Synthetic Methods

Catalytic Dehydrative Allylation of Alcohols**

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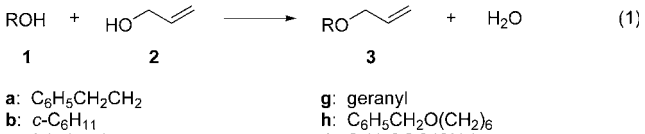
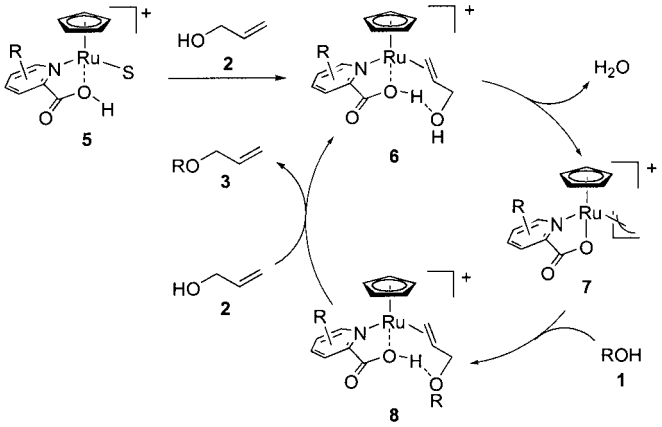
Allyl ethers are not only recognized as important starting materials for a wide range of organic reactions, including the 1,3 hydrogen shift, [3.3]-sigmatropic rearrangement, and polymerization,[1] but also constitute one of the most useful protecting groups for alcohols.[2] In contrast to the extensively studied allyl ether cleavage, the formation of allyl ethers is still under development and relies mainly on a Williamson-type ether synthesis that uses metal alkoxides and allyl halides or their equivalents.[3] Salt waste-free allylation of alcohols is desirable, and several catalytic methods utilizing allyl esters have been reported.[4] Ideally, the catalysis should directly convert a 1:1 mixture of alcohols **1** and 2-propen-1-ol (**2**) into allyl ethers **3** [Eq. (1)] in a solvent-free system without the need for any additional stoichiometric activators. As water should be the only co-product this dehydrative allylation is efficient, environmentally friendly, and simple to operate. However, the poor leaving ability of the hydroxy group as well as the low nucleophilicity of the alcoholic oxygen presents major difficulties.[5] Pioneering research in this area has been carried out by the Showa Denko company. As it is assumed that the reaction involves a π-allyl mechanism, various combinations of palladium or platinum compounds with mono- and bidentate phosphanes or phosphites were systematically examined.[6] Several similar approaches have been reported,[7] but to date none of them have been sufficiently developed to be useful from a generic synthetic perspective.[8] Herein, we report a highly efficient catalytic system for the direct dehydrative allylation of alcohols, which is effective even with only 1.0 equivalents of **2**.



a: $C_6H_5CH_2CH_2$
b: *c*-C_6H_{11}
c: 2-indanyl
d: $C_6H_5CH_2C(CH_3)_2$
e: $CH_2{=}CHCH_2CH_2CH_2CH_2$
f: C_6H_5
g: geranyl
h: $C_6H_5CH_2O(CH_2)_6$
i: $C_6H_5COO(CH_2)_6$
j: $CH_3OCH_2O(CH_2)_6$
k: $(t\text{-}C_4H_9)(C_6H_5)_2SiO(CH_2)_6$

We have developed a new catalytic system that consists of a cationic [CpRu] (Cp = cyclopentadienyl) complex and 2-pyridinecarboxylic acid derivatives for direct allyl ether cleavage in alcoholic solvents.[2] Taking into account the reversibility of the cleavage reaction, the catalytic cycle shown in Scheme 1 is assumed to operate during the allylation. In the formation of **6** the catalyst precursor **5** captures **2** through an Ru–olefin interaction together with a hydrogen bond interaction between the COOH moiety and the OH group. In this catalyst–substrate complex, the hydrogen bond interaction and the strong coordination of the σ-donating sp^2 nitrogen atom of the pyridine moiety and the monoanionic η^5-Cp ligand to the Ru atom synergistically enhance the electrophilicity of **2** and the nucleophilicity of the Ru center. This effect accelerates the oxidative addition of the Ru^{II} center onto **2** to generate a cationic $[CpRu^{IV}(C_3H_5)]^+$ carboxylate species **7**. Nucleophilic attack of **1** onto the π-allyl carbon, assisted by the good leaving ability of the carboxylate ligand, gives a catalyst–product complex **8**. Liberation of the product **3** revives the chain carrier **6**. All the elementary steps are essentially reversible, but the phase separation of water from the reaction system together with water's poor nucleophilicity may force the equilibrium to the allyl ether side.



Scheme 1. Supposed catalytic cycle for allyl ether formation.

Based on the above concept, the reaction conditions for the allylation of 2-phenylethan-1-ol (**1a**) with **2** were examined. Representative results of screening reactions are listed in Table 1. The allylation proceeds at 70 °C with 1.0 equivalents of **2** and 0.0005 equivalents of $[CpRu(CH_3CN)_3]PF_6$ (**9**)[9] and 2-quinolinecarboxylic acid (**10**) each to give **3a** in 90 % yield after 6 hours. Formation of the 1,3-hydrogen shifted isomer, 1-propenyl ether, was not observed. The substrate/catalyst (S/C) ratio of 10000 is acceptable, which approaches a turnover number (TON) of 6500 and a turnover frequency (TOF) of 5200 at 26 % conversion. At 50 °C, it requires 42 hours to attain 90 % yield. When heated to reflux, the shift of the equilibrium to the product side is retarded. The ligand acceleration efficiencies of 1-isoquinolinecarboxylic

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Supporting information for this article (preparation and characterization of all substrates and products, general procedures for allylations, ^1H NMR spectroscopic analysis, and X-ray crystallographic analysis) is available on the WWW under http://www.angewandte.org or from the author.

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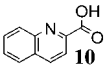
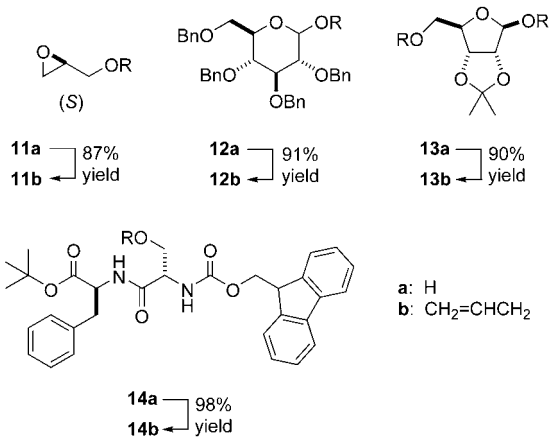
Table 1: Direct allylation of various monoalcohols with 2-propen-1-ol (**2**) catalyzed by [$CpRuPF_6$]–2-pyridinecarboxylic acid derivative combined systems [cf. Eq. (1)].[a]

Entry	Alcohol	Ligand	t [h][b]	Yield [%][b]
1	**1a**	 **10**	6 (3)	90 (93)
2	**1a**	**10**	0.5 (0.5)	66 (58[c])
3	**1a**		0.5 (0.5)	16 (11[c])
4	**1a**		0.5 (0.5)	20 (1.3[c])
5	**1a**		0.5 (0.5)	21 (5.7[c])
6	**1a**		0.5 (0.5)	2 (0[c])
7	**1b**	**10**	24 (24)	76 (90)
8	**1c**	**10**	12 (5)	84 (92)
9	**1d**	**10**	3 (24)	29 (30)
10	**1e**	**10**	12 (5)	90 [d] (97)
11	**1f**	**10**	12 (5)	24 (62)
12	**1g**	**10**	12 (3)	92 (91)
13	**1h**	**10**	10 (6)	90 (94)
14	**1i**	**10**	3 (6)	92 (94)
15	**1j**	**10**	12 (6)	93 (92)
16	**1k**	**10**	12 (6)	91 (97)

[a] Reactions were performed at 70 °C without solvent in a 2000:2000:1:1 ratio of **1**/**2**/[$CpRu(CH_3CN)_3$]PF_6(**9**)/ligand. The yields were determined by GC analysis, see the Supporting Information for details. [b] The values in parentheses are those obtained at reflux temperature in CH_2Cl_2 ([**1**] = [**2**] = 500 mM; [**9**] = [ligand] = 1 mM). [c] S/C = 100. [d] S/C = 1000.

acid, 3-isoquinolinecarboxylic acid, and 2-pyridinecarboxylic acid are 3–10 times lower than that of **10** in comparison to the initial rates (entries 2–5). Saturation of the pyridine ring retards catalytic activity (entry 6). Replacement of the COOH group of 2-pyridinecarboxylic acid with $COOCH_3$ or CH_2OH groups also abolishes the activity. Diphenylphosphanyl acetic acid gave an undesired 1,3-hydrogen shift-derived compound, 1,1-di(2-phenylethoxy)propane, in 27% yield after 24 hours. Secondary alcohols, such as **1b** and **1c**, are allylated in high yields (entries 7 and 8). Alcohol **1e**, which has a C=C bond at the 5-position, was converted into the corresponding allyl ether without any isomerization (entry 10). With geraniol (**1g**), only geranyl allyl ether (**3g**) was produced among many other possible diallyl ethers (entry 12). The low yields in the allylation of tertiary alcohol **1d** and aryl alcohol **1f** (entries 9 and 11) may be ascribed to the low nucleophilicity and the reversibility of the present catalysis. The chemoselectivity of the reaction was high; allylation was attained in > 90% yield without modifying the benzyl, benzoyl, methoxymethyl, and *tert*-butyldiphenylsilyl protecting groups (entries 13–16).

Furthermore, the present catalytic system is even more effective with a solvent and can be applied to the synthesis of multifunctional compounds, such as carbohydrates and peptides, where solvents are essential. For example, (*S*)-glycidol (**11a**) in 98% *ee* was allylated with 1.2 equivalents of **2** to give (*S*)-allyl glycidyl ether (**11b**) in 98% *ee* and in 87% yield (S/C = 100/1, CH_2Cl_2, reflux). No racemization was detectable by



high performance liquid chromatographic (HPLC) analysis. Optically active **11b** is widely used as a chiral unit not only for the synthesis of functionalized epoxy resins but also for a variety of natural products. However, there are problems associated with the preparation of (*S*)- or (*R*)-**11b**. The Williamson-type allylation often causes a Payne rearrangement, which decreases the optical purity.[10] Transformation from chiral glycerol derivatives involves several steps.[11] The hydroxy group at the anomeric C1 of **12a** was also smoothly allylated to give the allyloxy compound in 91% yield of isolated product, and 1,5-free furanose **13a** was diallylated in 90% yield of isolated product. *tert*-Butyl Fmoc-protected phenylalanyl serine **14a** was converted in a 98% yield to the corresponding allyl ether, leaving the Fmoc and *tert*-butyl ester intact (**12a**, **13a**, or **14a** = 100 mM, 2 equivalents of **2** for each OH group, CH_2Cl_2, reflux).

Consistent with the proposed catalytic cycle in Scheme 1, **9** was mixed with **10** in a 1:1 ratio in [D_6]acetone (each 10 mM) at 27 °C. A new set of signals was observed [δ = 8.01 (t, 1H, J = 7.57 Hz), 8.15 (t, 1H, J = 7.57 Hz), 8.32 (m, 2H), 8.84 (d, 1H, J = 8.26 Hz), 9.14 ppm (d, 1H, J = 8.26 Hz)] that could be assigned to **5** (S = CH_3CN, R = 5,6-$(CH)_4$).[12] The signals immediately disappeared when 1 equivalent of **2** was introduced at 27 °C to give another new set of signals characteristic of **7** [R = 5,6-$(CH)_4$] [π-allyl moiety: δ = 4.40 (dd, 1H (*syn*), J = 2.75, 5.85 Hz), 4.44 (dd, 1H (*syn*), J = 2.75, 6.20 Hz), 4.75 (d, 1H (*anti*), J = 9.64 Hz), 4.96 (d, 1H (*anti*)), 4.96–5.20 ppm (m, 1H (*center*)]. In solution, the complex is assumed to have an *endo* π-allyl structure with a narrowed dihedral angle φ defined by the coordination plane and the π-allyl plane.[13] This is supported by three observations: 1) the clear A_2B_2X allyl signal pattern, 2) the two H_{syn} protons resonating at a higher magnetic field than H_{anti} protons, and 3) the observation of 2–5% and approximately 8% enhancements of the two H_{anti} signals and the H_{syn} signal on irradiating CpH protons and C(8)H of the quinoline ring, respectively. Under the reaction conditions described herein no catalyst–substrate complex **6** was detected, which demonstrates the efficiency of

the bifunctional property of **6** to form **7**. The signals for **7** were unaffected by the introduction of 10 mole amounts each of **1a** and **2** at reflux while the allylation proceeded.[14] This indicates that the π-allyl species **7** is at the resting state in the catalysis. Complex **7** [R = 5,6-$(CH)_4$] was isolated as a single pale yellow crystal. The characteristic feature of the *endo* π-allyl conformation at a small value of φ is also seen in the X-ray crystallographic measurements (Figure 1). The

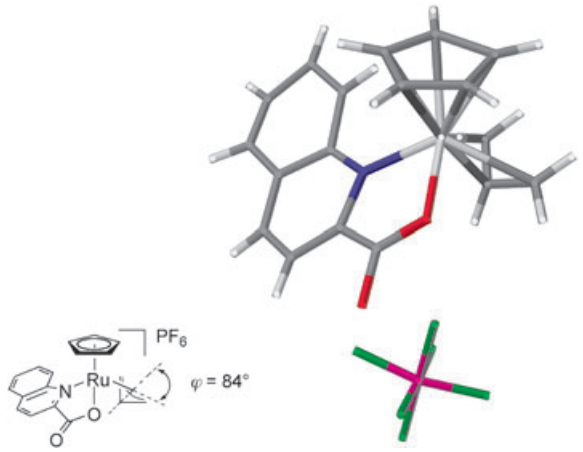


Figure 1. Molecular structure of [CpRu(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 [**7**; R = 5,6-$(CH)_4$] determined by X-ray crystallographic analysis.[15]

isolated Ru^{IV} complex acted as the allylation catalyst with higher reactivity than that of the corresponding 2-pyridinecarboxylic acid complex. The rate-determining reductive elimination of Ru^{IV} to a Ru^{II} center could be accelerated by a quinoline ring, which has a higher π-accepting ability than pyridine.

In conclusion, we have developed an efficient catalytic system for the dehydrative allylation of alcohols. The new methodology is superior to conventional synthetic routes[3–8] in many respects, and it increases the importance of allyl ethers not only as basic compounds but also as protecting groups in organic synthesis. Furthermore, a series of NMR spectroscopic and X-ray crystallographic studies on a key π-allyl intermediate has given insight into the probable reaction mechanism.

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[14] The ratio of **3a**, **2**, and diallyl ether after 30 minutes was approximately 40:20:20.

[15] Crystallographic analysis of **7** (R = 5,6-$(CH)_4$) pale yellow prism; $P\bar{1}$, $a = 7.94(6)$, $b = 8.3(1)$, $c = 14.3(1)$ Å, $\alpha = 106.2(5)°$, $\beta = 89.95(2)°$, $\gamma = 90.0(3)°$, $V = 906.7(19)$ Å^3, $Z = 2$, $R = 0.136$, $Rw = 0.163$. CCDC 251818 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

