Tetrahedron Letters 54 (2013) 5496–5499

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed aminocarbonylation of aryl iodides using aqueous ammonia

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ARTICLE INFO

Article history:
Received 4 July 2013
Revised 25 July 2013
Accepted 27 July 2013
Available online 3 August 2013

Keywords:
Palladium
Aminocarbonylation
Aqueous ammonia
Aryl iodide

ABSTRACT

Aminocarbonylation of aromatic iodides using aqueous ammonia in toluene has been developed. Various primary aromatic amides have been efficiently synthesized in good to excellent yields in the presence of catalytic quantities of $Pd(OAc)_2$/CYTOP®292. The usage of aqueous ammonia avoids the handling of two gases in the reaction.

Transition metal-catalyzed carbonylation reactions have become a powerful tool in organic synthesis.[1] As an inexpensive and readily available C1 source, carbon monoxide can be used to synthesize various carbonyl products, such as aldehydes, ketones, carboxylic acids, esters, and amides.[2] And a broad scope of substrates has been used for carbonylation reactions, including aromatic halides,[3] alkenes,[4] alkynes,[4] etc. Among the different types of carbonylation reactions, palladium-catalyzed coupling carbonylation reaction of aromatic halides with different nucleophiles, has been one of the most important methodologies for the synthesis of valuable carbonyl containing compounds both from academic and industrial perspectives.[5]

The amide is an important motif in natural products, agrochemicals, materials, and pharmaceutical molecules.[6] Coupling reagents (e.g., EDC, HOBt, CDI) or activated carboxylic acids (e.g., acid chlorides, esters, anhydrides) are usually used for the synthesis of amides.[7] Although efforts have been devoted to the efficient synthesis of amides, this methodology can produce stoichiometric amounts of waste, which increases the cost of commercial applications. In this respect, the atom-efficient palladium-catalyzed aminocarbonylation of aromatic halides has emerged as an alternative and promising strategy. Since the first work of Heck and co-workers in 1974,[8] an impressive amount of development of the palladium-catalyzed aminocarbonylation of aromatic halides has been devoted to the synthesis of aromatic secondary and tertiary amide.[9] There are only a few examples of the preparation of aromatic primary amides via the palladium-catalyzed aminocarbonylation. Some ammonia equivalents[10] have been developed to prepare primary amides, such as hexamethyldisilazane (HMDS), formamide, *N-tert*-butylamine, hydroxylamine, and a titanium–nitrogen complex. However ammonia, which is one of the most important chemical feedstocks for the chemical industry available at low cost, is the most desirable source of nitrogen to synthesize primary amides. Recently, Beller and Wu developed palladium catalysts based on $BuPAd_2$ or dppf as ligands for the synthesis of primary amides using gaseous ammonia as reagent and base. Although important progress has been accomplished,[11] the required handling of two gases still restricts the application of the method. Herein we reported a palladium-catalyzed aminocarbonylation of aromatic iodides to synthesize primary amides using aqueous ammonia as the nitrogen source.

In our initial studies, the aminocarbonylation of *p*-iodotoluene **1a** was chosen as the reactant for the optimization of the reaction conditions (Table 1). In the presence of 5 mol % $Pd(OAc)_2$ and 5 mol % dppf in 1,4-dioxane/aqueous ammonia (v/v = 15:1), amide **2a** was obtained in 31% isolated yield (entry 1). PPh_3 afforded **2a** in 35% yield while a phenyl-substituted phospha-adamantane ligand, CYTOP®292[12] (1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane) gave amide **2a** in 40% yield (entries 2 and 3). Additional base such as Cs_2CO_3 or $NaHCO_3$ did not improve the yield (entries 4 and 5). When the

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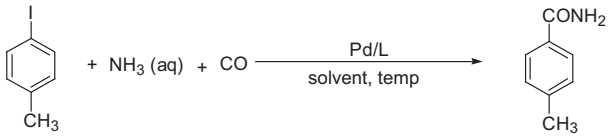
http://dx.doi.org/10.1016/j.tetlet.2013.07.143

Table 1
Screening of the reaction conditions[a]



1a **2a**

Entry	Cat. (mol %)	Ligand	Solvent	Temp. (°C)/P_{CO} (psi)	**2a**[b] (%)
1	5	dppf	1,4-Dioxane	100/200	31
2	5	PPh_3	1,4-Dioxane	100/200	35
3	5	CYTOP®292	1,4-Dioxane	100/200	40
4[c]	5	CYTOP®292	1,4-Dioxane	100/200	35
5[d]	5	CYTOP®292	1,4-Dioxane	100/200	25
6	5	CYTOP®292	1,4-Dioxane	100/200	65
7[e]	5	CYTOP®292	1,4-Dioxane	100/200	35
8	5	CYTOP®292	THF	100/200	86
9	5	CYTOP®292	Toluene	100/200	93
10	5	CYTOP®292	DCE	100/200	70
11[f]	5	CYTOP®292	H_2O	100/200	19
12	5	CYTOP®292	Toluene	80/200	30
13	2	CYTOP®292	Toluene	100/200	93
14	0.5	CYTOP®292	Toluene	100/200	50
15	2	CYTOP®292	Toluene	100/100	93
16	2	PPh_3	Toluene	100/100	88
17	2	CYTOP®292	Toluene	100/50	<5
18[g]	2	CYTOP®292	Toluene	100/100	47
19[h]	2	CYTOP®292	Toluene	130/100	95
20[h]	0.5	CYTOP®292	Toluene	130/100	98
21[h]	0.25	CYTOP®292	Toluene	130/100	<5
22[h]	0.5	DavePhos	Toluene	130/100	93
23[h]	0.5	JohnPhos	Toluene	130/100	96
24[h]	0.5	XPhos	Toluene	130/100	94

[a] Reagents and conditions: 0.5 mmol **1a**, 0.2 mL aqueous ammonia, $Pd(OAc)_2$/P = 1/2, entries 1–5, 3 mL solvent (0.17 M **1a**); entries 6–24, 10 mL solvent (0.05 M **1a**); 20 h.
[b] Isolated yield.
[c] 2 equiv Cs_2CO_3.
[d] 2 equiv $NaHCO_3$.
[e] 0.1 mL NH_3.
[f] 10 mol % TBAI was added.
[g] 8 h.
[h] 3 h.

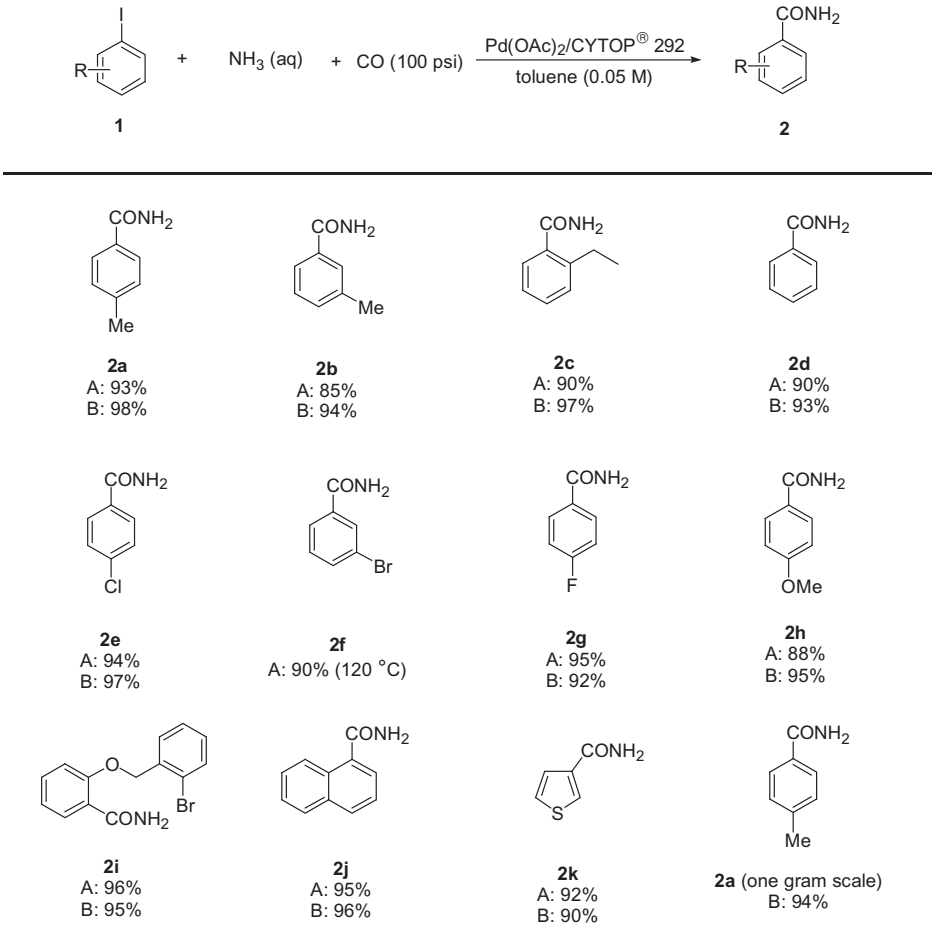
reaction concentration of **1a** was reduced to 0.05 M, the yield increased to 65% (entry 6). The yield decreased when the amount of aqueous ammonia was reduced to 0.1 mL (entry 7).

Different solvents were tested for this reaction (entries 8–11). When the reaction was carried out in THF and DCE, **2a** was obtained in 86% and 70% yields. Toluene was the best solvent and afforded **2a** in 93% yield. Water was also tried in the presence of 10 mol % tetrabutylammonium iodide (TBAI), only affording **2a** in 19% yield. The yield decreased dramatically at a lower reaction temperature such as at 80 °C (entry 12), indicating that temperature plays an important role in the reaction. The loading of the catalyst could be reduced to 2 mol % without decreasing the yield under lower pressure (100 psi) of carbon monoxide, while PPh_3 afforded 88% yield (entries 13–17). When we carried out the reaction at 130 °C with 0.5 mol % $Pd(OAc)_2$ and 1 mol % CYTOP®292, the aminocarbonylation could be completed in 3 h and afforded **2a** in 98% yield (entries 18–21). Other ligands such as DavePhos, JohnPhos, and XPhos were studied under these conditions, affording **2a** in slightly lower yields (93–96%, entries 22–24).

A variety of different aryl iodides were transformed to the corresponding primary amides using two types of reaction conditions (Scheme 1): Condition A, where the reaction was carried out for 20 h at 100 °C in the presence of 2 mol % $Pd(OAc)_2$/4 mol % CYTOP®292; and condition B, where the reaction was carried out at 130 °C but with shorter reaction times, in the presence of 0.5 mol % $Pd(OAc)_2$/1 mol % CYTOP®292. Amides with *ortho*-, *meta*-, or *para*-alkyl-substituents were isolated in high yields (85–98%, **2a**–**d**). Both electron-rich and electron-deficient aryl iodides gave good yields of the primary amide (**2e**–**i**). The aryl iodides were selectively transformed to the corresponding amides in the presence of other halogen substituents (F, Cl, Br) (**2e**–**g**). In the case of 1-bromo-3-iodobenzene, the aminocarbonylation should be effected at 120 °C under condition A. 1-Iodonaphthalene and 3-iodothiophene were also converted to the primary amides in high yield (**2j** and **2k**).

A one gram scale reaction of **1a** was carried out under condition B. After heating at 130 °C for 6 h, the reaction mixture was cooled, washed with water and then the organic phase was concentrated, affording the amide **2a** in 94% yield. This result indicates the potential application of the methodology.

In summary, the palladium-catalyzed aminocarbonylation of aromatic iodides using aqueous ammonia in toluene has been developed. The usage of aqueous ammonia avoided the handling of two gases and could be easily scaled up. Various primary aromatic amides have been efficiently synthesized in good to excellent yields in the presence of $Pd(OAc)_2$/CYTOP®292.



Scheme 1. Palladium-catalyzed aminocarbonylation of aryl iodides using aqueous ammonia. Reagents and conditions A: 0.5 mmol **1**, 0.2 mL aqueous ammonia, 2 mol % $Pd(OAc)_2$, 4 mol % CYTOP®292, 10 mL toluene, P_{CO} = 100 psi, 100 °C, 20 h. Conditions B: 0.5 mmol **1**, 0.2 mL aqueous ammonia, 0.5 mol % $Pd(OAc)_2$, 1 mol % CYTOP®292, 10 mL toluene, P_{CO} = 100 psi, 130 °C, 3–8 h.

Acknowledgments

We are grateful to Cytec Industries, Inc., and to the Natural Sciences and Engineering Research Council of Canada for supporting this research.

Supplementary data

Supplementary data (experimental procedures, ^{1}H and ^{13}C NMR data) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.143.

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