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A Versatile Ruthenium Catalyst for the Tetrahydropyranylation of Alcohols and Phenols

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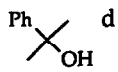
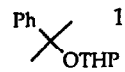
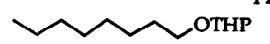
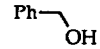
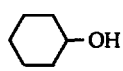
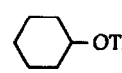
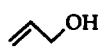
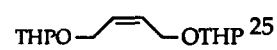
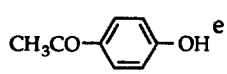
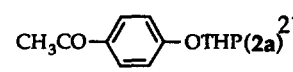
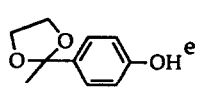
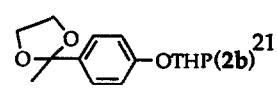
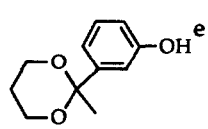
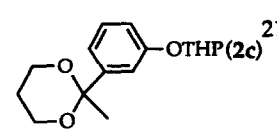
SUMMARY: The tetrahydropyranyl derivatives of alcohols and phenols are efficiently prepared in the presence of catalytic amounts of $[Ru(CH_3CN)_3(triphos)](OTf)_2$ (triphos = $CH_3C(CH_2PPh_2)_3$) under mild conditions, in good to excellent yields.

Tetrahydropyranylation is one of the most frequently used methods to protect alcohols and phenols, because of the stability of the resulting ethers to strongly basic media, Grignard reagents, oxidative alkylation and acylation reagents, reduction with hydrides, etc.[1] Thus, dihydropyran (DHP) is a reagent of choice for the protection of hydroxy groups in peptides, nucleotides, carbohydrates, and stereoids. These tetrahydropyranyl ethers have also been used as precursors for the synthesis of some key organic compounds.[2] Alcohols are converted to their tetrahydropyranyl derivatives using protic acids,[3-6] ion-exchange resins,[7] Lewis acids,[8] p-toluenesulfonates,[9,10] montmorillonite clay K-10[11] or charcoal,[12] as catalysts, as well as by other miscellaneous methods.[13] However, some of these procedures suffer from the need to use acidic conditions, and thus, cannot be used for acid-sensitive substrates, or when aqueous work-up should be avoided. Furthermore, the yields with sterically hindered alcohols are usually low. Thus, the development of more efficient catalysts for this reaction is still actively pursued by synthetic chemists.

Transition-metal complexes are playing an increasingly important role in organic synthesis:[14] Due to their unique reactivity, they are regarded as chemist's enzymes.[15] Recently, several transition metal cationic complexes have been shown to be versatile catalytst precursors for the acetalization of aldehydes and ketones.[16-18] We report here recent results showing that the ruthenium(II) complex $[Ru(CH_3CN)_3(triphos)](OTf)_2$,[19] where triphos is the terdentate ligand $H_3CC(CH_2PPh_2)_3$, is a mild and efficient catalyst precursor for the tetrahydropyranylation of alcohols and phenols, whereby the most suitable solvent is dichloromethane. Some of the results obtained are summarized in **Table 1**. The following general procedure was used: The catalyst precursor, $[Ru(CH_3CN)_3(triphos)](OTf)_2$ (28 mg, 1:2000) was added to a stirred solution of the alcohol or phenol (50 mmol) and DHP (55 mmol) in CH_2Cl_2 (25 mL) at rt. When the reaction was complete, as detected by GC,[20] neutral Al_2O_3(1.0 g) was added to remove the metal complexes. After filtration, the solvent was removed by rotary evaporation (for liquid products, Na_2CO_3(100 mg) was added at this stage to avoid their decomposition during the subsequent distillation), and the residue was submitted either to vacuum distillation, chromatography on silica gel, or recrystallization, to afford the corresponding tetrahydropyranyl derivative in pure form. The products were characterized by IR, MS, ^1H/ ^{13}C NMR spectra and by comparing their boiling or melting points with those reported in

Table 1. [Ru(CH$_3$CN)$_3$(triphos)](OTf)$_2$ Catalyzed Tetrahydropyranylation of Alcohols and Phenols

Entry	Alcohols (1)	Reaction Time(h)	Products (2)	Yield [a] (%)
1		4.5	 [3,b]	99.5 [c]
2		8	 [11]	91
3		8	 [24]	75
4	 [d]	6	 [13c]	83
5	Cholesterol [d]	7	CholesterylOTHP [4]	99.7
6		4.5	 [11]	97
7		1	 [11]	98.5
8	Ph-OH	2	Ph-OTHP [11]	79
9		6	 [6]	96
10		3.5	 [11]	77
11		1	 [7]	91
12		2	 [25]	81
13	 [e]	24	 [21]	60 [f]
14	 [e]	2	 [21]	80
15	 [e]	2	 [21]	81

a: Isolated yield unless otherwise stated; b: THP = tetrahydro-2H-pyranyl; c: Yield determined by GC using mesitylene as an internal standard; d: 1.5 equivalents of DHP were used; e: 4 equivalents of DHP were used, and the reaction was carried out in 2 mmol scale; f: This reaction is not clean, (**2a**) being the major product.

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the literature (see **Table 1**). The new products were also identified by elemental analysis.[21] However, the reaction of DHP with 1-butanol in absence of a solvent (21 h, yield: 42.5%), in benzene (6 h, 12%), THF (6 h, 9%), diethyl ether (28 h, 11%) at rt is slow, while in CH_3CN, no reaction occurs even after 28 h at rt.

As can be seen from the data in **Table 1**: The catalyst is highly active as only 0.05% is sufficient for all the reactions tested. Thus, (1) the catalyst is efficient not only for primary and secondary alcohols, but also for tertiary alcohols (Entries 3 and 4), which are converted with difficulty to their tetrahydropyranyl derivatives in satisfactory yields under most conditions;[10,22] (2) cholesterol, which requires several days with acid catalysts,[4,5,8] was also smoothly converted to its tetrahydropyranyl derivative (Entry 5); (3) compared with acidic catalysis, the present reaction gives better yields for phenols;[3] (4) this catalyst can tolerate several functional groups, such as carbon-carbon double and triple bonds (Entries 10, 11 and 12), and carbonyl groups (Entry 13); (5) although 1,3-dioxolanyl and 1,3-dioxanyl groups attached to aromatic rings were reported to be extremely sensitive to acid or moisture,[23] good yield were obtained even in these cases (Entries 14 and 15), the ketal groups remaing intact. However, 2-(N,N-diethylamino)etha nol, 2-(N-methylamino)ethanol, 2-aminoethanol, and (2R,3R)-(+)-phenylglycidol did not afford the corresponding products, probably due to the strong coordinating properties of the donor atoms present in these substrates.

In conclusion, the present method provides an excellent alternative method for the preparation of the tetrahydropyranyl derivatives from alcohols and phenols, with the added advantage that the reaction conditions are mild (rt), no aqueous work-up is needed and, last but not least, the reaction is efficient for tertiary alcohols, phenols, and some of acid-sensitive substrates. To the best of our knowledge, this is the first example of the use of a transition metal complex as catalyst for this transformation. Furthermore, preliminary experiments show that the rhodium(III) complex, $[Rh(CH_3CN)_3(triphos)](OTf)_3$,[16] is also an active catalyst for the tetrahydropyranylation reaction of alcohols, e.g., in the case of entry 4 in **Table 1**, the reaction afforded the product in 82% isolated yield within 1 h at rt. Finally, the catalytic activity towards the acetalization reaction of some optically active transition metal complexes[26] makes this reaction promising for the synthesis of chiral compounds. Further studies of this reaction are being carried out in this laboratory.

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20. GC condition: Instrument: GC 6000 Vega Series; Column: SE-54(25 m x 0.25 mm); Temperature: 80°C to (20°C/min.) 250°C(20 min.); H_2: 70 KPa; Air: 100 KPa; Argon: 90 KPa.
21. **Data of New Compounds**(^{1}H NMR: $CDCl_3$, 250 MHz; ^{13}C NMR: $CDCl_3$, 62.9 MHz):
(2a): mp. 89-90°C; ^{1}H NMR: 7.96(d, J = 7.6 Hz, 2H), 7.10(d, J = 7.6 Hz, 2H), 5.55(t, J = 3 Hz, 1H), 3.90(m, 1H), 3.68(m, 1H), 2.56(s, 3H), 2.10-1.50(m, 6H) ppm; ^{13}C NMR: 196.7, 161.0 131.0, 130.4, 115.9, 96.1, 62.0, 30.1, 26.3, 25.0, 18.5 ppm; MS: 220.1(M^+); Anal. : Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C: 70.93; H, 7.59.
(2b): mp. 82-84°C; ^{1}H NMR: 7.40(d, J = 7.6 Hz, 2H), 7.0(d, J = 7.6 Hz, 2H), 5.42(m, 1H), 4.02 (m, 2H), 3.90(m, 1H), 3.75(m, 2H), 3.60(m, 1H), 2.12-1.50(m, 9H) ppm; ^{13}C NMR: 156.7, 136.3, 126.5, 115.9, 108.8, 96.3, 64.4, 62.1, 30.4, 27.6, 25.2, 18.8 ppm; MS: 264.1(M^+); Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16, H, 7.63. Found: C, 68.29; H, 7.51.
(2c): oil; ^{1}H NMR: 7.30(t, J =7.9 Hz, 1H), 7.15-6.95(m, 3H), 5.45(t, J = 3.3 Hz, 1H), 4.00-3.70 (m, 5H), 3.60(m, 1H), 2.20-1.52(m, 7H), 1.47(s, 3H),1.20(bd, J = 13 Hz, 1H) ppm; ^{13}C NMR: 157.6, 142.9, 129.6, 120.0, 115.4, 115.3, 100.4, 96.4, 62.1, 61.2, 32.3, 30.4, 25.4, 25.2, 18.9 ppm; MS: 278.1(M^+); Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.98; H, 7.94.
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