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Palladium-Catalyzed Decarboxylative Coupling of Alkynyl Carboxylic Acids and Aryl Halides

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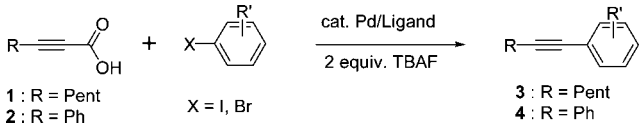

2-Octynoic acid and phenylpropiolic acid were employed for the palladium-catalyzed decarboxylative coupling reaction and with a variety of aryl halides. The former needed 1,4-bis(diphenylphosphino)butane (dppb) as a ligand and the latter tri-*tert*-butylphosphine (P^tBu_3), and both required 2 equiv of tetra-*n*-butylammonium fluoride (TBAF) for full conversion. These reactions showed high reactivities and tolerance of functional groups such as vinyl, ester, ether, ketone, and amine.

Palladium-catalyzed carbon−carbon bond formation reactions are very useful methods for constructing higher molecules such as materials and drugs for modern chemical and medical applications.[1] There are several types of reactions that depend on a variety of organometallic nucleophiles, such as the Kumada, Negishi, Stille, Suzuki, Hiyama, Sonogashira, and other related couplings.[2] Among them, the Sonogashira reaction, cross coupling of aryl halides or alkenyl halides and terminal alkynes, has been widely used as a powerful tool for the formation of sp carbon and sp^2 carbon bonds.[3] Arylalkynes and alkenylalkynes are important structures in pharmaceuticals,[4] natural products,[5] and polymers.[6] In particular, much attention has been given to π-extended molecules in the electrochemical and optical fields.[7]

In 1963, Castro and Stephens reported the coupling of an alkynylcopper reagent and aryl halides to produce arylalkynes.[8] Sonogashira showed the coupling of aryl halides and alkynes without use of stoichiometric amounts of copper reagent in 1975.[9] The most commonly used catalytic system in the Sonogashira reaction requires CuI as the cocatalyst with palladium and a phosphine ligand, amines, solvent, and the desired aryl halides and terminal alkynes.[10] Similar reaction types have been reported that used alkynyl metal reagents containing Mg,[11] Zn,[12] B,[13] Al,[14] Si,[15] or Sn[16] as the alkyne source instead of terminal alkynes. Among the alkynyl metals, trimethylsilylacetylene has been widely used as one of the protected alkynes in the synthesis of asymmetrically disubstituted arylalkynes,[17] and another protected alkyne, 2-methylbut-3-yn-2-ol, was also used.[18] However, they have some drawbacks. When alkynyl metal reagents are used, the reactions always produce stoichiometric amounts of metal waste, raising environmental problems. In the case of 2-methylbut-3-yn-2-ol, the range of usable substrates is low because a strong base is required. In the case of terminal acetylene as the alkyne source, the homocoupled product occurred as a byproduct in the presence of the copper cocatalyst[19] or this side product sometimes formed from the desired product in the absence of copper.[20]

Many improved versions of the Sonogashira reactions have been reported, including, for example, copper-free,[21] amine-

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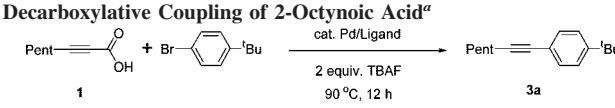
free,[22] and palladium-free[23] and applications for aryl chlorides;[24] however, there is still much room for improvement in the synthesis of arylalkynes from aryl halides.

Recently, we first reported a one-pot synthesis of unsymmetrically diarylalkynes using cascade reactions of the Sonogashira and decarboxylative coupling reactions.[25] In previous work, the optimized conditions of decarboxylative coupling were shown for only phenylpropiolic acid. In the present paper, the scope of useful substrates was expanded for decarboxylative couplings and applied to a variety of aryl halides, such as aryl bromides and chlorides, with phenylpropiolic acid and 2-octynoic acid employed as the alkyne coupling source.

When phenylpropiolic acid was used as decarboxylative coupling partner, the optimized catalytic conditions previously reported were: 1 equiv of aryl halide, 1 equiv of phenylpropiolic acid, 2.5 mol % of $Pd_2(dba)_3$ (dba, dibenzylideneacetone), 10 mol % of P^tBu_3, and 2 equiv of TBAF at 90 °C for 12 h. It required 6 equiv of TBAF when 1,1′-bis(diphenylphosphino)-ferrocene (dppf) was used as the ligand. Based on these results, the decarboxylative coupling was expanded to use alkylalkynyl carboxylic acids such as 2-octynoic acid. Screening reactions were performed with respect to ligand, palladium source, solvent, and the amount of catalysts and are summarized in Table 1. Unexpectedly, P^tBu_3, which was a suitable ligand for phenylpropiolic acid, afforded the desired product in low yield (30%) (entry 1). In addition, a variety of ligands were screened searching for the suitable ligand for 2-octynoic acid. The chelating ligands dppf and dppb showed good reactivities (entries 2 and 6), and the latter was chosen here for its low cost. Optimization with respect to the palladium source showed that $Pd(PPh_3)_2Cl_2$ was superior to all other choices (entry 10) and the yield increased as the ratio of ligand to palladium increased (entries 11 and 12). The solvent choice was the most important factor in this transformation. When the solvent was changed from *N*-methyl-2-pyrrolidone (NMP) to dimethyl sulfoxide (DMSO), the reaction dramatically improved, generating the desired coupling product in high yield (entry 17). Interestingly, the yield was little changed even as the amount of catalyst decreased (entries 18 and 19); however, the yield was low when 0.1 mol % of catalyst was used (entry 20), which meant that at least 1 mol % of catalyst was required for high yield.

TABLE 1. Screening of Palladium, Ligand, and Solvent for the Decarboxylative Coupling of 2-Octynoic Acid[a]

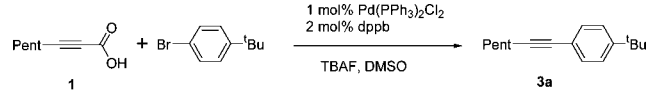


1 3a

entry	palladium	ligand	Pd/L (mol %)	solvent	yield[b] (%)
1	$Pd_2(dba)_3$	P^tBu_3	1/2 (5)	NMP	30
2	$Pd_2(dba)_3$	dppf [c]	1/1 (5)	NMP	45
3	$Pd_2(dba)_3$	BiphP^tBu_2 [d]	1/1 (5)	NMP	23
4	$Pd_2(dba)_3$	Xantphos[e]	1/1 (5)	NMP	37
5	$Pd_2(dba)_3$	PPh_3	1/1 (5)	NMP	12
6	$Pd_2(dba)_3$	dppb[f]	1/1 (5)	NMP	50
7	$Pd(CH_3CN)_2Cl_2$	dppb	1/1 (5)	NMP	15
8	$Pd(OAc)_2$	dppb	1/1 (5)	NMP	22
9	$Pd(acac)_2$	dppb	1/1 (5)	NMP	31
10	$Pd(PPh_3)_2Cl_2$	dppb	1/1 (5)	NMP	55
11	$Pd(PPh_3)_2Cl_2$	dppb	1/1.5 (5)	NMP	56
12	$Pd(PPh_3)_2Cl_2$	dppb	1/2 (5)	NMP	60
13	$Pd(PPh_3)_2Cl_2$	dppb	1/2 (5)	*p*-xylene	56
14	$Pd(PPh_3)_2Cl_2$	dppb	1/2 (5)	toluene	63
15	$Pd(PPh_3)_2Cl_2$	dppb	1/2 (5)	1,4-dioxane	70
16	$Pd(PPh_3)_2Cl_2$	dppb	1/2 (5)	DMF	66
17	$Pd(PPh_3)_2Cl_2$	dppb	1/2 (5)	DMSO	92
18	$Pd(PPh_3)_2Cl_2$	dppb	1/2 (2)	DMSO	94
19	$Pd(PPh_3)_2Cl_2$	dppb	1/2 (1)	DMSO	96
20	$Pd(PPh_3)_2Cl_2$	dppb	1/2 (0.1)	DMSO	73

[a] Reaction conditions: 1.0 mmol of 2-octynoic acid, 1.0 mmol of 4-butylbromobenzene, 2.0 mmol of TBAF, 3 mL of NMP at 90 °C for 12 h. [b] Yield determined by GC with an internal standard. [c] 1,1′-Bis-(diphenylphosphino)ferrocene. [d] 2-(Di-*tert*-butylphosphino)biphenyl. [e] 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthenes. [f] 1,4-Bis(diphenylphosphino)butane.

TABLE 2. Screening of Various Amounts of TBAF, Temperature, and Time for the Decarboxylative Coupling of 2-Octynoic Acid[a]



1 3a

entry	TBAF (equiv)	*T* (°C)	time (h)	conv (%)	yield[b] (%)
1	3.0	90	12	100	96
2	2.0	90	12	100	96
3	1.5	90	12	80	64
4	1.0	90	12	37	25
5	2.0	70	12	47	45
6	2.0	110	2	100	96

[a] Reaction conditions: 1.0 mmol of 2-octynoic acid, 1.0 mmol of 4-butylbromobenzene, 1 mol % of $Pd(PPh_3)_2Cl_2$, 2 mol % of dppb, and 3 mL of DMSO. [b] Yield determined by GC with an internal standard.

In the case of phenylpropiolic acid, the chelating ligand dppf required 6 equiv of TBAF to obtain a high yield. The effect of the amount of TBAF in reactions involving 2-octynoic acid was investigated by reactions with various equivalents of TBAF (Table 2). 2-Octynoic acid needed only 2 equiv of TBAF for a high product yield (entry 2). When the amount of TBAF was reduced from 2 to 1 equiv, the yield was lower (entry 4). At 110 °C, the reaction reached completion in 2 h (entry 6). Based on these results, the optimized conditions for the decarboxylative coupling of 2-octynoic acid were as follows: 1 mol % of $Pd(PPh_3)_2Cl_2$, 2 mol % of dppb, 2 equiv of TBAF, 1 equiv of aryl bromide, and 1 equiv of 2-octynoic acid reacted in DMSO solvent at 110 °C for 2 h.

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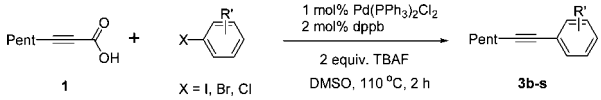
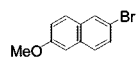
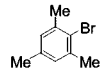
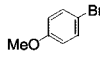
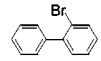
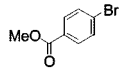
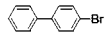
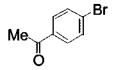
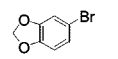
TABLE 3. Decarboxylative Coupling of Aryl Halides and 2-Octynoic Acid[a]



entry	ArX		yield(%)[b]	entry	ArX		yield (%)[b]
1		**3b**	X = I, 96				
2		**3b**	X = Br, 82	12		**3k**	84
3		**3b**	X =Cl, 2				
4		**3c**	94	13		**3l**	92
5		**3d**	88	14		**3m**	66
6		**3e**	99	15		**3n**	98
7		**3f**	93	16		**3o**	92
8		**3g**	99	17		**3p**	95
9		**3h**	99	18		**3q**	73
10		**3i**	91	19		**3r**	85
11		**3j**	92	20		**3s**	82

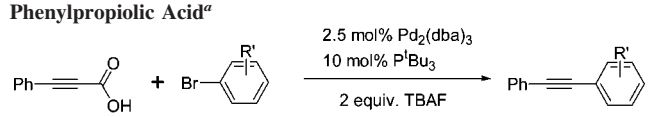
[a] Reaction conditions: 3.0 mmol of 2-octynoic acid and 3.0 mmol of aryl halides in 10 mL of DMSO. [b] Average of at least two runs.

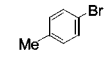
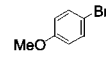
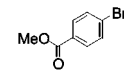
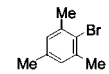
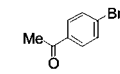
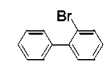
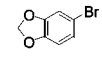
Next, a variety of aryl halides for use in the palladium-catalyzed decarboxylative coupling of 2-octynoic acid was explored (Table 3). In all cases, the homo-decarboxylative coupling product of 2-octynoic acid, tetradeca-6,8-diyne, was not detected in GC analysis.

Iodobenzene and bromobenzene afforded the desired product in high yield; however, chlorobenzene was not a suitable substrate for this transformation (entries 1−3). Monoalkyl-substituted bromobenzenes produced high yields (entry 4); however, multisubstituted bromobenzenes, such as the sterically bulky bromomesitylene, showed slightly lower yields (entry 5). All of the bromoanisole series, bromobiphenyl derivatives, and bromonaphthalene derivatives had high product yields (entries 6−12). Heteroaromatic bromides reacted with 2-octynoic acid resulted in the desired products in moderate to good yields (entries 13−15). In the case of 1-bromo-3-chlorobenzene, only bromide was reacted in this coupling reaction (entry 16), demonstrating that selectivity in coupling could be achieved between chloride and bromide. This decarboxylative coupling has a tolerance for functional groups, such as vinyls, esters, ketones, and ethers, and showed moderate to high yields (entries 17−20).

Finally, the optimized conditions, reported in the previous paper,[25] were applied to the decarboxylative coupling with the phenylpropiolic acid and aryl halides and the resulting yields summarized in Table 4. Electron-neutral, -withdrawing, and -donating substituted aryl halides were tested for their yield in decarboxylative coupling reactions. As expected, the reaction yields of the decarboxylative coupling of phenylpropiolic acid and aryl halides were higher than those from the one-pot reaction

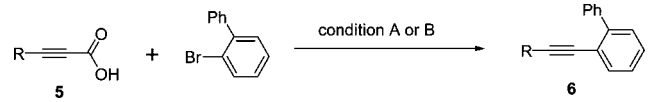
TABLE 4. Decarboxylative Coupling of Aryl Halides and Phenylpropiolic Acid[a]



entry	ArBr		yield(%)[b]	entry	ArBr		yield (%)[b]
1		**4a**	88	8		**4h**	92
2		**4b**	78	9		**4i**	63
3		**4c**	68	10		**4j**	83
4		**4d**	64	11		**4k**	92
5		**4e**	84	12		**4l**	74
6		**4f**	94	13		**4m**	68
7		**4g**	78	14		**4n**	75

[a] Reaction conditions: 3.0 mmol of phenylpropiolic acid and 3.0 mmol of aryl halides in 10 mL of NMP. [b] Average of at least two runs.

TABLE 5. Decarboxylative Coupling of 2-Bromobiphenyl and Alkynoic Acids



entry	R		condition[a]	product	yield[b] (%)
1	CH_3	**5a**	A	**6a**	82
2	2-$CH_3C_6H_4$	**5b**	B	**6b**	88

[a] Reaction condition A: 1.0 mol % of $Pd(PPh_3)_2Cl_2$, 2.0 mol % of dppb, 2 equiv of TBAF, DMSO, 110 °C, 2 h. Reaction condition B: 2.5 mol % of $Pd_2(dba)_3$, 10 mol % of $PtBu_3$, 2 equiv of TBAF, NMP, 90 °C, 12 h. [b] Average of at least two runs.

of propiolic acid, and all aryl halides showed similar reactivities to phenylpropiolic acid as to 2-octynoic acid. However, the product yields from phenylpropiolic acid were generally lower than those from 2-octynoic acid. When the reaction of phenylpropiolic acid and 4-*tert*-butylbromobenzene was carried out under the conditions optimized for 2-octynoic acid, the desired product was obtained in 68% yield.

As shown in Table 5, alkynoic acids such as 2-butynoic acid and *o*-tolylpropynoic acid were coupled with 2-bromobiphenyl. 2-Butynoic acid (**5a**) showed 82% yield (entry 1). 3-Arylalkynoic acids such as *o*-tolypropynoic acid (**5b**) gave desired products in 88% yield (entry 2).

In conclusion, effective decarboxylative coupling of aryl- and aryl-substituted alkynyl carboxylic acids with aryl halides was accomplished and it was found that dppb was a suitable ligand for the decarboxylative coupling of 2-octynoic acid, whereas P^tBu_3 afforded the decarboxylative product of phenylpropiolic acid in high yield. 2-Octynoic acid showed better reactivities than phenylpropiolic acid, with the former requiring 1 mol % of catalytic loading and the latter 5 mol%. In addition, the solvent proved an important factor in these reactions, with DMSO effective for 2-octynoic acid and NMP for phenylpro-

piolic acid. This catalytic system is more tolerant, versatile, and environmentally friendly than the coupling reactions utilizing metal alkynes. Moreover, this method does not produce side products, such as homocoupling of the alkynes and over-reacted compound.

Experimental Section

General Procedure for the Decarboxylative Coupling of 2-Octynoic Acid. $Pd(PPh_3)_2Cl_2$ (21.1 mg, 0.03 mmol), 1,4-bis(diphenylphosphino)butane (25.6 mg, 0.06 mmol), aryl halide (3.0 mmol), and 2-octynoic acid (420.5 mg, 3.0 mmol) were combined with TBAF (6.0 mL of 1 M solution in THF, 6.0 mmol) in DMSO (10.0 mL). The resulting mixture was placed in an oil bath at 110 °C for 2 h. The reaction was poured into 20 mL of saturated aqueous ammonium chloride and extracted with (3 × 20 mL) with Et_2O. The combined ether extracts were washed with brine (60 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum.

Compound 3a. 4-*tert*-Buylbromobenzene (639 mg, 3.0 mmol) was used as aryl halide. Purification by flash chromatography (hexane) afforded **3a** as a yellow oil (658 mg, 96%): R_f = 0.4 (hexane); IR (KBr, cm^{-1}) 3033, 2958, 2931, 2861, 2221, 1508, 1463; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.27 (m, 4H), 2.38 (ddd, J = 7.2, 7.0, 6.9 Hz, 2H), 1.60 (quintet, J = 6.9 Hz, 2H), 1.45−1.31 (m, 4H), 1.29 (s, 9H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 131.2, 125.1, 121.1, 89.6, 80.5, 34.6, 31.2, 31.1, 28.5, 22.2, 19.4, 14.0; MS (EI) *m*/*z* (relative intensity) 228 (M^+, 25), 213 (100), 171 (15), 141 (25), 129 (31), 115 (25), 91 (14), 67 (61). Anal. Calcd for $C_{17}H_{24}$: C, 89.41; H, 10.59. Found: C, 89.02; H, 10.37.

General Procedure for the Decarboxylative Coupling of Phenylpropiolic Acid. $Pd_2(dba)_3$ (68.7 mg, 0.075 mmol), tri-*tert*-butylphosphine (0.6 mL of 0.5 M solution in THF, 0.3 mmol), aryl halide (3.0 mmol), and phenylpropiolic acid (438.5 mg, 3.0 mmol) were combined with TBAF (6.0 mL of 1 M solution in THF, 6.0 mmol) in *N*-methylpyrrolidone (10.0 mL). The resulting mixture was placed in an oil bath at 90 °C for 12 h. The reaction was poured into 20 mL of saturated aqueous ammonium chloride and extracted with (3 × 20 mL) with Et_2O. The combined ether extracts were washed with brine (60 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum.

Compound 4a. 4-Bromotoluene (510 mg, 3.0 mmol) was used as aryl halide. Purification by flash chromatography (10% ethyl acetate in hexane) afforded **4a** as a white solid (550 mg, 88%): mp 72−73 °C; R_f = 0.5 (10% ethyl acetate in hexane); IR (KBr, cm^{-1}) 3046, 2962, 2216, 1510, 1440; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.34−7.31 (m, 3H), 7.13 (d, J = 7.9 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 131.5, 131.5, 129.1, 128.3, 128.1, 123.5, 120.2, 88.5, 88.7, 21.5.

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Supporting Information Available: Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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