

# Nickel-Catalyzed Cross-Coupling of Alkyl Carboxylic Acid Derivatives with Pyridinium Salts via C–N Bond Cleavage

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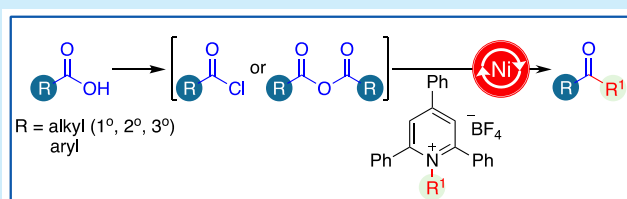


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**ABSTRACT:** The electrophile–electrophile cross-coupling of carboxylic acid derivatives and alkylpyridinium salts via C–N bond cleavage is developed. The method is distinguished by its simplicity and steers us through a variety of functionalized ketones in good to excellent yields. Besides acid chlorides, carboxylic acids were also employed as acylating agents, which enabled us to incorporate acid-sensitive functional groups such as MOM, BOC, and acetal. Control experiments with TEMPO revealed a radical pathway.



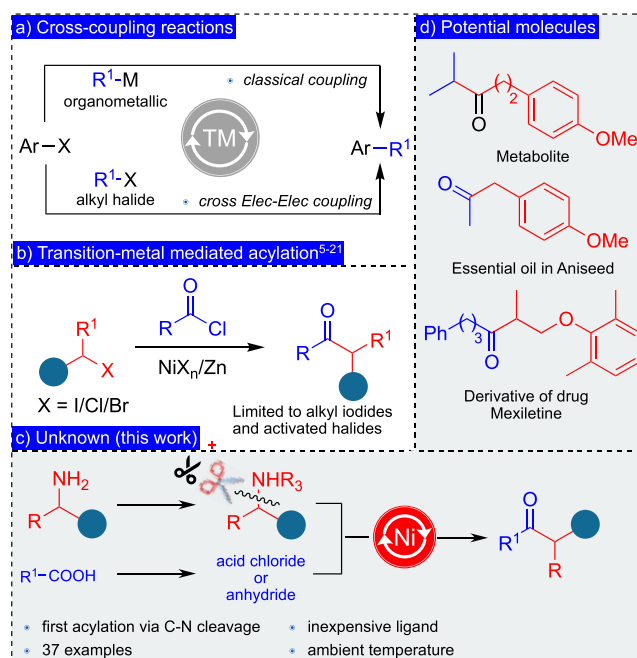
- Inexpensive bpy ligand
- No additive
- 37 examples
- Ambient temperature
- Abundant nickel catalyst
- Broad substrate scope

The ubiquity of ketones in pharmaceutical agents, natural products, agrochemicals, and synthetic applications<sup>1–4</sup> has led to the invention of various elegant strategies for accommodating this intrinsic group. A convergent acylation that utilizes carboxylic acid derivatives with preformed organometallic reagents is commonly found in the literature.<sup>3–5</sup> A further improvement to this acylation was achieved using transition metals, in which less reactive organometallic reagents such as organozinc,<sup>6</sup> organomagnesium,<sup>5,7</sup> organotin,<sup>8</sup> organoboron,<sup>9,10</sup> and organosilane<sup>11</sup> were successfully utilized. Despite these advancements, the instability and limited availability of the organometallic reagents drive the researchers to find potent alternative methods. Moreover, the alkyl organometallic reagents consisting of a  $\beta$ -leaving group are more prone to undergoing elimination.<sup>12</sup>

The electrophile–electrophile cross-coupling reactions are an attractive alternative to classical cross-coupling reactions (Scheme 1a). Although the strategy was reported a few decades ago,<sup>2,13,14</sup> it was not developed further until recently when Weix et al., Gong et al., and others showed that the alkyl halides could be cross-coupled with various electrophiles in the presence of nickel,<sup>15–21</sup> cobalt,<sup>22</sup> palladium,<sup>13</sup> and iron catalysts.<sup>23</sup> In this context, acylations via a cross electrophile–electrophile coupling reaction to afford ketone were also reported (Scheme 1a). Carboxylic acids<sup>10,21,24</sup> and their derivatives, including acyl halides,<sup>2,13,18–20</sup> anhydrides,<sup>21,25</sup> and esters,<sup>14,19</sup> were utilized as the source of the acylating agent. Mukaiyama et al. showed that the pyridyl ester could be coupled with alkyl iodides.<sup>14</sup> In the same year, Fujisawa et al. reported a palladium-mediated acylation of benzyl bromide.<sup>13</sup> The direct cross-coupling of carboxylic acids with alkyl halides has also been recently reported wherein the anhydrides were prepared *in situ* from carboxylic acids and Boc<sub>2</sub>O.<sup>21,24</sup>

Despite these significant advancements in transition metal-mediated electrophile–electrophile cross-coupling reactions

## Scheme 1. Electrophile–Electrophile Cross-Coupling Reactions



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(Scheme 1b), the acylation remains confined to the use of alkyl halides. However, the use of amines as an electrophilic coupling partner in transition metal-mediated acylation is unknown (Scheme 1c) despite its widespread availability.<sup>26–28</sup> Activation of kinetically inert C–N bonds in cross-coupling reactions is notoriously difficult, and a significant effort has been made to activate C–N bonds. Transition metal-mediated cleavage of C(sp<sup>2</sup>)–N and activated C(sp<sup>3</sup>)–N (strained, allylic, and benzylic) bonds is reported.<sup>29</sup> Recently, Watson,<sup>16,26,30</sup> Glorius,<sup>31</sup> Aggarwal,<sup>32</sup> and Rueping<sup>15</sup> et al. reported the activation of an unactivated C(sp<sup>3</sup>)–N bond by converting various amines into Katritzky pyridinium salts.<sup>33</sup>

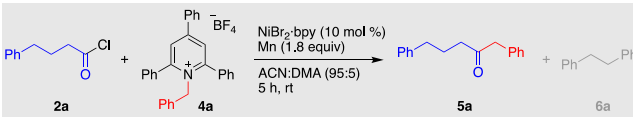
Perceiving the advantage of this approach and in accordance with our interest in nickel-mediated cross-coupling reactions,<sup>34</sup> herein, we demonstrate the feasibility of electrophile–electrophile cross-coupling reaction between amines and acid chlorides as well as carboxylic acids by the synthesis of vital molecules (Scheme 1c) in various facets of chemistry.

We commenced our study with acid chloride **2a**, which was readily prepared from the corresponding carboxylic acid **1a**. The pyridinium salt **4a** was prepared from benzyl amine in two steps. The optimized condition requires the use of NiBr<sub>2</sub>·bpy (10 mol %), 1.8 equiv of Mn, and 2.0 equiv of acid chloride **2a** in a 95:5 CH<sub>3</sub>CN/DMA mixture at room temperature. Under this ideal condition, we were delighted to obtain the ketone **5a**, a photochromic dye, in 92% isolated yield (Table 1, entry 1). Nickel complexes NiBr<sub>2</sub>·bpy<sup>35</sup> and NiBr<sub>2</sub>·bpy<sub>2</sub><sup>36</sup> offered excellent catalytic activity with similar yields, stressing that the coordination environment around the nickel center did not alter the reaction efficiency (entries 1 and 2, respectively),

whereas NiI<sub>2</sub> and Ni(acac)<sub>2</sub> yielded moderate results (entries 3 and 4, respectively) with the significant formation of byproduct **6a**. In the absence of a bipyridine ligand (entry 5), a substantial drop in the level of acylation (42% yield) was observed, suggesting the crucial role of a bipyridine ligand. The *in situ*-generated NiBr<sub>2</sub>·bpy from the trihydrated nickel(II) bromide offered a slightly lower yield (entry 6), whereas the *in situ*-generated NiCl<sub>2</sub>·bpy from nickel(II) chloride offered a poor yield with significant formation of byproduct **6a** (entry 7). Control experiments reveal that NiBr<sub>2</sub>·bpy and Mn are essential (entries 8 and 10, respectively), and a detrimental effect was observed when Mn was replaced with Zn (entry 9), demonstrating the potential role of Mn as a reductant to generate low-valent nickel and/or an alkyl radical intermediate from pyridinium salt. Decreasing the amount of either Mn or acid chloride decreased the yield (entry 11 or 12, respectively), presumably due to the partial hydrolysis of acid chloride. A brief screening of solvents showed that the cosolvent system CH<sub>3</sub>CN and DMA was the best in terms of chemical yield for acylation (entries 13 and 14, respectively), and a 95:5 solvent ratio (CH<sub>3</sub>CN:DMA) was optimal (see the Supporting Information). Remarkably, 5 mol % NiBr<sub>2</sub>·bpy offered a yield that was slightly lower than that of 10 mol % NiBr<sub>2</sub>·bpy (entry 15). A further decrease in catalyst load to 1 mol % reduced the yield of acylated product **5a** (entry 16). Because an anhydride can also be used as an acylating agent,<sup>21,25</sup> we employed the purified anhydride **3a** in place of acid chloride **2a** and obtained **5a** in 72% yield (entry 17). It is also necessary to purify the acid chloride **2a** prior to the reaction, or the undistilled crude acid chloride **2a** generated by the reaction of either oxalyl chloride or thionyl chloride offered moderate yields (entry 18 or 19, respectively). The reaction was also carried out with 1 mmol of **4a** and produced **5a** in 95% isolated yield with 10 mol % nickel catalyst and 87% isolated yield with 5 mol % nickel catalyst.

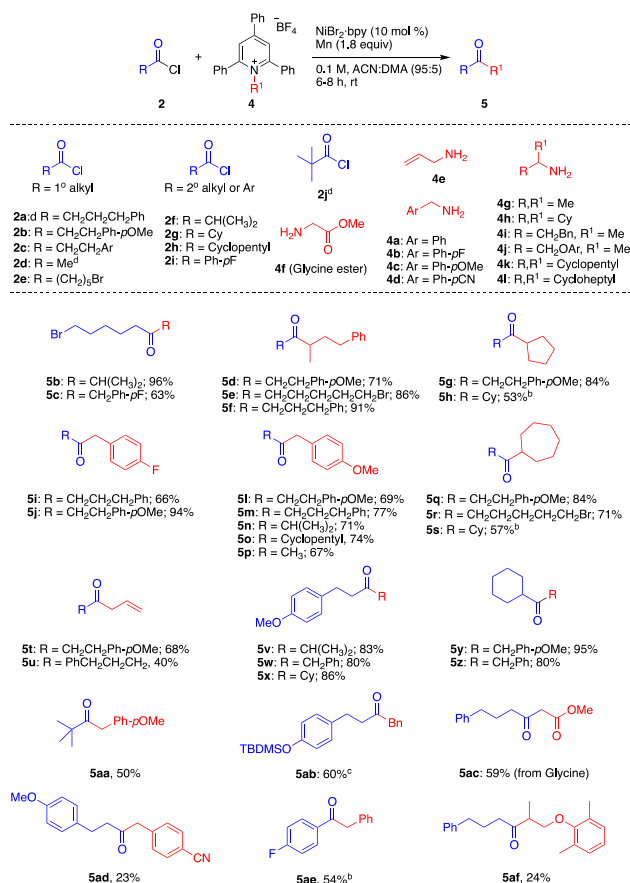
Having an optimized condition in hand, we further expanded the substrate scope, and the results are summarized in Table 2. A broad range of acid chlorides (10 in total) were conveniently prepared from the corresponding carboxylic acids, and the pyridinium salts (12 in total) were made from the corresponding amines via pyrylium salts (see the Supporting Information). Although the purified acid chloride **2a** offered a yield higher than that of the undistilled acid chloride (Table 1), some of the acid chlorides in Table 2 were utilized as a crude because they are prone to undergo decomposition during distillation. A range of acid chlorides, including the primary **2a–e** and secondary alkyl acid chlorides **2f–i**, smoothly underwent cross-coupling reactions with various pyridinium salts **4** to obtain the cross-coupled product in good to excellent yields. The sterically hindered tertiary alkyl acid chloride **2j** offered the cross-coupled product **5aa** in moderate yield. Aryl carboxylic acid chloride **2i** was also compatible to offer the coupled product **5ae** in 54% yield and can also be extended to various aryl acid chlorides, which is not within the scope of this paper. Strikingly, a substrate bearing alkyl bromide was also well tolerated, although the alkyl halides are also known to undergo cross-coupling reactions with acid halides.<sup>37</sup> The alkyl acid chloride **2e** underwent chemoselective cross-coupling reaction to afford the acylated products **5b** and **5c** in 96% and 63% yields, respectively. Various functional groups, including fluoride **2i**, alkene **4e**, ether **2b**, and carbonyl **4f**, were undeterred. The silyl-protected alcohol **2c** was also compatible and underwent smooth cross-coupling to afford

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



entry	deviation from standard conditions	6a (%) <sup>b</sup>	5a (%) <sup>b</sup>
1	none	ND <sup>g</sup>	93, 92 <sup>c</sup>
2	NiBr <sub>2</sub> ·bpy <sub>2</sub> instead of NiBr <sub>2</sub> ·bpy	5	90
3	NiI <sub>2</sub> ·bpy	18	55 <sup>d</sup>
4	Ni(acac) <sub>2</sub> + bpy	42	34
5	NiBr <sub>2</sub> in the absence of bpy	5	42 <sup>d</sup>
6	<i>in situ</i> NiBr <sub>2</sub> ·3H <sub>2</sub> O + bpy	ND <sup>g</sup>	89
7	<i>in situ</i> NiCl <sub>2</sub> + bpy	27	20 <sup>d</sup>
8	without NiBr <sub>2</sub> ·bpy	ND <sup>g</sup>	0
9	Zn instead of Mn	3	56 <sup>d</sup>
10	no Mn	ND <sup>g</sup>	0 <sup>d</sup>
11	1 equiv of <b>2a</b>	8	74 <sup>d</sup>
12	1.2 equiv of Mn	trace	49 <sup>d</sup>
13	CH <sub>3</sub> CN alone	ND <sup>g</sup>	48, <sup>d</sup> 65 <sup>d,e</sup>
14	DMA alone	6	67
15	5 mol % NiBr <sub>2</sub> ·bpy	2	89
16	1 mol % NiBr <sub>2</sub> ·bpy	ND <sup>g</sup>	60 <sup>f</sup>
17	anhydride instead of acid chloride	ND <sup>g</sup>	72
18	<i>in situ</i> <b>2a</b> from oxalyl chloride	3	60
19	<i>in situ</i> <b>2a</b> from thionyl chloride	ND <sup>g</sup>	32

<sup>a</sup>Reaction conditions: 0.295 mmol of **4a**, 0.59 mmol of **2a**, 0.0295 mmol of NiBr<sub>2</sub>·bpy, 0.53 mmol of Mn, 0.1 M CH<sub>3</sub>CN/DMA solution (95:5). <sup>b</sup>Yields determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup>Isolated yield. <sup>d</sup>Leftover **4a** was seen in TLC. <sup>e</sup>After 20 h. <sup>f</sup>Carried out with 2.06 mmol of **4a**. <sup>g</sup>Not detected.

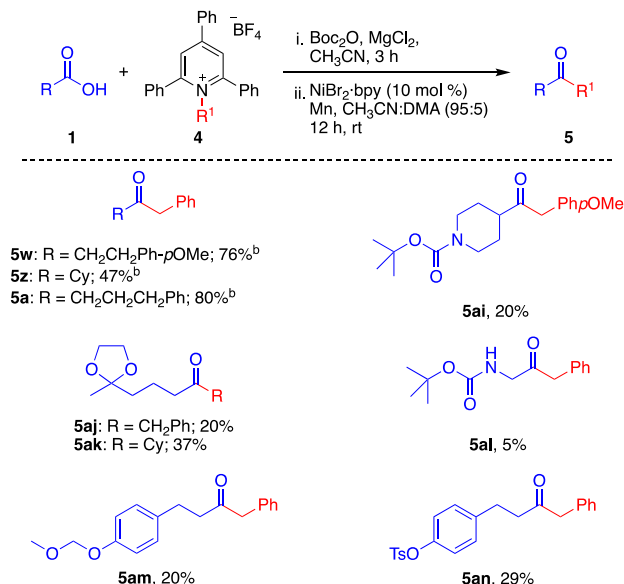
Table 2. Scope of Carboxylic Acid Chlorides as an Acylating Source<sup>a</sup>

<sup>a</sup>Reaction conditions: 1 equiv of **2**, 2 equiv of **4**, 10 mol % NiBr<sub>2</sub>·bpy, 1.8 equiv of Mn, 0.1 M CH<sub>3</sub>CN/DMA solution (95:5), 6–8 h, rt, isolated yield. <sup>b</sup>Reduced to the corresponding alcohol using NaBH<sub>4</sub> (3 equiv). <sup>c</sup>With 1.4 equiv of **2c**. <sup>d</sup>Commercial. Acid chlorides **2a**, **2b**, **2d**, and **2i** were purified by distillation, and **2e**, **2g**, and **2h** were used as crude acid chloride.

product **5ab** in 60% isolated yield. This provides an opportunity for further functionalization of the cross-coupled products. Given the importance of amino acids across various disciplines and their greater accessibility, glycine ester **4f** was successfully cross-coupled into the corresponding acylated product **5ac**. Ketones **5h**, **5s**, and **5ae** were reduced to the corresponding alcohols with NaBH<sub>4</sub> for successful isolation from the otherwise inseparable byproduct (triphenylpyridine). We also obtained **5p**, a naturally occurring essential oil in Aniseed,<sup>38</sup> and **5v**, a metabolite, in high yields.<sup>39</sup> It is noteworthy to mention that **5af**, a derivative of antiarrhythmic drug Mexiletine, was also prepared in 24% yield using this method.

Despite the success of acid chlorides as an acylating source, acid-sensitive protecting groups such as MOM, BOC, and acetals were not compatible in the synthesis of acid chlorides. Encouraged by the literature findings,<sup>21,24</sup> we anticipated that the carboxylic acids could be directly utilized via the *in situ* generation of anhydrides. Moreover, if successful, the acid-sensitive functional groups could be incorporated to diversify the functional group tolerance. We carried out a detailed investigation to optimize the *in situ* generation of anhydride using Boc<sub>2</sub>O and MgCl<sub>2</sub> in either THF or CH<sub>3</sub>CN (see the

Supporting Information).<sup>40</sup> The subsequent cross-coupling reaction proceeded smoothly in the presence of NiBr<sub>2</sub>·bpy (10 mol %) and Mn (1.8 equiv) to afford the ketones **5w** and **5a** in 76% and 80% yields, respectively. We then subjected the carboxylic acids, containing acid-sensitive protecting groups, including MOM, BOC, OTs, and acetal, to the optimized reaction condition and obtained the cross-coupled products in poor to moderate yields as shown in Table 3. These results can

Table 3. Scope of Carboxylic Acids as an Acylating Source<sup>a</sup>

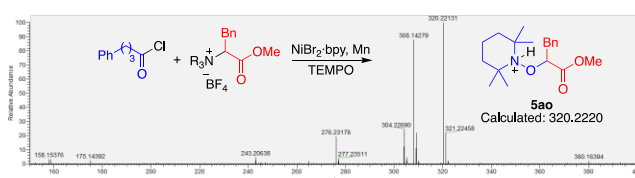
<sup>a</sup>Reaction conditions: 0.885 mmol of **2** (acid), 0.294 mmol of MgCl<sub>2</sub>, 1.03 mmol of Boc<sub>2</sub>O, and 0.9 mL of CH<sub>3</sub>CN (1 M) in step i. In step ii, 0.295 mmol of **4**, 0.0295 mmol of NiBr<sub>2</sub>·bpy, 0.53 mmol of Mn, 1.9 mL of CH<sub>3</sub>CN, and 0.15 mL of DMA were added (overall 0.1 M). <sup>b</sup>Yields were determined by <sup>1</sup>H NMR using 1,3,5-trimethoxybenzene as an internal standard, and **5a** was synthesized using THF instead of CH<sub>3</sub>CN.

be attributed to the formation of byproducts (biphenyl ethane and *tert*-butyl ester of the carboxylic acids) and the unstable nature of these acid-sensitive substrates.

In accordance with the literature, we expected the generation of an alkyl radical intermediate from pyridinium salt.<sup>15,30,32</sup> Hence, we introduced TEMPO under the optimized reaction condition and observed the complete inhibition of the reaction with consequent formation of TEMPO adduct **5ao**, which was confirmed by <sup>1</sup>H NMR (see the Supporting Information) and MS analysis (Scheme 2). The reaction was also inhibited when the reaction was carried out in the presence of radical inhibitor 1-chloro-2,4-dinitrobenzene.

It has been proposed in the literature that the nickel-catalyzed cross-coupling reactions may follow different path-

## Scheme 2. Radical Trap Experiment with TEMPO





ways rather than a universal catalytic cycle. Although we are working on a dedicated mechanistic study to identify the actual intermediates and mechanistic pathway (Figure 1), we present

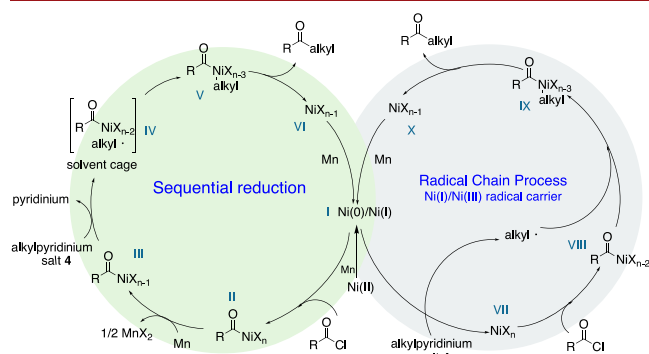


Figure 1. Mechanistic proposal.

here two possible mechanistic pathways based on the preceding literature: (i) sequential reduction and (ii) radical chain process. It has been proposed that the exposure of  $\text{Ni(II)X}_2$  to Zn or Mn will lead to the low-valent nickel [either  $\text{Ni(0)}$  or  $\text{Ni(I)}$ ];<sup>15,17a,41,42</sup> subsequently, it can follow two different mechanistic pathways. In sequential reduction, the low-valent nickel can undergo oxidative addition with acid chloride and resultant intermediate **II** could be reduced to intermediate **III**, which will in turn reduce the pyridinium salt **4** to intermediate **V** in a stepwise manner. Reductive elimination of intermediate **V** and further reduction with Mn could regenerate the active nickel species **I**. In the case of a radical chain process,<sup>17a,42,43</sup> the low-valent nickel species **I** may reduce pyridinium salt **4** to generate the intermediate **VII**, and subsequent oxidative addition with acid chloride will lead to the intermediate **VIII**, which in turn will combine with an alkyl radical to generate the intermediate **IX**. Subsequent reductive elimination followed by the Mn-mediated reduction could regenerate the active nickel species.

In summary, we have presented a nickel-mediated acylation of pyridinium salt for the first time. A broad range of acid chlorides, including sterically hindered, and pyridinium salts with varied functional groups underwent cross-coupling reactions to offer the acylated products in good yields. This protocol accommodates inexpensive bipyridine ligand, requires no additives, and proceeds at ambient temperature. We also showed that the carboxylic acids can be used directly in place of acid chloride to incorporate acid-sensitive functional groups, although the yields of these reactions ranged from poor to high. The presence of the radical intermediate is confirmed by the identification of the TEMPO adduct through NMR and MS analysis. We have presented two possible mechanistic pathways, namely, sequential reduction and radical chain process for the acylation via C–N bond cleavage. The process of finding the actual intermediates and mechanistic pathway is currently underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c00554>.

Additional supporting information (PDF)

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### Notes

The authors declare no competing financial interest.

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