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Carbamoylation of Aryl Halides by Molybdenum or Tungsten Carbonyl Amine Complexes

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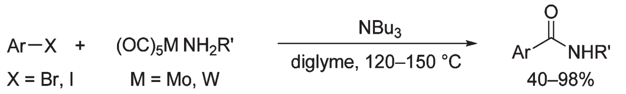

When aryl halide is treated with molybdenum carbonyl amine complex in the presence of base, carbamoylation proceeds to give amide in good yield. The proposed mechanism involves oxidative addition of aryl halide to molybdenum(0) complex, migratory insertion to carbon monoxide giving acyl(amino)molybdenum(II) or aryl(carbamoyl)molybdenum(II) intermediate, and reductive elimination of the amide. This method is simple and provides an alternative method to the conventional palladium-catalyzed amide formation using gaseous carbon monoxide.

Introduction

Amides are an important class of compounds in chemistry and biology that have been used as synthetic intermediates of many natural products and artificial functionalized materials.[1] Traditionally, amides have been synthesized by the reaction of activated carboxylic acid derivatives such as acid chlorides, anhydrides, and esters with amines.[2] Since Heck and coworkers reported the palladium-catalyzed three-component coupling of aromatic halide, carbon monoxide, and amine, this coupling has drawn much attention.[3,4] By using this reaction, one-carbon-elongated amides can be synthesized from aryl halides. The reaction proceeds with the catalytic mechanism depicted in Scheme 1. Oxidative addition of aryl halide to palladium(0) complex takes place to generate arylpalladium(II) intermediate A. Migratory insertion of carbon monoxide gives acylpalladium(II) complex B, followed by the reaction with amine, to afford amide with regeneration of palladium(0) catalyst. We recently proposed another possibility for palladium-catalyzed amide formation in the reaction of aryl halides and Group VI metal carbonyl amine complexes (Scheme 1, path B).[5] Other than the mechanism involving acylpalladium(II) intermediate B, we proposed one involving carbamoylpalladium(II) intermediate C. Although the mechanism was not clear, we could provide an alternative palladium-catalyzed amide formation without using gaseous carbon monoxide (Scheme 2).[6]

During the study on the above palladium-catalyzed amide synthesis by using Group VI metal carbonyl amine complexes, we found that the amides were obtained even without palladium catalyst when the reaction was performed at

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[1] (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. (b) Kim, J. W.; Kazuya, Y.; Mizuno, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 9249 and related reference therein.

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[3] (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327. (c) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761.

[4] (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109. (b) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 3931. (c) Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1996**, *61*, 7482. (d) Morera, E.; Ortar, G. *Tetrahedron Lett.* **1998**, *39*, 2835. (e) Schnyder, A.; Beller, M.; Mehltretter, G.; Nsenda, T.; Studer, M.; Indolese, A. F. *J. Org. Chem.* **2001**, *66*, 4311. (f) Schnyder, A.; Indolese, A. F. *J. Org. Chem.* **2002**, *67*, 594. (g) Skoda-Foldes, R.; Kollar, L. *Curr. Org. Chem.* **2002**, *6*, 1097. (h) Li, Y.; Alper, H.; Yu, Z. K. *Org. Lett.* **2006**, *8*, 5199. (i) Martinelli, J. R.; Clark, T. P.; Watson, D. A.; Munday, R. H.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8460. (j) Takacs, A.; Jakab, B.; Petz, A.; Kollar, L. *Tetrahedron* **2007**, *63*, 10372. (k) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402. (l) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102. (m) Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 7175. (n) Deagostino, A.; Larini, P.; Occhiato, E. G.; Pizzuto, L.; Prandi, C.; Venturello, P. *J. Org. Chem.* **2008**, *73*, 1941. (o) Takacs, A.; Farkas, R.; Kollar, L. *Tetrahedron* **2008**, *64*, 61. (p) Takacs, A.; Acs, P.; Farkas, R.; Kokotos, G.; Kollar, L. *Tetrahedron* **2008**, *64*, 9874. (q) Tambade, P. J.; Patil, Y. P.; Bhanushali, M. J.; Bhanage, B. M. *Synthesis* **2008**, *15*, 2347. (r) Csajagi, C.; Borcsek, B.; Niesz, K.; Kovacs, I.; Szekelyhidi, Z.; Bajko, Z.; Uerge, L.; Darvas, F. *Org. Lett.* **2008**, *10*, 1589. For a review, see: (s) Yasui, Y.; Takemoto, Y. *Chem. Rec.* **2008**, *8*, 386. (t) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

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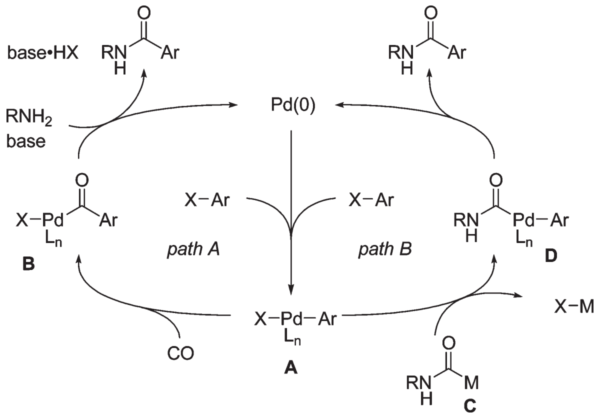
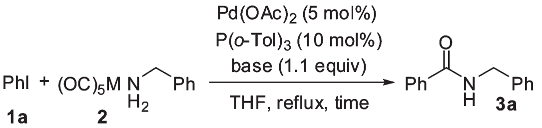
SCHEME 1. **Reported and Hypothetic Mechanism of Palladium-Catalyzed Amidation of Aryl Halides**

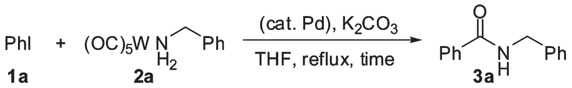


SCHEME 2. **Palladium-Catalyzed Carbamoylation of Phenyl Iodide with Group VI Metal Complexes**



	base	time	
2a (M = W)	LiHMDS	2 h	70%
	K_2CO_3	16 h	95%
2b (M = Mo)	K_2CO_3	20 h	90%
2c (M = Cr)	K_2CO_3	20 h	39%

SCHEME 3. **Carbamoylation of Iodobenzene in the Presence or Absence of Palladium Catalyst**



5 mol % $Pd(OAc)_2$ / 2P(o-Tol)$_3$	16 h	95%
without cat. Pd	72 h	< 4%

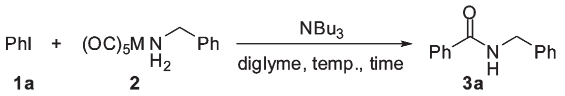
higher temperature. Here, we report molybdenum-mediated amide synthesis from aryl halides.

Results and Discussion

As shown in Scheme 3, we had reported that the palladium catalyst was indispensable for the carbamoylation of aryl halides using tungsten carbonyl amine complexes as the carbamoyl group source.[5] Without palladium catalyst, only a trace amount of product **3a** was obtained with some recovery of amine complex **2a** even after 72 h stirring in refluxing THF (bp 66 °C). Because the generation of a trace amount of the product suggests that a tungsten(0) intermediate can be a substitute for palladium catalyst, we performed the reactions in diglyme at higher temperatures (Table 1).

Although the results were not so much different when we performed the reaction at below 140 °C (entries 2 and 3), the product yield was dramatically increased up to 76% when we performed the reaction at 150 °C (entry 4). The tungsten complex was completely consumed within 3 h, and the amide **3a** was obtained in 76% yield. We checked the reactivity of the other group VI metal amine carbonyl complexes, and the corresponding molybdenum complex was found to provide an excellent yield of amide (entry 5). It is obvious that the molybdenum complex is more reactive than the tungsten complex, and 95% yield of amide **3a** was obtained when we performed the reaction even at 120 °C (entry 6). However, the chromium complex gave only a trace amount of the product (entry 8).

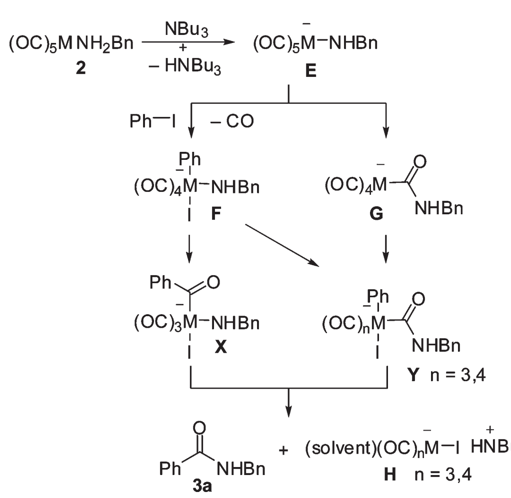
TABLE 1. **Carbamoylation of Iodobenzene with Group VI Metal Carbonyl Amine Complexes**[a]



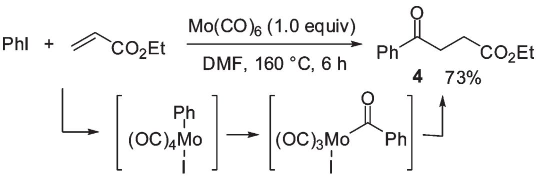
entry	M **2**	temp (°C)	time (h)	yield **3a** (%)	(%)[c]
1[b]	W **2a**	66	72	<4	(0)
2	W **2a**	100	20	6	(42)
3	W **2a**	120	18	6	(33)
4	W **2a**	150	3	76	(27)
5	Mo **2b**	150	1	97	(0)
6	Mo **2b**	120	1	95	(0)
7	Mo **2b**	90	20	6	(5)
8	Cr **2c**	150	3	tr	(0)

[a] Reactions were conducted with PhI (1.5 mmol), **2** (1.0 mmol), and NBu_3 (1.1 mmol) in diglyme. [b] K_2CO_3 and THF were used as the substitute for NBu_3 and diglyme. [c] Number in parentheses shows the recovery of **1a**.

SCHEME 4. **Proposed Mechanism of Carbamoylation of Iodobenzene**

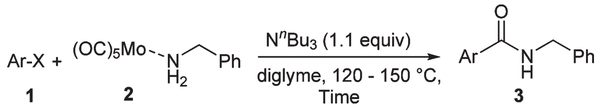


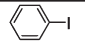
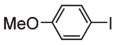
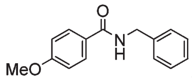
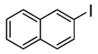
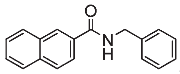
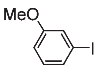
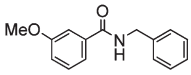
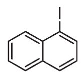
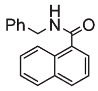
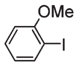
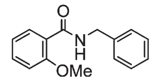
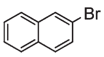
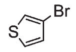
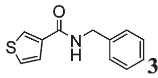
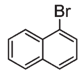
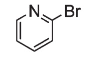
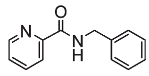
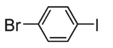
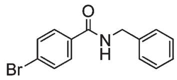
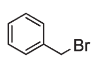
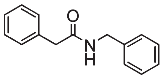
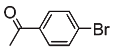
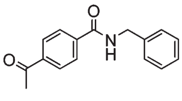
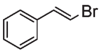
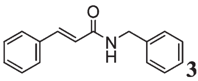
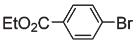
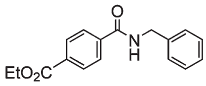
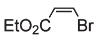
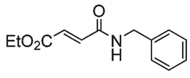
SCHEME 5. **Mo-Mediated Acylation of Acrylate Reported by Iwasawa**



Although the mechanism for this reaction is unclear, two possibilities must be taken into consideration as shown in Scheme 4. One involves generation of acyl metal intermediate **X**, and the other is generation of carbamoyl metal intermediate **Y**. Acyl metal intermediate **X** would be generated by the oxidative addition of iodobenzene to molybdenum complex **E**, followed by insertion of carbon monoxide to phenyl–molybdenum bond. Iwasawa and co-workers reported that aryl halides oxidatively added to low valent

TABLE 2. Carbamoylation of Organic Halides by $(CO)_5MoNH_2Bn$[a]



entry	Ar-X	product	time/ h	yield/ %	entry	Ar-X	product	time/ h	yield/ %
1		**3a**	1	95	9		 **3g**	1.5	95
2		 **3b**	1	95	10		 **3h**	1	80
3		 **3c**	1	87	11		 **3i**	1	88
4		**3b**	1	92	12		 **3j**	1.5	91
5		**3c**	1	87	13		 **3k**	1	49
6		 **3d**	0.5	75	14		 **3l**	1	78
7		 **3e**	3	89	15		 **3m**	1	93
8		 **3f**	3	88	16		 **3n**	5 min	57

[a]Reaction conditions: 1 (1.2 mmol), 2 (1.0 mmol), NBu_3 (1.1 mmol).

molybdenum complex at 160 °C in DMF and acylmolybdenum intermediate was formed in the reaction of acylation of alkenes (Scheme 5).[7,8] Carbamoyl metal complex **Y** would be generated from phenylmetal amide **F** or from carbamoyl metalate **G** by oxidative addition of iodobenzene. Although it is known that heteroatoms such as RO^- and R_2N^- on transition metals rarely migrate to carbon monoxide to form alkoxycarbonyl or carbamoyl metals,[9] we still cannot exclude the possibility of this mechanism involving carbamoyl metal intermediate. The formation of molybdenum(0) complex **H** was confirmed by isolating as $(OC)_4Mo(dppe)$ (74% yield) by adding dppe after the reaction.[10]

Thus, we found that molybdenum amine carbonyl complex gave the best yield, and then we examined the scope

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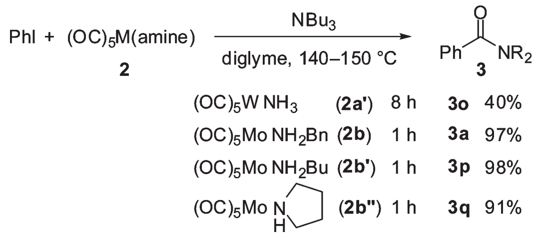
(10) A mixture of **2b** (0.44 g, 1.0 mmol), iodobenzene (0.306 g, 1.5 mmol), and $^nBu_3N$ (0.203 g, 1.1 mmol) in diglyme (10 mL) was heated at 150 °C for 1 h under N_2 atmosphere. The mixture was cooled to room temperature before 1,2-Bis(diphenylphosphino)ethane (dppe) (0.396 g, 1.0 mmol) was added, and the mixture was heated for another 1 h at 150 °C under N_2 atmosphere. Then the solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography (hexane/ethyl acetate = 10:1) to give **3a** (0.20 g, 0.95 mmol, yield 95%) as a white solid along with $(dppe)Mo(CO)_4$ (0.45 g, 0.74 mmol, yield 74%) as a white solid. For the NMR data of $(dppe)Mo(CO)_4$, see: Maitra, K. ; Nelson, J. H. *Polyhedron* **1999**, *18*, 203

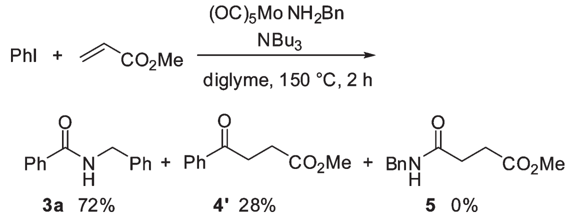
SCHEME 6. Carbamoylation of Iodobenzene with Some Molybdenum Amine Complexes



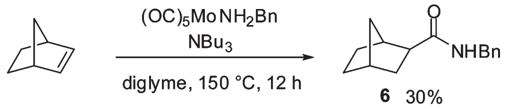
of the reaction by testing various kinds of aryl halides (Table 2). The reactions were carried out with 1:1.2 ratio of molybdenum benzylamine carbonyl complex and aryl halide in the presence of 1.1 molar amount of tributylamine as the base. Not limited to only aryl iodide, aryl bromide could also be applied for this carbamoylation reaction without decreasing the yields (entries 1−5). Aryl iodide, however, had better reactivity. This was proven by performing the reaction with 1-bromo-4-iodobenzene, and the selective formation of 4-bromobenzamide **3d** was confirmed (entry 6). Both electron-deficient and -rich aryl halides gave good yields (entries 7−9). Regardless of the substitution pattern, ortho, meta, or para, iodo(methoxy)benzenes gave the corresponding amides **3g**−**i** in good yields (entries 9−11). Not only aryl but also heteroaryl halides could be applied, although 2-bromopyridine gave the product **3k** in lower yield (49%) (entries 12 and 13). The low yield was probably due to the strong coordination of pyridine nitrogen to the molybdenum metal center. Benzyl bromide and alkenyl bromides were also applicable to this reaction, and 2-phenylacetoamide **3l** and α,*β*-unsaturated amides **3m**,**n** were obtained (entries 14−16). All reactions were completed in a short reaction time within 3 h, and this is in contrast to the fact that palladium-catalyzed carbamoylation of aryl halides with tungsten amine carbonyl complexes requires much longer reaction times (13−84 h).

We also investigated the scope of amine complexes for this reaction (Scheme 6). Because normally high temperature is necessary for palladium-catalyzed amide formation and using ammonia gas is hazardous and not very practical, the preparation of *N*-nonsubstituted amides is still fraught with difficulties.[11] Tungsten ammonia complex **2a**[12] was easily prepared from $(OC)_5WClNEt_4$ and ammonia solution in water and found to be utilizable for preparation of *N*-nonsubstituted benzamide **3o** in the reaction with iodobenzene. Primary amine **2b′** substituted by a primary alkyl group gave an excellent yield of amide **3p** (98%). Cyclic secondary amine complex **2b″** was also applicable for this reaction, and *N*-benzoylpyrrolidine **3q** was obtained in 91% yield.

SCHEME 7. Attempt To Trap the Molybdenum Intermediate by Acrylate



SCHEME 8. Attempt To Trap the Molybdenum Intermediate by Norbornene



To gain some insight on the mechanism of the reaction, we tested the reactions in the presence of reactive alkenes. If alkene could trap the organometallic intermediate, we could determine which mechanism depicted in Scheme 1 was correct, either the acylmolybdenum- or carbamoylmolybdenum-involving mechanism. Iwasawa reported aroylation of alkene when iodobenzene was reacted with ethyl acrylate in DMF at 160 °C as shown in Scheme 5.[8] When we tried the reaction in the presence of methyl acrylate, the similar aroylation product **4′** was obtained in 28% yield along with benzamide **3a** in 72% yield and no carbamoylation of acrylate took place (Scheme 7). Although the yield of the aroylation product **4′** was low, this finding supports the mechanism involving acylmolybdenum intermediate **X** (Scheme 4). We also tried the reaction in the presence of norbornene as the substitute for acrylate, however, it resulted in a complex mixture. When the reaction was performed without iodobenzene, it became rather clear and carbamoylated norbornane **6** was obtained in 30% yield (Scheme 8). This result indicates that the mechanism via carbamoylmolybdenum intermediate **Y** is still possible.

In conclusion, carbamoylation of aryl halides proceeded by using Group VI metal amine carbonyl complexes. It only requires a simple experimental procedure compared to conventional palladium-catalyzed amidation reactions. It does not require gaseous carbon monoxide and palladium catalysts.

Experimental Section

General Procedure for Carbamoylation of Aryl Halide Using Molybdenum Amine Carbonyl Complex. A mixture of $(OC)_5Mo\text{-}NH_2Bn$ (**2b**, 0.44 g, 1.0 mmol), aryl halide (1.2 mmol), and NBu_3 (0.203 g, 1.1 mmol) in diglyme (10 mL) was heated at the temperature indicated in Table 2 (120−150 °C) for 1−3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 8:1) to give the corresponding amide **3**.

4-Acetyl-*N*-benzylbenzamide (**3e**)[5]**.** White solid; mp 112−113 °C; IR (KBr) 3292, 3091, 3066, 2918, 1685, 1639, 1606, 1552, 1421, 1361, 1323, 1300, 1263, 985, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.60 (s, 3H), 4.63 (d, J = 5.6 Hz, 2H), 6.75 (br s, 1H), 7.28−7.35 (m, 5H), 7.86 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 26.7, 44.2, 127.3, 127.7, 127.9, 128.5, 128.8, 137.8, 138.2, 139.1, 166.4, 197.4.

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Supporting Information Available: General experimental procedures for the synthesis of complexes **2** and amides **3** and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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