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Pd-Catalyzed Chemoselective Carbonylation of Aminophenols with Iodoarenes: Alkoxycarbonylation vs Aminocarbonylation

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Supporting Information

ABSTRACT: Palladium-catalyzed chemoselective carbonylation of aminophenols with iodoarenes was realized by changing ligand and base. 3- or 4-Aminophenols afforded esters in high yields and selectivities using 1,3-bis(diphenylphosphino)propane as the ligand and K_2CO_3 as the base, and gave amides in high yields and selectivities using 1,3-bis(diisobutylphosphino)propane as the ligand and DBU as the base. 2-Aminophenol only gave amides in high yields under both conditions.

Transition metal-catalyzed carbonylation reactions are of value for a variety of organic syntheses.[1,2] As a relatively inexpensive and readily available C1 source, carbon monoxide can be used to prepare various carbonyl containing products from a broad scope of substrates.[3,4] Esters and amides are important motifs in natural products, agrochemicals, materials, and pharmaceutical agents.[5] Coupling reagents (e.g., EDC, HOBt, and CDI) or activated carboxylic acids (e.g., acid chlorides, esters, and anhydrides) are usually used for the synthesis of esters and amides.[6] However, the routes can produce stoichiometric amounts of waste, which increases the cost of commercial processes. In this respect, the atom-efficient palladium-catalyzed carbonylation of aromatic halides has been investigated extensively for the synthesis of esters and amides.[7]

The carbonylation of aniline and phenol derivatives has also been investigated extensively for the preparation of the corresponding amides and esters.[1,4] These reactions may proceed via (i) catalyst generation, (ii) oxidative addition, (iii) CO coordination, (iv) carbonyl insertion through ligand migration, (v) nucleophilic attack, and (vi) product release (Scheme 1).[8] Molecules containing both hydroxyl and amino functionalities are common in drug intermediates and natural products.[9] The question arises as to the pathway for the palladium-catalyzed carbonylation of aminophenols (eq 1). It is conceivable that the selectivity for amides would be high given that the amino group is a better nucleophile than the hydroxyl function. However, other pathways may take precedence. Herein we report useful methodology for the selective carbonylation of aminophenols with iodoarenes, leading to esters or amides as the principal reaction products.

Initially, 4-aminophenol (**1a**) was used as the model substrate to optimize the conditions for the reaction (Table 1). The carbonylation of 4-aminophenol (**1a**) and 4-iodotoluene (**2a**) was initially carried out in MeCN, using PPh_3 as the ligand and K_2CO_3 as the base, affording ester **3a** in high selectivity and in 80% isolated yield. The double carbonylation product **5a** was obtained in 2% yield, and no amide (**4a**) was formed (entry 1). Bases and solvents were investigated using PPh_3 as the ligand (see Supporting Information). Using KF gave **3a** in 82% yield, with **4a** and **5a** obtained in only 2% and 4% yields, respectively (entry 2). When the organic base, Et_3N, was used, **3a** was the major product (75%) together with a small amount of **4a** and **5a** (entry 3). Similar results were obtained using DMSO instead of acetonitrile (entry 4). When DMF was used as the solvent, **3a** and **4a** were obtained in 61% and 23% yields, respectively (entry 5). The yield of **4a** increased when DBU was used in MeCN or DMSO (entries 6 and 7). The ester **3a** was the major product when Et_3N was used in DMSO (entry 8). The effect of ligands on the carbonylation reaction was then investigated (see Supporting Information). Under conditions favoring ester formation (entry 1), the bidentate ligand 1,3-bis(diphenylphosphino)propane (DPPP) afforded **3a** as the major product in 85% yield (entry 9). When the isobutyl replaced the phenyl group in DPPP, trialkylphosphine ligands 1,3-bis(diisobutylphosphino)propane (DIBPP) gave **3a** and **4a** in 33% and 50% yields, respectively (entry 10). When DBU was used as the base, the amide **4a** was obtained in 81% yield, while **3a** was formed in only 8% yield (entry 11). The reactions were also carried out in the absence of ligand under the conditions of entries 9 and 11. K_2CO_3 gave the ester as the major product, and DBU gave the amide **4a** as the major product (entries 12 and 13), indicating that base also plays an important role in the selectivity.

Scheme 1. Conventional Mechanism for the Carbonylation of Aryl Halides

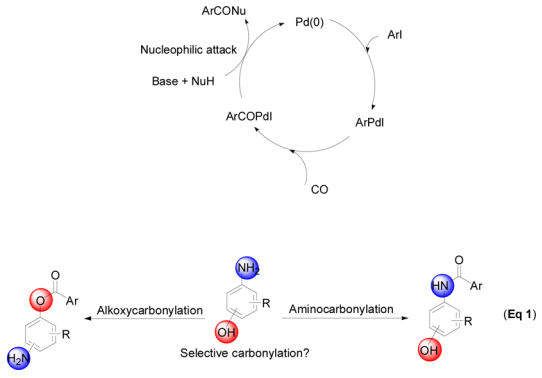

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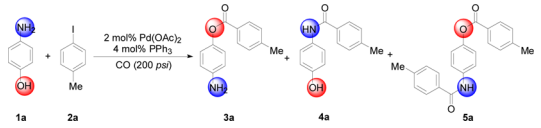
Table 1. Screening of the Reaction Conditions for the Carbonylation of 4-Aminophenol[a]



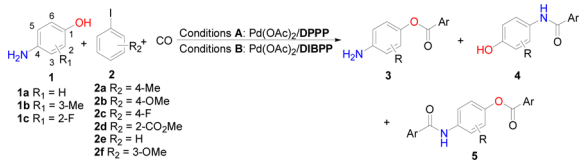
entry	ligand (mol %)	solvent	base	yield (%)[b] 3a	4a	5a
1	PPh_3	MeCN	K_2CO_3	80		2
2	PPh_3	MeCN	KF	82	2	4
3	PPh_3	MeCN	Et_3N	75	3	3
4	PPh_3	DMSO	K_2CO_3	80	2	4
5	PPh_3	DMF	K_2CO_3	61	23	2
6	PPh_3	MeCN	DBU	30	43	5
7	PPh_3	DMSO	DBU	13	60	3
8	PPh_3	DMSO	Et_3N	70	5	3
9	**DPPP**	**MeCN**	**K_2CO_3**	**85**		**1**
10	DIBPP	MeCN	K_2CO_3	33	50	5
11	**DIBPP**	**MeCN**	**DBU**	**8**	**81**	**4**
12		MeCN	K_2CO_3	58	9	5
13		MeCN	DBU	10	62	3

[a]Conditions: 0.5 mmol of 4-iodotoluene, 0.6 mmol of 4-aminophenol, 2 mol % $Pd(OAc)_2$, Pd/P = 1:2, 1 mmol of base, 5 mL of solvent, 200 psi CO, 100 °C, 15 h. [b]Isolated yield. DPPP = 1,3-bis(diphenylphosphino)propane. DIBPP = 1,3-bis(diisobutylphosphino)propane.

The selective carbonylation of 4-aminophenols was then applied under conditions **A** and **B** (Table 2). After completion, the reaction mixtures were analyzed by GC, and the product ratios were used to indicate the ester/amide selectivity. The results showed that the electronic property of substituents on the iodoarenes had no effect on the selectivity for the ester or amide. Iodoarene with electron-donating (Me and OMe, entries 1−4) or electron-withdrawing (F and CO_2Me, entries 4−8) substituents successfully afforded esters under conditions **A** or amides under conditions **B** in high yields and fine selectivities. Steric hindrance on the iodoarene did not affect the selectivity (entries 7−8). When methyl 2-iodobenzoate was reacted under conditions **B**, subsequent reaction between the amide and methoxycarbonyl substituent occurred to form isoindole-1,3-dione derivative **4d** in 67% yield (entry 8). Substituents on the 4-aminophenol influence the selectivity and yield (entries 9−12). A methyl substituent at the ortho position of the amino group had no effect on the selectivity and yield of ester **3e** under **A** conditions (entry 9), but steric hindrance decreased the selectivity of amide under **B** conditions (entry 10). The fluoride at the ortho position of the hydroxyl group did not influence the selectivity of the ester (**3f**) formation under conditions **A**, but the yield decreased (entry 11).

Our reaction conditions were next applied to the carbonylation of 3-aminophenol derivatives (Table 3). High selectivity for esters and amides was realized using conditions **A** or **B**. 3-Aminophenol reacted with 3-iodoanisole to selectively afford ester **3g** (conditions **A**) in 77% yield and amide **4g** (conditions **B**) in 84% yield (entries 1 and 2). With the methyl substituent at the 2-position, the selectivity for the amide decreased (entries 3 and 4). Steric hindrance apparently has greater influence on amide, rather than ester formation. When 6-methyl- and 6-methoxy-substrates **1f** and **1g** were reacted with 4-iodotoluene (entries 5−8), there was no noticeable influence on the extent of formation of amides under conditions **B**. A significant decrease in

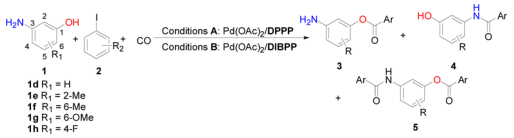
Table 2. Selective Carbonylation of 4-Aminophenol Derivatives[a]



entry	1	2		3/4[b]	Yield (%)[c] 3	4	5
1	**1a**	**2a**	**A**	>99/1	**3a** (85)	-	**5a** (1)
2	**1a**	**2a**	**B**	8/92	**3a** (8)	**4a** (81)	**5a** (4)
3	**1a**	**2b**	**A**	>99/1	**3b** (88)	-	-
4	**1a**	**2b**	**B**	16/84	**3b** (9)	**4b** (86)	-
5	**1a**	**2c**	**A**	>99/1	**3c** (85)	-	-
6	**1a**	**2c**	**B**	10/90	**3c** (4)	**4c** (85)	-
7	**1a**	**2d**	**A**	>99/1	**3d** (95)	-	-
8	**1a**	**2d**	**B**	1/99	-	 **4d** (67)	-
9	**1b**	**2a**	**A**	>99/1	**3e** (87)	-	-
10	**1b**	**2a**	**B**	20/80	**3e** (9)	**4e** (66)	**5e** (8)
11	**1c**	**2e**	**A**	95/5	**3f** (55)	-	**5f** (4)
12	**1c**	**2e**	**B**	5/95	-	**4f** (71)	-

[a]Conditions **A**: 0.6 mmol of **1**, 0.5 mmol of **2**, 2 mol % $Pd(OAc)_2$, 2−3 mmol % DPPP, 1 mmol of K_2CO_3, 5 mL of MeCN, 200 psi CO, 100 °C, 15 h. Conditions **B**: 0.6 mmol of **1**, 0.5 mmol of **2**, 2 mol % $Pd(OAc)_2$, 2−3 mmol % DIBPP, 1 mmol of DBU, 5 mL of MeCN, 200 psi CO, 100 °C, 15 h. [b]GC area ratio of **3**/**4**. [c]Isolated yield.

Table 3. Selective Carbonylation of 3-Aminophenol Derivatives[a]



entry	1	2		3/4[b]	yield (%)[c] 3	4	5
1	**1d**	**2f**	**A**	>99/1	**3g** (77)		
2	**1d**	**2f**	**B**	4/96		**4g** (84)	
3	**1e**	**2b**	**A**	99/1	**3h** (92)		
4	**1e**	**2b**	**B**	11/89	**3h** (6)	**4h** (75)	
5	**1f**	**2a**	**A**	97/3	**3i** (70)		**5i** (10)
6	**1f**	**2a**	**B**	3/97		**4i** (85)	
7	**1g**	**2a**	**A**	73/27	**3j** (41)	**4j** (10)	**5j** (10)
8	**1g**	**2a**	**B**	1/99		**4j** (80)	
9	**1h**	**2e**	**A**	97/3	**3k** (95)		
10	**1h**	**2e**	**B**	12/88	**3k** (8)	**4k** (73)	

[a]Conditions **A**: 0.6 mmol of **1**, 0.5 mmol of **2**, 2 mol % $Pd(OAc)_2$, 2−3 mmol % DPPP, 1 mmol of K_2CO_3, 5 mL of MeCN, 200 psi CO, 100 °C, 15 h. Conditions **B**: 0.6 mmol of **1**, 0.5 mmol of **2**, 2 mol % $Pd(OAc)_2$, 2−3 mmol % DIBPP, 1 mmol of DBU, 5 mL of MeCN, 200 psi CO, 100 °C, 15 h. [b]GC area ratio of **3**/**4**. [c]Isolated yield.

the selectivity for ester under conditions **A** was observed (entries 5 and 7), and **2a** was not consumed, indicating that the electronic effect was greater than the steric effect, and the electron-donating

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substituent disfavored the formation of the ester under conditions **A**. Substrate **1h** with the fluoride substituent on the para position of the hydroxyl group (entry 9) afforded the ester under conditions **A** in high yield and high selectivity, demonstrating that the electronic-withdrawing group favors ester formation.

When 2-aminophenol (**1i**) was carbonylated with 4-iodotoluene, only the amide (**4l**) was obtained in high yield under **A** or **B** conditions (see Supporting Information). The coordination at both nitrogen and oxygen might lead to this result.[10]

According to the conventional mechanism outlined in Scheme 1, the amide should be favored over the ester because the amino group is a better nucleophile than the hydroxyl group. However, in our case, the selectivity was dependent on the ligand and the base. Both are important in the process (Table 1, entries 9−13). To determine the selectivity, *p*-toluoyl chloride (**6**) was reacted with 4-aminophenol in MeCN using K_2CO_3 and DBU as the base, respectively (see Supporting Information). Surprisingly, the selectivity of **3a**/**4a** was the reverse of the palladium-catalyzed carbonylation of 4-aminophenol.

We then carried out two reactions using a mixture of 4-methylphenol (**7**) and 4-methylaniline (**8**) instead of 4-aminophenol under conditions **A** and **B**, respectively (see Supporting Information). The selectivity for ester (**9**) or amide (**10**) was consistent with the result of 4-aminophenol. Buchwald and co-workers observed that the ester was formed as an intermediate in the palladium-catalyzed aminocarbonylation of aryl chlorides using sodium phenoxide as the base.[11] However, in our work, we used excess aminophenol and base, and ester **3** did not convert to the amide even using 3 equiv of aminophenol. Prolonging the reaction time or raising the reaction temperature to 120 °C did not alter the selectivity, suggesting a different mechanism here. Lei and co-workers reported a base-induced mechanistic variation for the palladium-catalyzed alkoxycarbonylation of aryl iodides.[12] Sodium alkoxide was used instead of tertiary amines in their work, affording high yields of ester while tertiary amine gave low product yields. They proposed that transmetalation with sodium alkoxide led to the key intermediate. The ligand effect was not mentioned in their work.

Treatment of aroyl chlorides with Pd(0) catalysts can form ArCOPdCl.[13] Unfortunately, preparation of the complex ArCOPdCl bearing DPPP or DIBPP was fruitless. We prepared (*p*-TolCO)Pd(PPh_3)$_2$Cl from Pd(PPh_3)$_4$ and *p*-toluoyl chloride. Then (*p*-TolCO)Pd(PPh_3)$_2$Cl was used to react with 4-aminophenol quantitatively or to catalyze the carbonylation using K_2CO_3 or DBU as base (see Supporting Information), affording ester or amide selectively consistent to the palladium-catalyzed carbonylation of 4-aminophenol. The results indicate that ArCOPdX may be an intermediate, and coordination of NH_2 or OH to the palladium intermediate occurred in the process, affording products after reductive elimination. On the basis of the experimental results and literature reports, it is reasonable to conclude that the nature of ligand is key to the selectivity.[14] An electron-rich ligand favors the coordination of the amino group rather than the hydroxyl group. The base assists the selectivity. Inorganic base can react with phenol to form phenoxide, which facilitates transmetalation with the palladium intermediate to form ester.

A secondary aminophenol and an aliphatic aminoalcohol were subjected to the carbonylation reaction with 4-iodotoluene (see Supporting Information). We were pleased to observe that 4-isopropylaminophenol (**1j**) afforded the ester (**3m**) in 93% isolated yield under **A** conditions. Ester **3m** was also the major product (70% yield) under **B** conditions, indicating the potential importance of the steric factors for this reaction. Also, the coordination of nitrogen to the palladium intermediate may be critical to the catalytic process. 3-Aminopropanol gave the amide (**4n**) in 75% yield under **B** conditions, but poor selectivity resulted using **A** conditions. The method was also applied to the carbonylation of 4-methylphenol with 4-iodoaniline and 4-methylaniline with 4-iodophenol. The ester **13** was obtained in 75% yield under **A** conditions, and the amide **16** was obtained in 61% yield under **B** conditions.

In conclusion, the palladium-catalyzed selective carbonylation of 3- and 4-aminophenols was realized, affording esters in high yields and selectivities using 1,3-bis(diphenylphosphino)-propane as the ligand and K_2CO_3 as the base, while producing amides in high yields and selectivities using 1,3-bis-(diisobutylphosphino)propane as the ligand and DBU as the base. 2-Aminophenol only gave the amide in high yields under both conditions. These results demonstrate that the nature of the phosphine ligand is key to the selectivity of the catalytic reactions. These chemoselective reactions have considerable potential for organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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