Palladium-Catalysed Hydroxycarbonylation of Vinyl and Aryl Triflates:
Synthesis of α,β-Unsaturated and Aromatic Carboxylic Acids

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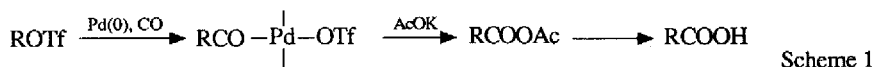
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Abstract: The palladium-catalysed hydroxycarbonylation of vinyl and aryl triflates, under a CO balloon, in the presence of potassium acetate affords α,β-unsaturated and aromatic carboxylic acids with one more carbon in good to high yield. The nature of the solvent and of the ligand have been proved to be crucial for the success of the reaction. Vinyl triflates undergo the hydroxycarbonylation at room temperature in DMF in the presence of Pd(OAc)$_2$(PPh$_3$)$_2$. Aryl triflates produce best results at 60 °C in DMSO in the presence of Pd(OAc)$_2$ and 1,1-bis (diphenylphosphino)ferrocene (dppf).

The previously reported formation of α,β-unsaturated and aryl esters and amides with one more carbon through the palladium-catalysed carbonylation of vinyl[1] and aryl[2] triflates in the presence of alcohols or amines represents a valuable method for a two-steps conversion of ketones and phenols into carboxylic acid derivatives.

Esters, however, are often intermediates on the way to carboxylic acids and an additional hydrolytic step is needed to attain the target compounds. For example, Holt and co-workers[3] recently reported the preparation of a series of steroidal carboxylic acids, a new class of steroid 5α-reductase inhibitors, via the sequence *vinyl/aryl triflates-carboxylic acid esters-carboxylic acids*. Clearly, the development of a method for the direct synthesis of carboxylic acids from vinyl and aryl triflates would be desirable. In the effect, during our studies on the palladium-catalysed synthesis of esters and amides from vinyl triflates,[1] we found that carboxylic acids could be obtained carrying out the reaction in the presence of formic acid and an excess of triethylamine, most likely through the intermediacy of an unstable[4] mixed formic anhydride.[5,6] However, although the formate-mediated palladium-catalysed approach to the hydroxycarbonylation of vinyl/aryl triflates can give good results in many cases, this procedure can be hardly considered a general synthetic method for the preparation of carboxylic acids. Indeed, depending on the nature of the starting triflate, reduction to alkenes[7] or arenes[8] and/or formylation to aldehydes[9] may represent significant side reactions or even the main reaction pathways.

Based on the idea that the substitution of acetate for formate could allow vinyl/aryl triflates to be involved in a catalytic cycle similar to that supposed to be operating in the formate-mediated hydroxycarbonylation, with the generation of carboxylic acids from mixed acetic anhydrides[10] (Scheme 1) and avoiding the reduction of σ-organopalladium intermediates, we attempted the conversion of vinyl and aryl triflates into carboxylic acids in the presence of potassium acetate.
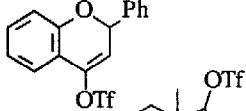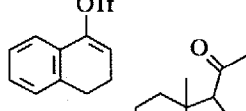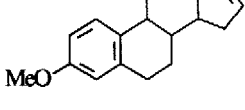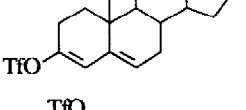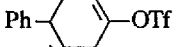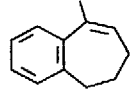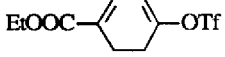
Scheme 1

In this letter, we wish to report that vinyl and aryl triflates can be successfully converted in good to high yield into α,β-unsaturated and aromatic carboxylic acids with one more carbon according to the following scheme

$$R\text{-OTf} \xrightarrow{\text{AcOK, CO}} R\text{-COOH}$$

1 → **2**

R= vinyl: Pd(OAc)$_2$(PPh$_3$)$_2$, 25 °C, DMF
R= aryl: Pd(OAc)$_2$/dppf, 60 °C, DMSO

Scheme 2

Vinyl triflates were converted into α,β-unsaturated carboxylic acids in the presence of Pd(OAc)$_2$(PPh$_3$)$_2$, AcOK, and CO in DMF at room temperature. Our results are summarized in Table 1.

Table 1. Palladium-Catalysed Hydroxycarbonylation of Vinyl Triflates.[a]

Vinyl Triflate 1	Reaction time (h)	Yield % of 2[b]	Vinyl Triflate 1	Reaction time (h)	Yield % of 2[b]
	4	94		2	77
	2	77		2[c]	84
Ph—⟨ ⟩—OTf	5	82		3	88
EtOOC—⟨ ⟩—OTf	3	89			

[a] Unless otherwise stated, reactions were carried out in DMF under a CO balloon, at room temperature, using the following molar ratios: **1**: AcOK: Pd(OAc)$_2$(PPh$_3$)$_2$ = 1: 4: 0.05. [b] Yields refer to single runs and are for pure, isolated products. All new compounds had satisfactory elemental analysis and spectral data consistent with postulated structures. [c] 60 °C.

A typical procedure for vinyl triflates is as follows: a mixture of 4-carbethoxy-3-methyl-1,3-cyclohexadienyl triflate (0.314 g, 1.0 mmol), potassium acetate (0.392 g, 4.0 mmol), bis(triphenylphosphine)palladium(II) diacetate (0.0375 g, 0.05 mmol) in DMF (6 ml) was purged with carbon monoxide for 5 min and stirred under a CO balloon at 25 °C for 3 h. The reaction mixture was diluted with water, acidified with 0.5 N hydrochloric acid and extracted with dichloromethane. The organic layer was washed with water, dried (Na$_2$SO$_4$), and evaporated under vacuum. The residue was chromatographed on silica gel eluting with petroleum ether (40-70 °C)/ethyl acetate/acetic acid 60: 40: 1 to give 4-carbethoxy-3-methyl-1,3-cyclohexadienyl carboxylic acid (0.187 g, 89%): mp = 91-92 °C (diethyl ether/n-hexane); IR (CHCl$_3$) 3019, 1678, 1210 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.33 (t, J = 7 Hz, 3 H), 2.23 (s, 3 H), 2.50 (bs, 4 H), 4.23 (q, J = 7 Hz, 2 H), 7.05 (s, 1 H), 10.66 (bs, 1 H).

Even though the obtained results appear to support our working hypothesis (Scheme 1), we didn't get experimental evidences supporting the formation of mixed acetic anhydrides. On the other hand, the acetate anion was found to play a crucial role for the success of the reaction. For example, the starting material was recovered in 98% yield when 4-phenylcyclohex-1-en-1-yl triflate was reacted under usual conditions omitting potassium acetate. Further studies should be performed to clear this point up.

The successful conversion of vinyl triflates into α,β-unsaturated carboxylic acids prompted us to extend the reaction to aryl triflates. However, the above conditions were proved to be unsatisfactory when applied to them (Table 2, entries a and b). This failure was not completely unexpected. It turns out quite often neither certain or garanteed[11] that reaction conditions found satisfactory with vinyl triflates work with aryl triflates in the same way. Therefore, we examined the possible effects of ligands and solvents on the reaction outcome. Some of the experiments carried out with 4-phenylphenyl triflate as the model system are reported in Table 2 (entries c-g). Best results were obtained when the reaction was carried out in the presence of both DMSO and dppf at 60 °C (Table 2, entry f). Then, a variety of aryl triflates were converted into the corresponding carboxylic acid derivatives under these conditions (Table 3).

Table 2. Ligand and Solvent in the Palladium-Catalysed Hydroxycarbonylation of 4-Phenylphenyl Triflate.[a]
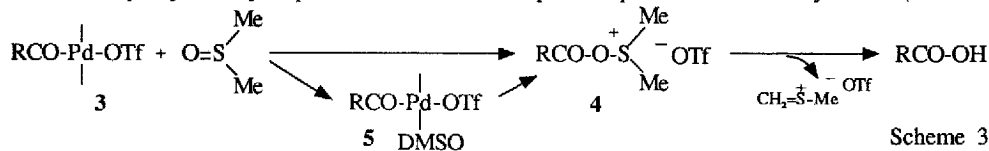
Entry	Ligand	Solvent	Reaction conditions	4-Phenyl benzoic acid % yield[b]	Recovered starting material % yield[b]
a	PPh3[c]	DMF	r.t., 19 h	-	93
b	"	"	60 °C, 18 h	-	92
c	dppf[d]	"	"	-	91
d	PPh3[c]	DMSO[d]	60 °C, 8 h	15	70
e	dppf[f]	"	60 °C, 16 h	45	40
f	dppf[d]	"	60 °C, 3 h	92	-
g[g]	"	"	60 °C, 3 h	43	50

[a] Unless otherwise stated, reactions were carried out under a CO balloon in the presence of Pd(OAc)2 (0.05 equiv) and AcOK (4 equiv). [b] Yields refer to single runs and are for pure, isolated products. [c] 0.1 equiv. [d] 0.2 equiv. [e] Anhydrous DMSO (Merck) on 4 Å molecular sieves. [f] 0.1 equiv. [g] In the absence of AcOK.
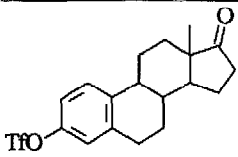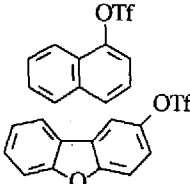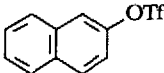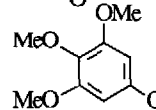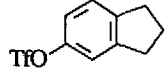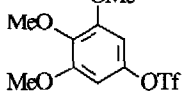
A typical procedure for aryl triflates is as follows: a mixture of 3,4,5-trimethoxyphenyl triflate (0.316 g, 1.0 mmol), potassium acetate (0.392 g, 4.0 mmol), palladium(II) diacetate (0.012 g, 0.05 mmol), dppf (0.111 g, 0.2 mmol), in DMSO (6 ml) was purged with carbon monoxide for 5 min and stirred under a CO balloon at 60 °C for 3 h. The reaction mixture was worked up as reported above and the residue was purified on a silica gel column eluting with petroleum ether (40-70 °C)/ethyl acetate/ acetic acid 70: 30: 1 to afford 3,4,5-trimethoxybenzoic acid (0.200 g, 94%): mp 169-170 °C (diethyl ether/acetone) (lit [12] mp = 171- 173 °C).

It is worth emphasizing that 4-phenyl benzoic acid was isolated in 43% yield even when the reaction was carried out under usual conditions used for aryl triflates omitting AcOK (Table 2, entry g). A possible explanation for this result envisions that the *in situ* generated σ-acylpalladium complex 3 is trapped with DMSO to produce the acyloxydimethylsulphonium 4 whose decomposition produces the carboxylic acid (Scheme 3).

Scheme 3

The conversion of 3 into 4 may occur *via* intermolecular nucleophilic attack of the oxygen of DMSO to the carbon of the carbonyl group or/and by previous coordination of the sulfoxide to palladium to give 5, followed by an intramolecular nucleophilic attack. Sulfoxides are known to form strong complexes with Pd(II).[13] Acyloxydimethylsulphonium intermediates have been supposed to be involved in the related conversion of acetyl chloride to acetic acid in the presence of DMSO[14] and in the well known oxidation of alcohols in the presence of DMSO and Ac2O.[15] Presumably, under the best conditions we found for aryl triflates, both DMSO and AcOK contribute to the formation of carboxylic acids.

Table 3. Palladium-Catalysed Hydroxycarbonylation of Aryl Triflates.[a]

Aryl Triflate 1	Reaction time (h)	Yield % of 2[b]	Aryl Triflate 1	Reaction time (h)	Yield % of 2[b]
	18	84		3	90
	4	95		2.5	73
	4	85		3	94

[a] Reactions were carried out under a CO balloon in DMSO, at 60 °C, using the following molar ratios: 1: AcOK: Pd(OAc)$_2$: dppf = 1: 4: 0.05: 0.2. [b] Yields refer to single runs and are for pure, isolated products. All new compounds had satisfactory elemental analysis and spectral data consistent with postulated structures.

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9. As an example, when we reacted 2-naphthyl triflate (1 equiv) with formic acid (2 equiv) and carbon monoxide (CO balloon) in the presence of Pd(OAc)$_2$(PPh$_3$)$_2$ (0.05 equiv) and Et$_3$N (3 equiv) in DMSO (60 °C, 3 h), naphthalene and 2-naphthaldehyde were isolated in 68 and 23% yield, respectively.
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