

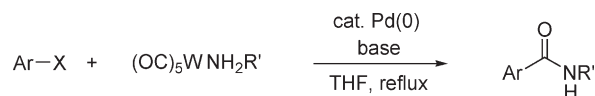
Palladium-Catalyzed Carbamoylation of Aryl Halides by Tungsten Carbonyl Amine Complex

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In the presence of aminepentacarbonyltungsten, base, and a catalytic amount of palladium(0) complex, carbamoylation of aryl halide proceeds to afford amide. The reaction may involve transmetalation between palladium(II) intermediate and carbamoyltungstenate that is generated in situ. This catalytic cross-coupling reaction provides an alternative method to the conventional palladium-catalyzed amidation by using gaseous carbon monoxide.

Introduction

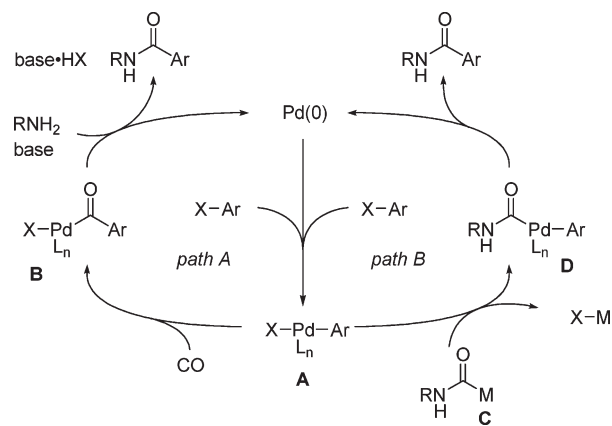
Since Heck and his co-worker first reported it,¹ the palladium-catalyzed three-component coupling reaction of aryl halides, carbon monoxide, and amine has been studied energetically because it is one of the practical catalytic methods for the preparation of amides.² By this method amides are prepared from organic halides and amines with one carbon elongation. The catalytic cycle is explained as depicted in path A in Scheme 1. Oxidative addition of aryl halide to palladium(0) proceeds to give arylpalladium(II) intermediate **A**. Migratory insertion of carbon monoxide gives acylpalladium(II) intermediate **B** that reacts with amine in the presence of a base to afford amide with regeneration of palladium(0) catalyst.

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To form acylpalladium(II) intermediate **B**, carbon monoxide is indispensable, and therefore the reactions are performed under gaseous carbon monoxide atmosphere. Sometimes a high pressure of carbon monoxide is necessary to realize efficient amide formation.^{2c,f,h,j,p-r} Recently it was reported that group VI metal carbonyl complexes could be used as a solid state of the carbon monoxide sources in the reaction under microwave irradiation.³

SCHEME 1. Reported and Hypothetic Mechanism of Palladium-Catalyzed Amidation of Aryl Halides



An alternative possible idea for palladium-catalyzed amide formation is depicted in path B in Scheme 1. This is totally a

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cross-coupling reaction between carbamoylmetal compounds and organic halides. The key step is the transmetalation between carbamoylmetal **C** and palladium(II) intermediate **A** to generate carbamoylpalladium(II) intermediate **D**. Although there is the advantage that gaseous carbon monoxide is not necessary, this type of catalytic reaction has never been reported so far. The reason is that useful nucleophilic carbamoylation reagents **C** have not been developed.

Only a few nucleophilic carbamoylation reagents have been found in the literature. For example, there are some reports on the preparation of carbamoyllithium,⁴ which is unstable for use in carbon–carbon bond formation reactions. Especially, carbamoyllithium having a hydrogen on its nitrogen atom is so unstable that a rearrangement takes place to form the azaenolate of formamide.^{4c} The carbamoylnickel complex is known as a rather stable intermediate and is used for the reaction with carbon electrophiles such as aryl halides.⁵ Recently the aluminum azaenolate of carbamoyltelluroate was reported as a synthon of carbamoyllithium and carbamoylation of carbonyl compounds was achieved.⁶ To the best of our knowledge, these are the only reagents for nucleophilic carbamoylation reactions.

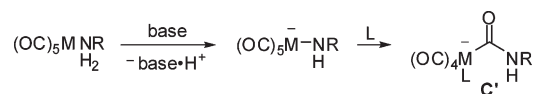
Acyl transition metal complexes are known to be used as nucleophilic acylation reagents.⁷ Especially, group VI metal carbonyl complexes, such as chromium, molybdenum, and tungsten complexes, are used for this purpose and a variety of nucleophilic acylation reactions are reported.⁸ Moreover, it is known that transmetalation between these acylmetalates and palladium(II) intermediates proceeds to generate acylpalladium(II) complexes.^{8c,d} Therefore, it was expected that group VI carbamoyl metal complexes could be used as nucleophilic carbamoylation reagents. So far carbamoyl complexes of group VI metals were mostly used as intermediates for the synthesis of alkoxy(amino)carbene metal complexes⁹ and the preparation of ureas¹⁰ or formamides,¹¹ while never being used for C–C bond formation reactions.

In this paper are present an investigation of in situ generation of carbamoylmetalate as a nucleophilic carbamoylation reagent and its application to palladium-catalyzed carbamoylation of aryl halides.

Results and Discussion

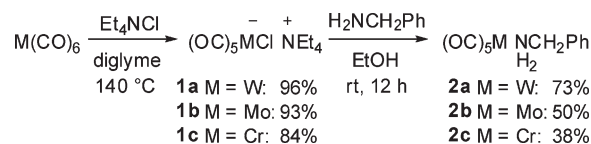
As shown in Scheme 2, we expected that group VI carbamoyl complexes **C'** would be generated by the combined use of bases and aminepentacarbonylmetal complexes that were known to be easily prepared as air-stable crystalline complexes in most cases.¹²

SCHEME 2. Generation of Carbamoyl Metalate



Actually, group VI metal benzylamine pentacarbonyl complexes **2** [(OC)₅MNH₂CH₂Ph; M = Cr, Mo, W] were prepared as air-stable solids in 2 steps from the corresponding hexacarbonyl complexes according to the reported procedure^{13,14} with some modifications (Scheme 3).

SCHEME 3. Preparation of Group VI Metal Carbonyl Amine Complexes



With the amine complexes in hand, we tried to investigate the palladium-catalyzed carbamoylation of aryl halides. First, iodobenzene was selected as the substrate. To a mixture of tungsten benzylamine complex **2a** (1 mmol) and base (1.1 mmol) in THF were added iodobenzene (1.5 mmol), Pd(OAc)₂ (0.05 mmol), and P(*o*-Tol)₃ (0.1 mmol) and the reaction mixture was heated to reflux (Scheme 4). When LiHMDS was used as the base, the reaction was completed in 2 h and benzamide **3a** was obtained in 70% yield. It was found that the use of K₂CO₃ gave an excellent yield (95%) although it required longer reaction time. In both cases a small amount of biphenyl (<3%) was obtained as the side product. When a control reaction was performed without Pd(OAc)₂ and P(*o*-Tol)₃, amide **3a** was obtained in <4% as a mixture of undefined compounds and benzylamine complex **2a** was recovered in 42%.¹⁵ Carbamoylation of iodobenzene

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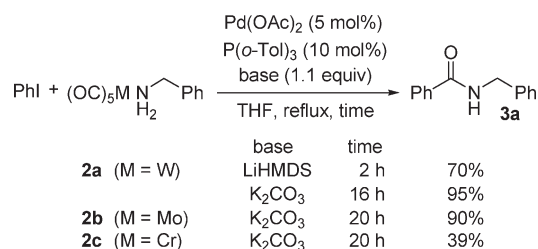
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was also performed by using other group VI metal benzylamine complexes **2b** and **2c**. Molybdenum complex **2b** gave good yield of **3a**; however, chromium complex **2c** gave only 39% yield.

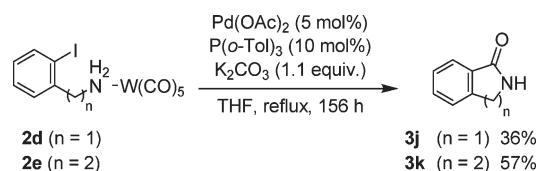
SCHEME 4. Palladium-Catalyzed Carbamoylation of Phenyl Iodide



Palladium-catalyzed carbamoylation of a variety of aryl halides was performed and the results are summarized in Table 1. It was found that not only aryl iodides but bromides could be used as the coupling partners although it requires longer reaction time and larger amounts of the catalyst loading (10 mol %). This higher reactivity of the iodide was applied for the chemoselective carbamoylation of 1-bromo-4-iodobenzene and 4-bromobenzamide **3e** was obtained selectively in good yield (entry 7). Functional group tolerance was tested by using 4-substituted phenyl halides and it was found that vinyl, acyl, ethoxycarbonyl, and methoxy groups were not affected under the reaction conditions (entries 8–10). This reaction was also applicable for the catalytic carbamoylation of heteroaromatic halides. 3-Thiophenecarboxamide **3i** was obtained from 3-bromothiophene in 63% yield (entry 11).

We applied this palladium-catalyzed carbamoylation reaction for a lactam synthesis. Tungsten amine complexes **2d** and **2e** having a 2-iodoaryl moiety were prepared and subjected to the palladium-catalyzed reaction conditions (Scheme 5). Intramolecular carbamoylation proceeded to give 5- and 6-membered ring lactams **3j** and **3k**.

SCHEME 5. Palladium-Catalyzed Intramolecular Carbamoylation



As stated in the Introduction, there are two possible mechanisms for the palladium-catalyzed amide formation. If amine and carbon monoxide are released from the tungsten center in the reaction conditions, the two mechanisms cannot be distinguished. To have some insight into the mechanism of this palladium-catalyzed carbamoylation, the following reactions were performed. The palladium-catalyzed reaction was performed with the combination of benzylamine and carbon monoxide (1 atm) instead of using tungsten amine carbonyl complex (Scheme 6). When 2-bromonaphthalene was subjected to the reaction, the corresponding amide **3c** was not obtained at all in spite of refluxing 36 h. It seems to be required that a higher

TABLE 1. Palladium-Catalyzed Carbamoylation of Aryl Halides^a

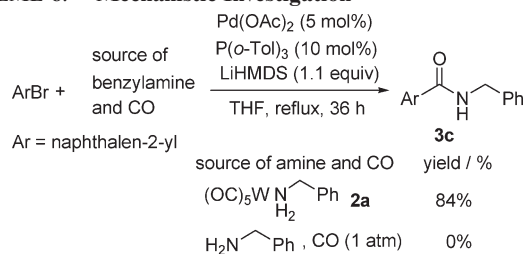
entry	Ar-X	product	time / h	yield / %
1		3a	16	95
			(72) ^b	(<4) ^{b,c}
2		3a	72	47
3		3b	20	85
4		3b R = -C(=O)CH ₃ ; 3b' R = -C(OH)(CH ₃) ₂	60	74 ^d
5		3c	68	86
6		3d	70	81
7		3e	13	84
8		3f	48	63
9		3g	84	64
10		3h	16	95
11		3i	72	63

^aReaction conditions: **2a** (1 mmol), Ar-X (1.5 mmol), K₂CO₃ (1.1 mmol), Pd(OAc)₂ (5 mol % for aryl iodide, 10 mol % for aryl bromide), P(*o*-Tol)₃ (10 mol % for aryl iodide, 20 mol % for aryl bromide). ^bWithout Pd(OAc)₂ and P(*o*-Tol)₃. ^c**2a** was recovered in 42%. ^d**3b** and **3b'** were obtained in 63% and 11% yields, respectively.

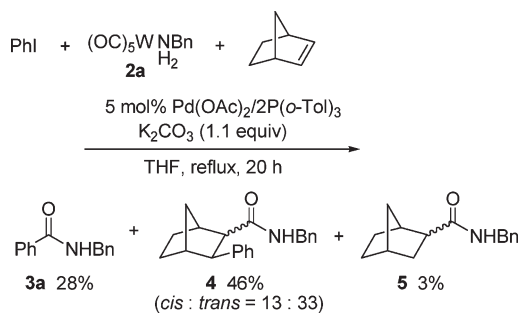
temperature or higher pressure of carbon monoxide is necessary to accomplish amide formation via path A (Scheme 1). On the contrary, tungsten benzylamine carbonyl complex gave the amide in 84% yield. Although we cannot completely exclude the possibility of path A, these results suggest the reaction proceeds via path B, transmetalation of carbamoylmetalate.

The main difference between path A and B is whether the reaction proceeds via acylpalladium intermediate (path A) or carbamoylpalladium intermediate (path B). Then we performed the palladium-catalyzed reaction in the presence of reactive alkene to trap the palladium intermediates (Scheme 7). When norbornene was added to the

SCHEME 6. Mechanistic Investigation



SCHEME 7. Attempt To Trap the Palladium Intermediate



palladium-catalyzed reaction of iodobenzene, phenylcarbamoylation products **4** were obtained in 46% yield as a mixture of *syn* and *anti* stereoisomers along with benzamide **3a** and a small amount of 2-carbamoylnorbornane **5**.¹⁶ The fact that not benzoyl- but carbamoylnorbornane was obtained suggests that the reaction proceeds via carbamoylpalladium intermediate (path B in Scheme 1) although there is still a possibility to form product **4** via CO insertion to the norbornanyl palladium intermediate.

(16) If the reaction proceeds via phenylpalladation of norbornene followed by reductive elimination, *cis-exo* stereoisomer should be obtained. For *cis-exo* addition in palladium-catalyzed arylacylation of norbornene, see: Yamane, M.; Kubota, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 331. The mechanism of the formation of the *trans*-stereoisomer of **4** and 2-carbamoylnorbornane **5** is not clear at this stage. Further experimental investigations are necessary to make it clear.

Conclusions

In conclusion, palladium-catalyzed carbamoylation of aryl halides was accomplished by using aminopentacarbonyltungsten(0). The reaction may involve transmetalation between carbamoylmetalate and palladium(II) intermediate although the mechanism is not clear yet. This reaction can be performed without using gaseous carbon monoxide and may provide an alternative method of conventional palladium-catalyzed three-component coupling reaction of aryl halide, carbon monoxide, and amine.

Experimental Section

General Procedure for Pd-Catalyzed Carbamoylation of Aryl Halides. A mixture of tungsten amine complex **2a** (0.44 g, 1.0 mmol), aryl halide (1.5 mmol), Pd(OAc)₂ (5 mol % in the case of aryl iodide, 10 mol % in the case of aryl bromide), P(*o*-Tol)₃ (10 mol % in the case of aryl iodide, 20 mol % in the case of aryl bromide), and K₂CO₃ (0.152 g, 1.1 mmol) in THF (10 mL) was heated to reflux. The reaction was monitored by thin-layer chromatography. The volatile materials were removed under reduced pressure and the residue was purified by flash column chromatography (SiO₂, hexane:ethyl acetate = 8: 1) to afford the pure products **3a–i**.

N-Benzyl-4-vinylbenzamide (3f). Amide **3f** (0.15 g, 0.63 mmol) was synthesized following the general procedure. White solid; mp 116–117 °C; IR (KBr) 3280, 3261, 3082, 3030, 2922, 1641, 1564, 1502, 1454, 1427, 1357, 1323, 1246, 1078, 856, 700 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 4.62 (d, *J* = 6.0 Hz, 2H), 5.35 (d, *J* = 11.0 Hz, 1H), 5.82 (d, *J* = 17.5 Hz, 1H), 6.62 (br s, 1H), 6.73 (dd, *J* = 11.0, 17.5 Hz, 1H), 7.27–7.35 (m, 5H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm) 44.0, 116.0, 126.2, 127.3, 127.5, 127.8, 128.7, 133.3, 135.9, 138.2, 140.6, 167.0; ESI-HRMS found *m/z* 238.1221, calcd for C₁₆H₁₆NO (M + H)⁺ 238.1232.

Acknowledgment. We thank Nanyang Technological University for generous financial support.

Supporting Information Available: General experimental procedures for the synthesis of compounds **3** and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.