

# Ketone Formation via Mild Nickel-Catalyzed Reductive Coupling of Alkyl Halides with Aryl Acid Chlorides

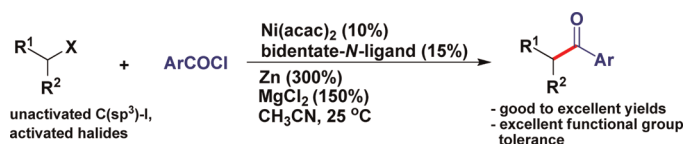
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## ABSTRACT



The present work highlights unprecedented Ni-catalyzed reductive coupling of unactivated alkyl iodides with aryl acid chlorides to efficiently generate alkyl aryl ketones under mild conditions.

In recent years, transition-metal-catalyzed acylation<sup>1–3</sup> and carbonylation<sup>4–6</sup> of carbon nucleophiles have advanced rapidly, leading to facile formation of ketones. In general, however, the catalytic ketone formation employing

aliphatic, particularly functionalized bulky secondary alkyl–metallic, nucleophiles has been less explored,<sup>1b,2a,2b,2f,3a,3c,3d</sup> probably owing to slow reductive elimination and  $\beta$ -elimination of the alkyl–organometallic intermediates.<sup>7</sup> These challenges are also evident in the recent development of Ni- and Pd-catalyzed coupling of secondary alkylzinc reagents with organic halides.<sup>8</sup> Moreover, preparation of alkyl–metallic reagents may be difficult, particularly for those bearing  $\beta$ -leaving groups as pointed out by Knochel.<sup>9</sup>

To avoid the limitation of using alkyl–metallic nucleophiles, syntheses of ketones via acylation or carbonylation of readily accessible alkyl electrophiles are intriguing alternatives.<sup>10</sup> While carbonylation of alkyl halides is restricted to scarce examples of radical and Pd-catalyzed methods under a high pressure of CO,<sup>11,12</sup> employment of acyl nucleophiles in catalytic reversed polarity strategies is efficient only for aryl and activated alkyl electrophiles.<sup>13</sup>

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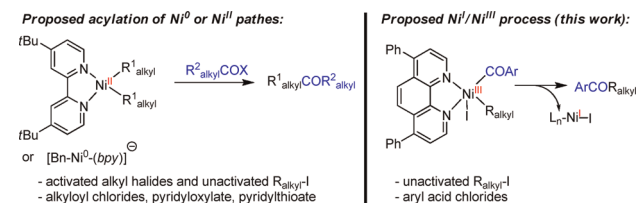
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On the other hand, direct coupling of acyl electrophiles with alkyl electrophiles would provide a straightforward means to ketones. The known methods, however, are effective for the coupling of activated halides and unactivated alkyl iodides with essentially alkyl acid derivatives.<sup>2a,14</sup> Addition of [BnNi<sup>0</sup>(bpy)]<sup>-</sup> and L<sub>n</sub>-Ni(alkyl)<sub>2</sub> to R<sub>alkyl</sub>COCl has been proposed for the Ni-catalyzed chemically and electrochemically reductive alkyl ketone synthesis (Figure 1).<sup>14</sup> Notably, coupling of unactivated alkyl bromides and synthesis of alkyl aryl ketones from readily available aryl acid chlorides remain challenging.

Recent advances of Ni- and Co-catalyzed reductive coupling of alkyl halides with alkyl, aryl, and allylic electrophiles<sup>15,16</sup> suggest redox pathways without involvement of in situ organometallic nucleophiles.<sup>17,2a,2b</sup> Similar to these strategies, we herein report a mild efficient Ni-catalyzed ketone formation via reductive coupling of unactivated alkyl iodides and activated halides with acid chlorides. This protocol accommodates sterically hindered secondary halides and a variety of alkyl and aryl acid chlorides using Zn as the reductant. Our initial studies are in favor of a probable unprecedented Ni<sup>I</sup>/Ni<sup>III</sup> redox process for the formation of alkyl aryl ketones (Figure 1).



**Figure 1.** Pathways for Ni-catalyzed reductive ketone formation.

We first examined the coupling of 4-iodo-1-tosylpiperidine **1a** and benzoyl chloride and identified that a

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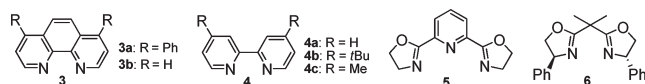
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combination of Ni(COD)<sub>2</sub>/**3a**/Zn/CH<sub>3</sub>CN gave the desired ketone **2a** in 85% yield (Table 1, entry 1). Whereas screening of other ligands (e.g., **3b**, **4a**, **5**, and **6**, entries 2–5 and Figure 2), reductants, and solvents did not yield better results, the survey of different Ni sources revealed that Ni(acac)<sub>2</sub> was comparable to Ni(COD)<sub>2</sub> (entry 6).<sup>18</sup> Addition of 1.5 equiv of MgCl<sub>2</sub> further boosted the yield to 91% (entries 7–8).<sup>18,19</sup> Use of 1.5 equiv of PhCOCl only slightly eroded the yield (88%). In general, the excess benzoyl chloride was converted to benzyl benzoate. The coupling of 4-bromo-1-tosylpiperidine **1b** with benzoyl chloride was also studied (entries 9–11).<sup>18</sup> An extensive search for the optimal reaction conditions only resulted in a best 40% yield under the Ni(COD)<sub>2</sub>/**3a**/Zn conditions in CH<sub>3</sub>CN (entry 10). Nearly 60% of **1b** was recovered while benzoyl chlorides were all consumed after 4 h.



**Figure 2.** Structures of ligands.

**Table 1.** Optimization for the Reaction of **1** and PhCOCl<sup>a</sup>

entry	1/Ni/ligand	additives	time (h)	yield <sup>b</sup> (%)
1	<b>1a</b> /Ni(COD) <sub>2</sub> / <b>3a</b>	none	12	85
2	<b>1a</b> /Ni(COD) <sub>2</sub> / <b>3b</b>	none	12	78
3	<b>1a</b> /Ni(COD) <sub>2</sub> / <b>4a</b>	none	12	75
4	<b>1a</b> /Ni(COD) <sub>2</sub> / <b>5</b>	none	12	30
5	<b>1a</b> /Ni(COD) <sub>2</sub> / <b>6</b>	none	12	68
6	<b>1a</b> /Ni(acac) <sub>2</sub> / <b>3a</b>	none	12	82
7	<b>1a</b> /Ni(acac) <sub>2</sub> / <b>3a</b>	MgCl <sub>2</sub> (150%)	12	91
8	<b>1a</b> /Ni(acac) <sub>2</sub> / <b>3a</b>	MgCl <sub>2</sub> (150%)	4	91
9	<b>1b</b> /Ni(COD) <sub>2</sub> / <b>3a</b>	none	12	40
10	<b>1b</b> /Ni(COD) <sub>2</sub> / <b>3b</b>	none	12	15
11	<b>1b</b> /Ni(COD) <sub>2</sub> / <b>3a</b>	MgCl <sub>2</sub> (150%)	12	33

<sup>a</sup> Reaction conditions: **1** (0.15 mmol, 100 mol %), benzoyl chloride (200 mol %), Ni source (10 mol %), ligand (15 mol %), Zn (300 mol %), CH<sub>3</sub>CN (1 mL). <sup>b</sup> Isolated yields.

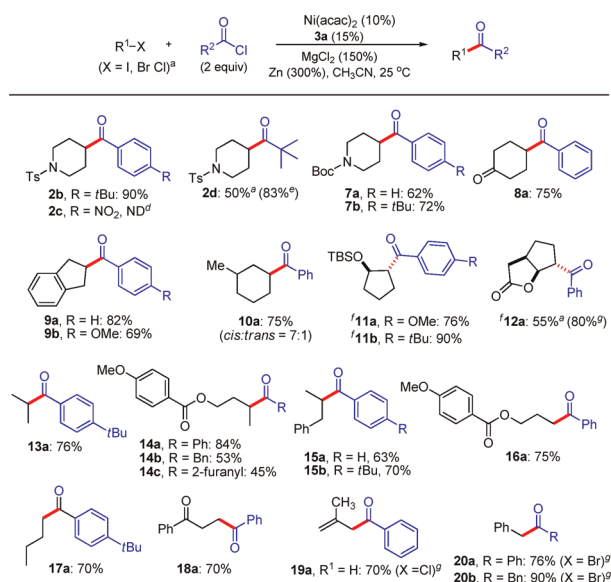
Extension of the optimized conditions (Table 1, entry 7) for the coupling of a wide range of unactivated alkyl iodides and acid chlorides is summarized in Figure 3.

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(18) See the Supporting Information for details.

(19) The role of MgCl<sub>2</sub> is not clear. We speculate that it may activate Zn by removing the salts on the surface of Zn.

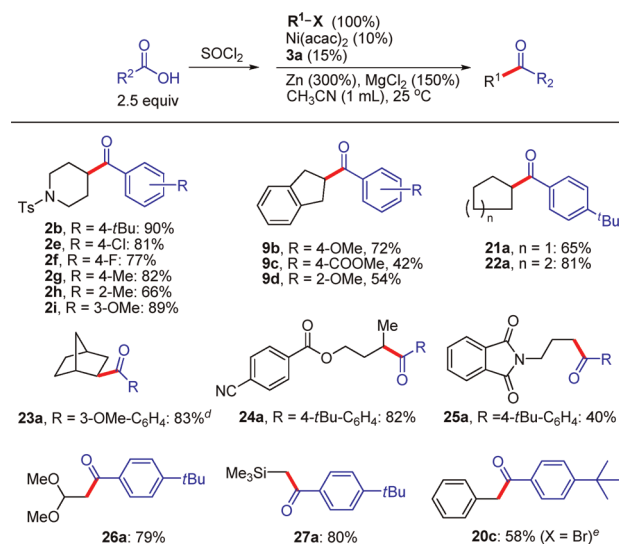
A variety of cyclic and open-chain secondary iodides provided ketones **2** and **7–15** in good to excellent yields. Good to excellent diastereoselectivities were observed for **10–12**. No product was observed when the 4-nitro group was introduced as in **2c**. Good coupling yields were also produced for primary iodides as evident in **16a–18a**. Alkyl acid chlorides, such as pivaloyl and 2-phenylacetyl chlorides, were also compatible with the reaction conditions, giving **2d** and **14b** in moderate to excellent yields. Moreover, employment of furan-2-carbonyl chloride generated **14c** in 45% yield. Using Ni(COD)<sub>2</sub>/**4b** catalytic conditions, the coupling protocol was also effective to generate allylic and benzylic ketones (**19–20**). In general, moderate to excellent yields were resulted. The control experiments indicated that no to low desired coupling products were produced with no Ni.



**Figure 3.** Coupling of alkyl halides with acid chlorides. (a) Standard conditions as in entry 7, Table 1. (b) Unless otherwise mentioned, X = I. (c) Isolated yields. (d) ND: not detected. (e) Standard conditions except Ni(COD)<sub>2</sub> was used. (f) dr > 20:1. (g) Standard conditions except Ni(COD)<sub>2</sub> and **4b** were used.

An additional survey of various substituted aromatic acid chlorides was carried out using freshly prepared crude acid chlorides by removal of excess thionyl chloride, wherein 2.5 equiv of acid was used to ensure the coupling effectiveness (Figure 4). This modified procedure allowed us to easily access ketones **2e–i** and **9b–d**. In general, aryl chlorides containing electron-withdrawing groups (e.g., **9c**) and *ortho*-substituents (e.g., **2h** and **9d**) diminished the yields. Other secondary and primary halides gave ketones **21a–27a**, also in good yields.

The collective examples in Figures 2 and 3 indicated that the coupling conditions displayed excellent functional group tolerance. These included ketone, acetal, fluorine and chlorine, cyanide, lactone, silyl, and alkene. Of special



**Figure 4.** Coupling of alkyl halides with freshly prepared crude acid chlorides. (a) Standard conditions as in entry 7, Table 1 except freshly prepared acid chlorides (<2.5 equiv) were used. (b) Unless otherwise mentioned, X = I. (c) Isolated yields. (d) dr > 20:1. (e) Standard conditions except Ni(COD)<sub>2</sub> and **4b** were used.

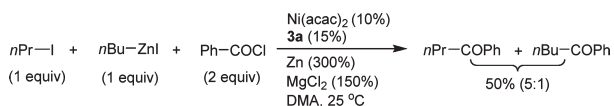
note is that high coupling efficiencies were attained for alkyl halides bearing neighboring groups that are sterically bulky or vulnerable to  $\beta$ -elimination as in **9a**, **11a,b**, **12a**, and **18a**.

To understand whether in situ Negishi mechanism operates, benzoyl chloride was first exposed to an equimolar mixture of *n*-Bu-ZnI and *n*-propyl iodide under optimized conditions (Scheme 1). 1-Phenylbutanone and 1-phenylpentanone were obtained in a ratio of 5:1, suggesting that a Negishi pathway is kinetically less feasible for unactivated alkyl iodides.<sup>20</sup> More importantly, treatment of PhC(O)O(CH<sub>2</sub>)<sub>3</sub>I (0.15 M in CH<sub>3</sub>CN) with Zn in the presence or absence of Ni(acac)<sub>2</sub> leads to formation of no or a trace amount of organozinc reagents even after 12 h. This again supports that a Negishi process is less likely to be involved. Interestingly, addition of MgCl<sub>2</sub> (150 mol %) led to complete conversion to organozinc after 3 h. These observations may explain why the yield was boosted from 82% (entry 6, Table 1) to 91% (entry 7, Table 1) by addition of MgCl<sub>2</sub>, possibly due to the participation of small amount of in situ organozinc, although the Negishi process is slower than the reductive coupling path.

Next, treatment of a 1:1 mixture of 2-iodo-2,3-dihydro-1*H*-indene and benzoyl chloride with Ni(COD)<sub>2</sub> (1 equiv)/**3a**/MgCl<sub>2</sub> (1:1:1.5) in CH<sub>3</sub>CN for 10 min led to about 75%

(20) Coupling of a 1:1:2 mixture of *n*-Pr-I, *n*-Bu-I, and PhCOCl gave *n*-Pr-COPh and *n*-BuCOPh in a 4:5 ratio and 55% total yield.

(21) Tracking the reaction progress for the coupling of PhCOCl (2 equiv) with 2-iodo-2,3-dihydro-1*H*-indene (1 equiv) under the optimized conditions disclosed that acylation completed after 30 min (see the Supporting Information), while for **1a**, it took 4 h, suggesting the former iodide is more reactive.

**Scheme 1.** Ni-Catalyzed Acylation of *n*-BuZnI and *n*-PrI

conversion of PhCOCl, and trace amount of conversion for the alkyl iodide.<sup>21</sup> Thus, PhCOCl is kinetically favored in oxidative addition to Ni<sup>0</sup>.<sup>22</sup>

The previous studies in the Ni-catalyzed Negishi coupling of alkyl halides suggest that oxidative addition of alkyl halides to a Ni<sup>I</sup> species<sup>23,24</sup> first involves generation of an alkyl radical and a Ni<sup>II</sup> intermediate which rapidly combine ( $k > 10^7$  s), leading to an alkyl-Ni<sup>III</sup> species.<sup>24c</sup> Acylation of **28** indeed produced a cyclization product **29a** in good yields, confirming that a radical intermediate may be involved, likely via oxidative addition of alkyl halide to PhCO-Ni<sup>I</sup> to produce a PhCO-Ni<sup>III</sup>-alkyl species (Scheme 2).<sup>24,25</sup> Although to our knowledge PhCO-Ni<sup>I</sup> is unknown, we propose that it could be generated by reduction of the PhCO-Ni<sup>II</sup> intermediate with Zn.<sup>26</sup> A working model for the catalytic process can thus be completed by reductive elimination of a PhCO-Ni<sup>III</sup>-alkyl intermediate to yield the ketone product and a Ni(I) species. Subsequent reduction of the Ni<sup>I</sup> to regenerate Ni<sup>0</sup> allows the catalysis to proceed.

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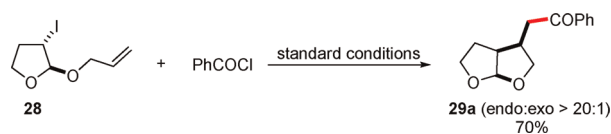
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(26) BnCONi(I) is evidenced in the electrochemical reduction process (ref 14c).

**Scheme 2.** Coupling of **28** and Benzoyl Chloride

In summary, we have disclosed an efficient Ni-catalyzed reductive coupling of alkyl halides with acid chlorides under mild conditions that are tolerant of various functional groups. A wide range of activated and unactivated alkyl halides as well as aryl and alkyl acid chlorides are competent, generally offering ketones in good yields. Our initial mechanistic studies suggest that for unactivated alkyl iodides a Ni<sup>I</sup>/Ni<sup>III</sup> process for the synthesis of alkyl aryl ketones may operate. The use of zinc powder as the terminal reductant avoids preparation of organozinc reagents, which would otherwise be difficult to achieve for alkyl halides bearing functional groups amenable for  $\beta$ -elimination. Further understanding the reaction mechanism for this mild, easy-to-operate ketone formation method is under investigation.

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**Supporting Information Available.** Spectral data of new compounds and experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.