Ligand-Free and Recyclable Palladium(II) Acetate Catalyzes the Decarboxylative Cross-Coupling of Alkynyl Carboxylic Acids with Arylboronic Acids in Aqueous PEG-400

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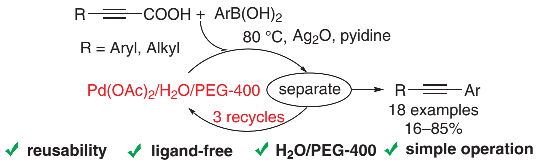

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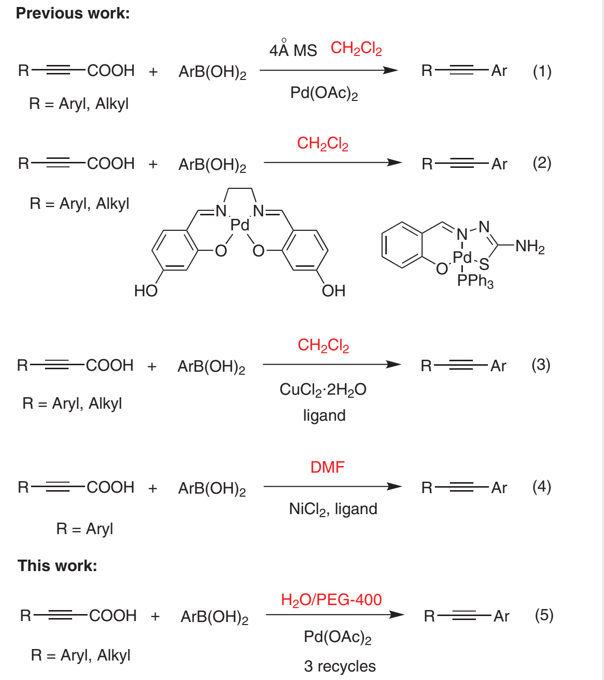
Abstract A novel and ligand-free method was developed for the decarboxylative cross-coupling of alkynylcarboxylic acids with arylboronic acids. By using an environmentally friendly H_2O–poly(ethylene glycol) (PEG-400) system as the reaction medium, a series of internal alkynes were synthesized in good yields and with remarkable selectivity. The $Pd(OAc)_2$–H_2O–PEG-400 catalytic system could be used for up to three cycles without any loss of activity, demonstrating the robustness of the approach.

Key words palladium catalysis, alkynylcarboxylic acids, arylboronic acids, decarboxylative cross-coupling, alkynes

Internal acetylenic bonds are key structural units of various bioactive natural products, synthetic pharmaceutical compounds, and molecular organic materials.[1–7] Because carboxylic acids are widely available, stable, and easy to handle and store, the decarboxylative coupling of alkynylcarboxylic acids is a crucial method for the formation of internal alkynes. For example, Lee and co-workers demonstrated syntheses of diarylalkynes by decarboxylation cross-coupling of propiolic acid with aryl halides or organosilanes.[8,9] In recent years, the decarboxylation cross-coupling of alkynylcarboxylic acids with arylboronic acids has been investigated in organic solvents.[10–14] Feng and Loh reported the first example of a highly efficient palladium-catalyzed synthesis of substituted alkynes by decarboxylative cross-coupling of carboxylic acids with arylboronic acids in CH_2Cl_2 (Scheme 1, eq 1).[10] Palladacycle-catalyzed decarboxylative cross-couplings of arylboronic acids in CH_2Cl_2 were developed and studied by Lee and Mao and their respective co-workers (Scheme 1, eq 2).[11,12] Jiao and co-workers reported a mild Cu-catalyzed procedure for the decarboxylative cross-coupling of aryl- or alkynylboronic acids for the construction of unsymmetrical substituted alkynes (Scheme 1, eq 3).[13] In 2016, Lee and co-workers developed a nickel-catalyzed oxidative decarboxylative coupling reaction of alkynylcarboxylic acids with arylboronic acids (Scheme 1, eq 4).[14]

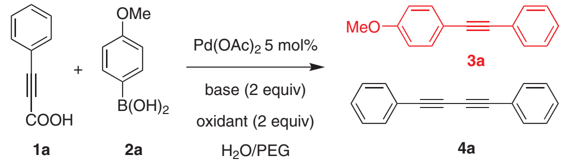


Scheme 1 Decarboxylative cross-coupling reactions of alkynylcarboxylic acids with arylboronic acids

Although interesting results have been achieved, the available decarboxylative cross-coupling reactions of alkynylcarboxylic acids with arylboronic acids have many drawbacks. Recycling of the catalysts remains challenging, and further research is needed to develop environmentally friendly solvents. It is widely accepted that modern organic syntheses should be based on the principles of green chemistry,[15–17] and one important approach to achieve this is by the use of environmentally benign reaction media to replace volatile and poisonous organic solvents.[17–22] Here, we report a simple, effective, ligand-free, method that uses a recyclable catalyst for the decarboxylative cross-coupling of alkynylcarboxylic acids with arylboronic acids in an environmentally friendly H_2O–poly(ethylene glycol) (PEG-400) medium (Scheme 1, eq 5).

We first studied the decarboxylative cross-coupling of 3-phenylpropiolic acid (**1a**) with (4-methoxyphenyl)boronic acid (**2a**) in the presence of $Pd(OAc)_2$ (5 mol%) as a model reaction. Our subsequent work focused on the optimization of this reaction by changing such reaction parameters as the oxidant, the base, and the reaction temperature (Table 1). Among the several oxidants screened, Ag_2O proved to be optimal in terms of the resultant yield (Table 1, entries 1–4). The decarboxylative cross-coupling reaction in the presence of pyridine as the base provided the cross-coupled product in an 80% yield, which was higher than those obtained in the presence of K_2CO_3, KOAc, or quinoline (entries 5–8). The ratio of H_2O and PEG-400 was also investigated, and the target products **3a** was isolated in yields of 76 and 63% yield by using 0:10 and 2:8 mixtures of H_2O and PEG-400, respectively (entries 9 and 10). Changing the reaction temperature also affected the yield. At 60 °C, the decarboxylative cross-coupling product was obtained in 73% yield, whereas at a 68% yield was obtained at 100 °C (entries 11 and 12). Finally, the use of PEG-200 or PEG-600 instead of PEG-400 resulted in slight reductions in the yield (entries 13 and 14).

Table 1 Optimization of the Reaction Conditions[a]

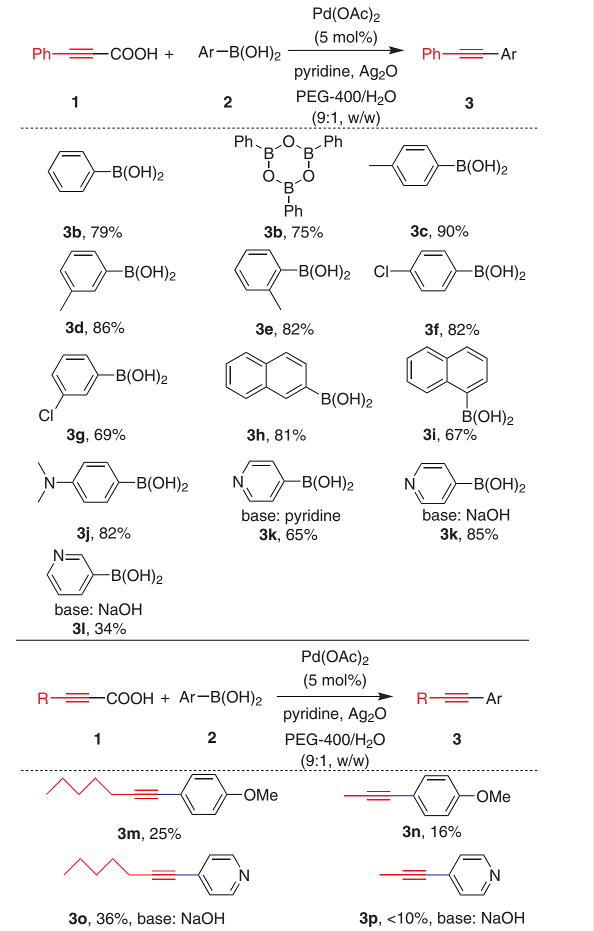


Entry	Base	Oxidant	Yield[b] (%) of **3a**	Yield[b] (%) of **4a**
1	Et_3N	Ag_2CO_3	<10	32
2	Et_3N	AgOAc	27	28
3	Et_3N	$AgNO_3$	<10	0
4	Et_3N	Ag_2O	58	28
5	K_2CO_3	Ag_2O	<10	<10
6	KOAc	Ag_2O	26	11
7	quinoline	Ag_2O	72	<10
8	**pyridine**	$\mathbf{Ag_2O}$	**80**	**<10**
9[c]	pyridine	Ag_2O	76	<10
10[d]	pyridine	Ag_2O	63	<10
11[e]	pyridine	Ag_2O	73	<10
12[f]	pyridine	Ag_2O	68	<10
13[g]	pyridine	Ag_2O	75	<10
14[h]	pyridine	Ag_2O	60	18

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), base (2 equiv), oxidant (2 equiv), H_2O (0.1 g), PEG-400 (0.9 g), air, 4 h, 80 °C.
[b] Isolated yield.
[c] H_2O/PEG-400 = 0:10.
[d] H_2O/PEG-400 = 2:8.
[e] 60 °C.
[f] 100 °C.
[g] PEG-200.
[h] PEG-600.

The decarboxylative cross-coupling reaction between various arylboronic acids and alkynylcarboxylic acids was subsequently evaluated by using $Pd(OAc)_2$ (5 mol%), pyridine (2 equiv), Ag_2O (2 equiv), H_2O (0.1 g), and PEG-400 (0.9 g) (Scheme 2). 3-Phenylpropiolic acid (**1a**) cross-coupled with phenylboronic acid or with 2,4,6-triphenyl-1,3,5,2,4,6-trioxatriborinane (0.2 mmol) to produce the corresponding product **3b** in yields of 79 and 75% , respectively. 3-Phenylpropiolic acid (**1a**) also reacted efficiently with *p*-, *m*-, or *o*-tolylboronic acids to give the products **3c**–**e** in yields of 82–90%, showing that steric effects have marginal influence on the decarboxylative cross-coupling reaction. The yields of the decarboxylative cross-coupling reaction were markedly dependent on the electronic and steric properties of the arylboronic acid (**3f** and **3g**, **3h** and **3i**, and **3k** and **3l**). Pleasingly, reactions of pyridin-4-ylboronic acid (**2k**) and of pyridin-3-ylboronic acid (**2l**) gave the desired products **3k** and **3l**, respectively. Furthermore, sodium hydroxide proved to be a superior base to pyridine in the former case, because of the electron withdrawing effect of **2k**. Aliphatic alkynylcarboxylic acids and arylboronic acids were then subjected to the optimized conditions in the H_2O–PEG-400 system, but unfortunately gave much lower yields of the decarboxylative cross-coupling products **3m**–**p**.

Palladium catalysts are expensive, which might limit their use in some cases. Consequently, the reusability of immobilized palladium catalysts has attracted considerable attention.[23–25] Generally, the preparation of immobilized palladium catalysts is a complex process that often involves the generation of various impurities. In recent years, we have carried out extensive research on carrier-free and reusable reaction systems.[26,27] Here, the decarboxylative coupling reaction of 3-phenylpropiolic acid with 4-methoxyphenylboronic acid or with pyridin-4-ylboronic acid was examined as potential ligand- and carrier-free method for the reuse of $Pd(OAc)_2$ (Table 2). Similar experimental results

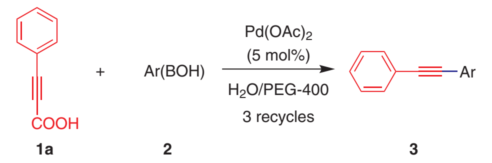


Scheme 2 $Pd(OAc)_2$-catalyzed decarboxylative cross-coupling of aryl- and alkynylcarboxylic acids with arylboronic acids in H_2O–PEG-400. *Reagents and conditions*: **1** (0.3 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), pyridine (2 equiv), Ag_2O (2 equiv), H_2O (0.1 g), PEG-400 (0.9 g), air, 4 h, 80 °C. Isolated yields are reported.

were obtained in three runs using the recovered $Pd(OAc)_2$–H_2O–PEG-400 system. However, the yield of the cross-coupling reaction fell sharply in the fourth cycle (not shown).

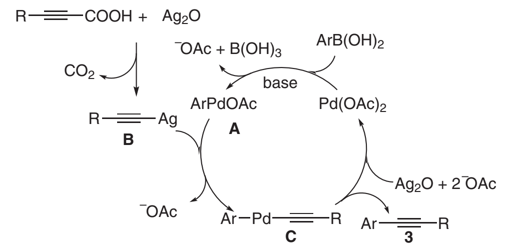
Based on related reported work,[10,13,14,27] a plausible mechanism for the decarboxylative cross-coupling is shown in Scheme 3. First, Pd(II), generated by oxidation of Pd(0) by Ag_2O, reacts with the arylboronic acid to form the arylpalladium intermediate **A**, and the alkynylcarboxylic acids reacts with Ag_2O to give alkynylsilver compound **B**. Intermediate **A** then reacts with alkynylsilver **B** to afford intermediate **C**. Finally, reductive elimination by intermediate **C** gives the desired product **3**.

Table 2 Reusability of the $Pd(OAc)_2$–H_2O–PEG-400 System in the Decarboxylative Cross-Coupling of 3-Phenylpropiolic Acid with Arylboronic Acids



Ar	Base	Cycle	Yield[a] (%)
4-$MeOC_6H_4$	pyridine	1[b]	78
		2[c]	75
		3[c]	74
pyridin-4-yl	NaOH	1[b]	82
		2[c]	80
		3[c]	77

[a] Isolated yield.
[b] Reaction conditions: **1a** (0.3 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), base (2 equiv), Ag_2O (2 equiv), H_2O/PEG-400 = 1:9 (1.5 g), air, 4 h, 80 °C.
[c] Reaction conditions: **1a** (0.3 mmol), **2** (0.5 mmol), base (2 equiv), Ag_2O (1 equiv), air, 4 h, 80 °C.



Scheme 3 A possible mechanism

In summary, we have successfully developed a $Pd(OAc)_2$-catalyzed decarboxylative cross-coupling reaction of alkynylcarboxylic acids with arylboronic acids that shows remarkable cross-coupling selectivity.[28] In comparison with previous reports, the described protocol has numerous advantages, in that it involves a ligand-free and recyclable system, requires simple operations, and does not require any carrier. Importantly, the reaction also uses an environmentally friendly solvent. Further work aimed at extending the range of applications of the recyclable Pd/water/PEG system to other coupling reactions is currently underway in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691736.

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(28) **Arylarynes 3; General Procedure** A Schlenk tube was charged with the appropriate alkynylcarboxylic acid **1** (0.3 mmol), arylboronic acid **2** (0.5 mmol), Pd(OAc)$_2$ (0.015 mmol), Ag$_2$O (0.6 mmol), pyridine (0.6 mmol), H$_2$O (0.1 g), and PEG-400 (0.9 g), and the reaction was allowed to proceed under air at 80 °C (oil-bath temperature) for 4 h. When the reaction was complete, the mixture was cooled to r.t., diluted with sat. aq NaCl (10 mL) and extracted with Et$_2$O (3 × 20 mL). The combined organic layer was dried (Na$_2$SO$_4$) and transferred to a round-bottomed flask. The combined organic extracts were concentrated in vacuum, and the resulting residue was purified by column chromatography (silica gel, PE–EtOAc). **1-Methoxy-4-(phenylethynyl)benzene (3a)**. White solid; yield: 50 mg (80%); mp 93.8–94.7 °C. ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 7.52–7.49$ (m, 2 H), 7.46 (d, $J = 8.8$ Hz, 2 H), 7.34–7.27 (m, 3 H), 6.86 (d, $J = 8.8$ Hz, 2 H), 3.80 (s, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 159.6$, 133.0, 131.4, 128.3, 127.9, 123.6, 115.3, 114.0, 89.4, 88.0, 55.2.