Ni-Catalyzed Reductive Coupling of Alkyl Acids with Unactivated Tertiary Alkyl and Glycosyl Halides

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ABSTRACT: This work highlights Ni-catalyzed reductive coupling of alkyl acids with alkyl halides, particularly sterically hindered unactivated tertiary alkyl bromides for the production of all carbon quaternary ketones. The reductive strategy is applicable to α-selective synthesis of saturated, fully oxygenated C-acyl glycosides through easy manipulations of the readily available sugar bromides and alkyl acids, avoiding otherwise difficult multistep conversions. Initial mechanistic studies suggest that a radical chain mechanism (cycle B, Scheme 1) may be plausible, wherein MgCl₂ promotes the reduction of Ni(II) complexes.

1. INTRODUCTION

In catalytic coupling reactions, tertiary alkyl−metallic reagents or tertiary alkyl electrophiles generally display pronounced difference and challenges as compared to their primary and secondary alkyl analogs, which require special and independent attentions. For instance, the recent development of catalytic coupling of unactivated secondary alkyl zinc reagents with aryl halides has only been extended to adamantylzinc reagents. Moreover, although catalytic formation of ketones involving alkyl nucleophiles has been widely explored, the employment of tertiary alkyl−metallic reagents is very rare. The challenge for the coupling of tertiary alkyl halides can be manifested in Oshima and Fu’s recent construction of quaternary carbon centers through Kumada coupling of allyl-/benzyl-Mg and Suzuki coupling of aryl-9-BBN, respectively. While the former is limited to special organometallics, the latter is very sensitive to the electronic nature of aryl moieties.

Therefore, it is not surprising to notice that although recent Ni-catalyzed reductive coupling of primary and secondary alkyl halides with other electrophiles including acid derivatives effectively generates C(sp³)−C(sp³) and C(sp³)−C(sp²) products (Figure 1), tertiary alkyl halides are not competent. Moreover, although we have extended the reductive protocol to ketone formation through the coupling of alkyl halides with in situ activated aryl acids, four equiv of aryl acids are necessary to ensure low to moderate coupling efficiency, and only alkyl iodides are compatible with limited aryl acids; alkyl acids prove to be ineffective. Hence, development of reductive ketone synthesis that allows for tertiary alkyl halides and alkyl acids is important.

In addition, although C-glycosides including C-acyl glycosides are believed to be important bioactive candidates, their preparation has not been achieved by reductive coupling of two electrophiles. The conventional transition-metal-catalyzed coupling methods, though have succeeded in C-aryl and alkyl glycosides, are generally not applicable to C-acyl glycosides. The challenges are apparent; glycosyl C1 (sp³) and acyl nucleophiles are notoriously difficult to prepare and participate in coupling reactions. Thus, far, benzoyl β-C-glucoside has been the sole example documented in a Pd-catalyzed acylation of 1-glycosyl-Sn method. As a result, much less efficient multistep conversions from 1-glycosyl acids, cyanides, alkyne and allenes dominate the current synthesis of C-acyl glycosides. The development of a general and straightforward method to C-acyl glycosides particularly the α-anomers is therefore highly needed.

We herein report an efficient Ni-catalyzed alkyl−alkyl ketone formation method with emphasis on the coupling of tertiary alkyl and glycosyl halides with alkyl acids using Zn as the reductant (Figure 1). To the best of our knowledge, this work...
demonstrates the first construction of all carbon quaternary centers via the reductive coupling of unactivated tertiary alkyl halides with a second electrophile other than Barbier-type radical addition to carbonyl or activated alkenes.\textsuperscript{27,28} It also represents the first reductive synthesis of α-C-glycosides via readily available electrophiles featuring α-selectivities. Finally, the initial mechanistic studies seem to support a radical chain mechanism, wherein MgCl$_2$ accelerates the reduction of the Ni$^{II}$ complexes.

2. RESULTS AND DISCUSSIONS

2.1. Coupling of Tertiary Alkyl Halides with Alkyl Acids. To identify whether alkyl acids and tertiary alkyl halides are competent, the coupling of tBuBr (1a) with 1.7 equiv of 3-phenylpropanoic acid was intensively surveyed in the presence of Boc$_2$O/Zn and 1.5 equiv of MgCl$_2$ (Table 1).\textsuperscript{29} With Ni(acac)$_2$ being the precatalyst, ligand 4a gave the ketone 2a in 24% yield in THF, which is superior than 3a and 3b (Table 1, entries 1–3). The effects of solvents were next carefully examined. With 4a as the ligand, DME was slightly better than DMSO (entries 4–5). While a mixture of DMSO/DME in a ratio of 8/2 (v/v) worked better than that of 2/8 (entries 6 and 7), addition of 1.5 equiv of Pr$_2$NEt to the latter conditions increased the yield to 47% (entry 8). Other ligands, e.g., 4b–c, 5a, and 6a did not yield better results (entries 9–12). Interestingly, whereas reduction of the amount of MgCl$_2$ from 1.5 to 1 equiv diminished the yield using ligand 4a (entries 8 vs 13), the yield was boosted to 65% from 19% when ligand 4b was employed (entries 9 vs 14). Decrease of Pr$_2$NEt from 1.5 to 0.85 equiv further enhanced the yield to 79% (entries 15). Raising the temperature from 25 to 30 °C resulted in a slight increase of the yield to 82% (entry 16). With these conditions (\textit{method A}), ligand 4a turned out to be much less efficient (entry 17).

With the optimized conditions (\textit{method A}, Table 1, entry 16) in hand, a wide set of acids were able to generate good to excellent yields when coupling with tBuBr as evident in 2a–f, except that a low yield was obtained for 2g using a secondary acid. The excellent compatibility of sterically more hindered tert-alkyl bromides was illustrated in 7–15 (Table 2). Notably, compound 14 was obtained in high \textit{trans}-diastereomeric selectivity (\textit{trans}-4-acyl/phenyl) from its \textit{cis}-bromo precursor (\textit{cis}-4-bromo/phenyl).\textsuperscript{29}

Table 1. Optimization for the Reaction of tBuBr (1a) with 3-Phenylpropanoic Acid$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>solvent</th>
<th>Pr$_2$NEt (%)</th>
<th>MgCl$_2$ (%)</th>
<th>°C</th>
<th>yield (%)$^b$</th>
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<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>THF</td>
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<td>16</td>
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<td>2</td>
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<td>THF</td>
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<td>150</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>4a</td>
<td>THF</td>
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<td>150</td>
<td>25</td>
<td>25</td>
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<td>4a</td>
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<tr>
<td>7</td>
<td>4a</td>
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<td>100</td>
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</table>

$^a$Reaction Conditions: tBuBr (0.3 mmol, 100 mol %), acid (170 mol %), Ni(acac)$_2$ (10 mol %), ligand (12 mol %), Boc$_2$O (200 mol %), Zn (300 mol %), MgCl$_2$ (100 mol %), solvent (1 mL).$^b$GC yields using dodecane as the internal standard (calibrated).

Table 2. Coupling of Unactivated tert-Alkyl Bromides with Acids$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>solvent</th>
<th>Pr$_2$NEt (%)</th>
<th>MgCl$_2$ (%)</th>
<th>°C</th>
<th>yield (%)$^b$</th>
</tr>
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<tr>
<td>1</td>
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<td>THF</td>
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</tr>
<tr>
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<tr>
<td>3</td>
<td>4b</td>
<td>DME</td>
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<td>150</td>
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<td>4b</td>
<td>DMSO/DME = 8:2</td>
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<td>150</td>
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<td>4b</td>
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<td>10</td>
<td>4b</td>
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<td>13</td>
<td>4b</td>
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<tr>
<td>14</td>
<td>4b</td>
<td>DMSO/DME = 2.8</td>
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<td>DMSO/DME = 2.8</td>
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<td>100</td>
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</table>

$^a$Reaction Conditions (\textit{method A}): tert-RBr (0.3 mmol, 100 mol %), acid (170 mol %), Ni(acac)$_2$ (10 mol %), 4b (12 mol %), MgCl$_2$ (100 mol %), iPr$_2$NEt (85 mol %), Boc$_2$O (200 mol %), Zn (300 mol %), DMSO/DME (0.2:0.8, v/v, 1 mL).$^b$Isolated yield after treatment of an inseparable mixture of product and tert-butyl alkoanoate (arising from Boc$_2$O) with TFA. \textit{Isolated yield.}$^c$15 mol % of Ni(acac)$_2$ and 15 mol % of 4b were used. $^d$The dr for isolated 14 was determined by GC-MS analysis which is different from the crude reaction mixture (dr = 19:1); the relative stereochemistry of 14 was determined by single crystal X-ray diffraction analysis (see Supporting Information).

2.2. Coupling of Tertiary Alkyl Halides with Aryl Acids.

With \textit{method A} (Table 1, entry 16), coupling of benzoic acid (1.7 equiv) with (3-bromo-3-methylbutyl)benzene 1b did not generate ketone 11c, nor did benzoic acid anhydride; the majority of the tertiary halide remains unreacted, while benzoic acid and its anhydride were converted into tert-butyl benzoate or decomposed. A control experiment by exposure of equimolar mixture of 3-phenylpropanoic (0.85 equiv) and benzoic acids to 1b gave ketones 11a in 60% yield, while 11c was not detected (eq 1). In addition, reaction of equimolar mixture of 1b and 4-bromo-1-tosylpiperidine (16a) with

benzaldehyde only generated 10% yield of the acylation product from the secondary halide, wherein most of 1b was recovered and 16a underwent hydroxide elimination (eq 2). These results suggest that alkyl acids are more efficient than aryl acids for tertiary alkyl halides in the catalytic ketone formation, and secondary alkyl halides appear to be more reactive than the tertiary ones when reacting with benzoic acid.

2.3. Coupling of Primary and Secondary Alkyl Halides with Alkyl Acids. Extension of the conditions for tertiary alkyl bromides (method A) to secondary halides proved to be ineffective or not general.29,30 Optimization for the reaction of 4-iodo-1-tosylpyperidine (16b) with 1.5 equiv of 3-phenylpropanoic acid in the presence of Boc2O/MgCl2/Zn indicated that a combination of Ni(acac)2/3a in CH3CN/THF (v/v = 2:3) at 25 °C gave ketone 17a in an optimal 95% yield (Table 3). The primary bromides were inert (e.g., 16a).

Table 3. Formation of Ketones from Alkyl Halides

<table>
<thead>
<tr>
<th>Sugar</th>
<th>RCOOR′</th>
<th>Method</th>
<th>Yield (%)</th>
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</thead>
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<tr>
<td>glucose</td>
<td>EtCO2H</td>
<td>B</td>
<td>97 (2.2:1)</td>
</tr>
<tr>
<td>galactose</td>
<td>EtCO2H</td>
<td>C</td>
<td>97 (2.2:1)</td>
</tr>
<tr>
<td>mannose</td>
<td>EtCO2H</td>
<td>C</td>
<td>99 (2.9:1)</td>
</tr>
<tr>
<td>5 glucose</td>
<td>EtCO2H</td>
<td>C</td>
<td>82 (2.6:1)</td>
</tr>
<tr>
<td>9 galactose</td>
<td>EtCO2H</td>
<td>B</td>
<td>90 (7.5:1)</td>
</tr>
<tr>
<td>10 galactose</td>
<td>EtCO2H</td>
<td>B</td>
<td>90 (8.7:1)</td>
</tr>
</tbody>
</table>

*Method A as in Table 2, Method B as in Table 3, Method C as in Table 4.

The general reactivity of the reductive method to C-acyl halides was exemplified in Table 4. A variety of alkyl acids were compatible when method C (for glucosyl and galactosyl bromides) and B (for mannosyl bromide) were used, generating the corresponding ketones 38–46 in good to high yields, while retaining similar α/β ratios to those observed in Table 4.

2.4. Application to the Synthesis of C-Glycosides. To showcase the applicability of this work, we extend the reaction conditions to the synthesis of C-acyl glycosides which are an important class of bioactive products or their intermediates.16,25,26 To our delight, the coupling of glucosyl bromides 32 with propionic acid and its anhydride (Table 4) using the optimized methods B, C and C1 (same as method C except DMF/CH3CN = 1:4) produced the desired C-acyl glucoside 35 in up to 99% yield with moderate α selectivity (α/β ratio up to 3:1). Method A proved to be ineffective (entries 1–7). With method B and C1, high yields were obtained for mannosyl and galactosyl bromides 33 and 34, giving 36 in pure α-form and 37 in high α selectivity (α/β = 8.7:1), respectively (entries 8–10).

The generality of the reduction methods to C-acyl halides was exemplified in Table 5. A variety of alkyl acids were compatible when method C1 (for glucosyl and galactosyl bromides) and B (for mannosyl bromide) were used, generating the corresponding ketones 38–46 in good to high yields, while retaining similar α/β ratios to those observed in Table 4.

2.5. Radical Chain versus Double Oxidative Addition Mechanism. 2.5.1. Proposed Catalytic Cycles. A control experiment indicated that 3-phenylpropanoic anhydride worked equally well as acid/Boc2O when it couples with 2-bromo-2-methylbutane. We reasoned that in situ formation of acid anhydride31 followed by oxidative addition to NiII giving R′C(O)−NiII−OC(O)R′ (I) may constitute the first steps of the catalytic process.32 Intermediate I may be reduced to R′C(O)−NiI (II) which undergoes oxidative addition of alkyl halide leading to a R(C)(O)NiII−R−alkyl (IV), possibly involving rapid combination of an alkyl radical and a NiII intermediate (III) that was generated by reduction of an alkyl halide with NiI (II) (Scheme 1, cycle A).33,34 An alternative radical chain
process is possible via combination of an alkyl radical with intermediate I, similar to the recent Hu’s Ni-catalyzed alkyl Kumada, Weix’s reductive arylation and Fu’s Negishi mechanisms (Scheme 1, cycle B).35 The alkyl radical can be generated by reaction of alkyl halide with the NiI (III) to give the NiII (IV). Initial generation of intermediate III may arise from halide abstraction of R−X with complex I to give R′C(O)−NiIII(OC(O)R)−X (V), followed by reductive elimination of acyl-X.

2.5.2. Radical Process. The radical nature of the reaction was verified in the reductive cyclization/coupling of 47-D with 3-phenylpropanoic acid giving endo-48-D with a 1:1 ratio of syn/anti for H−/H′ (eq 3), as well as the ring opening/coupling of (bromomethyl)cyclopropane with 3-phenylpropanoic acid (eq 4).36

2.5.3. Radical Chain versus Double Oxidative Addition Mechanism. Treatment of Ni(COD)2 with 4a and (iPrCO)2O or (nPrCO)2O in Et2O gave isolatable I-a (Figure 2) and I-b with I-b in DMSO/DME indicated that the reaction went to completion within 180 min, giving 2h in 46% yield (Supporting Information Figure S7). With 5 equiv of tBuBr, the reaction completed much faster, delivering 2h in 50% yield after 65 min.29 Similar results were also detected for the reactions of I-a with 16a (see Supporting Information Table S4), albeit much slower. The observations that Zn was not needed for the stoichiometric reactions of I with Ralkyl−X seem to be better explained by a radical chain mechanism (cycle B, Scheme 1), which involves addition of Ralkyl radical to I.35b Cycle A is less likely as it would require reduction of I by Zn to be a key step. When Zn was introduced, the equimolar reactions of I-b with tBuBr went to completion faster than those without Zn (eq 5). If cycle B operates (Scheme 1), Zn would be unnecessary for the stoichiometric reaction of I-b with tBuBr except reduction of NiII complex (IV) to Ni or Ni0. Generation of Ralkyl radicals by these low-valence Ni species is possible, which may in turn accelerate the reaction.36c

Addition of MgCl2 to the stoichiometric reactions of I-b with tBuBr without Zn did not seem to affect the yields and completion time as much as those with Zn (eq 5). In contrast, MgCl2 appears to be indispensable for the catalytic conditions as evident in the coupling of (3-bromo-3-methylbutyl)benzene (1b) with Ph(CH2)2CO2H, without which no 11a formed. One of its key roles seems to be to significantly accelerate the reduction rate of the Ni(II) complexes. Without MgCl2, most of I-a remained untouched after 3 h in the presence of excess Zn in DMF (Supporting Information Figure S2).29 With it, ~80% and ~100% of I-a were consumed in DMF and DMSF (2:3, v/v) after 1 h, respectively (Supporting Information Figures S3 and S4).29 1H NMR studies indicated that a different complex may form upon addition of MgCl2 to I-a in DMF (Figure 2).29,38 This may involve Cl−/[iPr C(O)O]− anion metathesis and interaction of the resultant iPrC(O)−Ni(Ln)Cl

Table 5. Examples of C-Acyl Glycosides Using Methods B and C1

<table>
<thead>
<tr>
<th>Method</th>
<th>Isolated yields (α/β ratio was determined by 1H NMR).</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>38 (R = iPr), 98% (α/β = 2.8:1)</td>
</tr>
<tr>
<td></td>
<td>39 (R = CH3), 99% (α/β = 2.7:1)</td>
</tr>
<tr>
<td></td>
<td>40 (R = OH), 90% (α/β = 2.8:1)</td>
</tr>
<tr>
<td></td>
<td>41 (R = Cl), 76% (α only)</td>
</tr>
<tr>
<td></td>
<td>42 (R = Br, 68% (α only)</td>
</tr>
<tr>
<td></td>
<td>43 (R = cyclopropanoyl), 99% (α/β = 2.3:1)</td>
</tr>
<tr>
<td>C</td>
<td>44 (R = OH), 94% (α/β = 7.5:1)</td>
</tr>
<tr>
<td></td>
<td>45 (R = Cl, 60% (α/β = 11:1)</td>
</tr>
<tr>
<td></td>
<td>46 (R = Cl, 96% (α/β = 7.7:1)</td>
</tr>
</tbody>
</table>

1H NMR spectra of I-a in DMF without (top) and with MgCl2, and I-c without and with (bottom) MgCl2.
(I-c) intermediate, with Mg²⁺, since addition of MgCl₂ to I-c prepared from oxidative addition of iPrCOCl to L₂-Ni(0) resulted in identical ¹H NMR spectra as that of I-a/MgCl₂ (Figure 2).³⁶ It should be noted that reduction of I-c is much faster than I-a in the absence of MgCl₂ (Supporting Information Figure S5), indicating anion metathesis plays an important role in reduction of I-a/MgCl₂. However, the role of Mg²⁺ cannot be eliminated, as we also observed that MgCl₂ can markedly enhance the rate of reduction of L₆-NiBr₂ (L₆ = 4a) by Zn. Without MgCl₂, most of L₆-NiBr₂ remained intact after 3 h (Supporting Information Figure S6).²⁹,⁴⁰

The effect of Zn²⁺ which is an in situ generated byproduct was also examined. By addition 1 equiv of ZnCl₂ to the catalytic reaction of tBuBr with 3-phenylproanoic acid, the yield of 2a was comparable to the optimized one (Table 1). Equimolar mixture of ZnCl₂ with I-b in DMSO showed that I-b decomposed within 1 h; however, addition of 1.5 equiv of MgCl₂ significantly suppresses the decomposition,²⁹ suggesting that the effect of Zn²⁺ on the catalytic reactions is not important.

To further differentiate the proposed cycles A and B, a radical clock 6-iodohex-1-ene was examined for the coupling with 3-phenylproanoic acid (Figure 3).³⁷,³⁸ A radical-cage-rebound process prepared from oxidative addition of MgCl₂ by Zn. Without MgCl₂, most of L₆-NiBr₂ remained intact after 3 h (Supporting Information Figure S6).²⁹,⁴⁰

The collective studies appear to favor the catalytic cycle B, although the details of the reaction mechanism require more evidence. For instance, the observation that Zn accelerates the stoichiometric reaction should not be simply attributed to reduction of complex IV to Ni²⁺ which is significantly enhanced by MgCl₂. Participation of Zn on promoting the formation of alkyl radicals cannot be excluded.³⁸

3. CONCLUSIONS

In summary, alkyl–alkyl ketones can be efficiently synthesized via Ni-catalyzed reductive coupling of alkyl halides with acids under mild conditions. The reactions accommodate various functional groups. A wide range of acids and alkyl halides are competent, particularly tertiary alkyl bromides. The easy-to-operate procedure avoids prepreparation of organometallic reagents and preactivation of acids, rendering it practical for ketone synthesis. The α-selective synthesis of potentially bioactive C-acyl glycosides is particularly intriguing, as it would otherwise be difficult to achieve using the conventional methods. The indispensable role of MgCl₂ in the catalytic process is evidenced by formation of a new complex with acyl–Ni²⁺ (e.g., I-a), which appears to accelerate the reduction of Ni²⁺ by Zn. The collective mechanistic studies seem to support a radical chain process proposed in cycle B, although more evidence are required for understanding the details.

ASSOCIATED CONTENT

† Supporting Information
Detailed experimental procedures, characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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(33) BnCONi(II) is evidenced in the electrochemical reduction process (ref 15c).


(37) Although a single crystal X-ray structure is not available, the formation of 1-a (or [1-a]) was evidenced by 1H, 13C NMR and ICP studies (see the Supporting Information for details).


(39) Very recently, Weix reported a similar synthesis of an alkyl acyl-Ni(II)−Cl complex in a THF solution with similar observation that Zn is not necessary but may enhance the reaction rate, see: Wotal, A. C.; Ribson, R. D.; Weix, D. J. Organometall. 2014, 33, 5874.

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