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Highly reactive and chemoselective cleavage of allyl esters using an air- and moisture-stable [CpRu(IV)(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 catalyst

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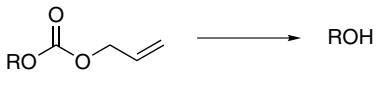
Abstract

A new catalytic process for allyl ester cleavage has been developed by using a robust cationic CpRu(IV) π-allyl complex of 2-quinolinecarboxylic acid that can be stored for over six months in air without any loss of catalytic activity. The deprotection of various alcohols and acids can be attained simply with high reactivity and chemoselectivity under mild conditions. Furthermore, with continuous removal of the low-boiling point coproduct, a turnover number of 1 000 000 can be achieved.

Keywords: Deallylation; Alcoholic solvent; Allyl ester; Ruthenium; π-Allyl complex

1. Introduction

Allyl esters provide well-established and highly reliable protecting groups for alcohols and acids [1]. Among others, allyloxycarbonyl (AOC) [2] -protected alcohols **1** are frequently used. Their deprotection to **2** is achievable in the presence of typically a 0.05 mol amount of $Pd(P(C_6H_5)_3)_4$ or related soluble Pd complexes in aprotic solvents [3]. A drawback of deprotection, however, is that a stoichiometric or excess amount of an appropriate nucleophile, including metal carboxylates, metal alkoxides, aliphatic or aromatic amines, ammonium formates, formic acid, metal hydrides, and malonates or dimedone, must be used [1,3,4]. This necessity decreases the atom economy and operational simplicity, two features that are advantageous in catalysis, and more seriously it sometimes leads to difficulties in isolating the deprotected product, in particular, polar compounds such as peptides [5], oligonucleotides [6], and oligosaccharides [7]. 1-Isopropylallyloxycarbonyl (IPAoc), invented by Tsuji, provides a solution to this problem [8]. Decarboxylation, followed by β-hydrogen elimination from the intermediary π-allyl palladium complex, gives the product along with only the coproducts of CO_2 and 4-methyl-1,3-pentadiene. Although the reflux temperature of dioxane is required, a one-pot synthesis of various di- or tripeptides can be attained in 69–80% isolated yields. Herein, we report another method for the efficient catalytic deprotection of alcohols and acids protected by AOC and allyl esters, respectively, without the need for additional nucleophiles other than an alcoholic solvent.



1 **2**

a: R = $C_6H_5CH_2CH_2$
b: R = *c*-C_6H_{11}
c: R = $C_6H_5CH_2C(CH_3)_2$
d: R = C_6H_5
e: R = $C_6H_5CH_2O(CH_2)_6$
f: R = $C_6H_5COO(CH_2)_6$
g: R = $CH_3OCH_2O(CH_2)_6$
h: R = (*t*-C_4H_9)(C_6H_5)$_2$SiO(CH_2)$_6$

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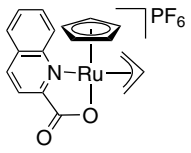
2. Results and discussion

We recently found that various allyl ethers could be cleaved by a combination of $[CpRu(CH_3CN)_3]PF_6$ and 2-quinolinecarboxylic acid in alcoholic solvents [9]. Our preliminary mechanistic study [9,10], as well as other reports on the CpRu complexes [11], have indicated that the π-allyl complex **3** is involved both as a key intermediate and in the resting state of the catalysis. This led us to try to isolate **3** and to remove an AOC group by catalysis using **3**. Thus, mixing $[CpRu(CH_3CN)_3]PF_6$, 2-quinolinecarboxylic acid, and 2-propen-1-ol in a 1:1:1 ratio in acetone at room temperature gave, in 99% isolated yield, complex **3** as a pale yellow solid, the stability of which in both air and moisture was high enough for easy handling (vide infra) [12]. Table 1 lists representative results of the deprotection of alcohols catalyzed by **3**. The standard substrate was set to an AOC-protected 2-phenylethan-1-ol (**1a**), and the conditions were optimized as a starting point of [**1a**] = 100 mM, [**3**] = 0.2 mM, CH_3OH, and 30 °C. Under these conditions, **1a** was converted to 2-phenylethan-1-ol (**2a**) in >99% yield within 0.5 h (entry 1). The substrate concentration could be increased to 500 mM (entry 2) but, with [**1a**] = 1 M, the yield tended to be lowered by 2–5% owing to the formation of allyl 2-phenylethyl ether, a decarboxylative allylation product (entry 3) [13]. The substrate/catalyst (S/C) ratio could be increased by a factor of 20 without a significant decrease in the yield (entry 4). The S/C could be further increased to 1 000 000 by the continuous addition of methanol and removal of the volatile coproduct, allyl methyl ether, at 70 °C (entry 5), with the corresponding turnover number (TON) and turnover frequency (TOF) approaching 1 000 000 and 10 000 h^{-1}, respectively. Ethanol and 2-propanol were the solvents of choice (entries 6 and 7). *tert*-Butyl alcohol could be used, but it had less reactivity (entry 8), possibly due to the low solubility of the catalyst. Methanol containing water, DMF, THF, or dichloromethane could be used (entries 9–12), not only to facilitate the dissolution of a wide range of substrates but also to provide a potential application to solid-phase synthesis. Acetonitrile was found to be a poor cosolvent that significantly lowered the reactivity (entry 13). The AOC groups of primary, secondary, and tertiary alkanols, such as **1a**, **1b**, and **1c** and phenol **1d**, were quantitatively removed by the catalyst (entries 14–16).



3

Table 1
Catalytic deallyloxycarbonylation of alcohols by the $[CpRu(\pi\text{-}C_3H_5)(2\text{-quinolinecarboxylato})]PF_6$ complex (**3**)[a]

Entry	Substrate	S/C[b]	Solvent	Time (h)	Yield (%)[c]
1	**1a**	500	CH_3OH	0.5	>99
2	**1a**[d]	500	CH_3OH	0.5	>99
3	**1a**[e]	1000	CH_3OH	0.5	98[f]
4[g]	**1a**[d]	10 000	CH_3OH	6	99
5[h]	**1a**[d]	1 000 000	CH_3OH	9 days	99
6	**1a**	500	C_2H_5OH	1	>99
7	**1a**	500	*i*-C_3H_7OH	1	>99
8	**1a**	500	*t*-C_4H_9OH	6	11
9	**1a**	500	1:1 CH_3OH–H_2O	2	>99
10	**1a**	500	1:1 CH_3OH–DMF	1	>99
11	**1a**	500	1:1 CH_3OH–THF	1	>99
12	**1a**	500	1:1 CH_3OH–CH_2Cl_2	1	>99
13	**1a**	500	1:1 CH_3OH–CH_3CN	3	99
14	**1b**[d]	500	CH_3OH	0.5	>99
15	**1c**[d]	500	CH_3OH	0.5	>99
16	**1d**[d]	500	CH_3OH	0.5	>99
17	**1e**[d]	500	CH_3OH	3	>99
18	**1f**[d]	500	CH_3OH	3	>99
19	**1g**[d]	500	CH_3OH	3	>99
20	**1h**[d]	500	CH_3OH	3	>99

[a] The reactions were carried out at 30 °C with [**1**] = 100 mM unless otherwise specified.
[b] S/C = substrate/catalyst.
[c] Determined by ^1H NMR analysis.
[d] [**1**] = 500 mM.
[e] [**1**] = 1 M.
[f] 2% of allyl 2-phenylethyl ether was formed.
[g] 50 °C.
[h] Reaction was operated under an argon stream at 70 °C.

The high chemoselectivity of this method was further demonstrated by using a series of mono-AOC-protected diols, **1e**–**h**, in which another hydroxy group was protected as the benzyl (Bn) ether, benzoate (Bz), methoxymethyl (MOM) ether, or *tert*-butyldiphenylsilyl (TBDPS) ether. Under the conditions [**1e**–**h**] = 500 mM, [**3**] = 1 mM, CH_3OH, and 30 °C, **1e**–**h** were completely converted after 3 h to give the corresponding monools in >99% yield without modification of the Bn, Bz, MOM, and TBDPS groups at all (entries 17–20).

Analogous to the removal of AOC, the present catalysis was found to be applicable to other allyl esters **4**. Thus, as shown in Table 2, the allyl esters of primary alkyl, secondary alkyl, tertiary alkyl, and aryl carboxylic acids in **4a**–**e**, as well as the phosphonic acid diallyl ester **4f**, were converted to the corresponding acids **5a**–**f** in quantitative yields (entries 1–6). In methanol, the primary alkanoates were found to undergo allyl/methyl ester exchange. The side reaction could be avoided by using 2-propanol instead of methanol. The reactivity was found to be about 10 times as high as that of $[CpRu(P(C_6H_5)_3)(CH_3CN)_2]PF_6$ [14], which is also known to catalyze allyl ester cleavage in methanol. Whereas the $CpRu\text{–}P(C_6H_5)_3$ complex isomerized allyl 5-hexenoate (**4e**) to the internal olefin, the complex **3** smoothly removed the allyl group without any isomerization, giving **5e** in >99% yield. The chemoselective cleavage of allyl esters in multifunctional molecules such as **6a** and **7a** was also found to be possible. Each of the *tert*-butyl, Fmoc, and allyl groups in a protected α-amino carboxylic acid or dipeptide was

Table 2
Catalytic cleavage of allyl esters by the [CpRu(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 complex (**3**)[a]

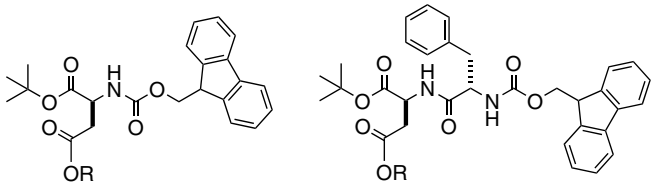
Entry	Substrate **4**	Solvent	Time (h)	Yield (%)[b]
1	**a**	*i*-C_3H_7OH	20	99
2	**b**	CH_3OH	9	>99
3	**c**	CH_3OH	18	>99
4	**d**	CH_3OH	9	>99
5	**e**	*i*-C_3H_7OH	14	>99
6[c]	**f**	CH_3OH	16	>99

[a] Conditions: [**4**] = 100 mM, [[CpRu(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 (**3**)] = 0.2 mM, temperature = 30 °C.
[b] Determined by ^1H NMR analysis.
[c] [**4**] = 500 mM, [**3**] = 1 mM.

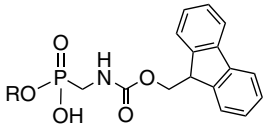
selectively cleaved, without any interference from each other, by using CF_3COOH, piperidine, and **3**, respectively. The compounds **6b** and **7b**, which were deprotected for only the allyl group, were isolated in >99% yield (**6a**: S/C = 1000, 30 °C, 1 h, CH_3OH. **7a**: S/C = 1000, 30 °C, 1 h, 1:1 CH_3OH–CH_2Cl_2). Finally, the method could be applied to the selective and quantitative conversion of the allyl- and *N*-Fmoc-protected α-amino phosphonic acid **8a** to **8b** (S/C = 1000, 30 °C, 18 h, CH_3OH).

4 **5**

a: A = C, *n* = 1, R = $C_6H_5CH_2CH_2$
b: A = C, *n* = 1, R = *c*-C_6H_{11}
c: A = C, *n* = 1, R = *t*-C_4H_9
d: A = C, *n* = 1, R = C_6H_5
e: A = C, *n* = 1, R = CH_2=$CH(CH_2)_3$
f: A = P, *n* = 2, R = C_6H_5



6 **7**



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a: R = CH_2CH=CH_2
b: R = H

In summary, we have found that a [CpRu(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 complex (**3**) functions as a highly reactive, chemoselective, and robust catalyst for removing the AOC group from various alcohols. Allyl carboxylic esters, as well as allyl phosphonic esters, can be also similarly removed. The system operates in environmentally benign alcoholic solvents under very mild reaction conditions, and its substrates require no additional nucleophiles to give the corresponding alcohols and acids. The nature of the protecting group often plays a critical role in the completion of synthesis. In particular, deprotection, which tends to be performed in the later stage of synthesis, requires conditions under which the targeted protective group is removed selectively and quickly. The present system, which satisfies such requirements, should open a new door to the liquid- or solid-phase synthesis of a wide range of natural and unnatural peptides [15], in which allyl esters are widely used.

3. Experimental

A mixture of allyl 2-phenylethyl carbonate (**1a**) (10.8 g, 52.2 mmol) and methanol (95 mL), which was placed in a 150-mL Schlenk tube containing a Teflon-coated magnetic stirring bar under argon atmosphere, was degassed by three freeze–thaw cycles. To this solution, [CpRu(π-C_3H_5)-(2-quinolinecarboxylato)]PF_6 (55.0 mg, 105 μmol) was added. The inlet was sealed by a glass stopper coated in silicon grease. The yellow solution was stirred for 0.5 h at 30 °C. The reaction mixture was concentrated under reduced pressure (100 mmHg) to give a crude product in which the yield and purity were determined to be >99% by ^1H NMR analysis ((600 MHz, $CDCl_3$) **1a**: δ 4.35 (t, 2H, J = 6.91 Hz, CH_2CH_2O), **2a**: δ 3.87 (q, 2H, J = 6.19 Hz, CH_2CH_2OH)). This product was distilled (55 °C/0.01 mmHg) to give **2a** (6.28 g) in 99% isolated yield.

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