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$CpRu^{II}PF_6$/Quinaldic Acid-Catalyzed Chemoselective Allyl Ether Cleavage. A Simple and Practical Method for Hydroxyl Deprotection

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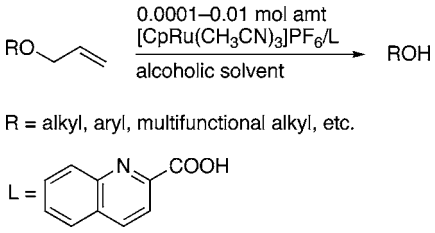
ABSTRACT



A cationic $CpRu^{II}$ complex in combination with quinaldic acid shows high reactivity and chemoselectivity for the catalytic deprotection of hydroxyl groups protected as allyl ethers. The catalyst operates in alcoholic solvents without the need for any additional nucleophiles, satisfying the practical requirements of operational simplicity, safety, and environmental friendliness. The wide applicability of this deprotection strategy to a variety of multifunctional molecules, including peptides and nucleosides, may provide new opportunities in protective group chemistry.

Protecting groups play a crucial, though often inconspicuous, role in multistep syntheses of organic molecules having a variety of functional groups.[1] Deprotection, performed in the later steps of a synthetic sequence, requires particularly mild reaction conditions with high reactivity and chemoselectivity. From both economic and environmental points of view, the operational simplicity as well as the efficiency of the reaction are issues that need to be addressed successfully. Among others, the allyl, or 2-propenyl group, is a simple and attractive choice for the protection of the hydroxyl functionality. The corresponding alkyl or aryl allyl ethers formed are stable in both acidic and basic conditions and have a high potential for removal by catalytic deallylation processes.[2] In fact, a strong base such as *tert*-C_4H_9OK or transition metal compounds containing Ru, Rh, Ir, or Pd do catalyze the isomerization of allyl ethers to the 1-propenyl ethers, which are then converted to the alcohols under acidic or oxidative conditions.[3] A Ni,[4] Pd,[5] or Os[6] catalyst can more directly remove the allyl group in the presence of excess acid, base, reducing agent, or oxidizing agent. However, all of them have disadvantages that lessen their practical attractiveness for general use such as a low level of chemoselectivity, reactivity, and/or atom economy. Herein, we report a

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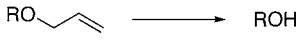
new CpRu-based catalytic system that efficiently brings about the single-step deprotection of allyl ethers without the need for any additional reagent other than an alcoholic solvent.



1 **2**

a: $C_6H_5CH_2CH_2$
b: 2-indanyl
c: $C_6H_5CH_2(CH_3)_2C$
d: C_6H_5
e: $CH_2{=}CHCH_2CH_2CH_2$
f: $CH{\equiv}CCH_2CH_2CH_2$

A 1:1 mixture of cyclopentadienyltris(acetonitrile)ruthenium(II) hexafluorophosphate ($[CpRu(CH_3CN)_3]PF_6$) (**3**) and triphenylphosphine ($P(C_6H_5)_3$) catalytically deprotects allyl esters in methanol via a π-allyl mechanism,[7] but the system is completely inert for the cleavage of allyl ethers.[8] With this result as the starting point, the ligand acceleration effect for $[CpRu(CH_3CN)_3]PF_6$ (**3**) was combinatorially examined for the deprotection of allyl 2-phenylethyl ether (**1a**) in methanol at 30 °C for 3 h with the standard fixed concentrations of [**1a**] = 100 mM, [ligand] = 1 mM, and [**3**] = 1 mM. Among the many ligands tested, including phosphines, sulfides, amines, and pyridines and their derivatives possessing amino, hydroxyl, alkoxyl, carboxyl, or alkoxycarbonyl functionalities, 2-pyridinecarboxylic acid showed a particularly high reactivity, affording 2-phenylethanol (**2a**) in >99% yield. When the hexahydropyridine derivative, 2-piperidinecarboxylic acid, was used as a ligand, the reactivity dramatically decreased. The use of pyridine, benzoic acid, pyridinium benzoate, sodium 2-pyridinecarboxylate, 3-pyridinecarboxylic acid, 4-pyridinecarboxylic acid, 8-quinolinecarboxylic acid, 2-(hydroxymethyl)pyridine, and 2-(aminomethyl)pyridine as ligands resulted in virtually no reactivity. These results clearly indicate the importance of a synergetic effect between the ligand sp^2-hybridized N atom and the adjacent COOH group of the pyridinecarboxylic acid producing a five-membered chelating ring with the $CpRu^{II}$ catalyst precursor.

As shown in Table 1, use of quinaldic acid (**4**), 2-quinolinecarboxylic acid, even further increases the reactivity, resulting in complete reaction within 30 min (entry 1).Deprotection is possible with a substrate/catalyst (S/C) ratio as high as 1000 (entry 3) at 30 °C; this ratio can be further increased 10 000 at 70 °C (entry 4). Under the conditions of entry 4, the turnover number (TON) is 4000 and the turnover frequency (TOF) is 700 h^{-1}. In addition to methanol, ethanol and *iso*-propyl alcohol can also be used as solvents, while *tert*-butyl alcohol gives a lower yield because of the low solubility of the catalyst system (entries 5−7) in that solvent. When water, DMF, THF, or dichloromethane is used as a cosolvent with methanol (entries 8, 9, 11, and 12) the yield remains high. However, a solvent mixture of 1:1 acetonitrile significantly lowers the reactivity (entry 10).

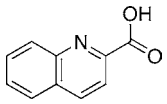


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Table 1. Catalytic Deprotection of Allyl Ethers **1** by Use of a $[CpRu(CH_3CN)_3]PF_6$ (**3**)−Quinaldic Acid (**4**) Combined System[a]

entry	substrate (mM)	S/C[b]	solvent	time, h	% yield[c]
1	**1a** (100)	100	CH_3OH	0.5	>99
2	**1a** (500)	500	CH_3OH	3	99
3	**1a** (1000)	1000	CH_3OH	3	98[d]
4[e,f]	**1a** (1000)	10 000	CH_3OH	17	41
5	**1a** (100)	100	C_2H_5OH	2	99
6	**1a** (100)	100	*i*-C_3H_7OH	3	98
7	**1a** (100)	100	*t*-C_4H_9OH	13	82[g]
8	**1a** (100)	100	1:1 CH_3OH-H_2O	6	99
9	**1a** (100)	100	1:1 CH_3OH−DMF	6	99
10	**1a** (100)	100	1:1 CH_3OH-CH_3CN	3	18
11	**1a** (100)	100	1:1 CH_3OH−THF	0.5	99
12	**1a** (100)	100	1:1 $CH_3OH-CH_2Cl_2$	0.5	99
13	**1b** (500)	500	CH_3OH	3	99
14	**1c** (500)	500	CH_3OH	3	>99
15	**1d** (100)	100	CH_3OH	3	>99
16	**1e** (500)	500	CH_3OH	3	97
17	**1f** (500)	500	CH_3OH	3	94

[a] Reactions were carried out in CH_3OH at 30 °C with [**3**] = [**4**] = 1 mM unless otherwise specified. [b] S/C = substrate/catalyst. [c] Determined by GC analysis. For details, see Supporting Information. [d] Under 200 mmHg Ar. [e] T = 70 °C. [f] [Catalyst] = 0.1 mM. [g] Catalyst was insoluble.

The generality of this new catalytic deprotection process is high. The allyl groups of the primary, secondary, and tertiary alkanols such as **1a**, **1b**, and **1c** are quantitatively removed (entries 2, 13, and 14). Both aliphatic allyl ethers and allyl phenyl ether (**1d**) are smoothly deprotected (entry 15). Allyl 4-pentenyl ether (**1e**) is converted to 4-pentenol without any olefin isomerization (entry16). An acetylene-containing alkyl allyl ether **1f** can also be used (entry 17).

The high chemoselectivity is further demonstrated by the reactions of a series of diprotected *trans*-1,2-cyclopentanediols **5a**−**d**, in which one hydroxyl functionality is protected as the allyl ether and the other as the benzoate, benzyl ether, methoxymethyl ether, or *tert*-butyldiphenylsilyl ether. Even more highly multifunctionalized molecules such as dipeptide **6a**, possessing *tert*-butyl ester and Fmoc protecting group, and nucleoside **7a** are deprotected with high chemoselectivity. In all these cases, only the allyl group is removed in >99% yield ([**5a**−**d**] = [**6a**] = [**7a**] = 100 mM, [catalyst] = 1 mM, 30 °C, 0.5−4 h).

The allyl cleavage is assumed to proceed via a π-allylruthenium(IV) species, which reacts with the alcoholic solvent to give the corresponding alcohols.[7] Although the reaction is reversible, excess solvent forces the equilibrium to the product side. Consistent with this view, nearly

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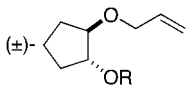
(8) The Ru−phosphine complex isomerizes allyl ethers to the corresponding alkenyl ethers, although the reactivity is low.[3a,b]



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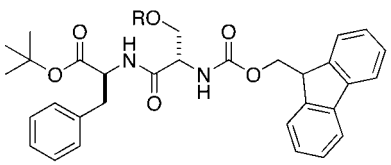
a: R = C_6H_5CO
b: R = $C_6H_5CH_2$
c: R = CH_3OCH_2
d: R = $(t\text{-}C_4H_9)(C_6H_5)_2Si$



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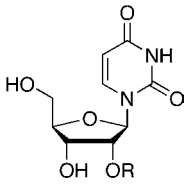

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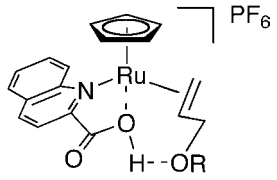
a: R = $CH_2{=}CHCH_2$
b: R = H

quantitative generation of allyl methyl-d_3 ether was observed in a ^{1}H NMR experiment in CD_3OD ([**1a**] = 100 mM, [**3**] = [**4**] = 1 mM, 30 °C). Neither (*Z*)- nor (*E*)-1-propenyl methyl-d_3 ether was produced. The high reactivity of this CpRu-based catalytic system may be ascribed to the donor−acceptor bifunctional ability[9] of the $CpRu^{II}PF_6$/**4** system, which can form a catalyst−substrate complex such as **8**. Here, the hydrogen bond between the COOH group in the catalyst and the ether O atom of the substrate increases the electrophilicity of the allyl group, while the strong coordination of the σ-donating sp^2-hydridized N atom of quinaldic acid to the Ru^{II} center enhances the metal nucleophilicity. Such a cooperative electronic effect accelerates the oxidative addition to Ru^{II}, even in conjunction with the less reactive allyl ether, to give a cationic $CpRu^{IV}(\pi\text{-}C_3H_5)$ carboxylate species.[10] Of importance here is the combination of the weak carboxylic acid with the $CpRu^{II}$ salt of the strong acid HPF_6. This prevents a shift of the acid−base equilibrium to the $CpRu^{II}$ carboxylate/HPF_6 side, where the bifunctional property is essentially nonexistent.



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The new $CpRuPF_6$-quinaldic acid catalyst described here functions as *a highly reactive and chemoselective allyl ether cleaver in alcoholic solvents under very mild and additive-free conditions*. The only coproduct is a volatile ether. The efficiency and simplicity of the reaction should further increase the practical utility of allyl ethers for hydroxyl protection in organic synthesis.

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Supporting Information Available: Preparation and characterization of all substrates and products and general procedures for deprotection of allyl ethers. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Exo/endo conformation of the π-allyl ligand is unknown. The related complex $Cp^*RuCl_2(C_6H_5CHCHCH_2)$ takes the endo structure in crystals.[11]

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