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An efficient method for *para*-methoxybenzyl ether formation with lanthanum triflate

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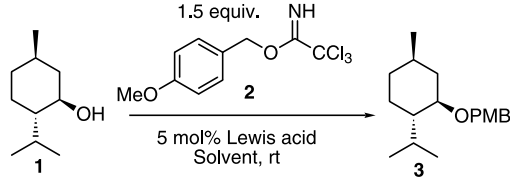
Abstract—PMB ethers of alcohols are prepared in high yields and short reaction times using the trichloroacetimidate of PMB alcohol and lanthanum triflate. The mild conditions allow protection of acid-sensitive alcohols.

The *para*-methoxybenzyl (PMB) group has found application in organic synthesis as a protecting group for alcohols due to the robustness of its ether linkage to basic, nucleophilic, and mildly acidic conditions.[1] Deprotection of the PMB group can be accomplished under oxidative, reductive or acidic conditions.[1,2] For substrates which are not base sensitive, the most common method for installation of the protecting group involves treatment of the alcohol with a base such as sodium hydride in the presence of a *para*-methoxybenzyl halide.[1] However, for substrates which are not stable under these basic conditions, protection can be effected by reaction of the alcohol with the trichloroacetimidate of *para*-methoxybenzyl alcohol (PMBTCA, **2**) in the presence of Brønsted acids such as *para*-toluenesulfonic acid, triflic acid, or camphorsulfonic acid.[3] Lewis acids such as $BF_3{\cdot}OEt_2$, $TrBF_4$, TMSOTf, $Sn(OTf)_2$, and $TrClO_4$ have also been used as catalysts.[3b,4] While other methods for formation of PMB ethers have been reported,[5] the trichloroacetimidate continues to find extensive use due to its ease of preparation.[4a]

We recently found that attempts at protection of a multifunctional alcohol using PMBTCA along with several commonly used promoters resulted in either recovery of the starting material or decomposition of the reagents to an intractable mixture (vide infra). Prompted by these failures, we sought to identify milder conditions for installation of the PMB ether using the trichloroacetimidate. We now report that metal triflates, especially the lanthanide triflates, are highly effective in catalyzing the desired transformation. We began by examining the protection of (−)-menthol under various conditions (Table 1). A variety of magnesium, copper, and zinc salts were screened, and each of

Table 1. Reaction of (−)-menthol and PMBTCA with various catalysts/solvents



Entry	Catalyst	Solvent	Time	Conversion (%)[a]
1	$Mg(OTf)_2$	CH_2Cl_2	4 h	89 (64)
2	$Cu(OTf)_2$	CH_2Cl_2	2 h	74 (67)
3	$Zn(OTf)_2$	CH_2Cl_2	2 h	58
4	$MgBr_2$	CH_2Cl_2	72 h	55
5	$Cu(OTf)_2$	Toluene	30 min	97
6[b]	$CuSO_4$	Toluene	72 h	21
7	$Yb(OTf)_3$	Toluene	<5 min	79
8	$Sc(OTf)_3$	Toluene	<5 min	96
9	$La(OTf)_3$	Toluene	<5 min	98 (85)
10	$La(OTf)_3$	CH_3CN	<5 min	92
11[c]	$La(OTf)_3$	Toluene	<5 min	85
12[d]	$La(OTf)_3$	Toluene	<5 min	81

[a] Conversion was determined by GC analysis of the crude reaction mixtures and refers to the ratio of product to alcohol starting material. Numbers in parentheses refer to isolated yields.
[b] Anhydrous copper sulfate was used.
[c] The toluene was saturated with water prior to use.
[d] 1.0 equiv. of PMBTCA was used.

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the salts afforded product within a few hours in dichloromethane (entries 1–4). Of these salts, copper triflate was the most effective, and changing the reaction solvent from dichloromethane to toluene resulted in a four-fold increase in the rate of the reaction, which was complete in thirty minutes. Even copper sulfate was somewhat effective in toluene, providing 21% conversion to product after 72 h.

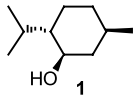
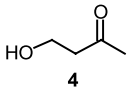
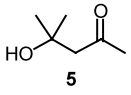
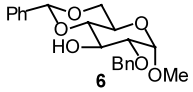
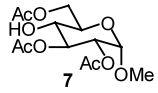
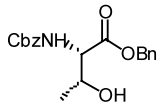
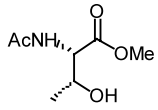
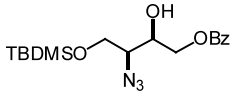
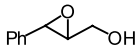
We next examined a series of lanthanide triflates as possible promoters (entries 7–9). Lanthanum triflate and scandium triflate were excellent catalysts, providing essentially quantitative formation of product within minutes of their addition (entries 8 and 9). Lanthanide triflates are known to be effective Lewis acids in polar and aqueous solutions.[6] In our studies, this characteristic was borne out by reactions which proceeded with high conversions in acetonitrile as well as toluene which had been saturated with water (entries 10 and 11).[7] A reaction using one equivalent of PMBTCA also proceeded with high conversion, albeit not to completion (entry 12).

For preparative reactions with $La(OTf)_3$ we used toluene as the reaction solvent, with 1.5 equivalents of PMBTCA as the PMB donor. We then examined the scope of the reaction with a variety of alcohols (Table 2). In each case examined, the reaction was complete in approximately 5 min, as monitored by TLC.[8] The β-hydroxy ketones **4** and **5** both underwent reaction smoothly to provide the corresponding ethers without any evidence of dehydration, even for the tertiary alcohol **5**. The glucose derivatives **6** and **7** were protected in 91 and 93% isolated yields, respectively. The carbamate and acetamide protected threonine esters **8** and **9** were also protected efficiently as their PMB ethers.

The utility of the lanthanides as promoters was illustrated by the successful etherification of the alcohols **10** and **11**. The differentially protected triol **10** provided the PMB ether in 89% isolated yield.[9] Previous attempts to etherify **10** with the imidate **2** using boron trifluoride, triflic acid, or *para*-toluenesulfonic acid either resulted in no reaction or decomposition of the alcohol. Notably, the use of lanthanum triflate allows the etherification of the acid sensitive epoxy alcohol **11** derived from cinnamyl alcohol. Etherification of **11** under our standard conditions (5 mol% $La(OTf)_3$, toluene, rt) resulted in rapid decomposition of the alcohol, and no desired product was isolated. However, when the reaction was carried out at −78°C, the alcohol was consumed within 5 min, and the epoxy ether was isolated in 34% yield. The use of boron trifluoride under these low temperature conditions resulted in an 8% yield of the PMB ether. We speculated that the poor yield was due to cation induced decomposition of the styryl epoxide moiety. Inclusion of the carbocation scavenger thioanisole in the reaction mixture increased the yield of the ether to 61%, consistent with this hypothesis.

In summary, the reaction of alcohols with PMBTCA in the presence of catalytic amounts of $La(OTf)_3$ rapidly affords the corresponding PMB ethers in high yields.

Table 2. Formation of PMB ether by reaction of alcohols with PMBTCA and $La(OTf)_3$

Entry	Substrate	Isolated Yield(%)
1[a]	 **1**	85
2[b]	 **4**	88
3[b]	 **5**	92
4[b]	 **6**	91
5[a]	 **7**	93
6[a]	 **8**	82
7[a]	 **9**	87
8[a]	 **10**	89
9[c]	 **11**	61

a) 5 mol% $La(OTf)_3$. b) 2 mol% $La(OTf)_3$. c) 5 mol% $La(OTf)_3$; -78 °C, 1 eq. thioanisole

The rapid reaction times, even at −78°C, low catalyst loading, along with the ease of handling and moisture tolerance of $La(OTf)_3$ should render this a useful method for the preparation of PMB ethers.

Acknowledgements

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7. When the reaction was carried out in wet toluene using *para*-methoxybenzyl *alcohol* in place of the imidate **2**, no product was observed, indicating that etherification in entry 11 proceeded via the imidate and hydrolysis of **2** was not significant under the reaction conditions.
8. **Representative procedure for PMB protection using La(OTf)$_3$**: PMBTCA was prepared via the method of Audia et al. (Ref. 4a). All PMB ethers with the exception of that derived from **11** were prepared using the representative procedure described below. A solution of menthol (20 mg, 0.128 mmol) and *p*-methoxybenzyl trichloroacetimidate (54 mg, 0.192 mmol) in toluene (3 ml) was treated with La(OTf)$_3$ (4 mg, 0.006 mmol) at room temperature. After completion of the reaction (<5 min), the reaction mixture was concentrated and purified by column chromatography (1:9 ethyl acetate:hexane) to afford 30 mg (85%) of **3**.

   Characterization data for PMB ethers of 1, 4–11:

   Compound **1**: R_f=0.5 (ethyl acetate/hexane, 1/9); ^{1}H NMR, HRMS—Reported in *J. Org. Chem.* **1999**, *64*, 8943; ^{13}C NMR: (100 MHz) δ 15.7, 20.7, 22.0, 22.9, 25.1, 31.2, 34.2, 39.9, 47.9, 54.9, 69.7, 78.0, 113.3, 129.0, 130.9, 158.7.

   Compound **4**: R_f=0.4 (ethyl acetate/hexane, 15/85); ^{1}H NMR (300 MHz) δ 2.16 (s, 3H), 2.69 (t, 2H, J=6.2 Hz), 3.70 (t, 2H, J=6.4), 3.0 (s, 3H), 4.43 (s, 2H), 6.87 (d, 2H, J=8.5), 7.24 (d, 2H, J=8.6); ^{13}C NMR (100 MHz) δ 30.4, 43.8, 55.3, 64.9, 72.9, 113.8, 129.3, 130.1, 159.2; HRMS calcd for $[C_{12}H_{16}O_3+Na]^+$ 231.0997, obsd. 231.1002.

   Compound **5**: R_f=0.5 (ethyl acetate/hexane, 1/9); ^{1}H NMR (300 MHz) δ 1.35 (s, 6H), 2.19 (s, 3H), 2.66 (s, 2H), 3.79 (s, 3H), 4.39 (s, 2H), 6.86 (d, 2H, J=8.4), 7.24 (d, 2H, J=9.7); ^{13}C NMR (100 MHz) δ 25.5, 32.5, 54.5, 55.3, 63.6, 74.7, 113.8, 128.8, 131.3, 158.9, 208.2; HRMS calcd for $[C_{14}H_{20}O_3+Na]^+$ 259.1310, obsd. 259.1302.

   Compound **6**: R_f=0.6 (ethyl acetate/hexane, 1/4); ^{1}H NMR (300 MHz) δ 3.40 (s, 3H), 3.53 (dd, 1H, J=9.2, 3.4), 3.57 (t, 1H, J=9.5), 3.69 (t, 1H, J=10), 3.78 (s, 3H), 3.82 (dt, 1H, J=8.1, 4.5), 4.02 (t, 1H, J=9.2), 4.26 (dd, 1H, J=9.8, 4.5), 4.58 (d, 1H, J=3.6), 4.67–4.87 (ab, 2H, J=12.1), 4.74–4.85 (ab, 2H, J=10.8), 5.54 (s, 1H), 6.82 (d, 2H, J=8.5), 7.25–7.50 (m, 12 H); ^{13}C NMR (100 MHz) δ 55.1, 55.2, 62.2, 68.9, 73.6, 74.9, 78.2, 79.1, 82.0, 99.2, 101.1, 113.6, 125.9, 127.8, 128.0, 128.1, 128.4, 128.8, 129.6, 130.8, 137.4, 138.1, 159.1; HRMS calcd for $[C_{29}H_{32}O_7+H]^+$ 493.2226, obsd. 493.2246.

   Compound **7**: R_f=0.7 (ethyl acetate/hexane, 1/1); ^{1}H NMR (300 MHz) δ 2.02 (s, 3H), 2.07 (s, 6H), 3.37 (s, 3H), 3.60 (t, 1H, J=9.2), 3.80 (s, 3H), 3.88 (ddd, 1H, J=9.9, 4.1, 2.3), 4.23 (dd, 1H, J=12, 4.2), 4.31 (dd, 1H, J=12, 2.3), 4.44–4.56 (ab, 2H, J=10.8), 4.82–4.86 (m, 2H), 5.51–5.58 (m, 1H), 6.85–6.88 (m, 2H), 7.17–7.19 (m, 2H); ^{13}C NMR (100 MHz) δ 20.7, 20.8, 20.9, 55.2, 55.3, 62.6, 68.3, 71.2, 72.2, 74.1, 75.3, 96.8, 113.9, 129.3, 129.8, 159.5, 169.8, 170.4, 171.6; HRMS calcd for $[C_{21}H_{28}O_{10}+Na]^+$ 463.1580, obsd. 463.1579.

   Compound **8**: R_f=0.5 (ethyl acetate/hexane, 9/1); ^{1}H NMR (300 MHz) δ 1.21 (d, 3H, J=6.3), 3.76 (s, 3H), 4.12 (dq, 1H, J=6.3, 2.1), 4.17–4.41 (ab, 2H, J=11.5), 4.37–4.41 (dd, 1H, J=9.5, 2.2), 5.06–5.17 (ab, 2H, J=13), 5.12 (s, 2H), 5.37 (d, 1H, J=9.6), 6.78–6.82 (m, 2H), 7.05–7.08 (m, 2H), 7.23–7.36 (m, 10H); ^{13}C NMR (100 MHz) δ 16.3, 55.2, 58.8, 67.0, 67.2, 70.4, 73.8, 113.7, 127.9, 128.1, 128.3, 128.4, 128.49, 128.54, 129.2, 129.8, 135.3, 136.3, 156.8, 159.2, 170.7; HRMS calcd for $[C_{27}H_{29}NO_6+Na]^+$ 486.1893, obsd. 486.1893.

   Compound **9**: R_f=0.5 (ethyl acetate/hexane, 8/2); ^{1}H NMR (300 MHz) δ 1.19 (d, 3H, J=6.3), 2.06 (s, 3H), 3.67 (s, 3H), 3.80 (s, 3H), 4.10 (dq, 1H, J=6.3, 2.2), 4.28–4.51 (ab, 2H, J=11.4), 4.66 (dd, 2H, J=9.3 2.2), 6.16 (d, 1H, J=8.7), 6.85–6.89 (m, 2H), 7.16–7.19 (m, 2H); ^{13}C NMR (100 MHz) δ 16.3, 23.2, 52.3, 55.3, 56.6, 70.5, 73.8, 113.8, 129.4, 129.8, 159.3, 170.5, 171.2; HRMS calcd for $[C_{15}H_{21}NO_5+Na]^+$ 318.1317 obsd. 318.1312.

   Compound **10**: R_f=0.3 (ethyl acetate/hexane, 7/93); ^{1}H NMR (300 MHz) δ 0.09 (s, 6H), 0.90 (s, 9H), 3.58–3.63 (m, 1H), 3.75–3.84 (m, 2H), 3.80 (s, 3H), 3.86–3.92 (m, 1H), 4.43–4.54 (m, 2H), 4.56–4.74 (ab, 2H, J=11.1), 6.86 (d, 2H, J=8.6), 7.2 (d, 2H, J=8.3), 7.44–7.49 (m, 2H), 7.57–7.62 (m, 1H), 8.02–8.04 (m, 2H); ^{13}C NMR (100 MHz) δ −5.56, −5.53, 18.1, 25.8, 55.2, 62.9, 63.7, 63.8, 72.7, 75.2, 113.8, 128.4, 129.6, 129.7, 129.8, 133.6, 159.4, 166.2; HRMS calcd for $[C_{25}H_{35}O_5Si+Na]^+$ 508.2244, obsd. 508.2258.

   Compound **11**: R_f=0.5 (ethyl acetate/hexane, 15/85); ^{1}H NMR (300 MHz) δ 3.21–3.25 (m, 1H), 3.60 (dd, 1H, J=11.5, 5.2 Hz), 3.76–3.78 (m, 1H), 3.80 (s, 3H), 3.82 (dd, 1H, J=11.5, 3.1), 4.56 (d, 2H, J=2.6), 6.88 (d, 2H, J=8.6 Hz), 7.26–7.36 (m, 7H); ^{13}C NMR (100 MHz) δ 55.3, 55.9, 61.2, 69.6, 73.1, 113.8, 125.7, 128.1, 128.2, 129.4, 129.9, 136.9, 159.3; HRMS calcd for $[C_{17}H_{18}O_3+Na]^+$ 293.1154, obsd. 293.1163.
9. Compound **10** was prepared from the corresponding azidotriol via benzoylation of the dibutylstannylene ketal followed by silylation. Full experimental details will be published elsewhere.