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LETTERS

A Palladium-Catalyzed Carbonylative Route to Primary Amides

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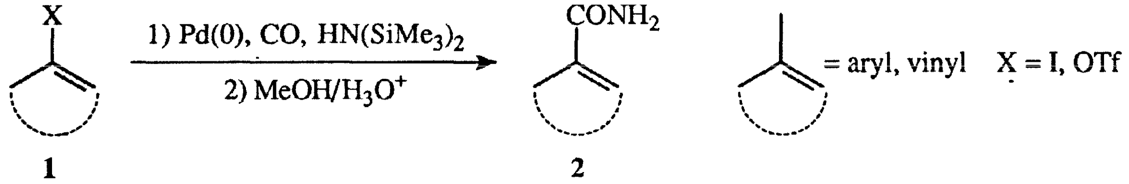
Abstract: The palladium-catalyzed reaction of aryl and vinyl iodides and triflates with carbon monoxide in the presence of hexamethyldisilazane followed by hydrolytic work-up affords aromatic and α,β-unsaturated primary amides in good to high yields under relatively mild conditions.

Palladium-catalyzed carbonylation reactions of sp^2-carbon halides and triflates in the presence of primary or secondary amines represent a well documented method for the preparation of secondary or tertiary aromatic and α,β-unsaturated amides.[1] To our knowledge there are however no examples of aminocarbonylations resulting in the formation of primary amides, despite the potential usefulness of this extension.

The traditional and more general methods of primary amides synthesis involve reactions of carboxylic acids or related derivatives with ammonia or, occasionally, ammonia equivalents.[2] Hexamethyldisilazane (HMDS) in particular has been reported in 1985 to behave as a useful synthon for ammonia in ammonolysis reactions and a variety of primary amides were obtained in 50-92% yields by treatment of the corresponding acyl chlorides with HMDS.[3] Metal derivatives of HMDS have been exploited as nitrogen sources in palladium-catalyzed aminations of allyl chloride[4] and in coupling reactions with aryl iodides.[5]

These precedents prompted us to explore the effectiveness of HMDS as nucleophilic partner in carbon monoxide insertion reactions and we wish to report here that aryl and vinyl iodides and triflates (**1**) undergo palladium-catalyzed carboamidation in the presence of HMDS to give primary amides **2** after hydrolytic work-up in good to high yields.



The carbonylation of aryl iodides was first examined and found to proceed quite satisfactorily under conditions modelled on those developed originally by Heck.[6] Thus, treatment of 1-iodonaphthalene (**1b**) with HMDS and a catalytic amount of $PdCl_2/2PPh_3$ in DMF under a CO atmosphere at 80°C for 1h afforded, after hydrolytic work-up, the amide **2b** in 94% yield.[7] As shown in the Table, a variety of aryl iodides was successfully aminocarbonylated under similar conditions (entries 1-7). It should be noted that, when tested as nucleophilic traps in the carbonylation of **1b**, ammonium acetate and aqueous ammonia afforded **2b** in low yield and not at all, respectively. In the case of ammonium acetate, the main product was the carboxylic acid, while with

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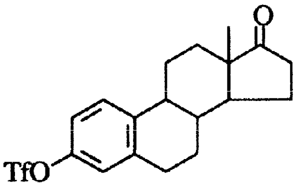
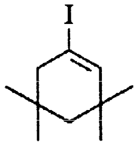
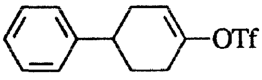
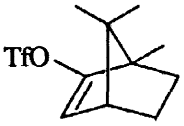
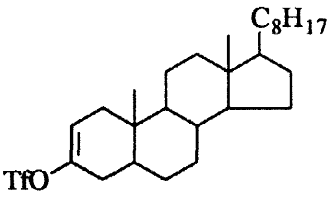
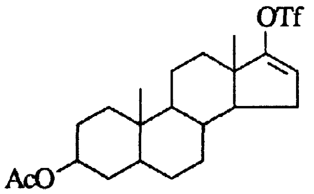
Table. Palladium-Catalyzed Aminocarbonylation of Organic Iodides and Triflates **1**[a]

Entry	Organic Iodide or Triflate 1	Catalyst (mol%)	Reaction conditions (solvent, temp., time)	Yield (%) of Amide 2[b]
1	iodobenzene (**a**)	$PdCl_2/2PPh_3$ (3)	DMF, 80 °C, 1.5 h	76
2	1-iodonaphthalene (**b**)	$PdCl_2/2PPh_3$ (3)	DMF, 80 °C, 1 h	94
3	9-iodophenanthrene (**c**)	$PdCl_2/2PPh_3$ (5)	DMF, 80 °C, 1 h	93[c]
4	4-MeC_6H_4I (**d**)	$PdCl_2/2PPh_3$ (3)	DMF, 80 °C, 1 h	84
5	4-$MeOC_6H_4I$ (**e**)	$PdCl_2/2PPh_3$ (3)	DMF, 80 °C, 1.5 h	76
6	3-$MeO_2CC_6H_4I$ (**f**)	$PdCl_2/2PPh_3$ (3)	DMF, 80 °C, 1 h	81
7	4-$MeO_2CC_6H_4I$ (**g**)	$PdCl_2/2PPh_3$ (3)	DMF, 80 °C, 1 h	88
8	2-naphthyl triflate (**h**)	$PdCl_2/2PPh_3$ (3)	DMF, 80 °C, 2.5 h	92
9	1-naphthyl triflate (**i**)	$PdCl_2/2PPh_3$ (5)	DMF, 80 °C, 6 h	40[d]
10	"	$PdCl_2$/dppp (5)	DMF, 80 °C, 4 h	86
11	4-$MeOC_6H_4OTf$ (**j**)	$PdCl_2$/dppp (5)	DMF, 100 °C, 2.5 h	80[e]
12	 **k**	$PdCl_2$/2dppp (5)	DMF, 100 °C, 16 h[f]	75
13	 **l**	$PdCl_2/2PPh_3$ (3)	DMF, 80 °C, 1.5 h	13[g]
14		$PdCl_2/2PPh_3$ (5)	DMPU, 100 °C, 4 h	73[e]
15	 **m**	$PdCl_2/2PPh_3$ (3)	DMF, 80 °C, 1.5 h	49[h]
16		$PdCl_2/2PPh_3$ (5)	DMPU, 80 °C, 4 h	81
17	 **n**	$PdCl_2/2PPh_3$ (5)	DMPU, 80 °C, 2h	72

(continued)

Table. (continued)

Entry	Organic Iodide or Triflate 1	Catalyst (mol%)	Reaction conditions (solvent, temp., time)	Yield (%) of Amide 2[b]
18	 **o**	$PdCl_2/4PPh_3$ (5)	DMPU, 80 °C, 5 h	59
19	 **p**	$PdCl_2/2PPh_3$ (5)	DMPU, 80 °C, 5 h	88

[a] All reactions were carried out in the same manner as described in the note 7, unless otherwise indicated. The progress of the reactions was followed by TLC. [b] Yields of isolated material. All the products were adequately characterized spectroscopically (IR, ^1H NMR). Mp's of known amides (2a-h) were in good agreement with those reported in the literature. [c] Using 3 mol% of the catalyst, the reaction was incomplete after 6 h and the yield of 2c was 55%. [d] Incomplete reaction. [e] The reaction does not proceed appreciably at 80 °C. [f] Further 4 mmol of HMDS were added after 15 h. [g] 29% of the formimide RCONHCHO and 27% of the tertiary amide $RCONMe_2$ were also isolated. [h] 7% of the formimide RCONHCHO and 35% of the tertiary amide $RCONMe_2$ were also isolated.

ammonia the reaction did not proceed appreciably.

Aryl triflates also underwent the carbonylation reaction, but their behaviour was less homogeneous. Thus, while the use of PPh_3 as the ligand was found to be satisfactory for 2-naphthyl triflate (**1h**, entry 8), the recourse to the bidentate phosphine ligand 1,3-bis(diphenylphosphino)propane (dppp) was necessary to produce effective rates and good yields with the other aryl triflates examined (entries 9-12). Similar observations regarding the beneficial effect of bidentate ligands in carbonylation reactions have been reported by Crisp,[8] Dolle,[9] and ourselves.[10] In addition, the use of 2 mol of dppp per mole of palladium in the case of aryl triflate **1k** (entry 12) proved to be essential for avoiding premature catalyst precipitation and incomplete conversion.

The study was finally extended to vinyl substrates. The reaction of vinyl iodide **1l** under standard conditions produced, beside the expected primary amide, mainly the imide RCONHCHO and the tertiary amide $RCONMe_2$ (R = 3,3,5,5-tetramethylcyclohexenyl) which arise most likely from reaction of some organopalladium intermediate with DMF (entry 13). An analogous result was observed with 4-phenyl cyclohexenyl triflate (**1m**, entry 15, R = 4-phenylcyclohexenyl). Side reactions with amide solvents resulting from palladium-assisted solvent dissociation have been previously reported by Perry and the intervention of an acylpalladium iodide has been assumed.[11]

In order to suppress the formation of the imide and of the tertiary amide, the carbonylations of **1l** and **1m** were conducted in other solvents. The use of acetonitrile at 80 °C led to slow reactions and incomplete consumption of the starting material. Satisfactory results were obtained with 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU)[12] (entries 14 and 16). The protocol was successfully applied to the vinyl triflates **1n-p** (entries 17-19). The use of 4 mol of PPh_3 per mole of palladium in the case of cholest-2-en-3-yl triflate (**1o**, entry 18) was found necessary to prolonge the lifetime of the catalyst enough to allow a complete conversion.

As concerns the mechanism of the reactions, various routes are conceivable, by analogy to the Heck amidation with primary and secondary amines.[6,13] Owing to the low nucleophilicity of HMDS, it seems reasonable to assume that the rate-determining step involves the nucleophilic attack of HMDS, either free or coordinated, on an acylpalladium iodide (or triflate), itself formed by oxidative addition and CO insertion. Nucleophilic attack on acylpalladium intermediates has been proposed as the rate-determining step in the case of carboxylates[14] and of alcohols[15] while, for more reactive amines, an attack on the CO coordinated to an arylpalladium complex (thus prior to the CO insertion) with formation of a carbamoyl species has been assumed.[16] The reasons for the differences observed between aryl and vinyl substrates in terms of side reactions with DMF are at present unclear.

In conclusion, we have shown that HMDS serves as a convenient ammonia equivalent in the palladium-catalyzed carboamidation of aryl and vinyl iodides and triflates. This protocol further expands the scope of catalytic aminocarbonylations and allows the conversion of aryl iodides or phenols to aromatic primary amides and of ketones to α,β-unsaturated primary amides.

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7. A mixture of **1b** (254 mg, 1 mmol), HMDS (0.83 mL, 4 mmol), $PdCl_2$ (5 mg, 0.03 mmol), and PPh_3 (16 mg, 0.06 mmol) in dry DMF (3 mL) was purged with carbon monoxide for 5 min and then stirred under a CO balloon at 80 °C for 1 h. After cooling to room temperature, MeOH (0.5 mL) was added and stirring was continued for 10 min. The mixture was then diluted with 2N H_2SO_4 (20 mL) and extracted with AcOEt (3x50 mL). The organic layers were washed successively with saturated aqueous $NaHCO_3$ (20 mL) and brine (2x20 mL), combined, dried (Na_2SO_4), and evaporated. The residue (190 mg) was chromatographed on silica gel (7 g) using CH_2Cl_2/AcOEt = 8/2 as eluent to give 161 mg (94%) of **2b**: mp 208-209 °C (EtOH) (lit.[17] mp 205.8 °C); IR (KBr) 3337, 1659, 1628 cm^{-1}.
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