

Pd-Catalyzed Carbonylative Reactions of Aryl Iodides and Alkynyl Carboxylic Acids via Decarboxylative Couplings

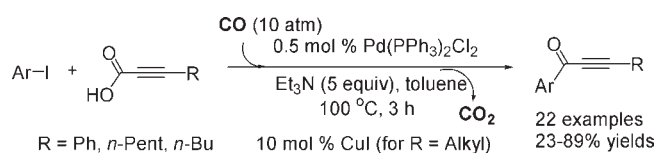
Ahbyeol Park, Kyungho Park, Yong Kim, and Sunwoo Lee*

Department of Chemistry, Institute of Basic Science, Chonnam National University, Gwangju, 500-757, Republic of Korea

sunwoo@chonnam.ac.kr

Received December 10, 2010

ABSTRACT



Alkynyl carboxylic acids reacted with aryl iodides under a CO atmosphere in the presence of a palladium catalyst to produce α,β -alkynyl aryl ketones in good yields. The maximum turnover number was 16 800. The desired carbonylative coupling was formed from phenyl propionic acid without any formation of a noncarbonylative coupling product in the absence of CuI. However, the reaction with alkyl-substituted alkynyl carboxylic acids required CuI as a cocatalyst for high yield.

The palladium-catalyzed carbonylation of aryl halides to give carboxylic acid derivatives has been widely used as a valuable tool in organic synthesis.¹ These reactions share the incorporation of carbon monoxide into aryl halides in the presence of a variety of nucleophiles. Since Heck first reported palladium-catalyzed aminocarbonylation and alkoxy carbonylation in 1974,² a number of related reaction methods have been developed. As a nucleophile, amines, alcohols, hydrogen, aryl metal reagents, and alkynes have been employed in the palladium-catalyzed carbonylation. However, the carbonylative Sonogashira reaction, which is the carbonylative three-component cross coupling of aryl halides with a terminal alkyne, has received little attention even though its product, which is an α,β -alkynyl ketone, is

a crucial moiety in many biologically active molecules,³ natural products,⁴ and pharmaceutical materials.⁵

A traditional route to synthesize the α,β -alkynyl ketone involves the coupling reaction of alkynyl organometallic reagents and acid chlorides.⁶ However, these methods have the drawback of needing to be handled in dry solvent under an inert atmosphere.⁷

To solve this problem, the palladium-catalyzed coupling reactions of aryl halides and alkyne source in the presence of carbon monoxide have been used as an alternative

(1) (a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation, Direct Synthesis of Carbonyl Compounds*; Plenum: New York, 1991. (b) Beller, M. In *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 1; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996; pp 148–159. (c) Skoda-Földes, R.; Kollár, L. *Curr. Org. Chem.* **2002**, *6*, 1097–1119. (d) Brennfürer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114–4133.

(2) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318–3326. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.

(3) (a) Savarin, C. G.; Murry, J. A.; Dormer, P. G. *Org. Lett.* **2002**, *4*, 2071–2074. (b) Karpov, A. S.; Muller, T. J. *Org. Lett.* **2003**, *5*, 3451–3454.

(4) (a) Vong, B. G.; Kim, S. H.; Abraham, S.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3947–3951. (b) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2004**, *126*, 13942–13944.

(5) (a) Chang, K.-T.; Choi, S.-H.; Kim, S.-H.; Yoon, Y.-J.; Lee, W. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 207–210. (b) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95–98.

(6) (a) Walton, D. R. M.; Waught, F. J. *Organomet. Chem.* **1972**, *37*, 45–56. (b) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549–2553.

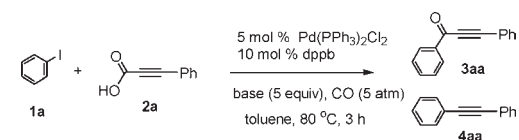
(7) (a) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777–778. (b) Alonso, D. A.; Najera, C.; Pacheco, M. C. *J. Org. Chem.* **2004**, *69*, 1615–1619. (c) Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J. P. H.; Kantacha, A. *Chem. Commun.* **2005**, 1037–1039.

approach. However, they also suffer two disadvantages: the metalated alkynes such as alkynylstannanes⁸ or alkynylsilanes⁹ have a waste problem due to the metal salts, and the terminal alkyne requires a high reaction temperature and high carbon monoxide pressure.¹⁰ An alternative pathway for the synthesis of α,β -alkynyl ketone is the palladium-catalyzed carbonylative coupling reaction of terminal alkynes with aryl iodides. Since Mori reported the carbonylative Sonogashira coupling reaction under mild conditions,¹¹ a variety of reaction methods have been developed, including copper-free, water solvent, ionic liquids, microflow, and recyclable catalytic systems.¹² In addition, a copper-catalyzed, palladium-free carbonylative Sonogashira coupling reaction has also been reported.¹³ However, they suffer the following drawbacks: long reaction time, high catalytic loading, high carbon monoxide pressure, and the formation of noncarbonylative Sonogashira product as a byproduct.

Due to their environmental friendliness as a leaving group, carboxylic acids have recently been considered candidates for the coupling partner in the transition metal-catalyzed coupling reactions.¹⁴ Since we first reported the palladium-catalyzed decarboxylative coupling of the alkynyl carboxylic acid,¹⁵ several other groups have employed the alkynyl carboxylic acid as the coupling substrate in a variety of coupling reactions.¹⁶

Palladium-catalyzed decarboxylative carbonylations have been reported.¹⁷ However, in the absence of any report on the use of alkynyl carboxylic acid in the carbonylation

Table 1. Optimization of the Bases and the Solvents for the Carbonylation^a



entry	base	solvent	conv (%) ^b	yield (%) ^b	
				3aa	4aa
1	DBU	DMSO	100	5	22
2 ^c	DBU	DMSO	100	0	98
3	DBU	Toluene	52	23	8
4	DBU	CH ₃ CN	23	6	5
5	Et ₃ N	Toluene	68	54	1
6	Pyridine	Toluene	3	0	0
7	PhN(Et) ₂	Toluene	0	0	0
8	(<i>n</i> -Pr) ₃ N	Toluene	2	0	0
9	N(<i>i</i> -Pr) ₂ Et	Toluene	10	0	0
10	Na ₂ CO ₃	Toluene	0	0	0
11	K ₂ CO ₃	Toluene	0	0	0
12	Cs ₂ CO ₃	Toluene	59	42	4
13	Et ₃ N	Xylene	59	52	5
14	Et ₃ N	DMSO	99	46	44
15	Et ₃ N	DMF	68	49	2
16	Et ₃ N	Dioxane	70	52	3
17	Et ₃ N	H ₂ O	0	0	0

^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), Pd (0.015 mmol), dppb (0.03 mmol), base (1.5 mmol), DMSO (1.0 mL), CO (5 atm) at 80 °C for 3 h. ^b Yield was determined by GC. ^c In the presence of CuI (0.03 mmol).

(8) (a) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417–6422. (b) Grisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500–7506.

(9) Arcadi, A.; Cacchi, S.; Marinelli, F.; Pace, P.; Sanzi, G. *Synlett* **1995**, 823–824.

(10) Delaude, L.; Masdeu, A. M.; Alper, H. *Synthesis* **1994**, 1149–1151.

(11) Mohamed Ahmed, M. S.; Mori, A. *Org. Lett.* **2003**, *5*, 3057–3060.

(12) (a) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391–393. (b) Liang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 6097–6100. (c) Fukuyama, T.; Yamaura, R.; Ryu, I. *Can. J. Chem.* **2005**, *83*, 711–715. (d) Liu, J.; Peng, X.; Sun, W.; Zhao, Y.; Xia, C. *Org. Lett.* **2008**, *10*, 3933–3936. (e) Liu, J.; Chen, J.; Xia, C. *J. Catal.* **2008**, *253*, 50–56.

(13) Tambade, P. J.; Patil, Y. P.; Nandurkar, N. S.; Bhanage, B. M. *Synlett* **2008**, 886–888.

(14) For some selected examples: (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664. (b) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312–6314. (c) Miyasaki, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674–3677. (d) Bilodeau, F.; Brochu, M.-C.; Guimond, N.; Thesen, K. H.; Forgione, P. *J. Org. Chem.* **2010**, *75*, 1550–1560. (e) Goossen, L. J.; Rodríguez, N.; Lange, P. P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111–1114. (f) Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 592–595. (g) Zhang, S.-L.; Fu, Y.; Shang, R.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 638–646.

(15) (a) Moon, J.; Jeong, M.; Nam, H.; Ju, J.; Moon, J. H.; Jung, H. M.; Lee, S. *Org. Lett.* **2008**, *10*, 945–948. (b) Moon, J.; Jang, M.; Lee, S. *J. Org. Chem.* **2009**, *74*, 1403–1406. (c) Park, K.; Bae, G.; Moon, J.; Choe, J.; Song, K. H.; Lee, S. *J. Org. Chem.* **2010**, *75*, 6244–6251.

(16) (a) Kim, H.; Lee, P. H. *Adv. Synth. Catal.* **2009**, *351*, 2827–2932. (b) Zhang, W.-W.; Zhang, X.-G.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 5259–5264. (c) Feng, C.; Loh, T.-P. *Chem. Commun.* **2010**, 46, 4779–4781. (d) Kolarović, A.; Fáberováč, Z. *J. Org. Chem.* **2009**, *74*, 7199–7202. (e) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000–2003.

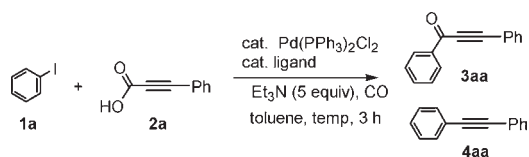
(17) (a) Knight, J. G.; Lawson, I. M.; Johnson, C. N. *Synthesis* **2006**, 227–230. (b) Zheng, Z.; Alper, H. *Org. Lett.* **2009**, *11*, 3278–3281.

reaction, we investigated the decarboxylative carbonylation of alkynyl carboxylic acid and aryl iodide.

We studied the optimized conditions for the carbonylation of decarboxylative coupling with phenyl iodide and phenyl propiolic acid as the substrate (Table 1).

First, the reaction was carried out in the presence of carbon monoxide according to our previously reported optimization conditions for the decarboxylative coupling of phenyl iodide and phenyl propiolic acid. Unfortunately, the desired carbonylative product was obtained in only 5% yield, and a noncarbonylative decarboxylative coupling product was formed in 22% yield (entry 1). However, following the addition of CuI as a cocatalyst, only noncarbonylative coupling product **4aa** was produced in 98% yield (entry 2). Using toluene and acetonitrile instead of DMSO solvent, toluene gave the desired product **3aa** in 23% yield but acetonitrile showed only a 6% yield of product (entries 3 and 4). In toluene solvent, a variety of bases were tested. In the case of organic bases, only Et₃N afforded the desired carbonylative product **3aa** in 54% yield (entry 5), whereas the other tertiary amines did not produce any coupling products (entries 6–9). Among the tested inorganic bases, Cs₂CO₃ resulted in a 42% yield of product (entry 12). In the presence of Et₃N as a base, a variety of solvents were tested. Although most solvents

Table 2. Effects of Ligands, Temperature, Amount of Catalyst, and Pressure of Carbon Monoxide^a



entry	Pd (mol %)	ligand	CO (atm)	temp (°C)	conv (%) ^b	yield (%) ^b	
						3aa	4aa
1	5	Dppm	5	80	46	43	6
2	5	Dppe	5	80	60	50	5
3	5	Dppbz ^c	5	80	48	23	5
4	5	Xantphos ^f	5	80	69	38	4
5	5	-	5	80	99	82	5
6 ^c	5	-	5	80	40	33	0
7 ^d	5	-	5	80	44	25	0
8	1	-	5	80	99	86	5
9	1	-	10	100	100	89	0
10	0.5	-	10	100	100	91	0
11	0.05	-	10	100	91	87	0
12	0.005	-	10	100	87	84	0

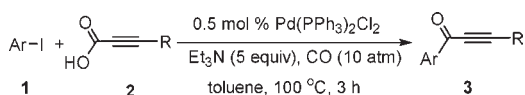
^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), Pd(PPh₃)₂Cl₂ (0.015–0.003 mmol), ligand (0.03 mmol), Et₃N (1.5 mmol), DMSO (1.0 mL), CO (5–10 atm) at 80–100 °C for 3 h. ^b Yield was determined by GC. ^c Pd(OAc)₂ was employed. ^d Pd(dba)₂ was employed. ^e 1,2-Bis(diphenylphosphino)benzene. ^f 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

showed similar product yields, DMSO afforded almost equal amounts of **3aa** and **4aa** (entry 14). Water, which was a good solvent in the case of terminal acetylene, did not show any coupled product (entry 17). Toluene was the most suitable solvent due to its high selectivity for the carbonylation.

Next, we tested other conditions such as a variety of ligands, palladium sources, carbon monoxide pressures, reaction temperatures, and amounts of catalyst as shown in Table 2.

In the presence of chelating phosphine ligands, the yield was not improved (entries 1–4). Interestingly, Pd(PPh₃)₂Cl₂ resulted in an 82% yield of **3aa** and a 5% yield of **4aa** in the absence of any additional ligand (entry 5). However, other palladium sources bearing nonphosphine ligands such as Pd(OAc)₂ and Pd(dba)₂ produced low yields (entries 6 and 7). With a decreasing palladium amount, the product yield was increased to 86%; however, the yield of byproduct was not decreased (entry 8). When the carbon monoxide pressure and reaction temperature were increased to 10 atm and 100 °C, respectively, only **3aa** was obtained without any **4aa** being formed (entry 9). Finally, 0.5 mol % of Pd(PPh₃)₂Cl₂ afforded a 91% yield of **3aa** under 10 atm and 100 °C. When the catalyst amount was decreased to 0.05 mol %, the conversion was not completed (entry 11). At a catalyst loading of 0.005 mol % catalyst, the turnover number was 16 800 (entry 12).

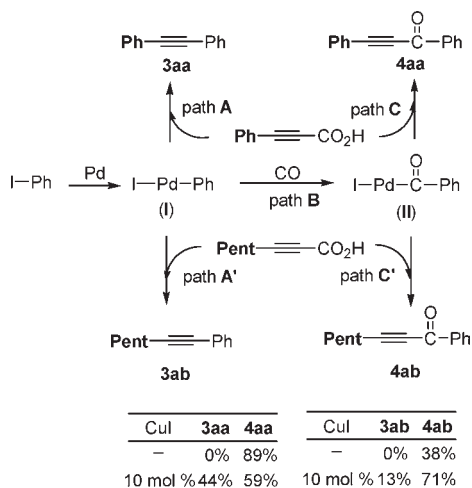
Table 3. Carbonylation of Alkynyl Carboxylic Acids with Aryl Iodides^a



entry	Arl	R	product ^b			
			yield (%)	3		
1		1a	Ph	2a	89	3aa
2		1b	Ph	2a	83	3ba
3		1c	Ph	2a	84	3ca
4		1d	Ph	2a	65	3da
5		1e	Ph	2a	77	3ea
6		1f	Ph	2a	80	3fa
7		1g	Ph	2a	81	3ga
8		1h	Ph	2a	78	3ha
9		1i	Ph	2a	87	3ia
10		1j	Ph	2a	87	3ja
11		1k	Ph	2a	42	3ka
12		1l	Ph	2a	52	3la
13		1m	Ph	2a	78	3ma
14		1n	Ph	2a	58	3na
15		1o	Ph	2a	53	3oa
16		1p	Ph	2a	63	3pa
17		1a	<i>n</i> -Pent	2b	38(81 ^c)	3ab
18		1f	<i>n</i> -Pent	2b	42(57 ^c)	3fb
19		1l	<i>n</i> -Pent	2b	23(42 ^c)	3lb
20		1a	<i>n</i> -Pr	2c	35(58 ^c)	3ac
21		1o	<i>n</i> -Pr	2c	32(57 ^c)	3oc
22		1q	<i>n</i> -Pr	2c	43(78 ^c)	3qc

^a Reaction conditions: **1** (2.0 mmol), **2** (2.0 mmol), Pd(PPh₃)₂Cl₂ (0.015 mmol), Et₃N (10.0 mmol), solvent (5.0 mL), CO (10 atm) at 100 °C for 3 h. ^b Isolated yields. ^c The reaction was carried out in the presence of 10 mol % CuI.

We intended to expand the scope of aryl iodide and propiolic acid derivatives for the palladium-catalyzed carbonylation of decarboxylative coupling. The results are summarized in Table 3. Iodobenzene afforded the desired product in 89% isolated yield (entry 1), while *ortho*-, *meta*- and *para*-iodotoluene produced the corresponding carbonylative coupling products in 83%, 84%, and 65% yields, respectively (entries 2–4). All iodoanisoles showed good yields (entries 5–7). 1-Iodonaphthalene (**1h**) afforded the desired product in 78% yield (entry 8).

Scheme 1. Effect of CuI in the Carbonylation

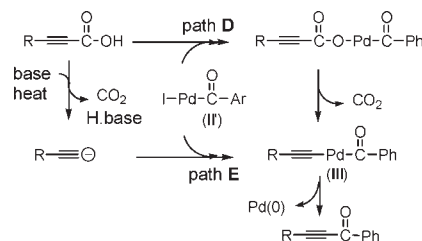
Aryl iodides bearing electron-withdrawing groups such as trifluoromethyl, chloro, nitrile, methyl ester, and acetyl afforded the corresponding carbonylative coupling products in 87%, 87%, 42%, 52%, and 78% yields, respectively (entries 9–13). 2,4-Dimethyliodobenzene (**1n**) resulted in a 58% yield (entry 14). Heteroaromatic aryl iodides such as 2-iodothiophene and 3-iodopyridine afforded the desired product in 53% and 63% yields, respectively (entries 15 and 16). Although the alkyl-substituted alkynyl carboxylic acids such as **2b** and **2c** produced low yields, the yields were increased when the reaction was carried out in the presence of 10 mol % CuI (entries 17–22).

The aryl iodides showed similar reactivities in the carbonylation of decarboxylative coupling independent of the substituted group's electronic properties. However, in the competition reaction, when equal amounts of 4-trifluoromethyliodobenzene and 4-iodoanisole were treated with phenyl propiolic acid under carbonylation coupling conditions, a 4-trifluoromethyliodobenzene-coupled product was obtained as a major product (**3ga/3ia** = 18%/70%).¹⁸ In addition, when equal amounts of phenyl propiolic acid (**2a**) and octynoic acid (**2b**) were reacted with iodobenzene in the absence of CuI, more product was formed from phenyl propiolic acid than from octynoic acid.¹⁹ The reactivity of octynoic acid was less than that of phenyl propiolic acid in the carbonylative decarboxylative coupling reaction.

A copper cocatalyst is known to accelerate the carbonylative and noncarbonylative Sonogashira reactions of terminal alkynes.¹¹ We found that CuI afforded a noncarbonylative coupling product dominantly as shown in entry 2 of Table 1. Based on this result, we studied the effect of CuI under our optimized conditions (Scheme 1).

(18) See Supporting Information.

(19) **3aa** (64%)/**3ab** (28%); see Supporting Information.

Scheme 2. Proposed Mechanism

In the case of the phenyl propiolic acid **2a**, the carbonylative product **4aa** was dominant in the absence of CuI, whereas the noncarbonylative coupling product **3aa** was also produced in a 44% yield in the presence of CuI. Our results indicated that the rate of the transmetalation of phenyl propiolic acid toward arylpalladium iodide complex **I** was slower than that of the insertion of carbon monoxide toward arylpalladium iodide complex **I** in the absence of CuI, which preferentially supports the formation of carbonylative coupling product **4aa** (path A < path B). However, in the presence of CuI, the yields of both products were similar due to the similarity in their rates (path A ≤ path B). In the case of octynoic acid **2b**, the formation of the carbonylative product **4ab** was predominant both with and without CuI, even though its yield was low in the absence of CuI. We suggested two possible pathways for the decarboxylation to form the alkynyl acylpalladium complex **III** as shown in Scheme 2. One is the initial reaction with alkynyl carboxylic acid and alkynyl carboxylic acid, followed by decarboxylation (path D). The other is the decarboxylation induced first by base and thermal heating, followed by reaction with an acylpalladium complex (path E). The mechanism of this reaction has not been fully elucidated, and further mechanistic studies are needed.

In conclusion, we employed alkynyl carboxylic acid derivatives as substrates in the palladium-catalyzed carbonylation of aryl iodide. The decarboxylation occurred even under high carbon monoxide pressure. The desired carbonylative coupling was formed from phenyl propiolic acid without any formation of a noncarbonylative coupling product in the absence of CuI. However, in the case of alkyl-substituted alkynyl carboxylic acids, CuI was required as a cocatalyst to ensure a high yield of the desired carbonylative product, as this was formed in low yield in the absence of CuI.

Acknowledgment. This work was supported by a National Research Foundation of Korea grant funded by the Korean Government (2009-0077677)

Supporting Information Available. Reaction procedures and spectral and analytical data for reaction products. This material is available free of charge via the Internet at <http://pubs.acs.org>.