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$(P(C_6H_5)_3)CpRu^+$-Catalyzed Deprotection of Allyl Carboxylic Esters

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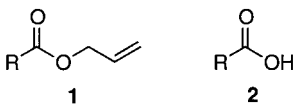
Abstract: A new and efficient catalytic method for deprotection of allyl carboxylic esters using a transition metal complex is reported. The reaction proceeds with a high substrate/catalyst ratio and without use of additional nucleophiles, giving the deprotected carboxylic acid in a quantitative yield. A variety of substrates, including the multifunctional amino acids and peptides, are also usable. The new method is more efficient, safe, and operationally simple in comparison to the conventional palladium-catalyzed method.

Considered selection of a protective group is crucial for success or failure in the synthesis of organic compounds, especially multifunctional molecules.[1] The protective group must be easily and selectively introduced and removed, while it must also be stable to the projected reactions. Among the many useful protective groups so far developed for this purpose, the allyloxycarbonyl function has attracted much attention[2] since Tsuji−Trost Pd chemistry was first reported in 1980.[3] The allyl groups for protecting carboxylic acid are now generally used for the liquid- or solid-phase synthesis of a wide range of natural and unnatural synthetic products.[4] The protection can be removed in an appropriate aprotic solvent containing, typically, a 0.05 mol amount of $Pd(P(C_6H_5)_3)_4$[5] or other soluble Pd complexes and a stoichiometric amount of nucleophile such as potasium carboxylate, alkoxide, morpholine, pyrrolidine, formate, tributyltin hydride, borohydride, and silane. The use of excess nucleophile, however, decreases the atom efficiency and sometimes causes problems during purification of the products. In this report, we describe a new and efficient method for the deprotection of allyl carboxylic esters.

The 8-, 9-, and 10-group transition metal complexes known to form π-allyl intermediates[6] have been combinatorially screened in the deprotection of allyl benzoate (**1a**) under the standard conditions of CH_3OH as the solvent, [**1a**] = 100 mM, [catalyst] = 1 mM, and 25 °C. The chemical yield of benzoic acid (**2a**) was determined by ^1H NMR analysis of the signal intensities of allyl and phenyl moieties (**1a**, δ 6.01−6.08 (m, 1H, CCH=C); **2a**, δ 8.13 (d, 2H, J = 7.33 Hz, aromatic)), after evaporation of all volatiles.



1 **2**

a: R = C_6H_5
b: R = (*E*)-C_6H_5CH=CH
c: R = C_6H_5C≡C
d: R = $C_6H_5CH_2CH_2$
e: R = *c*-C_6H_{11}
f: R = *tert*-C_4H_9
g: R = CH_2=$CHCH_2CH_2$
h: R = CH_2=$CHCH_2CH_2CH_2$
i: R = $C_6H_5CH_2OCH_2CH_2CH_2$
j: R = $(CH_3)_2NCH_2CH_2CH_2$
k: R = $ClCH_2CH_2CH_2$

As shown in Table 1, one cationic complex [$CpRu(P(C_6H_5)_3)(CH_3CN)_2$]$PF_6$ (**3**),[7] among others, was found to catalyze the deprotection of **1a** to give **2a** quantitatively. After 6 h under standard conditions, benzoic acid (**2a**) was isolated in 98% yield. The substrate concentration can be increased to 1 M without any problems. Use of a 0.001 mol amount of **3** completes the reaction within 24 h at 25 °C. With the reaction temperature increased to

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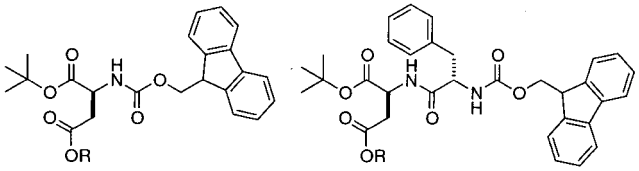
TABLE 1. Screening Results in the Catalytic Removal of the Allyl Group of Allyl Carboxylic Esters (1) with a Cationic Complex [CpRu(P(C$_6$H$_5$)$_3$)(CH$_3$CN)$_2$]PF$_6$ (3)[a]

entry	substrate	concn, mM: 1	concn, mM: 3	solvent	time, h	% convn
1	**1a**	100	1	CH_3OH	6	98[b]
2	**1a**	1000	1	CH_3OH	24	>99
3[c]	**1a**	1000	0.1	CH_3OH	12	98
4	**1a**	100	1	C_2H_5OH	6	>99
5	**1a**	100	1	*i*-C_3H_7OH	6	96
6	**1a**	100	1	*t*-C_4H_9OH	6	99
7	**1a**	100	1	1:1 $CH_3OH-CH_2Cl_2$	6	>99
8	**1a**	100	1	1:1 CH_3OH-H_2O	6	>99
9	**1a**	100	1	1:1 CH_3OH−THF	6	>99
10	**1a**	100	1	1:1 CH_3OH−DMF	6	71
11	**1a**	100	1	1:1 CH_3OH-CH_3CN	6	4
12	**1b**	100	1	CH_3OH	6	99[b]
13	**1c**	100	1	CH_3OH	17	0
14	**1d**	100	1	CH_3OH	17	93[b]
15	**1e**	100	1	CH_3OH	17	97[b]
16	**1f**	100	1	CD_3OD	10	97[d]
17	**1g**	100	1	CD_3OD	48	20[d]
18	**1h**	100	1	CH_3OH	14	93[b,e]
19	**1i**	100	1	CH_3OH	14	97[b]
20	**1j**	100	1	CD_3OD	100	96[d]
21	**1k**	100	1	CH_3OH	12	97[b]

[a] Reactions were carried out at 25 °C under an argon atmosphere unless otherwise specified. [b] Isolated yield. [c] Temperature = 50 °C. [d] Reaction was carried out in CD_3OD containing mesitylene (100 mM) as an internal standard. [e] Product was obtained as a 1:9 mixture of 5-hexenoic acid and 4-hexenoic acid.

50 °C, the substrate to catalyst ratio (S/C) can be increased to 10 000, with which the reaction runs to completion within 12 h. With an S/C value of 100 000, 50% of **1a** was converted to **2a** at 70 °C in 24 h, the turnover number and the turnover frequency being calculated to be 50 000 and 2000/h, respectively. Methanol, ethanol, *iso*-propyl alcohol, and *tert*-butyl alcohol are the solvents of choice. Dichloromethane, water, or THF can be used as a cosolvent in methanol without significant decrease in the reactivity. Methanol containing 50% DMF is also usable, although the reactivity is reduced by 71%. The reactivity in 1:1 methanol−acetonitrile was very low. A mixed system of [CpRu(CH$_3$CN)$_3$]PF$_6$ and P(C$_6$H$_5$)$_3$ also removes the allyl group, but the catalytic activity is ca. 10 times lower than that of **3** itself. The reactivity is halved by the use of a 2 mol amount of P(C$_6$H$_5$)$_3$ with [CpRu(CH$_3$CN)$_3$]PF$_6$, and increasing the mol amount of P(C$_6$H$_5$)$_3$ to 3 mol completely inhibits the catalysis. Tricyclohexylphosphine behaves similarly, while electron-deficient phosphines such as P(C$_6$F$_5$)$_3$ and P(OCH$_3$)$_3$ somewhat reduce the reactivity. CpRuCl(P(C$_6$H$_5$)$_3$)$_2$,[8] [Cp*RuCl$_2$]$_n$,[9] and [Ir(cod)Cl]$_2$[10] also showed catalytic activity, the yields of **2a** being 99, 48, and 87%, respectively (S/C = 100, 70 °C, 12 h). Other Ru complexes, including [Ru(*p*-cymene)Cl$_2$]$_2$, [Ru(cod)Cl$_2$]$_n$, RuCl$_2$(P(C$_6$H$_5$)$_3$)$_3$, RuHCl(P(C$_6$H$_5$)$_3$)$_3$, and RuH$_2$(P(C$_6$H$_5$)$_3$)$_4$, were not effective under the standard conditions.

The allyl ester of alkenyl carboxylic acid **1b** can be converted to **2b** with a reactivity similar to that of **1a**. Allyl alkynyl carboxylate **1c** was not deprotected under the standard conditions. The allyl groups of the primary, secondary, and tertiary alkyl carboxylic esters, **1d**−**f**, respectively, were also quantitatively removed, but the rates were reduced by a factor of 2−3. The reactivity of allyl 4-pentenonate (**1g**) was very low, but no isomerization to the internal olefin occurred. Allyl 5-hexenoate (**1h**) was converted to carboxylic acid with ca. 90% isomerization of the terminal olefin to the internal olefin. Other allyl esters possessing ether, tertiary amine, and halogen (**1i**−**k**, respectively) were also converted to the corresponding carboxylic acids in high yields, but the rate of **1j** was reduced by ca. 16. The present method was applied to multifunctional molecules. Each of the *tert*-butyl, Fmoc,[11] and allyl groups in a protected aspartic acid **4** is selectively cleaved, without any interference from each other, by use of CF$_3$COOH,[12] piperidine,[13] and [CpRu(P(C$_6$H$_5$)$_3$)(CH$_3$CN)$_2$]PF$_6$ (**3**), respectively. Under the above standard conditions (CH_3OH, S/C = 100, 25 °C, 17 h), the only allyl-deprotected **5** was isolated in >99% yield. Increasing the temperature to 90 °C in ethanol afforded **5** quantitatively after 2 h even with the S/C of 1000. A protected dipeptide **6**, aspargyl-phenylalanine derivative, could also act as a substrate. In a 1:1 mixture of ethanol and dichloromethane used to increase the solubility of **6**, the allyl group was quantitatively removed to give the corresponding acid **7** (S/C = 100, 25 °C, 17 h or S/C = 1000, 90 °C, 2 h).



4: R = $CH_2CH{=}CH_2$
5: R = H

6: R = $CH_2CH{=}CH_2$
7: R = H

The allyl cleavage in an allyl carboxylic ester is assumed to occur via a π-allylruthenium(IV) species,[14] which reacts with the alcoholic solvent to give the acid and allyl alkyl ether. Tracing the reaction of allyl benzoate (**1a**, 35 mM) with **3** (3.5 mM) in CD_3OD at 25 °C, by ^{1}H NMR, we observe complete consumption of **1a** after 18 h to yield **2a** together with a 73:27 mixture of $CD_3OCH_2CH{=}CH_2$ (δ 3.91 (ddd, 2H, J = 1.37, 1.83, 5.80 Hz, $OCH_2C{=}C$), 5.16 (ddt, 1H, J = 1.37, 1.83, 10.5 Hz, $C{=}CH_2$), 5.25 (ddt, 1H, J = 1.37, 1.83, 17.3 Hz, $C{=}CH_2$), 5.84−5.93 (m, 1H, $CCH{=}C$)) and (*E*)-$CD_3OCH{=}CHCH_3$ (δ 1.50−1.53 (m, 3H, CH_3), 4.69−4.74 (m, 1H, $C{=}CHC$), 6.26 (dq, 1H, J = 1.37, 12.4 Hz, $OCH{=}C$)). After 148 h, allyl methyl-d_3 ether was converted to the (*E*)-propenyl ether. Neither the methyl ester nor the propanal dimethyl ketal is formed. This excludes a mechanism via the 1,3-hydrogen shift of allyl esters to 1-propenyl esters.

In conclusion, a new efficient catalytic method for the deprotection of allyl carboxylic esters using a P(C$_6$H$_5$)$_3$-

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and Cp-coordinated cationic Ru complex is reported. The reaction proceeds with high selectivity to give the deprotected carboxylic acid in quantitative yield. Use of only millimol amounts of catalyst is sufficient even for multifunctional molecules such as amino acids and peptides. The reaction is clean and operationally simple. Since ethers are the only side products, the complete evaporation of volatiles from the reaction mixture yields virtually pure products. Related studies on solid-phase synthesis of peptides and nucleotides and on the mechanism involved are being carried out. These results will be reported in due course.

Experimental Section

General Procedure for Deprotection. Compound **1a** (1.05 g, 6.5 mmol) and CH_3OH (65 mL) were placed into a dry argon-filled 20 mL Schlenk tube, and the vessel was degassed by three freeze−thaw cycles. The solution was transferred via a stainless cannula to another 20 mL Schlenk tube containing [CpRu-$(P(C_6H_5)_3)(CH_3CN)_2]PF_6$ (**3**, 43 mg, 65 μmol) under argon pressure. The pale yellow mixture was stirred at 25 °C for 6 h. The reaction mixture was concentrated under reduced pressure to give a crude product. This was chromatographed on silica gel (AP350, 50 g; eluent, 1:1 hexanes−ethyl acetate) to give benzoic acid (**2a**, 780 mg, 6.4 mmol, 98% yield) as a white solid. ^{1}H and ^{13}C NMR spectra were consistent with the commercially available authentic sample.

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Supporting Information Available: Generality of the deprotection and characterization of all substrates and products obtained by the present method. This material is available free of charge via the Internet at http://pubs.acs.org.

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