# An Economic and Practical Synthesis of the 2-Tetrahydrofuranyl Ether Protective Group

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## Abstract

Primary, secondary, and tertiary alcohols as well as phenols and carbohydrates are efficiently transformed into the corresponding 2-tetrahydrofuranyl ethers by a combination of Mn(0) powder and $CCl_4$ in tetrahydrofuran.

## Keywords

Protecting group; Manganese; Radical reaction; Tetrahydrofuran

Despite its well-established reputation[1] as a versatile, orthogonal[2] protecting group, the 2-tetrahydrofuranyl (THF) ether is often disregarded in favor of its homologous relative, the tetrahydropyranyl (THP) ether. This is due, in large measure, to limitations in the extant procedures for its introduction, i.e., the required reagents not commercially available, corrosive, incompatible with sensitive functionality, and/or unstable.[2-11] To address these issues, we introduced a convenient protocol utilizing $CrCl_2$ and $CCl_4$ in tetrahydrofuran.[12] However, the high costs of $CrCl_2$, the need for a large excess of reagent, and chromium's toxicity spurred us to seek a more economic and environmentally benign alternative.

Initially, a panel of readily available, eco-friendly metals was evaluated for their ability to promoted the 2-tetrahydrofuranylation of *n*-octanol (**1**) under a standard set of reaction conditions (0.4 M in THF, 65°C, 15 h, 1.5 equiv of $CCl_4$). Fe(0) and Zn(0) furnished only modest yields of **2**[13] (73% and 63%, respectively). Mg(0), with the largest reduction potential of all the metals tested, gave rise to a disappointing 5% of the desired THF ether. The most consistent results were obtained with Mn(0) powder.[14] Just 1.5 equivalents of Mn(0) provided an excellent yield of **2** (Table 1, entry 1); fewer equivalents of Mn(0) led to portionately lower yields of **2**.

Likewise, secondary[12] (entry 2), allylic[15] (entry 3), and benzylic[12] (entry 4) THF ethers were easily obtained from alcohols **3**, **5**, and **7**, respectively. Less reactive hydroxyls such as phenol (**9**) and the highly hindered dimethylphenylcarbinol **11** were transformed without complication into their THF derivatives **10**[12] (entry 5) and **12**[12] (entry 6), respectively. Importantly, a variety of common funtionality proved compatible with the standard reaction conditions. For instance, methylenedioxy (entry 7), acetonide (entry 8), and silyl (entry 9) groups were all well tolerated and led accordingly to THF ethers **14**,[12] **16**,[15] and **18**.[15] The successful protection of labile

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1,1,1-trichloride **19**[12], acid sensitive epoxide **21**, and α,β-unsaturated steroidal ketone **23**, all in excellent yields, are especially notable.[15]

The mechanism of the tetrahydrofuranylation most like parallels that of the CrCl$_2$-mediated reaction,[12] i.e., single electron transfer from Mn(0)[16] to CCl$_4$ during the initiation phase generates the well-known trichloromethyl radical (Scheme 1). This radical subsequently abstracts a hydrogen atom from the tetrahydrofuran methylene adjacent to oxygen in the first step of the propagation phase forming chloroform and a heteroatom stabilized radical that is chlorinated by a second molecule of CCl$_4$. The newly evolved trichloromethyl radical can either propagate the reaction via hydrogen atom abstraction from another equivalent of tetrahydrofuran or is further reduced and in the process consumes the HCl produced during the etherification step.

**General Procedure**: CCl$_4$ (0.145 mL, 1.5mmol, 1.5 equiv) was added via syringe to a stirring suspension of alcohol (1 mmol, 1.0 equiv) and Mn(0) powder[14] (83 mg, 1.5 mmol, 1.5 equiv) in anhydrous THF (3 mL) under an argon atmosphere and then warmed to 65°C. A white precipitate of MnCl$_2$ accumulated during the course of the reaction. After the times indicated in Table 1, the reaction mixture was cooled to room temperature, diluted with ether (20 mL), filtered through a pad of silica gel, and the filter cake was washed with ether. In most cases, the residue after concentration *in vacuo* required no further purification, but if necessary, was passed over a SiO$_2$ column to give the corresponding THF ether in indicated yields (Table 1).

In summary, an operationally simple, inexpensive, and efficient method to make THF ethers has been developed. Its mild reaction conditions and general tolerance of most functional groups make it widely applicable in the synthesis of complex molecules.
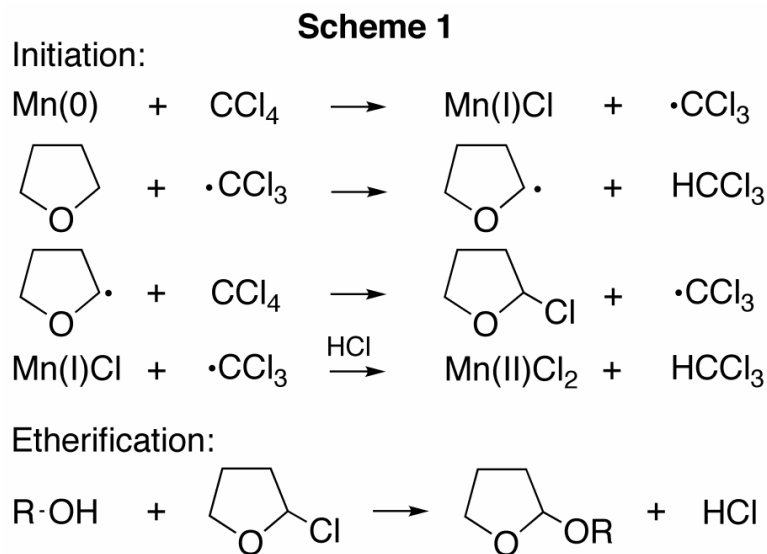
## Scheme 1



Initiation:

$$Mn(0) + CCl_4 \longrightarrow Mn(I)Cl + \cdot CCl_3$$

Etherification:

**1. .**
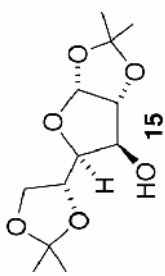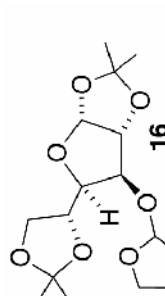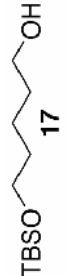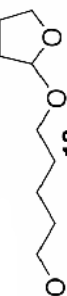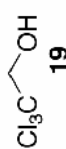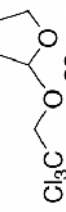
# References

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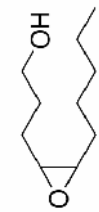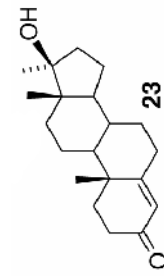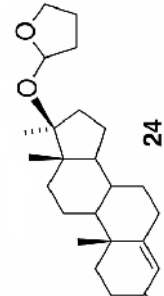6. Kruse CG, Poels EK, Jonkers FL, van der Gen A. J. Org. Chem 1978;43:3548.Acetal exchange

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14. Mn(0) powder was purchased from Aldrich Chem. (99%,-325 mesh). While it could be weighed and handled without special precautions, it was stored under an inert atmosphere to help retain its full reactivity

15. Spectral data for **6** (~1:1 diastereomeric mixture): $^1$H NMR (300 MHz, $CDCl_3$) δ 5.86-5.68 (m, 4H), 5.32 (dd, J = 4.2, 2.1 Hz, 1H), 5.29 (dd, J = 4.2, 1.8 Hz, 1H), 4.18-4.11 (m, 2H), 3.94-3.82 (m, 4H), 2.02-1.84 (m, 20H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 131.0, 130.6, 129.2, 127.9, 103.3, 102.0, 70.9, 69.7, 66.8 (2C), 32.9, 32.7, 30.5, 28.4, 25.3, 25.2, 23.7 (2C), 19.6, 19.4; HRMS (CI, $CH_4$) calcd for $C_{10}H_{17}O_2$ (M + 1) *m/e* 169.1228, found 169.1230. Compound **16** (~1:1 diastereomeric mixture): H NMR (400 MHz, $CDCl_3$) δ 5.87 (d, *J* = 4.0 Hz, 1H), 5.84 (d, *J* = 3.2 Hz, 1H), 5.31 (t, *J* = 2.8 Hz, 1H), 5.24 (br s, 1H), 4.60 (d, *J* = 3.2 Hz, 1H), 4.51 (d, *J* = 3.6 Hz, 1H), 4.31 (d, *J* = 3.6 Hz, 1H), 4.26-4.16 (m, 4H), 4.11-3.99 (m, 2H), 3.98-3.86 (m, 6H), 1.99-1.83 (m, 8H), 1.49 (s, 6H), 1.42 (s, 6H), 1.34 (s, 6H), 1.31 (s, 6H); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 111.8, 109.0, 108.8, 105.3, 101.2, 84.2, 82.4, 81.1, 80.2, 76.4, 72.8, 72.7, 67.4, 67.20, 67.16, 67.1, 32.4, 27.0, 26.9, 26.7, 26.3, 25.5, 23.4, 23.0. Compound **18** (~1:1 diastereomeric mixture): $^1$H NMR (400 MHz, $CDCl_3$) δ 5.09 (d, *J* = 3.2 Hz, 1H), 3.88-3.81 (m, 2H), 3.68-3.60 (m, 3H), 3.40-3.34 (m, 1H), 2.01-1.79 (m, 4H), 1.61-1.54 (m, 4H), 0.91 (s, 9H), 0.03 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 103.9, 67.1, 66.8, 63.1, 32.4, 29.7, 26.3, 26.1 (3C), 23.6, 18.5,-5.1 (2C); HRMS (CI, $CH_4$) calcd for $C_{15}H_{33}O3Si$ (M + 1) *m/e* 289.2199, found 289.2198. Compound **22**: 1:1 diastereo mixture; $^1$H NMR (300 MHz, $CDCl_3$): δ = 5.38 (dd, *J* = 4.2Hz, 1.8Hz, 1H), 5.13 (dd, *J* = 4.2Hz, 1.8Hz, 1H), 3.89-3.59 (m, 10H), 3.50-3.41 (m, 2H), 1.84-1.71 (m, 16H), 1.58-1.20 (m, 18H), 0.81-0.77 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): δ = 104.0, 103.0, 82.6, 80.0, 78.1, 77.8, 77.7, 68.5, 68.0, 67.0, 66.8, 32.6, 32.5, 32.2, 32.1, 32.0, 30.8, 28.5, 27.3, 26.2, 26.0, 25.6, 25.2, 23.7, 22.8, 22.7, 14.1 (2C); HRMS (CI, $CH_4$) calcd for $C_{14}H_{27}O_3$ (M + 1) *m/e* 243.1960, found 243.1960. Compound **24** (~1:1 diastereomeric mixture): $^1$H NMR (300 MHz, $CDCl_3$) δ 5.72 (s, 2H), 5.39-5.37 (m, 1H), 5.34-5.32 (m, 1H), 3.94-3.88 (m, 2H), 3.79-3.74 (m, 2H), 2.50-2.22 (m, 8H), 2.19-1.24 (m, 26H), 1.24 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 1.02-0.86 (m, 4H), 0.85 (s, 3H), 0.84 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 199.8 (2C), 171.1, 171.6, 124.0 (2C), 100.0, 99.6, 86.2, 85.8, 66.9, 66.7, 54.0 (2C), 49.9, 49.8 (2C), 46.6, 46.1, 38.8, 36.6, 36.5, 36.4, 36.1, 35.9 (2C), 34.1 (2C), 33.6, 33.5, 33.0 (2C), 32.6, 32.0 (2C), 31.7, 24.1 (2C), 23.7, 23.3, 23.2, 22.5, 20.9, 20.8, 17.6 (2C), 14.4, 14.2; HRMS (CI, $CH_4$) calcd for $C_{24}H_{37}O_3$ (M + 1) *m/e* 373.2743, found 373.2740

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**Table 1**
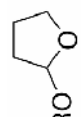
preparation of THF ethers.

$$R\text{-OH} \xrightarrow[\text{THF, 65°C}]{\text{Mn(0)/CCl}_4} RO$$

| Entry | Alcohol | THF Ether | Time(h) | yield(%) |
|-------|---------|-----------|---------|----------|
| 1 | $n\text{-C}_8\text{H}_{17}\text{-OH}$ **1** | $n\text{-C}_8\text{H}_{17}\text{-O}$ **2** | 15 | 96 |
| 2 | **3** | **4** | 15 | 99[a] |
| 3 | **5** | **6** | 7 | 85[a] |
| 4 | **7** | **8** | 4 | 93 |
| 5 | **9** | **10** | 6 | 91 |
| 6 | **11** | **12** | 6 | 88[a] |
| 7 | **13** | **14** | 14 | 90 |

| Entry | Alcohol | THF Ether | Time(h) | yield(%) |
|---|---|---|---|---|
| 8 | **15** | **16** | 6 | 99, [a][b] |
| 9 | **17** | **18** | 3 | 96 |
| 10 | **19** | **20** | 4 | 88[b] |
| 11 | **21** | **22** | 13 | 85[a] |
| 12 | **23** | **24** | 8 | 91, [a][b] |

[a] ~1:1 diastereomeric mixture by NMR analysis.

[b] 2 equiv each of Mn(0) and ccl4 were used.