we conducted several reactions of structurally varied carbonyl compounds with the TMS–ether **1** (Table 2) under this optimized set of reaction conditions [0.5 mol% $Cu(OTf)_2$, Et_3SiH, CH_2Cl_2, room temperature]. Benzyl ethers, which are stable in most acidic and basic environments,[11] are widely applied as permanent protecting groups in organic synthesis. On the other hand, the substituted benzyl ethers can be selectively cleaved with appropriate conditions and serve as orthogonal protecting groups.[12] With these considerations, a variety of aryl aldehydes were investigated first. In entries 1–5, reductive etherification of compounds **3**, **5**, **7**, **9**, and **11** led to the corresponding *n*-octyl ethers **4**,[13] **6**, **8**,[14] **10** and **12**[15] in good yields, respectively. 1-Naphthaldehyde **13** (entry 6) remained inert under the conditions, even after prolonged reaction time, presumably due to the steric hindrance offered by H8. Nevertheless, this steric barrier could be overcome by conducting the same reaction at refluxed temperature, delivering the expected ether **14** in 81% yield. In case of aliphatic aldehydes, conversion of *n*-hexanal **15** (entry 7) to the corresponding ether **16** (68%) was successfully carried out when high concentration of catalyst (10 mol% $Cu(OTf)_2$, 5 mL/g CH_2Cl_2) was employed to speed up the reaction and circumvent the formation of possible side products. Reaction of aliphatic ketone **17** was sluggish and demanded similar high reactant concentration and temperature to furnish the desired ether **18** in 71% yield (entry 8). Notably, the cyclic ketones worked well under the optimized set of conditions. As illustrated in entries 9 and 10, cyclohexanone **19** underwent a facile ether bond formation to provide *n*-octyl cyclohexyl ether **20**[5c] in 72% yield, while *l*-menthone **21** gave a single diastereomer **22**[16] (63%) in an exclusive manner. The stereochemistry was unambiguously determined through chemical correlation. The authentic equatorial compound and its axial counterpart were obtained by Williamson's etherification of *l*-menthol and its C1-epimer with *n*-octyl bromide, respectively. ^1H NMR spectrum of the later showed a close resemblance with that of compound **22**, affirming that the newly formed ether bond oriented axially.

Of particular interest was the differentiation of the 2,3-diequatorial dihydroxy groups in the D-glucopyranosides. Benzylation of the bis-TMS ether **23** followed by work-up with tetra-*n*-butylammonium fluoride yielded the corresponding 2-alcohol **24**[16] (72%) and the diol **25** (19%) without isolation of the 2-OBn isomer. This also revealed that the acid-labile benzylidene acetal could survive under these reaction conditions.

In conclusion, we have successfully developed a Et_3SiH-reductive etherification of the trimethylsilyl ethers with various carbonyl compounds in dichloromethane employing 0.5 mol% $Cu(OTf)_2$ as an extremely efficient catalyst. These reactions can be advantageously conducted at room temperature. $Cu(OTf)_2$, a cheaper

Table 2. Et_3SiH-reductive etherification of compound **1** with a variety of carbonyl compounds employing 0.5 mol% $Cu(OTf)_2$ as the catalyst

entry	R^1COR^2	t (h)	product	yield (%)
1	 **3**	7	 **4**	88
2	 **5**	7	 **6**	61
3	 **7**	5.5	 **8**	81
4	 **9**	5.5	 **10**	63
5	 **11**	5	 **12**	72
6	 **13**	16	 **14**	81[a]
7	 **15**	2	 **16**	68[b]
8	 **17**	24	 **18**	71[a,b]
9	 **19**	7	 **20**	72
10	 **21**	6	 **22**	63

a. The reaction was carried out at refluxed temperature.
b. 10 mol% of $Cu(OTf)_2$, 5 mL/g dichloromethane.

$M(OTf)_n$ agent, is equally suitable for the preparation of substituted and unsubstituted benzyl ethers and thus offers a unique opportunity to install an orthogonal set of protecting groups.

General procedure of etherification. A suspension of freshly dried $Cu(OTf)_2$ (10 mg, 27.6 μmol) in dichloromethane (12 mL) was prepared in a round bottom flask equipped with a rubber septum, nitrogen

inlet and magnetic stirring bar. *n*-Octyl trimethylsilyl ether (1.12 g, 5.53 mmol), the carbonyl compound (6.08 mmol) and triethylsilane (0.97 mL, 6.08 mmol) were sequentially added to the flask at room temperature under nitrogen, and the reaction was kept stirring for 2.5–7 h. Water (10 mL) was added to the solution, and the mixture was extracted with EtOAc (3×10 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give a residue, which was purified by flash column chromatography on silica gel to afford the desired ether product.

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16. Spectral data of selected new compounds. Compound **22**. $[\alpha]_D^{24}$ +17.5 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) 2925, 2868, 1457, 1368, 1331, 1198, 1093, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (d, $J=2.2$ Hz, 1H), 3.49 (dt, $J=9.1$, 6.4 Hz, 1H), 3.14 (dt, $J=9.1$, 6.4 Hz, 1H), 1.97 (ddt, $J=13.7$, 2.2, 5.9 Hz, 1H), 1.69–1.56 (m, 4H), 1.50 (quint, $J=6.4$ Hz, 2H), 1.36–1.25 (m, 10H), 0.87–0.74 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.97 (CH), 68.16 (CH_2), 48.33 (CH), 37.76 (CH_2), 35.29 (CH_2), 31.84 (CH_2), 30.28 (CH_2), 29.42 (CH_2), 29.29 (CH_2), 28.96 (CH), 26.33 (CH_2), 25.95 (CH), 24.90 (CH_2), 22.63 (CH_2), 22.47 (CH_3), 21.10 (CH_3), 20.95 (CH_3), 14.07 (CH_3); HRMS (FAB, M-H^+) calcd for $C_{18}H_{35}O$ 267.2688, found 267.2694. Compound **24**. $[\alpha]_D^{25}$ −43.6 (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) 3368, 3033, 2973, 2912, 2898, 2864, 1497, 1452, 1366, 1089, 1009, 746, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H, PhH), 7.39–7.26 (m, 8H, PhH), 5.56 (s, 1H, PhCH), 4.96 (d, $J=11.7$ Hz, 1H, $PhCH_2$), 4.80 (d, $J=11.7$ Hz, 1H, $PhCH_2$), 4.45 (d, $J=9.2$ Hz, 1H, H-1), 4.34 (dd, $J=10.4$, 5.0 Hz, 1H, H-6_{eq}), 3.76 (t, $J=10.4$ Hz, 1H, H-6_{ax}), 3.70 (t, $J=9.2$ Hz, 1H, H-4), 3.66 (t, $J=9.2$ Hz, 1H, H-3), 3.57 (t, $J=9.2$ Hz, 1H, H-2), 3.48 (ddd, $J=10.4$, 9.2, 5.0 Hz, 1H, H-5), 2.73 (dq, $J=7.4$, 3.0, 2H, SCH_2), 2.50 (bs, 1H, OH-2), 1.30 (t, $J=7.4$, 3H, SCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.28 (C), 137.20 (C), 128.98 (CH), 128.43 (CH), 128.23 (CH), 128.02 (CH), 127.81 (CH), 126.24 (CH), 125.99 (CH), 101.25 (CH), 86.57 (CH), 81.56 (CH), 81.21 (CH), 77.20 (CH), 74.69 (CH_2), 72.99 (CH), 70.74 (CH), 68.63 (CH_2), 24.54 (CH_2), 15.21 (CH_3); HRMS (FAB, MH^+) calcd for $C_{22}H_{27}O_5S$ 403.1579, found 403.1583.