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One-Pot Synthesis of Diarylalkynes Using Palladium-Catalyzed Sonogashira Reaction and Decarboxylative Coupling of sp Carbon and sp^2 Carbon

Jeongju Moon,[†] Miso Jeong,[†] Hyungoog Nam,[†] Jinhun Ju,[†] Joong Ho Moon,[‡] Hyun Min Jung,[§] and Sunwoo Lee*,[†]

Department of Chemistry, Chonnam National University, 300 Yongbong-dong, Buk-gu, Gwangju, 500-757, Republic of Korea, ICx Nomadics, Inc., 215 First Street, Suite 105, Cambridge, Massachusetts 02142, and Advanced Materials Division, Korea Research Institute of Chemical Technology, 100 Jang-dong, Yuseong-gu, Daejeon, 305-600, Republic of Korea

sunwoo@chonnam.ac.kr

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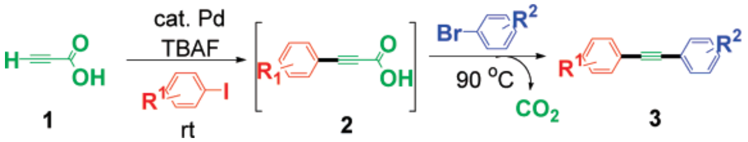
ABSTRACT



Decarboxylative coupling of sp-sp^2 carbons is possible by palladium catalyst. Employing propiolic acid (1) as a difunctional alkyne, and using the consecutive reactions of the Sonogashira reaction and the decarboxylative coupling, unsymmetrically substituted diaryl alkynes were obtained in moderate to good yield.

The Sonogashira reaction of terminal alkynes with aryl or alkenyl halides is the most straightforward and powerful existing method for constructing C(sp)−C(sp^2) bonds[1] and has been used for the synthesis of pharmaceuticals, natural products, and advanced functional materials. Generally, the Sonogashira reaction is carried out in the presence of a palladium catalyst and copper iodide, using an amine as solvent. Since its inception, many new developments related to the Sonogashira reaction have been reported in chemical literature, including improvements in the catalytic efficiency of the process,[2] copper- and/or amine-free versions,[3] and the ability to run the reaction in aqueous media or without solvent.[4] In order to synthesize unsymmetrically substituted diaryl alkynes using the Sonogashira reaction, acetylenes protected with silanes or other metals (Sn, Zn, and B) and aryl halides activated by copper and a base are generally required.[5]

However, these methods are not ideal because they require relatively long synthetic procedures for the protection and deprotection of alkynes, and thus are not economical. They

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[†] Chonnam National University.
[‡] ICx Nomadics, Inc.
[§] Korea Research Institute of Chemical Technology.

(1) For recent selected reviews, see: (a) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (c) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (d) Jutand, A. *Pure Appl. Chem.* **2004**, *76*, 565.

(2) (a) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993. (b) Köllhfer, A.; Pullmann, T.; Plenio, H. *Adv. Synth. Catal.* **2005**, *347*, 1295. (c) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2005**, *46*, 1717.

(3) For selected examples, see: (a) Ljungdahl, T.; Pettersson, K.; Albinsson, B.; Märtensson, J. *J. Org. Chem.* **2006**, *71*, 1677. (b) Li, P.-H.; Wang, L. *Adv. Synth. Catal.* **2006**, *348*, 681. (c) Ruiz, J.; Cutillas, N.; Lopez, F.; Lopez, G.; Bautista, D. *Organometallics* **2006**, *25*, 5768. (d) Gonzalez-Arellano, C.; Abad, A.; Corma, A.; Garcia, H.; Iglesias, M.; Sanchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1536.

(4) Marsden, J. A.; Haley, M. M. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 6.

(5) We presented the related works in Poster Session 1 at Tetrahedron 50th Anniversary Meeting Challenges in Organic Chemistry, Eight Tetrahedron Symposium, 26−29 June 2007, Berlin, Germany, 2007; pp 1, 44.

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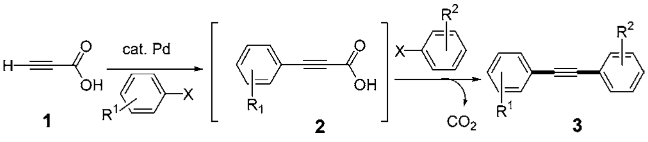
also produce an equivalent of metal complex as waste. Therefore, it is vital to develop an environmentally friendly, economical, and copper-free palladium catalytic system, such as we describe here, to apply the Sonogashira reaction intensively in chemical industry. Here, we introduce a decarboxylative coupling method using propiolic acid (**1**) and aryl halides with a copper-free palladium catalyst to produce unsymmetrically substituted diaryl alkyne **3** (Scheme 1).

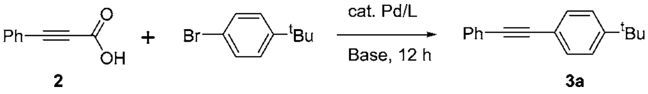
Scheme 1. One-Pot Synthesis of Diarylalkynes from Propiolic Acid



In devising this reaction, we first investigated the catalytic applicability of the decarboxylative coupling of aryl bromide and phenylpropiolic acid, since decarboxylative coupling of sp carbon and sp^2 carbon has never been reported.[6] To the best of our knowledge, decarboxylative cross-coupling has so far only been reported for sp^3-sp^3, sp^2-sp^2, and $sp-sp^3$ bond formation.[7]

We screened a variety of palladium sources, ligands, and additives for use in the decarboxylative coupling of phenylpropiolic acid and 4-*tert*-butyl-bromobenzene. As shown in Table 1, monodentate arylphosphines, such as PPh_3, showed very low yield. Among bidentate phosphine ligands, 1,1′-bis(diphenylphosphino)ferrocene (dppf) afforded the highest yield (entry 4). Among monodentate alkylphosphines, P^tBu_3 showed the best result (entry 8). Decreasing the ratio of palladium to ligand to 1/1, the product yield was decreased to 53% (entry 10). A palladium to ligand ratio of 1/2 was found to provide the best conditions for obtaining the desired product with high yield. Most palladium sources showed good yields, but $Pd_2(dba)_3$ (dba = dibenzylideneacetone) yielded the best results (entry 8). The temperature required for this reaction is above 90 °C, as inferior results were obtained at 60 °C (entry 14). Decreasing the amount of TBAF decreased the reaction yields (entry 13). Varying the base used also had a significant effect on the reaction. Tetrabutylammonium fluoride (TBAF) gave the product in 97% yield, while other types of tetrabutylammonium salts afforded no desired product or produced low yield (entries 15−17).

Table 1. Palladium-Catalyzed Decarboxylative Coupling Reaction of Phenylpropiolic Acid and 4-*tert*-Butyl-bromobenzene[a]



entry	ligand	Pd/L	base (equiv)	convn (%)	yield (%)[b]
1	PPh_3	1/2	TBAF(2)	56	19
2	Dppm	1/2	TBAF(2)	54	14
3	Dppe	1/2	TBAF(2)	51	28
4	Dppf	1/2	TBAF(2)	88	45
5	Xantphos[c]	1/2	TBAF(2)	70	30
6	PCy_3	1/2	TBAF(2)	64	54
7	$BiphP^tBu_2$	1/2	TBAF(2)	55	22
8	P^tBu_3	1/2	TBAF(2)	100	97
9	P^tBu_3	1/1.5	TBAF(2)	80	67
10	P^tBu_3	1/1	TBAF(2)	62	53
11[d]	P^tBu_3	1/2	TBAF(2)	100	72
12[e]	P^tBu_3	1/2	TBAF(2)	100	68
13	P^tBu_3	1/2	TBAF(1)	90	53
14[f]	P^tBu_3	1/2	TBAF(2)	27	15
15	P^tBu_3	1/2	TBAI(2)	15	2
16	P^tBu_3	1/2	TBABr(2)	11	0
17	P^tBu_3	1/2	TBACl(2)	13	0
18	P^tBu_3	1/2	NEt_3 (2)	0	0
19	Dppf	1/1	TBAF(2)	78	48
20	Dppf	1/1	TBAF(4)	100	70
21	Dppf	1/1	TBAF(6)	100	88

[a] Reaction conditions; 1.0 mmol phenylpropiolic acid, 1.0 mmol 4-*tert*-butyl-bromobenzene, 3 mL NMP, 5 mol % Pd ($Pd_2(dba)_3$). [b] Yield was determined by GC. [c] 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. [d] $Pd(OAc)_2$ was used instead of $Pd_2(dba)_3$. [e] $Pd(CH_3CN)_2Cl_2$ was used instead of $Pd_2(dba)_3$ [f] Reaction temperature is 60 °C.

Triethylamine, which is typically employed to accelerate the Sonogashira reaction, failed to give the desired product under this reaction condition (entry 18). When dppf′ was used as ligand, a palladium to ligand ratio of 1:1 showed high yield of desired product. However, 6 equiv of TBAF were required to obtain a high yield of product (entry 21). It is noteworthy that this catalytic system produces no trace of a diyne compound derived from the dimerization of alkynes, a common byproduct that plagues Sonogashira reactions. In addition, this reaction method could exclude the phenylacetylene-added side product which is often produced when phenylacetylene is used as an alkyne source.

Based on the reaction conditions of the decarboxylative couplings, we attempted to expand this transformation to the synthesis of unsymmetrically substituted diaryl alkynes from propiolic acid. To achieve this goal, we first had to identify appropriate reaction conditions for the synthesis of phenylpropiolic acid (step A), which is employed in the decarboxylative coupling (step B), from propiolic acid (**1**) and aryl halides (Table 2).

Propiolic acid (**1**) and iodobenzene were reacted under catalytic conditions with $Pd_2(dba)_3$ and P^tBu_3 at 90 °C. The conversion of iodobenzene was 100%. However, the diphenylacetylene (**4a**) was obtained as the major product (entry 1). Decreasing the reaction temperature caused a decrease

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(6) sp^3-sp^3 bond formation: (a) Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977. (b) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002. sp^2-sp^2 bond formation: (c) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (d) Becht, J.-M.; Catala, C.; Drian, C. L.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781. (e) Goossen, L. J.; Rodríguez, N.; Melzer, G.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. $sp-sp^3$ bond formation: (f) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510.

(7) For selected papers on the role of tetrabutylammonium ion in the cross-coupling reactions: (a) Calo, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. *J. Org. Chem.* **2003**, *68*, 2929. (b) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559.

Table 2. Synthesis of Unsymmetrically Substituted Diaryl Alkynes from Propiolic Acid[a]

entry	step[a]	% Pd[b], L, equiv of TBAF	temp (C°)	yield (%)[c]			
				convn	**2**[d]	**3a**	**4a**
1	A	5, P^{t}Bu$_3$, (2)	90	100	4	*e*	42
2	A	5, P^{t}Bu$_3$, (2)	60	100	11	*e*	27
3	A	5, P^{t}Bu$_3$, (2)	25	46	31	*e*	6
4	A	5, P^{t}Bu$_3$, (4)	25	32	20	*e*	8
5	A	5, P^{t}Bu$_3$, (6)	25	30	21	*e*	6
6	A	5, dppf, (2)	25	65	58	*e*	trace
7	A	10, dppf, (2)	25	100	94	*e*	trace
8[f]	A+B	10, dppf, (2)	25, 90	100	–	72	trace
9[f]	A+B	10, dppf, (6)	25, 90	100	–	90	trace

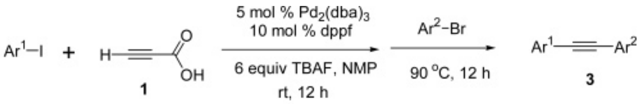
[a] Reaction conditions; step A: 1.0 mmol PhI, 1.0 mmol **1**, 3 mL NMP, Pd/L = 1/2 (for entries 1–5), Pd/L = 1/1 (for entries 6–9), TBAF were reacted for 12 h; step B: after step A, 1.0 mmol 4-^{t}BuC$_6$H$_4$Br was added and reacted for 12 h. [b] Mol % of Pd (from Pd$_2$(dba)$_3$ with respect to PhI). [c] Yield was determined by GC. [d] The product was converted to methyl ester using BF$_3$Et$_2$O with methanol. [e] No subject. [f] Step A at 25 °C for 12 h and step B at 90 °C for 12 h.

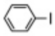
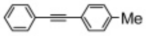
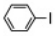
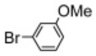
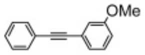
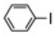
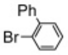
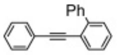
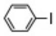
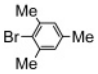
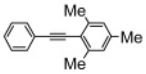
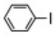
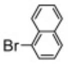
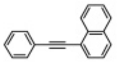
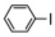
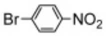
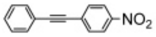
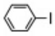
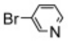
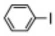
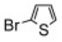
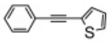
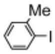
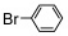
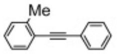
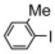
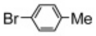
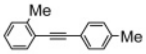
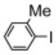
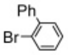
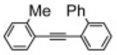
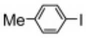
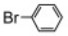
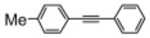
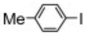
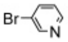
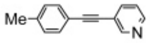
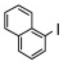
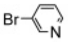
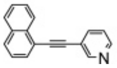
in both conversion and **4a** yield, and the desired product yield was increased but not sufficiently (entry 3). Using P^{t}Bu$_3$ as ligand and increasing the amount of TBAF to 6 equiv did not increase the yield of **2** (entry 5). Replacing the ligand P^{t}Bu$_3$ with dppf, and increasing the mol % of the catalyst, afforded phenylpropiolic acid in 94% yield as well as a trace amount of **4a** (entry 7). Based on these reaction conditions, after the Sonogashira reaction of propiolic acid (**1**) and iodobenzene, the decarboxylation using 4-*tert*-butyl-bromobenzene proceeded at 90 °C to afford the unsymmetrically diarylated acetylene **3a** with 72% (entry 8) yield. A dramatic improvement was observed when the amount of TBAF was increased by up to 6 equiv (entry 9).

The scope of the one-pot synthesis of unsymmetrical diaryl alkynes was explored. Aryl iodide was employed for the Sonogashira reaction with propiolic acid (**1**). Next, aryl bromide was employed for the decarboxylative coupling, and the reaction was carried out at 90 °C. The results are summarized in Table 3.

The one-pot reaction proceeded smoothly to produce unsymmetric diarylalkynes in moderate to good yield. Considering the reaction yields, electron-neutral and -rich aryl iodides all seemed to be coupled with propiolic acid to give the corresponding arylpropiolic acid. When using aryl bromide as a partner for the decarboxylative coupling reactions, all electron-neutral, -donating, and -withdrawing substituents in the substrates afforded the desired coupled products in good yields. In particular, 2-bromobiphenyl afforded a 94% yield of the corresponding diarylalkynes (entry 3). In our reaction, ortho-substituted aryl bromides afforded high yields (entries 3–5 and 11). Moreover, a sterically congested aryl bromide, such as bromomesitylene, also gave the desired coupling products in 91% yield (entry 4). However, an electron-rich meta-substituted aryl bromide showed low yield (entry 2). The heterocyclic bromides, such as 3-bromopyridine and 2-bromothiophene, also react smoothly in the decarboxylative couplings (entries 7, 8, 13, and 14).

Table 3. Synthesis of Unsymmetrical Diaryl Alkynes[a]

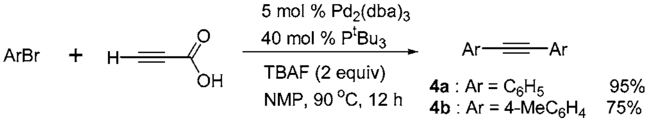


entry	Ar^{1}I	Ar^{2}Br	Ar^1–≡–Ar^2		yield (%)[b]
1				**3b**	86
2				**3c**	48
3				**3d**	94
4				**3e**	91
5				**3f**	70
6				**3g**	62
7				**3h**	70
8				**3i**	61
9				**3j**	75
10				**3k**	64
11				**3l**	81
12				**3b**	71
13				**3m**	69
14				**3n**	76

[a] Reaction conditions: 1.0 equiv of aryl iodides, 1.0 equiv of propiolic acid, 5 mol % Pd$_2$(dba)$_3$, 10 mol % dppf, 6.0 equiv of TBAF and NMP (0.15 M halides) at room temperature for 12 h and 1.0 equiv of aryl bromides at 90 °C for 12 h. Reaction time was not optimized. [b] Yield of isolated product.

Symmetrical diarylalkynes were also obtained from propiolic acid and 2 equiv of aryl bromide. Using P^{t}Bu$_3$ as ligand, only 2 equiv of TBAF are required for this reaction (Scheme 2).

Scheme 2. Synthesis of Symmetric Diaryl Alkynes



4a : Ar = C$_6$H$_5$ 95%
4b : Ar = 4-MeC$_6$H$_4$ 75%

This reaction method has several advantages: (1) propiolic acid (**1**) is relatively inexpensive compared to trimethylsilylacetylene, which is widely used as an alkyne source. (2) The byproduct is CO$_2$, which makes the reaction environmentally friendly. (3) Consecutive addition of different aryl halides, without adding a second portion of palladium catalyst, followed by changing the temperature in the reaction mixture yields an unsymmetrically substituted diaryl alkyne. (4) No diyne byproduct was generated from the dimerization of alkynes.

In summary, we demonstrate a simple synthetic method for the one-pot synthesis of diarylalkynes using propiolic acid (**1**). By modulating difunctional reactivity of the propiolic acid at different temperatures, we successfully coupled various aryl halides via a combination of the Sonogashira reaction and decarboxylative coupling. This method offers a new strategy to construct sp carbon and sp^2 carbon bonds difunctionally that is very useful for hetero-coupled alkyne derivatives. Synthetic applications for elucidating conjugated oligomers and polymers, using the difunctionality of propiolic acid in palladium-catalyzed coupling, are under investigation.

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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

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