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Palladium-Catalyzed Sonogashira Reaction for the Synthesis of Arylalkynecarboxylic Acids from Aryl Bromides at Low Temperature

Kyungho Park,[a] Jung-Min You,[a] Seungwon Jeon,*[a] and Sunwoo Lee*[a]

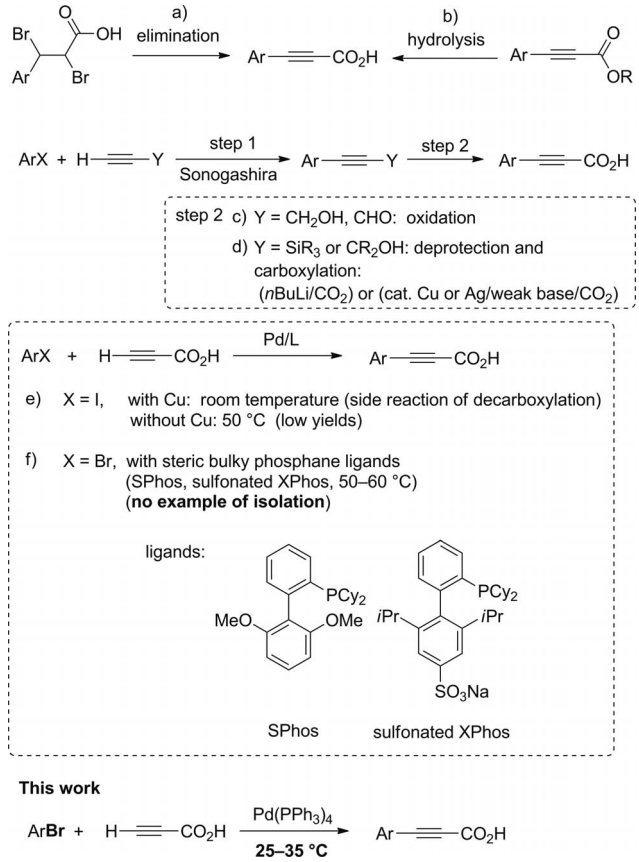
Keywords: Alkynecarboxylic acids / C–C coupling / Palladium / Aryl bromides / Electrochemistry

A variety of aryl bromides were coupled with propiolic acid in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and catalyst $Pd(PPh_3)_4$ to afford the corresponding arylalkynecarboxylic acids in good yields at low temperature. This method showed good tolerance toward functional groups such as alkoxy, ketone, ester, aldehyde, cyano, nitro, and hydroxy. Under these conditions, propiolic acid showed higher reactivity than any other compound containing terminal alkyne groups. According to the mechanistic studies, the key reaction step for the high reactivity of propiolic acid might be ligand exchange between the acetylide and bromide at palladium, and/or reductive elimination, but not the oxidative addition step.

Introduction

Aryl alkynes are important building blocks in the material and pharmaceutical fields.[1] The Sonogashira reaction, the coupling of terminal alkynes and aryl halides, is the most frequently used method for synthesizing aryl alkynes by forming a bond between aryl and alkynyl carbon atoms.[2] The use of alkynecarboxylic acids instead of terminal alkynes as the alkyne synthon has attracted attention in decarboxylative coupling reactions since we first reported the coupling of alkynecarboxylic acid with aryl halides in 2008.[3] We and several other research groups have used alkynecarboxylic acids because of their easy handling and storage.[4]

As shown in Scheme 1, there are various methods to prepare alkynecarboxylic acids, including the elimination of bromo-substituted carboxylic acids [Scheme 1, a)],[5] the hydrolysis of alkynyl carboxylates [Scheme 1, b)],[6] the oxidation of alkynyl alcohols[7a] and aldehydes[7b] [Scheme 1, c)], and the carboxylation of alkynes [Scheme 1, d)].[8] Most of them use aryl alkynyl derivatives, which are prepared by using Sonogashira coupling reactions. Although Sonogashira coupling reactions have been widely used, they still have some limitations. For example, alkynes bearing electron-withdrawing groups show very low reactivity in Sonogashira reactions.[9]



Scheme 1. Synthesis of arylalkynecarboxylic acids.

Very recently, we and the Muthusubramanian group reported the direct synthesis of arylalkynecarboxylic acid from the site-selective coupling reaction of propiolic acid with aryl iodides [Scheme 1, e)].[10] Two possible approaches can be used to expand this reaction to aryl bromides: elevat-

[a] Department of Chemistry, Chonnam National University, Gwangju 500-757, Republic of Korea
Fax: +82-62-530-3389
E-mail: swjeon3380@naver.com
sunwoo@chonnam.ac.kr
Homepage: http://cnuanalytical.tistory.com/
http://altair.chonnam.ac.kr/~sunwoo

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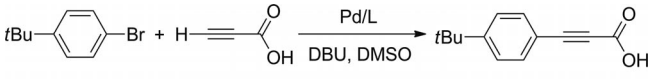
ing temperature or adding ligands. Running the coupling reaction of aryl bromides at higher temperature is the general method, because the reactivity of aryl bromides is lower than that of aryl iodides. However, at elevated temperatures, the double coupling products such as diaryl acetylenes tend to be produced through the Sonogashira reaction and the decarboxylative coupling.[4b]The Gooβen group recently reported that the reaction was conducted at low temperature in the presence of sterically bulky phosphane ligands to prevent the competitive decarboxylative coupling reaction [Scheme 1, f)].[11] The Buchwald group also reported the coupling reaction of aryl bromides and propiolic acid by using sulfonated XPhos as a ligand.[12] However, despite being commercially available, these ligands are very expensive.

To address these problems, we tried to discover a catalytic system that allows the reaction to run at low temperature to prevent the decarboxylative coupling. A number of methods for the Sonogashira reaction of aryl bromides at room or low temperature (< 40 °C) have been reported. However, most of them required sterically bulky phosphanes,[13] and in some cases they had a narrow scope of aryl bromides.[14] To the best of our knowledge, only one example has been reported for the coupling reaction of aryl bromides at low temperature in the Sonogashira reaction with PPh_3 as a ligand.[15] Here, we report the site-selective coupling reaction of propiolic acid with aryl bromides by using a simple reaction system familiar to most organic chemists.

Results and Discussion

To optimize the reaction for the coupling reaction of aryl bromides and **2a**, we first screened a variety of catalytic systems at low temperature. Compound **1a** was chosen as a model substrate. The results are summarized in Table 1. The catalytic system of $Pd(PPh_3)_2Cl_2$ and chelating ligands such as dppb and Xantphos showed no reactivity at 35 °C (entries 1 and 2). However, when $Pd(MeCN)_2Cl_2$ was used as a palladium source with the same chelating ligands, the desired product was obtained, albeit in very low yields (entries 3 and 4). We chose and screened monophosphane ligands that are commercially available, inexpensive, and stable toward oxygen and moisture. The reaction with *i*$PrPPh_2$ and $CyPPh_2$ as ligands gave the coupling product in 15 and 17% yields, respectively (entries 5 and 6). However, when the most sterically demanding ligand, Cy_2PPh, was used, no product could be obtained (entry 7). Interestingly, with

Table 1. Screening of palladium sources and ligands.[a]

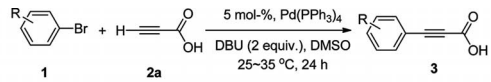


1a 2a 3a

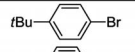
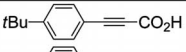
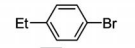
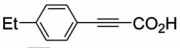
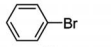
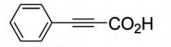
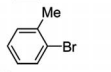
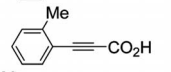
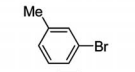
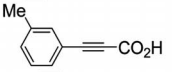
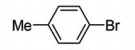
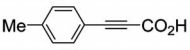
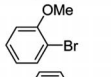
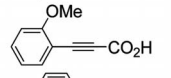
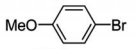
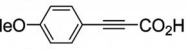
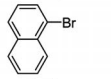
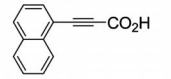
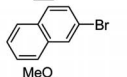
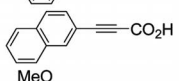
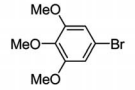
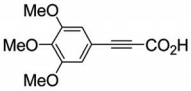
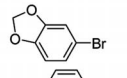
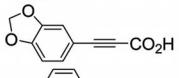
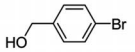
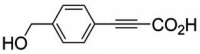
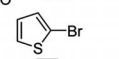
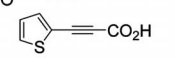
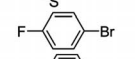
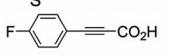
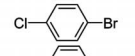
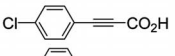
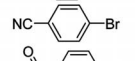
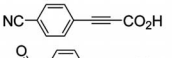
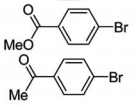
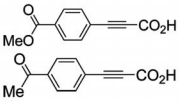
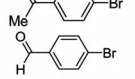
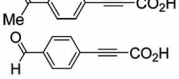
Entry	Pd source [amount] (mol-%)	Ligand [amount] (mol-%)	Conv. (%)[b]	Yield (%)[b]
1	$Pd(PPh_3)_2Cl_2$ [5]	dppb [10]	0	0
2	$Pd(PPh_3)_2Cl_2$ [5]	Xantphos [10]	0	0
3	$Pd(MeCN)_2Cl_2$ [5]	dppb [10]	5	2
4	$Pd(MeCN)_2Cl_2$ [5]	Xantphos [10]	19	13
5	$Pd(MeCN)_2Cl_2$ [5]	*i*$PrPPh_2$ [20]	22	15
6	$Pd(MeCN)_2Cl_2$ [5]	$CyPPh_2$ [20]	26	17
7	$Pd(MeCN)_2Cl_2$ [5]	Cy_2PPh [20]	0	0
8	$Pd(MeCN)_2Cl_2$ [5]	PPh_3 [20]	54	50
9	$Pd(PPh_3)_4$ [5]	–	89	85

[a] Reactants and reaction conditions: **1a** (0.20 mmol), **2a** (0.22 mmol), Pd catalyst (5 mol-%), ligand, DBU (0.44 mmol), and DMSO (1.0 mL) were heated at 35 °C for 24 h. [b] Determined by gas chromatography with internal standard naphthalene after esterification with CH_3I.

Table 2. Palladium-catalyzed coupling reaction of aryl bromides and propiolic acid.[a]



1 2a 3

Entry	ArBr		Product		Temp. (°C)	Yield (%)
1		**1a**		**3a**	35	83
2		**1b**		**3b**	35	86
3		**1c**		**3c**	35	93
4		**1d**		**3d**	35	82
5		**1e**		**3e**	35	84
6		**1f**		**3f**	35	76
7		**1g**		**3g**	35	77
8		**1h**		**3h**	35	78
9		**1i**		**3i**	35	87
10		**1j**		**3j**	35	81
11		**1k**		**3k**	35	74
12		**1l**		**3l**	35	86
13		**1m**		**3m**	35	93
14		**1n**		**3n**	35	72
15		**1o**		**3o**	35	82
16		**1p**		**3p**	25	79
17		**1q**		**3q**	25	85
18		**1r**		**3r**	25	87
19		**1s**		**3s**	25	81
20		**1t**		**3t**	25	93
21		**1u**		**3u**	25	83

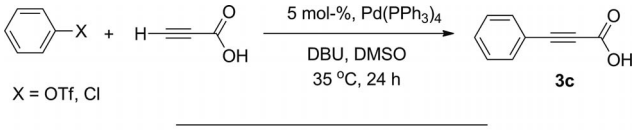
[a] Reactants and reaction conditions: **1** (5.0 mmol), **2a** (5.5 mmol), $Pd(PPh_3)_4$ (0.25 mmol), and DBU (11.0 mmol) were reacted in DMSO for 24 h.

PPh_3 as the ligand, the reaction afforded the desired product in 50% yield (entry 8). This result encouraged us to use $Pd(PPh_3)_4$ as a catalyst without an extra ligand. Surprisingly,the reaction with $Pd(PPh_3)_4$ gave the product in 85% yield (entry 9).

We studied the scope of the aryl bromides under the optimized conditions. The results are summarized in Table 2. As expected, 4-bromo-4-*tert*-butylbenzene and 4-bromo-4-ethylbenzene afforded the desired products **3a** and **3b** in 83 and 86% yields, respectively (entries 1 and 2). Bromobenzene gave phenylpropiolic acid in 93% yield (entry 3). All bromotoluene and bromoanisole derivatives led to good product yields (entries 4–8). Reactions with 1- and 2-bromonaphthalene gave the corresponding alkynecarboxylic acids in 87 and 81% yields, respectively (entries 9 and 10). Alkoxy-substituted aryl bromides such as **1k** and **1l** afforded the desired carboxylic acids in good yields (entries 11 and 12).

An aryl bromide bearing a hydroxy group also reacted to give the product in 93% yield (entry 13). The coupling of 2-bromothiophene with propiolic acid afforded the desired product in 72% yield (entry 14). Fluoro- and chloro-substituted aryl bromides were selectively coupled at the bromo position to afford **3o** and **3p** in 82 and 79% yields, respectively (entries 15 and 16). The reactions of aryl bromides having cyano, ester, ketone, aldehyde, and nitro groups gave the corresponding alkynecarboxylic acids in 85, 87, 81, 93, and 83% yields, respectively (entries 17–21).

We applied the $Pd(PPh_3)_4$ catalyst system to phenyl triflate and phenyl chloride (Scheme 2). Phenyl triflate gave the desired phenylpropiolic acid in 84% yield. However, no coupling product was formed from phenyl chloride, despite the elevated reaction temperature.

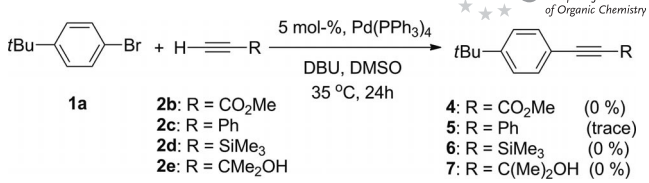


X	**3c** Yield (%)
OTf	84
Cl	0

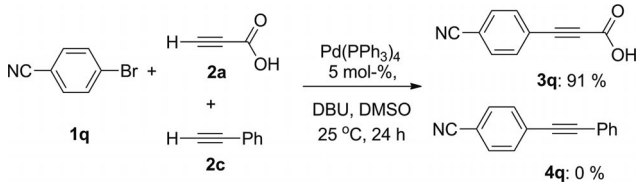
Scheme 2. Palladium-catalyzed coupling reaction of propiolic acid with phenyl triflate and phenyl chloride.

To investigate the catalytic system of $Pd(PPh_3)_4$ in the Sonogashira reaction of aryl bromides, a variety of terminal acetylenes were used as the coupling partner under our optimized conditions. As shown in Scheme 3, no terminal alkynes gave the coupling product at 35 °C after 24 h.

To investigate why the reactivity of **2a** in the coupling reactions with aryl bromides is higher than that of other terminal alkynes, the competitive reaction was carried out as shown in Scheme 4. When **1q** was treated with **2a** and **2c** under optimized conditions in the same reaction vessel, the product of the coupling with propiolic acid, **3q**, was dominantly formed in 91% yield; however, that of the coupling with phenyl acetylene, **4q**, was not formed.

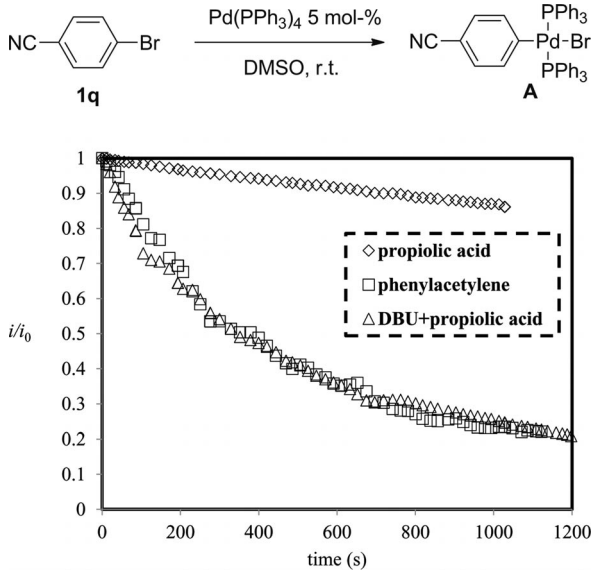


Scheme 3. Attempt to couple a variety of alkynes with **1a**.



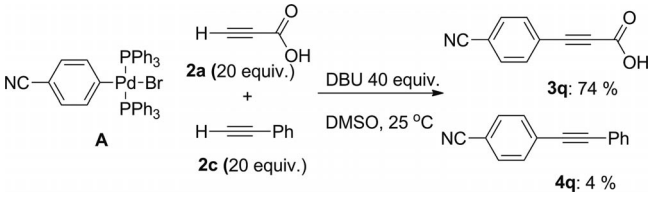
Scheme 4. Competitive reactions of **2a** and **2c**.

To investigate the reactivity of **2a** in $Pd(PPh_3)_4$-catalzyed coupling reactions with aryl bromides, we studied the rate of oxidation of $Pd(PPh_3)_4$ with **1q** to produce oxidative adduct **A**[16] by chronoamperometry (CA),[17] which was performed with a Au electrode (1.6 mm diameter, polarized at +0.05 V) vs. a Ag/AgCl electrode (3.0 M NaCl) on the oxidation wave of $Pd(PPh_3)_4$. The decay of the oxidation current with respect to time provided the apparent rate of the oxidative addition step of **1q** to $Pd(PPh_3)_4$. As shown in Scheme 5, we found, from the slope of i/i_0, that the rate of the oxidation step was very slow in the presence of only **2a**. However, the rate increased with the addition of DBU and was almost the same as that in the presence of **2c**. These results suggest that the rate of the oxidative addition step is not the key factor to explain the different reactivity between propiolic acid and phenylacetylene under these optimized reaction conditions.



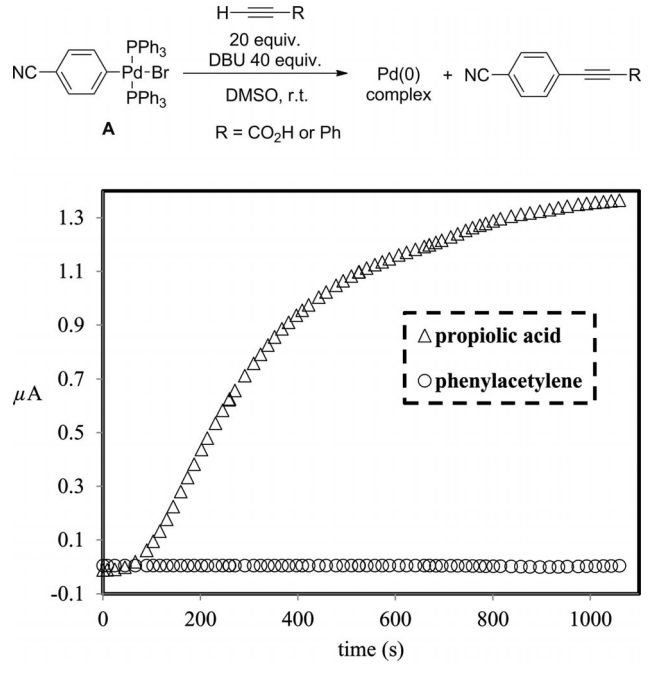
Scheme 5. Competitive reactions of **2a** and **2c**; plot of i/i_0 [i: intensity of the oxidation current (μ**A**) of Pd^0 from the $Pd(PPh_3)_4$ (1 mM) in DMSO at room temperature], in the presence of **2a** (20 mM) [◇], in the presence of **2c** (20 mM) [□], and in the presence of both **2a** (20 mM) and DBU (20 mM) [Δ].

Next, we investigated the rate of the next step to produce the coupling product as shown in Scheme 6. When the oxidative adduct, palladium complex **A**,[16] was treated with propiolic acid and phenyl acetylene in the presence of DBU in the same reaction vessel, arylalkynecarboxylic acid **3q**, coupled with propiolic acid, was formed in 74% yield, and diaryl alkyne **4q**, coupled with phenyl acetylene, was formed in 4% yield.



Scheme 6. Competitive coupling reaction of palladium complex **A** with **2a** and **2c**.

When the chronoamperometric analysis of palladium complex **A** was conducted in the presence of **2a** or **2c** as shown in Scheme 7, the oxidation current of palladium complex **A** increased in the presence of **2a**, but no change was found in the presence of **2c**. These results showed that palladium complex **A** could be treated with **2a** to produce the coupling product and was reduced to the palladium(0) complex. However, palladium complex **A** could not react with **2c** to afford the coupling product.



Scheme 7. Chronoamperometric analysis of palladium complex **A**: plot of the oxidation current (μA) of Pd^0 generated in situ by the reduction of complex **A** (1 mM) in DMSO at room temperature in the presence of DBU (40 mM) with **2c** (20 mM) [○] and in the presence DBU (40 mM) with **2a** (20 mM) [Δ].

On the basis of these results, we suggest that the key step responsible to the high reactivity of **2a** in the coupling reaction with aryl bromides might be the ligand exchange between the acetylide and bromide at palladium and/or the reductive elimination step, but it is not the oxidative addition step.

Conclusions

In summary, we developed a method to synthesize arylalkynecarboxylic acids from the Sonogashira coupling reaction of aryl bromides and propiolic acid in the presence of $Pd(PPh_3)_4$ at 25 or 35 °C. This method shows high functional group tolerance toward alkoxy, fluoro, chloro, ketone, ester, cyano, aldehyde, hydroxy, and nitro groups. In addition, the method does not require an expensive or sensitive ligand, which ensures a simple and easy handling for the preparation of arylalkynecarboxylic acid. Furthermore, we have found that the ligand exchange between the acetylide and bromide at palladium and/or the reductive elimination steps might be more important than the oxidative addition step. This could probably explain the high reactivity of propiolic acid in the coupling reaction with aryl bromides catalyzed by $Pd(PPh_3)_4$.

Experimental Section

General Information for the Electrochemical Measurements: A three-electrode assembled cell, consisting of a Au electrode (1.6 mm diameter) as the working electrode, a platinum coil as the counter electrode, and a Ag/AgCl electrode (3.0 M NaCl) as the reference electrode, was employed. Electrochemical techniques, including cyclic voltammetry (CV) and chronoamperometry (CA), were performed with a BAS 100B/W voltammetric analyzer (Bioanalytical Systems, West Lafayette, IN, USA) in a grounded Faraday cage. The Au electrode was polished successively with 1.0 and 0.05 μm alumina slurry. After successive sonication in methanol and deionized water, the electrode was dried under Ar. The voltammogram for a solution of nBu$_4$NBF$_4$ (1.2 mmol, 395.1 mg) and $Pd(PPh_3)_4$ (0.004 mmol, 4.6 mg) in DMSO (4 mL) showed an oxidation peak near 32 mV. Therefore, CA was performed with 50 mV as the optimum applied potential. The kinetics in Scheme 5 and Scheme 7 were measured by using a Au electrode with stirring. All experiments were carried out under Ar at room temperature.

Monitoring the Oxidative Addition Reactions of NCC_6H_4Br: A solution of nBu$_4$NBF$_4$ (0.3 M) and complex **A** (1 mM) in DMSO (4 mL) was poured into the cell. The reaction was monitored by CA while a solution of nBu$_4$NBF$_4$ (0.3 M), propiolic acid (2.0 M), and DBU (4.0 M) in DMSO (40 μL) was added.

General Method for the Synthesis of Arylalkynecarboxylic Acids from Aryl Bromides and Propiolic Acid: Propiolic acid (5.5 mmol, 385.3 mg) was diluted with DMSO (3.0 mL). The solution was added to a mixture of $Pd(PPh_3)_4$ (0.25 mmol, 288.9 mg), aryl bromide (5.0 mmol), DBU (11.0 mmol, 1.67 g), and DMSO (7.0 mL) in a small round-bottom flask. The resulting mixture was stirred at 35 or 25 °C, poured into ethyl acetate (25.0 mL), and extracted with saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated, acidified to pH 2.0 by adding cold HCl (1 N), and extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by flash chromatography on silica gel [ethyl acetate/hexane, 1:4 with HOAc (1%, v/v)].

3-(4-*tert*-Butylphenyl)propiolic Acid (3a):[8b] 1-Bromo-4-*tert*-butylbenzene (5.0 mmol, 1.07 g) gave **3a** (839.3 mg, 83%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.57 (d, J = 9.0 Hz, 2 H), 7.52 (d, J = 9.0 Hz, 2 H), 1.33 (s, 9 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 155.2, 154.6, 133.5, 126.7, 117.4, 86.3, 81.4, 35.6, 31.3 ppm. HRMS (ESI): calcd. for $C_{13}H_{13}O_2$ [M – H]$^-$ 201.0916; found 201.0914.

3-(4-Ethylphenyl)propiolic Acid (3b): 1-Bromo-4-ethylbenzene (5.0 mmol, 870.4 mg) gave **3b** (749.1 mg, 86%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.55 (d, J = 6.0 Hz, 2 H), 7.33 (d, J = 9.0 Hz, 2 H), 2.73–2.66 (m, 2 H), 1.25–1.20 (m, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.5, 148.6, 133.7, 129.3, 117.6, 86.4, 81.3, 29.4, 15.6 ppm. HRMS (ESI): calcd. for $C_{11}H_9O_2$ [M – H]$^-$ 173.0603; found 173.0609.

3-Phenylpropiolic Acid (3c):[10] Bromobenzene (5.0 mmol, 785.1 mg) gave **3c** (679.6 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, J = 6.0 Hz, 2 H), 7.54–7.44 (m, 1 H), 7.42–7.37 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5, 133.4, 131.3, 128.8, 119.2, 89.2, 80.2 ppm. HRMS (ESI): calcd. for $C_{11}H_9O_2$ [M – H]$^-$ 145.0290; found 145.031.

3-*o*-Tolylpropiolic Acid (3d):[10] 1-Bromo-2-methylbenzene (5.0 mmol, 855.2 mg) gave **3d** (656.7 mg, 82%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.50 (d, J = 9.0 Hz, 1 H), 7.43–7.30 (m, 1 H), 7.30–7.12 (m, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.8, 142.6, 133.9, 131.5, 130.6, 126.7, 120.0, 85.5, 85.2, 20.4 ppm. HRMS (ESI): calcd. for $C_{10}H_7O_2$ [M – H]$^-$ 159.0446; found 159.0441.

3-*m*-Tolylpropiolic Acid (3e):[18] 1-Bromo-3-methylbenzene (5.0 mmol, 855.2 mg) gave **3e** (672.7 mg, 84%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.41–7.39 (m, 2 H), 7.34–7.32 (m, 2 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.6, 139.6, 134.0, 132.5, 130.7, 129.7, 120.3, 86.31, 81.5, 21.1 ppm. HRMS (ESI): calcd. for $C_{10}H_7O_2$ [M – H]$^-$ 159.0446; found 159.0443.

3-*p*-Tolylpropiolic Acid (3f):[10] 1-Bromo-4-methylbenzene (5.0 mmol, 855.2 mg) gave **3f** (608.6 mg, 76%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.52 (d, J = 9.0 Hz, 2 H), 7.29 (d, J = 6.0 Hz, 2 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.6, 142.3, 133.6, 130.4, 117.4, 86.4, 81.4, 21.6 ppm. HRMS (ESI): calcd. for $C_{10}H_7O_2$ [M – H]$^-$ 159.0446; found 159.0493.

3-(2-Methoxyphenyl)propiolic Acid (3g):[10] 1-Bromo-2-methoxybenzene (5.0 mmol, 935.2 mg) gave **3g** (678.2 mg, 77%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.51 (d, J = 6.0 Hz, 1 H), 7.49–7.40 (m, 1 H), 7.06 (d, J = 9.0 Hz, 1 H), 6.98 (t, J = 7.1 Hz, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 162.4, 154.8, 135.3, 133.4, 121.4, 112.1, 109.3, 85.5, 83.5, 56.2 ppm. HRMS (ESI): calcd. for $C_{10}H_7O_3$ [M – H]$^-$ 175.0395; found 175.0393.

3-(4-Methoxyphenyl)propiolic Acid (3h):[10] 1-Bromo-4-methoxybenzene (5.0 mmol, 935.2 mg) gave **3h** (687.1 mg, 78%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.56 (d, J = 9.0 Hz, 2 H), 7.00 (d, J = 9.0 Hz, 2 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 161.8, 154.1, 134.7, 114.6, 111.2, 86.0, 80.3, 55.0 ppm. HRMS (ESI): calcd. for $C_{10}H_7O_3$ [M – H]$^-$ 175.0395; found 175.0389.

3-(Naphthalen-1-yl)propiolic Acid (3i):[10] 1-Bromonaphthalene (5.0 mmol, 1.04 g) gave **3i** (852.8 mg, 87%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 8.29 (d, J = 9.0 Hz, 1 H), 7.98 (d, J = 9.0 Hz, 1 H), 7.90 (d, J = 9.0 Hz, 1 H), 7.85 (d, J = 6.0 Hz, 1 H), 7.62 (t, J = 6.0 Hz, 1 H), 7.54 (t, J = 6.0 Hz, 1 H), 7.51–7.41 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.8, 134.1, 133.8, 133.6, 132.1, 129.4, 128.5, 127.7, 126.0, 125.9, 117.6, 86.5, 84.3 ppm. HRMS (ESI): calcd. for $C_{13}H_7O_2$ [M – H]$^-$ 195.0446; found 195.0441.

3-(Naphthalen-2-yl)propiolic Acid (3j): 2-Bromonaphthalene (5.0 mmol, 1.04 g) gave **3j** (794.0 mg, 81%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 8.26 (s, 1 H), 7.99–7.94 (m, 3 H), 7.63–7.59 (m, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.6, 134.8 (2 C), 133.7, 129.6, 129.1, 129.0, 129.0, 128.8, 128.1, 117.7, 86.4, 82.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{11}O_5$ [M – H]$^-$ 195.0446; found 195.0447.

3-(3,4,5-Trimethoxyphenyl)propiolic Acid (3k):[19] 1-Bromo-3,4,5-trimethoxybenzene (5.0 mmol, 1.24 g) gave **3k** (873.5 mg, 74%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 6.93 (s, 2 H), 3.88 (s, 6 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.7, 154.6, 142.2, 115.1, 111.3, 86.7, 80.9, 60.8, 56.7 ppm. HRMS (ESI): calcd. for $C_{12}H_{11}O_5$ [M – H]$^-$ 235.0607; found 235.0604.

3-(Benzo[*d*][1,3]dioxol-5-yl)propiolic Acid (3l):[19] 5-Bromobenzo[*d*][1,3]dioxole (5.0 mmol, 1.01 g) gave **3l** (817.6 mg, 86%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.18 (d, J = 3.0 Hz, 1 H), 7.07 (d, J = 3.0 Hz, 1 H), 6.93 (d, J = 9.0 Hz, 1 H), 6.11 (s, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.7, 151.2, 149.0, 129.6, 113.4, 112.9, 109.7, 103.1, 86.5, 80.6 ppm. HRMS (ESI): calcd. for $C_{10}H_5O_4$ [M – H]$^-$ 189.0188; found 189.0187.

3-[4-(Hydroxymethyl)phenyl]propiolic Acid (3m):[8d] (4-Bromophenyl)methanol (5.0 mmol, 935.2 mg) gave **3m** (819.2 mg, 93%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.60 (d, J = 9.0 Hz, 2 H), 7.47 (d, J = 9.0 Hz, 2 H), 4.70 (s, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.7, 146.9, 133.6, 127.6, 118.7, 86.25, 81.5, 64.1 ppm. HRMS (ESI): calcd. for $C_{10}H_7O_3$ [M – H]$^-$ 175.0395; found 175.0396.

3-(Thiophen-2-yl)propiolic Acid (3n):[20] 2-Bromothiophene (5.0 mmol, 815.2 mg) gave **3n** (547.8 mg, 72%). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 7.79 (d, J = 3.0 Hz, 1 H), 7.62 (d, J = 3.0 Hz, 1 H), 7.25–7.12 (m, 1 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]acetone): δ = 154.4, 137.7, 132.9, 128.9, 119.8, 85.9, 79.8 ppm. HRMS (ESI): calcd. for $C_7H_3O_2S$ [M – H]$^-$ 150.9854: found 150.9854.

3-(4-Fluorophenyl)propiolic Acid (3o):[10] 1-Bromo-4-fluorobenzene (5.0 mmol, 875.0 mg) gave **3o** (672.9 mg, 82%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.68 (dd, J = 9.0, 5.4 Hz, 2 H), 7.26–7.20 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 164.8 (d, $J_{C,F}$ = 255.0 Hz), 154.8, 136.3 (d, $J_{C,F}$ = 7.5 Hz), 117.2 (d, $J_{C,F}$ = 22.5 Hz), 116.9, 84.9, 81.8 ppm. HRMS (ESI): calcd. for $C_9H_4FO_2$ [M – H]$^-$ 163.0195; found 163.0193.

3-(4-Chlorophenyl)propiolic Acid (3p):[10] 1-Bromo-4-chlorobenzene (5.0 mmol, 957.3 mg) gave **3p** (711.0 mg, 79%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.66 (d, J = 9.0 Hz, 2 H), 7.52 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.1, 137.0, 134.9, 129.8, 119.0, 84.1, 82.4 ppm. HRMS (ESI): calcd. for $C_9H_4ClO_2$ [M – H]$^-$ 178.9900; found 178.9902.

3-(4-Cyanophenyl)propiolic Acid (3q):[8d] 4-Bromobenzonitrile (5.0 mmol, 910.1 mg) gave **3q** (727.4 mg, 85%). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 7.91 (d, J = 6.0 Hz, 2 H), 7.85 (d, J = 6.0 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]acetone): δ = 154.1, 134.3, 133.5, 125.2, 118.6, 114.9, 84.4, 83.5 ppm. HRMS (ESI): calcd. for $C_{10}H_4NO_2$ [M – H]$^-$ 170.0242; found 170.0249.

3-[4-(Methoxycarbonyl)phenyl]propiolic Acid (3r):[10] Methyl 4-bromobenzoate (5.0 mmol, 1.8 g) gave **3r** (888.2 mg, 87%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.00 (d, J = 9.0 Hz, 2 H), 7.76

(d, J = 9.0 Hz, 2 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 165.4, 154.0, 132.9, 131.2, 129.5, 123.6, 83.8, 82.8, 52.5 ppm. HRMS (ESI): calcd. for $C_{11}H_7O_4$ [M – H]$^-$ 203.0344; found 203.0345.

3-(4-Acetylphenyl)propiolic Acid (3s):[10] 1-(4-Bromophenyl)ethanone (5.0 mmol, 995.2 mg) gave **3s** (762.1 mg, 81%). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 8.07 (d, J = 5.0 Hz, 2 H), 7.77 (d, J = 10.0 Hz, 2 H), 2.63 (s, 3 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]-acetone): δ = 197.4, 154.3, 139.3, 133.8, 129.4, 124.7, 84.6, 83.7, 26.9 ppm. HRMS (ESI): calcd. for $C_{11}H_7O_3$ [M – H]$^-$ 187.0395; found 187.0393.

3-(4-Formylphenyl)propiolic Acid (3t):[8d] 4-Bromobenzaldehyde (5.0 mmol, 925.1 mg) gave **3t** (809.8 mg, 93%). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 10.12 (s, 1 H), 8.03 (d, J = 5.0 Hz, 2 H), 7.86 (d, J = 5.0 Hz, 2 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]-acetone): δ = 192.4, 154.2, 138.5, 134.2, 130.5, 126.0, 84.3, 84.1 ppm. HRMS (ESI): calcd. for $C_{10}H_5O_3$ [M – H]$^-$ 173.0239; found 173.0240.

3-(4-Nitrophenyl)propiolic Acid (3u):[8d] 1-Bromo-4-nitrobenzene (5.0 mmol, 1.01 g) gave **3u** (789.1 mg, 83%). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 8.32 (d, J = 9.0 Hz, 2 H), 7.92 (d, J = 6.0 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 154.0, 149.7, 134.8, 127.0, 124.8, 85.0, 83.2 ppm. HRMS (ESI): calcd. for $C_9H_4NO_4$ [M – H]$^-$ 190.0140; found 190.0141.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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