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# Nickel-catalyzed oxidative decarboxylative coupling reactions between alkynyl carboxylic acids and arylboronic acids

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One of the most frequently used methods for the formation of

sp<sup>2</sup>-sp carbon-carbon bonds is the Sonogashira reaction, which

is a coupling reaction between aryl halides and terminal alkynes

in the presence of Pd/Cu catalysts.<sup>1</sup> Since its first report in 1975,

this reaction has been modified, improved, and widely employed

in organic synthesis, especially in the medicinal and material

chemistry fields.<sup>2</sup> Notably, it represents a very useful tool for the

synthesis of conjugated polymers bearing an aryl alkyne

alkyne moieties since their decarboxylative coupling reaction was

reported in 2008.<sup>4</sup> Alkynyl carboxylic acids offer several advan-

tages. For example, propiolic acid is easier to handle and store as an alkyne source compared to acetylene, and less expensive than

other acetylene surrogates such as trimethylsilylacetylene and

bis(tributylstannyl)acetylene.<sup>5</sup> In addition, aryl alkynyl carboxylic

acid derivatives are easily prepared and no chromatography purifi-

halides with alkynyl carboxylic acids in the presence of a palla-

dium catalyst. Aryl iodide, bromide, and chloride were successfully used as coupling partners in the decarboxylative coupling reaction

In a first Letter, we described the coupling reaction of aryl

Alkynyl carboxylic acid derivatives such as propiolic acid have received much attention as alkyne sources for the synthesis of aryl

#### ARTICLE INFO

## ABSTRACT

vields.

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Introduction

backbone.<sup>3</sup>

(Scheme 1a).<sup>7</sup> In particular, benzyl bromide and chloride were coupled to give benzyl alkynes in good yields.<sup>8</sup> Recently, the coupling of benzoxazole and indolizine with alkynyl carboxylic acids through decarboxylation was also reported.<sup>9</sup> In addition, the formation of bonds involving heteroatoms such as phosphorus, nitrogen, and sulfur has also been reported using decarboxylative

Nickel-catalyzed decarboxylative coupling reactions between aryl alkynyl carboxylic acids and aryl-

boronic acids were developed. When aryl alkynyl carboxylic acids were reacted with arylboronic acids

in the presence of NiCl<sub>2</sub> (10 mol %), 2,2'-bipyridine (20 mol %), Na<sub>2</sub>CO<sub>3</sub> (1.0 equiv), and Ag<sub>2</sub>CO<sub>3</sub> (1.0 equiv)

in DMF at 80 °C for 18 h, the corresponding diaryl alkynes products were formed in moderate to good

coupling reactions of alkynyl carboxylic acids.<sup>10</sup> In most cases of decarboxylative coupling reactions, palladium or copper were generally employed as major catalysts, although a few example of nickel catalysts were reported.<sup>11</sup> More recently, we described decarboxylative coupling reactions with organosilanes using a nickel catalyst (Scheme 1b).<sup>12</sup> This success prompted us to develop a nickel-catalyzed decarboxylative coupling using organoboranes. Although the oxidative decarboxylative coupling with aryl boronic acids was reported in the presence of a palladium catalyst or a copper catalyst (Scheme 1c),<sup>13</sup> a nickel-based catalytic system has not been developed so far. Herein, we report a decarboxylative coupling reaction between alkynyl carboxylic acids and organoboranes using a nickel catalyst (Scheme 1d). This method offers several advantages since nickel is abundant and much cheaper than palladium,<sup>14</sup> and a greater variety of organoborane derivatives are commercially available compared to organosilanes.

In order to find the optimal conditions, phenyl propiolic acid (**1a**) and phenylboronic acid (**2a**) were reacted with Na<sub>2</sub>CO<sub>3</sub> and Ag<sub>2</sub>CO<sub>3</sub> under a variety of reaction conditions. First, different nickel sources, ligands, and solvents were tested, and the corresponding results are summarized in Table 1. Reactions conducted in the

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cation step is required.<sup>6</sup>

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Scheme 1. Transition-metal-catalyzed decarboxylative coupling reactions.

presence of Ni(acac)<sub>2</sub>, Ni(OAc)<sub>2</sub>, and Ni(OH)<sub>2</sub> afforded very poor yields of product **3a** (entries 1–3), while Ni(NO<sub>3</sub>)<sub>2</sub> and NiBr<sub>2</sub> provided the desired product in 22% and 28% yields, respectively (entries 4 and 5). The use of NiCl<sub>2</sub> led to an improvement of the product yield to 51% and a decrease of the yield of by-product **4** to 1% (entry 6), whereas NiF<sub>2</sub> gave a very poor yield (entry 7). The replacement of 2,2'-bipyridine (**L1**) with either 4,4'-bis-*tert*butylbipyridine (**L2**) or 1,10-phenanthroline (**L3**) did not increase the product yield (entries 8 and 9). No product was formed in the reaction with sterically hindered **L4** or L-proline (**L5**) (entries 10 and 11). Among the phosphine ligands, only Xantphos (**L9**) provided the desired product in 26% yield (entry 15). With respect to the solvents tested, polar solvents such as DMAc, NMP, and DMSO provided **3a** in 28–45% yields (entries 16–18). However, ethers and aromatic solvents showed no activity (entries 19–22).

Since the decarboxylative coupling reaction between **1a** and **2a** is an oxidative coupling, the oxidant is also an important factor, thus a number of different reagents were tested. As shown in

# Table 1

Effect of nickel source, ligand, and solvent in the oxidative decarboxylative coupling<sup>a</sup>

Entry	Ni	Ligand <sup>c</sup>	Solvent	<b>3a</b> yield <sup>b</sup> (%)	<b>4</b> yield <sup>b</sup> (%)
1	Ni(acac) <sub>2</sub>	L1	DMF	9	5
2	$Ni(OAc)_2$	L1	DMF	8	4
3	Ni(OH) <sub>2</sub>	L1	DMF	3	2
4	$Ni(NO_3)_2$	L1	DMF	22	5
5	NiBr <sub>2</sub>	L1	DMF	28	8
6	NiCl <sub>2</sub>	L1	DMF	51	1
7	NiF <sub>2</sub>	L1	DMF	4	2
8	NiCl <sub>2</sub>	L2	DMF	30	19
9	NiCl <sub>2</sub>	L3	DMF	29	2
10	NiCl <sub>2</sub>	L4	DMF	_	1
11	NiCl <sub>2</sub>	L5	DMF	_	4
12	NiCl <sub>2</sub>	L6	DMF	_	6
13	NiCl <sub>2</sub>	L7	DMF	_	12
14	NiCl <sub>2</sub>	L8	DMF	_	22
15	NiCl <sub>2</sub>	L9	DMF	26	5
16	NiCl <sub>2</sub>	L1	DMAc	38	2
17	NiCl <sub>2</sub>	L1	NMP	28	6
18	NiCl <sub>2</sub>	L1	DMSO	45	3
19	NiCl <sub>2</sub>	L1	Diglyme	_	1
20	NiCl <sub>2</sub>	L1	Dioxane	_	5
21	NiCl <sub>2</sub>	L1	Toluene	_	-
22	NiCl <sub>2</sub>	L1	Xylene	-	-

<sup>a</sup> Reaction condition: **1a** (0.3 mmol), **2a** (0.3 mmol), Ni (0.03 mmol), ligand (0.06 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.3 mmol), and Ag<sub>2</sub>CO<sub>3</sub> (0.3 mmol) were reacted at 80 °C for 18 h. The reaction was conducted under air condition.

<sup>b</sup> Determined by gas chromatography with internal standard.

<sup>c</sup> Ligand structure



#### Table 2

Effect of base, oxidant, and temperature in the oxidative decarboxylative coupling<sup>a</sup>



Entry	Ratio ( <b>1a/2a)</b>	Base	Oxidant	Temp	<b>3a</b> yield <sup>b</sup> (%)	<b>4</b> yield <sup>b</sup> (%)
1	1:1	Na <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> O	80	45	8
2	1:1	Na <sub>2</sub> CO <sub>3</sub>	AgOAc	80	6	24
3	1:1	Na <sub>2</sub> CO <sub>3</sub>	$Cu(OAc)_2$	80	24	22
4	1:1	Na <sub>2</sub> CO <sub>3</sub>	$Cu(OTf)_2$	80	24	7
5	1:1	Na <sub>2</sub> CO <sub>3</sub>	02	80	5	1
6	1:1	K <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	80	38	14
7	1:1	Cs <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	80	17	10
8	1:1	CsF	Ag <sub>2</sub> CO <sub>3</sub>	80	18	5
9	1:1	KF	Ag <sub>2</sub> CO <sub>3</sub>	80	15	2
10	1:1	NaOH	Ag <sub>2</sub> CO <sub>3</sub>	80	2	1
11	1:1	КОН	Ag <sub>2</sub> CO <sub>3</sub>	80	_	-
12	1:1	KO <sup>t</sup> Bu	$Ag_2CO_3$	80	11	36
13	1:1	NaO <sup>t</sup> Bu	$Ag_2CO_3$	80	19	5
14	1:1	Na <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	110	42	21
15	1:1	Na <sub>2</sub> CO <sub>3</sub>	Ag <sub>2</sub> CO <sub>3</sub>	60	16	3
16	1:2	Na <sub>2</sub> CO <sub>3</sub>	$Ag_2CO_3$	80	86	5
17	1:2	Na <sub>2</sub> CO <sub>3</sub>	$Ag_2CO_3$	110	75	8

<sup>a</sup> Reaction condition: 1a (0.3 mmol), 2a (0.3 mmol), NiCl<sub>2</sub> (0.03 mmol), L1 (0.06 mmol), base (0.3 mmol), and oxidant (0.3 mmol) were reacted in DMF at 80 °C for 18 h. The reaction was conducted under air condition. <sup>b</sup> Determined by gas chromatography with internal standard.

### Table 3

Nickel-catalyzed oxidative decarboxylative coupling reaction with alkynyl carboxylic acids and arylboronic acids<sup>a</sup>

0		10 mol% NiCl <sub>2</sub> 20 mol% <b>L1</b>	Ar1Ar2
Ar <sup>1</sup> ————————————————————————————————————	(HO) <sub>2</sub> B-Ar <sup>2</sup>	Na <sub>2</sub> CO <sub>3</sub> (1.0 equiv)	AI AI
1	2	Ag <sub>2</sub> CO <sub>3</sub> (1.0 equiv)	3
		DMF, 80 <sup>o</sup> C, 18 h	

Entry	Ar <sup>1</sup>	Ar <sup>2</sup>	Product	Yield <sup>b</sup> (%)
1	() <sup>2</sup>	2-MeC <sub>6</sub> H <sub>4</sub>	3b	34
2	() <sup>2</sup>	3-MeC <sub>6</sub> H <sub>4</sub>	3c	95
3	() <sup>2</sup>	4-MeC <sub>6</sub> H <sub>4</sub>	3d	82
4	() <sup>2</sup>	4-EtC <sub>6</sub> H <sub>4</sub>	Зе	94
5	C 2	4-MeCOC <sub>6</sub> H <sub>4</sub>	3f	71
6	O2N	2-MeC <sub>6</sub> H <sub>4</sub>	3g	58
7	NC	2-MeC <sub>6</sub> H <sub>4</sub>	3h	52
8	O2N	3-MeC <sub>6</sub> H <sub>4</sub>	3i	41
9	NC	3-MeC <sub>6</sub> H <sub>4</sub>	3j	34
10	MeO MeO OMe	3-MeC <sub>6</sub> H <sub>4</sub>	3k	55

Table 3 (continued)

Entry	Ar <sup>1</sup>	Ar <sup>2</sup>	Product	Yield <sup>b</sup> (%)
11	Me	3-MeC <sub>6</sub> H <sub>4</sub>	31	63
12	MeO	4-MeC <sub>6</sub> H <sub>4</sub>	3m	31
13	Me	4-MeC <sub>6</sub> H <sub>4</sub>	3n	54
14	NC	4-MeC <sub>6</sub> H <sub>4</sub>	30	41
15	NC	4-EtC <sub>6</sub> H <sub>4</sub>	3р	58
16	Me	4-EtC <sub>6</sub> H <sub>4</sub>	3q	56
17	MeO MeO OMe	4-MeCOC <sub>6</sub> H <sub>4</sub>	3r	45
18	NC	4-MeCOC <sub>6</sub> H <sub>4</sub>	3s	32
19	MeO	4-MeCOC <sub>6</sub> H <sub>4</sub>	3t	38

<sup>a</sup> Reaction condition: 1 (2.0 mmol), 2 (4.0 mmol), NiCl<sub>2</sub> (0.2 mmol), 2,2'-bipyridine (0.4 mmol), Na<sub>2</sub>CO<sub>3</sub> (2.0 mmol), and Ag<sub>2</sub>CO<sub>3</sub> (2.0 mmol) react in DMF at 80 °C for 18 h. The reaction was conducted under air condition.

<sup>b</sup> Isolated yield.

Table 2,  $Ag_2O$  afforded 45% yield (entry 1), however, other oxidants including copper and oxygen showed lower activities (entries 2–5). Next, other bases were employed in place of  $Na_2CO_3$ . The use of  $K_2CO_3$ ,  $Cs_2CO_3$ ,  $Cs_F$ , and KF did not improve the yield of compound **3a** (entries 6–9), while strong bases led to poor yields (entries 10–13). No improvement was observed at high temperature (entry 14), and when the reaction temperature decreased to 60 °C, the yield dropped to 16% (entry 15). Finally, when the amount of **2a** was increased to 2.0 equiv, the desired product was obtained in 86% yield (entry 16). However, when the reaction was carried out at high temperature, no further improvement was observed (entry 17).

Based on these results, the optimal conditions can be summarized as follows: alkynyl carboxylic acid (1.0 equiv), arylboronic acid (2.0 equiv), NiCl<sub>2</sub> (10 mol %), 2,2'-bipyridine (20 mol %), Na<sub>2</sub>-CO<sub>3</sub> (1.0 equiv), and Ag<sub>2</sub>CO<sub>3</sub> (1.0 equiv) were reacted in DMF at 80 °C for 18 h. To evaluate this optimized protocol, a variety of arylboronic acids were employed in the decarboxylative coupling reaction with phenyl propiolic acid. The corresponding results are summarized in Table 3. Alkyl substituted phenylboronic acids afforded coupling products in good yields (entries 1-4), with the exception of 2-methylphenylboronic acid that gave a low yield due to steric hindrance. The reaction between phenyl propiolic acid and 4-acetylphenylboronic acid gave the desired product in 71% yield (entry 5). 4-Nitro or 4-cyano substituted phenyl propiolic acids reacted with 2- or 3-methyl phenyl boronic acids affording 3g, 3h, 3i, and 3j in 58%, 52%, 41%, and 34% yield, respectively (entries 6-9). 3,4,5-Trimethoxy and 4-acetyl substituted phenyl propiolic acids reacted with 3-methyl phenylboronic acid to provide 3k and 3l in 55% and 63% yield, respectively (entries 10 and 11). 4-Alkyl substituted phenyl propiolic acids produced the desired products in moderate yields (entries 12-16). The reaction of 4-methoxycarbonylphenylboronic acid led to moderate yields of products (entries 17–19). Unfortunately, when octynoic acid was reacted with phenylboronic acid under this optimized condition, no desired coupled product was formed.

In order to investigate the reactivity of the nickel catalyst in this coupling reaction, diphenylacetylene was employed as a starting material in place of phenylpropiolic acid. When diphenylacetylene was reacted under the optimized conditions, it did not undergo further reaction with phenylboronic acid. Based on this result, it was found that the coupled product was stable under these reaction conditions even when two equivalents of arylboronic acid were employed.

To study the reaction mechanism, a model reaction was conducted under the optimized conditions in the presence of TEMPO (1 equiv), which is known to be a radical scavenger. Since the yield of the resulting product did not change, a possible radical pathway could be ruled out. Based on these results and a previous Letter,<sup>13a</sup>



Base = Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, Ag<sub>2</sub>CO<sub>3</sub>

we proposed the reaction pathway shown in Scheme 2. The arylboronic acid reacts with nickel(II) to give aryl nickel complex **I**, which then reacts with the decarboxylated alkyne to provide aryl alkynyl nickel complex **II**. The subsequent reductive elimination affords the desired coupled product and nickel(0). In this catalytic cycle,  $Ag_2CO_3$  acts as an oxidant for the oxidation of nickel(0) to nickel(II).

In summary, we developed a nickel-catalyzed oxidative decarboxylative coupling reaction between alkynyl carboxylic acids and aryl boronic acids. Under the optimized conditions, the reaction was carried out in the presence of NiCl<sub>2</sub> (10 mol %), 2,2'-bipyridine (20 mol %), Na<sub>2</sub>CO<sub>3</sub> (1.0 equiv), and Ag<sub>2</sub>CO<sub>3</sub> (1.0 equiv) in DMF at 80 °C for 18 h. A variety of aryl boronic acids bearing different groups reacted with aryl alkynyl carboxylic acids to give the desired diaryl alkynes in good yields. Mechanistic studies revealed that this nickel-based catalytic cycle involved an ionic rather than a radical process.

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