JOC*Note*

Catalytic Removal of *N*-Allyloxycarbonyl Groups Using the [CpRu(IV)(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 Complex. A New Efficient Deprotecting Method in Peptide Synthesis

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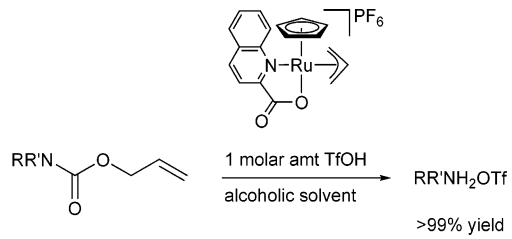
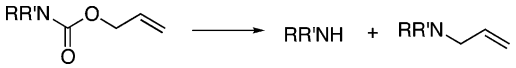


R = primary, secondary, and tertiary alkyl, R' = H or
RR'N = cyclic secondary amine

A variety of amines including even sterically less demanding and highly nucleophilic secondary amines have been efficiently deprotected without decarboxylative N-allylation from the corresponding *N*-allyloxycarbonyl (*N*-AOC) compounds by using a catalytic amount of [CpRu(IV)(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 in the presence of 1 molar amount of trifluoromethanesulfonic acid, the general utility of which has been demonstrated by the efficient synthesis of a collagen protein unit tripeptide, Pro-Pro-Gly.

Among the many sophisticated protecting groups for primary and secondary amines, carbamates (e.g., *N*-AOC, -Z, -BOC, and -Fmoc) are widely used in organic synthesis, particularly for the synthesis of natural and unnatural peptides and nucleotides.[1] The popularity of these protecting groups arises from their efficient coupling, using the corresponding chloride or anhydride derivatives, and their neutralization or suppression of basicity or nucleophilicity of the reactive amino functionality. Thus, the structurally simple *N*-AOC derivatives can satisfy a key requisite for multistep synthesis by conferring high stability under a wide range of different conditions (e.g., pH, temperature) for both nucleophilic or electrophilic molecules.[2] Furthermore, the development of Tsuji−Trost chemistry[3] has facilitated the straightforward removal of the protecting group, increasing the utility of the AOC reagent.[4] One drawback associated with the AOC derivatives is the competitive decarboxylative N-allylation, caused by the high nucleophilicity of the deprotected free amine toward a Pd-π-allyl complex.[5] The use of metal hydrides[6] in combination with the Pd catalysis has been reported to lessen the degree of the N-allylation by producing the metal carbamate and propene. An excess amount of nucleophilic amines[7] and other nucleophiles[8] has also been reported to facilitate the deprotection. The presence of an excessive amount of these additives often leads to difficulties during the isolation of the deprotected product. The problem becomes particularly serious during the synthesis of biologically relevant polar oligomers, such as peptides and nucleotides.



We recently reported a new catalyst, [CpRu(IV)(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 (**3**), for the efficient chemoselective cleavage and formation of allyl ethers.[9] First, we have applied the catalytic system to the removal of the AOC group from an AOC-protected 2-phenylethan-1-ol (**1a** to **2a**). The reaction completed within 30 min in methanol at 30 °C with a substrate/catalyst (S/C) ratio of 500, and a turnover number (TON) of 10^6 was achieved by continuous removal of the low-boiling-point coproduct, allyl methyl ether, from the reaction mixture ([**1a**] = 500 mM, [**3**] = 0.5 μM, 9 days, 70 °C). As shown in Scheme 1, the π-allyl complex first reacts with methanol solvent to form a cationic Ru(II) species **4** through reductive elimination of allyl methyl ether. The nucleophilicity of the Ru atom of the complex **4** is enhanced by the simultaneous coordination of monoanionic η^5Cp ligand and the highly donative sp^2N atom of the quinoline moiety, while the H atom of COOH acts as an acceptor of the O atom of AOC-protected alcohol **1a**.[10] The donor−acceptor functionality[11] dramatically accelerates the

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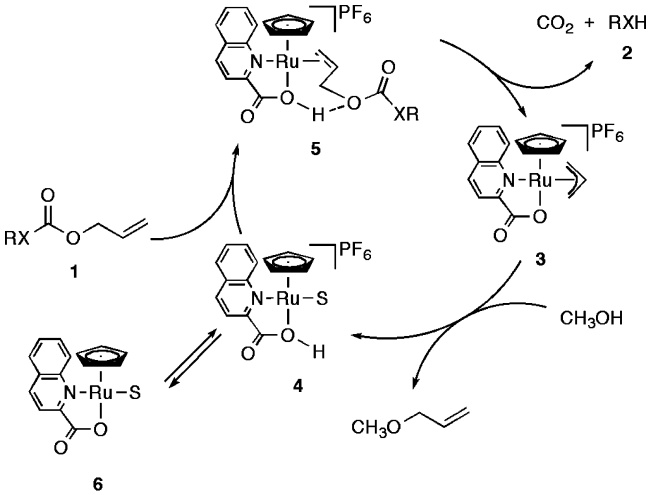
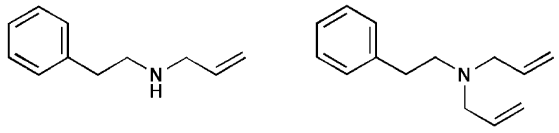
SCHEME 1



a: X = O, R = $C_6H_5CH_2CH_2$
b: X = NH, R = $C_6H_5CH_2CH_2$
c: X = NH, R = C_6H_{11}
d: X = NH, R = $C_6H_5CH_2(CH_3)_2C$
e: X = NH, R = C_6H_5
f: X–R = $N(CH_2CH_2)_2O$
g: X–R = $NCH_2CH_2CH_2CHCOO(t\text{-}C_4H_9)$



7 **8**

oxidative addition of **1a** onto the Ru(II) of **4**, probably via a catalyst-substrate complex **5**, regenerating the Ru(IV)-π-allyl complex **3** with the liberation of the deprotected alcohol **2a**. However, when X = O is replaced by X = N, the reactivity of *N*-AOC phenylethylamine (**1b**) is reduced by 1 order of magnitude, and the desired deprotected amine **2b** is produced in only 23% yield under standard conditions: *N*-allyl phenylethylamine (**7**) and *N*,*N*-diallyl phenylethylamine (**8**) are produced in 70% and 7% yield, respectively (vide infra). The low reactivity may be ascribed to the formation of the neutral Ru(II) complex **6**.[12] The deprotected amine acts as a base to deprotonate from the catalytic species **4**. We reasoned that suppression of amine basicity by the addition of an acid will not only maintain the concentration of chain carrier but also inhibit the N-allylation problem, thereby facilitating the efficient *N*-AOC deprotection of amines.

On the above assumption, the affect of acid was examined in the reaction of **1b** to **2b** under standard conditions as follows: [**1b**] = 100 mM, [**3**] = 1 mM, CH_3OH, and 30 °C. Addition of 1 molar amount of CF_3SO_3H converted **1b** to **2b** in >99% yield within 1 h (entry 1 in Table 1), and virtually no N-allylation products **7** and **8** were observed. One molar amount of CF_3SO_3H is essential, because halving the quantity of acid gave **7** and **8** in 38% and 5% yield, respectively. A 2 molar amount of CF_3SO_3H reduces the reactivity, although no allylation occurs under these conditions. Nafion, a solid-supported sulfonic acid, gave results (entry 4) very similar to those of CF_3SO_3H. It is also possible to use CH_3SO_3H (entry 5) in place of CF_3SO_3H. Using aqueous 12 M HCl, *N*,*N*-diallyl compound **8** was formed in 8% yield (entry 6). The degree of N-allylation was further increased with the less acidic CH_3COOH (entry 7). The total amount of **7** and **8** was reduced to 5% by use of a 10 molar amount of CH_3COOH (entry 8). The higher yield of **2** with the lower pK_a indicates the validity of the proposed mechanism outlined in Scheme 1. Methanol, ethanol, and 2-propanol were the best solvents tested in this study (entries 9 and 10). *tert*-Butyl alcohol as solvent reduced the reactivity (entry 11), possibly because of the low solubility of the catalyst. Methanol containing water, DMF, THF, dichloromethane, or acetonitrile was also tested (entries 12−16). These solvent systems not only dissolve a wide range of the substrates but also provide a potential application for the reaction with polymer-supported synthesis.

TABLE 1. Catalytic Deallyloxycarbonylation of Allyl Carbamate 1b by Use of [CpRu(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 Complex[a]

				% yield[b]		
entry	acid (molar amt)	solvent	time, h	**2b**	**7**	**8**
1	CF_3SO_3H (1)	CH_3OH	1	>99	0	0
2	CF_3SO_3H (0.5)	CH_3OH	5	57	38	5
3	CF_3SO_3H (2)	CH_3OH	5	>99	0	0
4	Nafion (1)	CH_3OH	11	99	0	0
5	CH_3SO_3H (1)	CH_3OH	1	>99	0	0
6	12 M HClaq (1)	CH_3OH	3	92	0	8
7	CH_3COOH (1)	CH_3OH	3	42	50	8
8	CH_3COOH (10)	CH_3OH	1	95	0	5
9	CF_3SO_3H (1)	C_2H_5OH	0.5	>99	0	0
10	CF_3SO_3H (1)	*i*-C_3H_7OH	3	>99	0	0
11	CF_3SO_3H (1)	*t*-C_4H_9OH	12	45	0	0
12	CF_3SO_3H (1)	1:1 CH_3OH-H_2O	1	>99	0	0
13	CF_3SO_3H (1)	1:1 CH_3OH−DMF	1	97	0	3
14	CF_3SO_3H (1)	1:1 CH_3OH−THF	3	>99	0	0
15	CF_3SO_3H (1)	1:1 $CH_3OH-CH_2Cl_2$	1	>99	0	0
16	CF_3SO_3H (1)	1:1 CH_3OH-CH_3CN	1	>99	0	0

[a] Conditions: [**1b**] = 100 mM; [**3**] = 1 mM; temp, 30 °C. [b] Determined by ^1H NMR analysis.

The AOC groups of the primary, secondary and tertiary alkyl primary amines, such as **1b**, **1c**, and **1d**, are quantitatively removed in the presence of 1 molar amount of CF_3SO_3H (entries 1−3 in Table 2). With the lower basicity of the parent primary amine, the more decarboxylative N-allylation product is formed. Thus, *N*-AOC aniline (**1e**) is converted to aniline together with 10% of *N*-allyl aniline, whereas no N-allylation occurs with **1b**−**1d** even in the presence of only 1 molar amount of CF_3SO_3H (entry 4). [CpRu(IV)(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 catalyst combined with CF_3SO_3H has been applied to morpholine (entry 5), which possesses a less hindered and highly nucleophilic secondary amine. In this case, deprotection of the *N*-AOC derivative by use of Pd chemistry is often problematic, and the compound is even used as an allyl trapping agent in Tsuji−Trost chemistry.[7] AOC-(*S*)-Pro-O*t*Bu (**1g**), another cyclic secondary amine, is quantitatively converted to (*S*)-proline *tert*-butyl ester (**2g**) without any racemizaion.[13] The *tert*-butyl ester moiety is intact under all *N*-AOC removal conditions.

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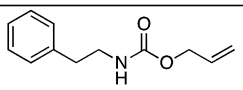
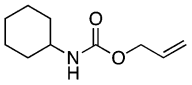
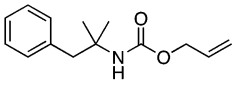
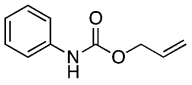
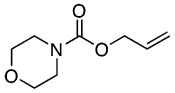
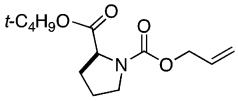
(12) A mixture of sodium 2-pyridinecarboxylate and [$CpRu(CH_3CN)_3$]PF_6 showed virtually no reactivity toward the catalytic allyl ether cleavage (see ref 10a).

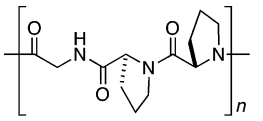
TABLE 2. [CpRu(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 (3)-Catalyzed Removal of the *N*-AOC Group from Allyl Carbamate[a]

entry	substrate	time, h	% yield
1	 **1b**	1	>99
2	 **1c**	2	>99
3	 **1d**	0.5	>99
4	 **1e**	1	88
5	 **1f**	1	99
6	 (*S*)-**1g**	6	>99[b]

[a] Conditions: [**1**] = 100 mM; [CF_3SO_3H] = 100 mM; [**3**] = 1 mM; solvent, CH_3OH; temp, 30 °C. [b] Solvent, CD_3OD.

The advantage of the **3**/acid combined system has been demonstrated by the liquid-phase synthesis of a collagen-like tripeptide repeat unit, Pro-Pro-Gly (**9**, $n = 1$).[14] Glycine *tert*-butyl ester was combined with *N*-AOC-(*S*)-Pro-OH (**10**) by the PyBOP method (dichloromethane, 30 °C, 4 h), giving *N*-AOC-(*S*)-Pro-Gly-O*t*Bu (**11**) in 98.5% yield. The AOC group of the dipeptide **11** was chemoselectively and quantitatively removed by the CpRu-π-allyl method ([**11**] = 10 mM, [**3**] = 0.1 mM, [CF_3SO_3H] = 10 mM, CH_3OH, 30 °C, 2 h). The PyBOP condensation of *H*-(*S*)-Pro-Gly-O*t*Bu with **10** followed by *N*-AOC deprotection afforded **12** in 98% total yield. Treatment of **12** with CF_3COOH at 30 °C for 2 h quantitatively yielded **9** ($n = 1$).

In summary, [CpRu(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 (**3**) has been found to catalyze the efficient removal of *N*-AOC from various amines in the presence of 1 molar amount of an appropriate acid. Even highly nucleophilic morpholine and pyrrolidine derivatives can be obtained without any complications associated with N-allylation. The neutral-acidic conditions exert little effect on other peptide-related protecting groups, such as *t*-Bu, Bn, and Fmoc. The general utility of this approach in peptide chemistry has been demonstrated by the successful synthesis of a tripeptide.[1]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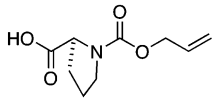
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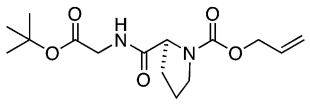
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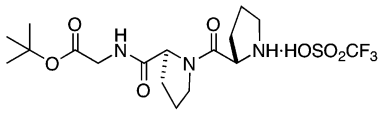
12

Experimental Section

General Procedure of Deallylation. A mixture of allyl 2-phenylethyl carbamate (**1b**) (61.5 mg, 0.300 mmol), trifluoromethanesulfonic acid (45.0 mg, 0.300 mmol), and methanol (3 mL) was placed in a 20-mL Schlenk tube equipped with a Young's tap containing a Teflon-coated magnetic stirring bar under an atmosphere of argon and degassed by three freeze−thaw cycles. To this solution was added [CpRu(π-C_3H_5)(2-quinolinecarboxylato)]PF_6 (1.6 mg, 3.0 μmol). The inlet was sealed by a Young's tap. The yellow solution was stirred for 1 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 was determined to be >99% by ^{1}H NMR analysis (600 MHz, acetone-d_6). For the details, see Supporting Information.

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Supporting Information Available: Information on *O*-AOC deprotection and generality of the *N*-AOC 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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(13) The ee value of the product was estimated by HPLC analysis after conversion to proline by removal of the *tert*-butyl group using the CF_3COOH method. Conditions: column, CHIRALPAK WH; eluent, a 0.25 mM aqueous copper sulfate; flow rate, 1.5 mL/min; detection at 254 nm. For details, see Supporting Information.

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