

# A Transition-Metal-Free Synthesis of Arylcarboxyamides from Aryl Diazonium Salts and Isocyanides

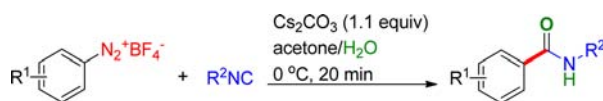
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## ABSTRACT



A transition-metal-free carboxyamidation process, using aryl diazonium tetrafluoroborates and isocyanides under mild conditions, has been developed. This novel conversion was initiated by a base and solvent induced aryl radical, followed by radical addition to isocyanide and single electron transfer (SET) oxidation, affording the corresponding arylcarboxyamide upon hydration of the nitrilium intermediate.

The transition-metal-catalyzed carbonylation reaction of aryl (pseudo) halides is a well-established approach to various aryl carbonyl derivatives, depending on the nucleophiles utilized.<sup>1</sup> For example, when primary or secondary amines are used as nucleophiles, corresponding arylcarboxyamides are produced following CO insertion and reductive elimination.<sup>2</sup> Aryl diazonium salts<sup>3</sup> are recognized as more reactive electrophiles than corresponding aryl iodides in palladium-catalyzed cross-coupling or carbonylative coupling reactions,<sup>4</sup> although the most well-known transformations associated with aryl diazonium salts are the Sandmeyer reaction<sup>5</sup> and the Meerwein arylation.<sup>6</sup> Nucleophiles applied in palladium-catalyzed carbonylative couplings using aryl diazonium salts as electrophiles include water, hydrides, alcohols, acids, and

organometallic reagents to furnish aryl carboxylic acids,<sup>7</sup> aldehydes,<sup>8</sup> esters,<sup>9</sup> mixed anhydrides,<sup>10</sup> and ketones,<sup>11</sup> respectively (Scheme 1). However, arylcarboxyamides cannot be obtained by direct aminocarbonylation of aryl diazonium salts in the presence of CO and amines or anilines, because adducts between aryl diazonium salts and amines or anilines will form quickly.<sup>12</sup>

Isocyanide contains a stable formal divalent carbon which can act as both a nucleophile and an electrophile in reactions such as the Passerini and Ugi multicomponent reactions.<sup>13</sup> The terminal carbon of isocyanide can also be attacked by a radical species, generating an imido radical intermediate for subsequent reactions.<sup>14</sup> In addition,

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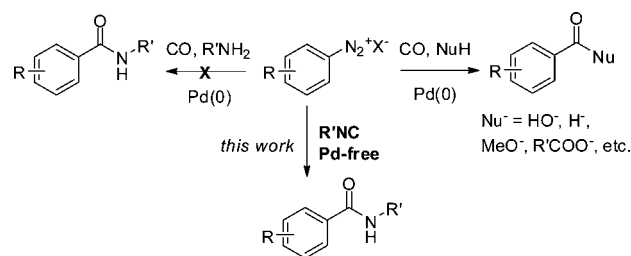
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**Scheme 1.** Palladium-Catalyzed Carbonylative Couplings of Aryl Diazonium Salts



reactions using isocyanides as isoelectronic equivalents of carbon monoxide in palladium-catalyzed isocyanide insertion have grown rapidly in recent years.<sup>15</sup> Based on our continuing interest on isocyanide chemistry,<sup>16</sup> we anticipate that aryl diazonium salts could be used as electrophiles in palladium-catalyzed isocyanide insertion, affording arylcarboxyamides.<sup>17</sup> Research following this hypothesis revealed that aryl diazonium tetrafluoroborates can react with isocyanides in the absence of palladium. This formal aminocarbonylation process occurs in the absence of CO and amines or anilines in aqueous media at 0 °C.<sup>18</sup> Mechanistic studies suggest that radical intermediates are involved in the process.

In an initial attempt, *p*-nitrophenyl diazonium tetrafluoroborate **1a** and *tert*-butyl isocyanide **2a** were used as model substrates in the presence of Pd(OAc)<sub>2</sub> (5 mol %) in acetone/H<sub>2</sub>O (2.5:1) at 0 °C (entry 1, Table 1). As we expected, the corresponding *N*-(*tert*-butyl)-4-nitrobenzamide **3a** was isolated in 9% yield. However, a control reaction without a palladium catalyst also produces **3a** in 16% yield, indicating that **1a** could react with **2a** through a different mechanism as we anticipated. Addition of base significantly improves the yield of **3a** (entries 3–6). In the case of using cesium carbonate (1.1 equiv) as a base, the

**Table 1.** Optimization of the Reaction Condition<sup>a</sup>

entry	promoter (equiv)	<b>2a</b> (equiv)	solvent	yield (%) <sup>b</sup>
1	Pd(OAc) <sub>2</sub> (0.05)	2	acetone/H <sub>2</sub> O	9
2	none	2	acetone/H <sub>2</sub> O	16
3	K <sub>2</sub> CO <sub>3</sub> (1.1)	2	acetone/H <sub>2</sub> O	61
4	Cs <sub>2</sub> CO <sub>3</sub> (1.1)	2	acetone/H <sub>2</sub> O	67
5	NaOAc (1.1)	2	acetone/H <sub>2</sub> O	42
6	<i>t</i> -BuOK (1.1)	2	acetone/H <sub>2</sub> O	65
7	Cp <sub>2</sub> Fe (0.1)	2	acetone/H <sub>2</sub> O	65
8	FeCl <sub>2</sub> (0.1)	2	acetone/H <sub>2</sub> O	12
9 <sup>c</sup>	Cs <sub>2</sub> CO <sub>3</sub> (1.1)	2	acetone/H <sub>2</sub> O	65
10	Cs <sub>2</sub> CO <sub>3</sub> (1.1)	2	CH <sub>3</sub> CN/H <sub>2</sub> O	36
11	Cs <sub>2</sub> CO <sub>3</sub> (1.1)	2	DMSO/H <sub>2</sub> O	36
12	Cs <sub>2</sub> CO <sub>3</sub> (1.1)	2	DMF/H <sub>2</sub> O	40
13	Cs <sub>2</sub> CO <sub>3</sub> (1.1)	3	acetone/H <sub>2</sub> O	73
<b>14<sup>d</sup></b>	<b>Cs<sub>2</sub>CO<sub>3</sub> (1.1)</b>	<b>3</b>	<b>acetone/H<sub>2</sub>O</b>	<b>80</b>
15 <sup>d</sup>	Cs <sub>2</sub> CO <sub>3</sub> (1.1)	5	acetone/H <sub>2</sub> O	83

<sup>a</sup> Reaction conditions: All reactions were performed with **1a** (0.2 mmol) and **2a** (2–5 equiv), in 0.4 mL of H<sub>2</sub>O and 1.0 mL of organic solvent at 0 °C, in air, for 20 min. <sup>b</sup> Isolated yields of **3a**. <sup>c</sup> The reaction was carried out in darkness. <sup>d</sup> The reaction was carried out in argon.

desired product **3a** was obtained in 67% yield. Interestingly, ferrocene (10 mol %) is also a good catalyst in promoting this transformation, which suggests that this reaction might proceed through a radical mechanism (entry 7).<sup>19</sup> When the reaction was carried out in darkness, a similar yield of 65% was obtained, ruling out the possibility that the reaction was initiated by light induced decomposition of aryl diazonium salt (entry 9).<sup>20</sup> In addition, it was observed that the reaction was less efficient in other organic solvents with water as a cosolvent (entries 10–12). Finally, the yield of **3a** was improved to 80% under the optimized reaction conditions involving 1.1 equiv of Cs<sub>2</sub>CO<sub>3</sub> and 3 equiv of *tert*-butyl isocyanide **2a** in argon (entry 14). Notably, this palladium-free carboxyamidation of aryl diazonium tetrafluoroborate occurs rapidly at low temperature, providing a formal aminocarbonylation reaction of aryl diazonium salts in the absence of CO and amines or anilines.

A series of substituted aryl diazonium tetrafluoroborates were reacted with isocyanide **2a** under the optimized reaction conditions (Figure 1). Aryl diazonium tetrafluoroborates bearing electron-withdrawing groups in the *para*

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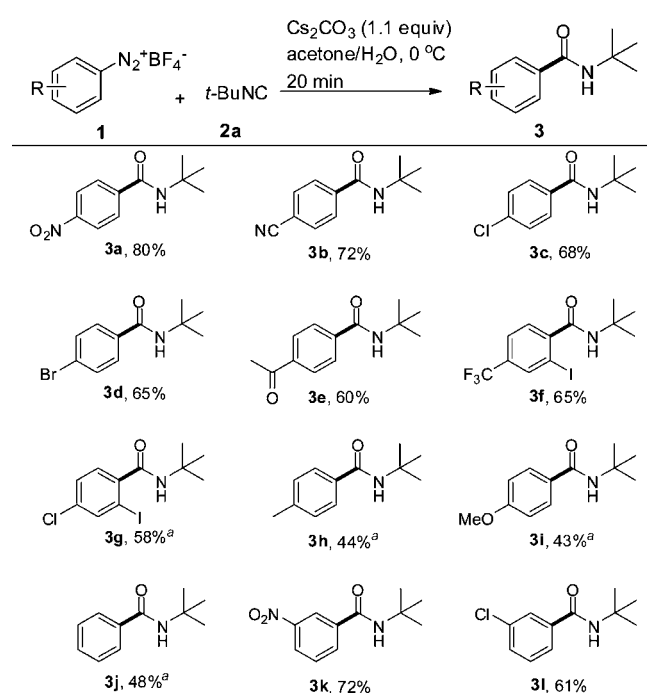
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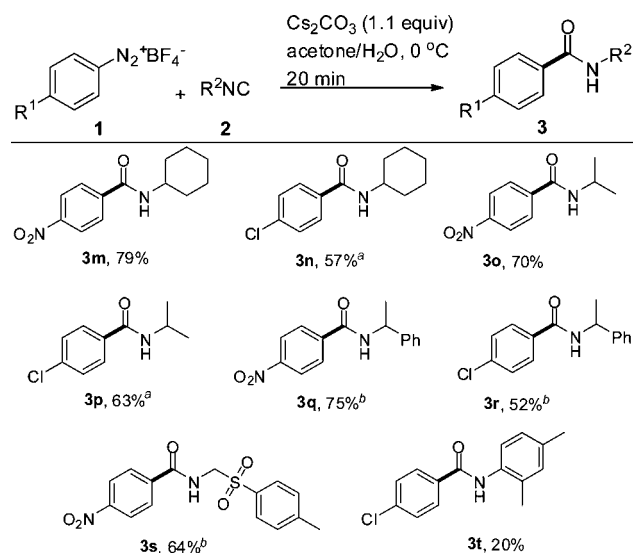
position, such as CN, Cl, Br, COCH<sub>3</sub>, and CF<sub>3</sub>, afforded corresponding amides **3b–3g** in moderate to good yields. It is notable that iodides also survive the reaction conditions (**3f–3g**), providing possibilities in diversification of the products. The synthesis of these iodine-containing carboxyamides would be challenging by the existing transition-metal-catalyzed methodologies. However, electron-neutral or -rich substrates give the amidated products in much lower yields even in the presence of 5 equiv of **2a** (**3h–3j**), indicating that the reaction is significantly affected by the electronic density of the substrates. *Meta* NO<sub>2</sub> or Cl substituted aryl diazonium tetrafluoroborates reacted smoothly with **2a**, providing **3k** and **3l** in 72% and 61% yields, respectively.



**Figure 1.** Scope of aryl diazonium salts. Reaction conditions: All reactions were performed with **1** (0.2 mmol) and **2a** (3 equiv), in 0.4 mL of H<sub>2</sub>O and 1.0 mL of acetone at 0 °C, in Ar, for 20 min; isolated yields of **3**. <sup>a</sup>The reaction was performed with 5 equiv of **2a**.

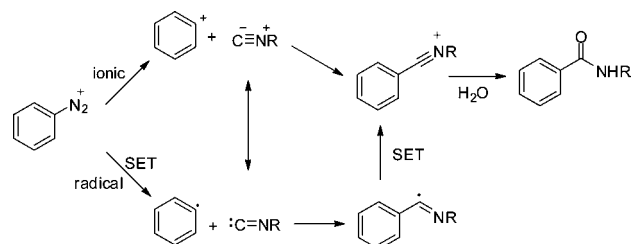
Other isocyanides were briefly investigated in reactions with *para* NO<sub>2</sub> or Cl substituted aryl diazonium tetrafluoroborates (Figure 2). Cyclohexyl, isopropyl, and  $\alpha$ -methyl benzyl isocyanides are all suitable carboxyamidation reagents in the reaction with aryl diazonium tetrafluoroborates, although they are less effective than *tert*-butyl isocyanide **2a** (**3m–3r**). Structurally more complicated 4-nitro-*N*-(tosylmethyl)benzamide **3s** can also be produced in 64% yield under modified conditions. Unfortunately, aryl isocyanide is less compatible with the current protocol, affording corresponding amide **3t** in low yield.

There are two possible reaction pathways involved in this novel carboxyamidation process: ionic or radical mechanism (Scheme 2). To gain insight into the reaction mechanism, radical trapping experiments were performed

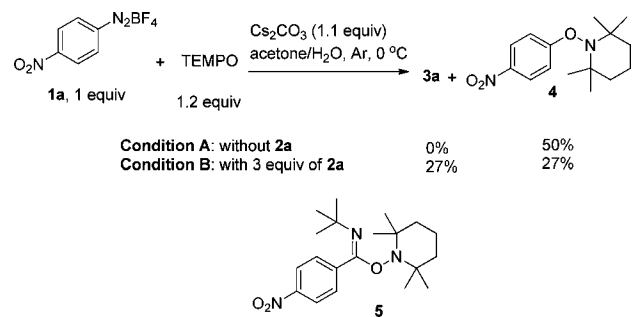


**Figure 2.** Scope of isocyanides. Reaction conditions: All reactions were performed with **1** (0.2 mmol) and **2** (3 equiv), in 0.4 mL of H<sub>2</sub>O and 1.0 mL of acetone at 0 °C, in Ar, for 20 min; isolated yields of **3**. <sup>a</sup> The reaction was performed with 5 equiv of **2**. <sup>b</sup> The reaction was performed with 3 equiv of **1**, and **2** (0.2 mmol, 1 equiv).

## Scheme 2. Two Possible Reaction Pathways

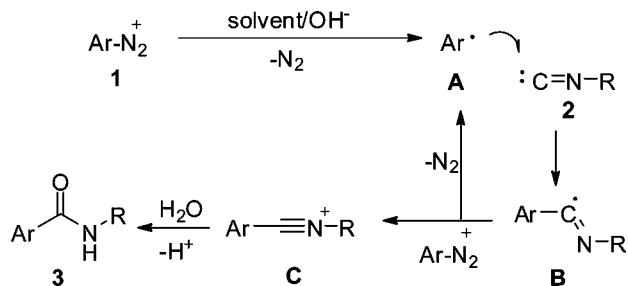


## Scheme 3. Radical Trapping by TEMPO



(Scheme 3). When 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO), a radical scavenger, is added to a reaction in the absence of isocyanide **2a** under otherwise identical conditions, the arylate TEMPO **4** is isolated in 50% yield,

**Scheme 4.** Proposed Reaction Mechanism



proving that an aryl radical is formed under the reaction conditions. When both isocyanide **2a** and TEMPO are present, the TEMPO adduct **4** is formed in 27% yield together with the amidated product **3a** (27%). Although we did not isolate the adduct **5** between the imidoyl radical intermediate and TEMPO, a free radical mechanism is highly likely involved in the reaction. However, the coexistence of an ionic pathway cannot be ruled out at this stage.<sup>21</sup>

According to previous studies on aryl diazonium salts<sup>22</sup> and the above results, a radical mechanism via hydroxide and/or polar solvent induced dediazonation is proposed

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(Scheme 4). Initially, aryl radical **A** is formed through single electron transfer (SET) from hydroxide and/or acetone to aryl diazonium salt **1** followed by homolytic dediazonation. The resulting aryl radical **A** reacts with isocyanide **2** to afford an imidoyl radical intermediate **B** which is oxidized by aryl diazonium cation **1** via SET, giving a nitrilium intermediate **C** and aryl radical **A** upon dediazonation. Finally, hydration and tautomerization of the nitrilium intermediate affords the desired arylcarboxyamide **3**.

In summary, we have reported a transition-metal-free arylation of isocyanides through aryl radical intermediates initiated by base and solvent induced SET reductive dediazonation of aryl diazonium tetrafluoroborates. A range of electron-deficient aryl diazonium tetrafluoroborates react with alkyl isocyanides rapidly at low temperature, in the absence of transition-metal catalysts and ligands. This carboxyamidation process provides a formal aminocarbonylation reaction using aryl diazonium salts as electrophiles in the absence of a palladium catalyst, CO, and amines.

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**Supporting Information Available.** Experimental procedure; characterization data for all new compounds. This material is free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.