Pd/C-Catalyzed Oxidative Alkylation of Secondary Alcohols with Primary Alcohols

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Transition metal-catalyzed carbon-carbon coupling protocol has been widely used as a powerful tool in synthetic organic chemistry.1 In connection with this report, during the course of our studies directed towards a ruthenium-catalyzed carbon-carbon bond forming reaction,2-5 we recently found a new ruthenium-catalyzed coupling reactions between ketones (or secondary alcohols) and primary alcohols. The coupling of ketones A with primary alcohols B preferentially afforded coupled ketones C (Scheme 1, route a)2-5 or coupled secondary alcohols D (Scheme 1, route b)7 according to the molar ratio of B to A. In addition, secondary alcohols E were also found to be coupled with B to afford D (Scheme 1, route c).4 Under these circumstances,8 this report describes a new Pd/C-catalyzed coupling route between E and B leading to oxidative coupled products C (Scheme 1, route d).9

The results of several attempted oxidative alkylation of 1-phenylethanol (1a) with butanol (2a) under several conditions are listed in Table 1. Treatment of 1a with 2 equiv. of 2a in the presence of a catalytic amount of 5% Pd/C (5 mol%) along with KOH in dioxane for 40 h afforded oxidative coupled product 1-phenylhexan-1-one (3a), coupled secondary alcohol 1-phenylhexan-1-ol (4), and acetophenone (5) in 2%, 3%, and 2% yields, respectively, with low conversion of 1a (run 1). However, when 1-decene was further added as a sacrificial hydrogen acceptor, the reaction rate was enhanced toward 3a and 5 formation with complete conversion of 1a, whereas 4 remains nearly constant (run 2). It appears that 1-decene works as a sacrificial hydrogen acceptor for a faster regeneration of [Pd] from [Pd]H2 generated during the course of the initial oxidations of 1a to 5 and 2a to butyraldehyde.10 The molar ratio of 2a to 1a affects the product distribution (runs 3, 4). The oxidized product 5 was formed in preference to 3a and 4 under lower molar ratio ([2a]/[1a] = 1) (run 3) and a lower selectivity between coupled products was observed with higher molar ratio ([2a]/[1a] = 3) (run 4). In spite of further elaboration for the optimization of reaction conditions (run 5, 6), the best result in terms of the yield of oxidative alkylated product 3a and the selectivity of 3a to 4 is best accomplished under the standard set of condition shown in run 2 of Table 1.

Table 1. Optimization of conditions for the reaction of 1a with 2a°

<table>
<thead>
<tr>
<th>Run</th>
<th>[2a]/[1a]</th>
<th>Additive</th>
<th>Conv. (%) of 1a</th>
<th>3a</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>–</td>
<td>21</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1-decene</td>
<td>99</td>
<td>60-62°</td>
<td>2-4°</td>
<td>26-32°</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1-decene</td>
<td>100</td>
<td>23</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1-decene</td>
<td>95</td>
<td>41</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>5’</td>
<td>2</td>
<td>1-decene</td>
<td>95</td>
<td>29</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>6’</td>
<td>2</td>
<td>1-decene</td>
<td>98</td>
<td>47</td>
<td>3</td>
<td>24</td>
</tr>
</tbody>
</table>

°Reaction conditions: 1a (1 mmol), 5% Pd/C (0.05 mmol), KOH (3 mmol), 1-decene (3 mmol), dioxane (2 mL), 100 °C, for 40 h.
°Determined by GLC. Several runs: For 24 h. Pd/C (0.02 mmol).

Table 2 Pd/C-catalyzed oxidative alkylation of 1 with 2a

<table>
<thead>
<tr>
<th>Secondary alcohol 1</th>
<th>Primary alcohol 2</th>
<th>Coupled ketone 3</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ar = Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a R = Pr</td>
<td>2a R = Bu</td>
<td>3a</td>
<td>62</td>
</tr>
<tr>
<td>1b R = Bu</td>
<td>3b</td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>2a R = pentyl</td>
<td>3c</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>2a R = undecyl</td>
<td>3d</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>2a R = phenethyl</td>
<td>3e</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>2b R = 3-pentyl</td>
<td>3f</td>
<td></td>
<td>71</td>
</tr>
<tr>
<td>2g R = Bu</td>
<td>3g</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>1h R = Pr</td>
<td>3h</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>11 R = 1Bu</td>
<td>3i</td>
<td></td>
<td>77</td>
</tr>
</tbody>
</table>

1b Ar = 4-MeC6H4
1c Ar = 4-MeC6H4
1d Ar = 2-naphthyl

8 Reaction conditions: 1 (1 mmol), 2 (2 mmol), 5% Pd/C (0.05 mmol), KOH (3 mmol), 1-decene (5 mmol), dioxane (2 mL), 100 °C, for 40 h.
9 GLC yield.

site, coupled carbonyl 2-butyl-1-tetralol was absolutely produced in preference to usual coupled ketone. This result indicates that the carbonyl reduction of benzo-fused cyclic ketone is faster than that of acyclic ketone under the present Pd/C-catalyzed conditions. From alkyl(methyl) carbonyl 1f, neither coupled ketone nor coupled carbonyl were satisfactorily formed. In the reaction of 1-ferrocenylinehan (1g), the oxidative alkylation occurred under the employed conditions to give coupled ketone along with acetylferrrocene (46% yield).

In summary, it has been shown that ary(methyl) carbonyl 1s undergo an oxidative coupling with primary alcohols in the presence of a catalytic amount of Pd/C along with KOH to give the corresponding coupled ketones in moderate to good yields. The present reaction is a straightforward one-pot process for the oxidative alkylation of secondary alcohols.11

Experimental Section

1H and 13C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. GLC analyses were carried out with a Shimadzu GC-17A instrument equipped with a CBP10-525-050 column (Shimadzu, fused silica capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using nitrogen as carrier gas. The isolation of pure products was carried out via thin layer chromatography (silica gel 60 GF254, Merck). Commercially available organic and inorganic compounds were used without further purification.

General experimental procedure. A mixture of 1a (0.122 g, 1 mmol), 2a (0.148 g, 2 mmol), palladium, 5 wt%, on activated carbon (0.106 g, 0.05 mmol), KOH (0.165 g, 3 mmol) and 1-decene (0.701 g, 5 mmol) in dioxane (2 mL) was placed in a 5 mL screw-capped vial and allowed to react at 100 °C for 40 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate-hexane mixture) to eliminate inorganic salts. To the extract was added appropriate amount of undecane as an internal standard and analyzed by GLC for the determination of the conversion of 1a (99%) and the yield of 5 (26%). Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate-hexane mixture) to give 3a (0.109 g, 62%) and 4 (0.007 g, 4%). All products prepared by the above procedure were identified by comparison with samples noted in our recent report except for 3b, 3d, 3f, 3j-1, and 3o.22,25,26

1-Phenylheptan-1-one (3b).12 Oil; 1H NMR (CDCl3) δ 0.89 (t, J = 7.5 Hz, 3H), 1.31-1.40 (m, 6H), 1.67-1.77 (m, 2H), 2.95 (t, J = 7.5 Hz, 2H), 7.43-7.46 (m, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.95 (d, J = 7.6 Hz, 2H); 13C NMR (CDCl3) δ 14.4, 22.4, 24.7, 29.4, 32.1, 39.0, 128.4, 128.9, 133.2, 137.5, 200.9.

1-Phenyltetradecan-1-one (3d). Solid (hexane); mp 53-55 °C (lit.13 52.5 °C); 1H NMR (CDCl3) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26-1.40 (m, 20H), 1.67-1.72 (m, 2H), 2.94 (t, J = 7.8 Hz, 2H), 7.43-7.47 (m, 2H), 7.52-7.57 (m, 1H), 7.94-7.97 (m, 2H); 13C NMR (CDCl3) δ 14.50, 23.08, 24.78, 29.74, 29.77, 29.88, 29.90, 30.01, 30.03 (× 2), 30.06, 32.31, 39.02, 124.88, 131.21, 137.51, 200.97.

1-Phenylethyl-phenylhexan-1-one (3f).14 Oil; 1H NMR (CDCl3) δ 0.88 (t, J = 7.3 Hz, 6H), 1.26-1.38 (m, 5H), 1.67-1.72 (m, 2H), 2.94 (t, J = 7.8 Hz, 2H), 7.43-7.47 (m, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.95-7.97 (m, 2H); 13C NMR (CDCl3) δ 11.2, 25.7, 27.6, 36.5, 40.5, 128.4, 128.9, 133.2, 137.5, 201.3.

1-(4-Methylphenyl)hexan-1-one (3j).15 Oil; 1H NMR (CDCl3) δ 0.91 (t, J = 7.0 Hz, 3H), 1.34-1.38 (m, 4H), 1.69-1.77 (m, 2H), 2.40 (s, 3H), 2.93 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H); 13C NMR (CDCl3) δ 14.3, 22.0, 22.9, 24.6, 32.0, 38.9, 128.6, 129.6, 135.0, 143.9, 200.7.

1-(4-Methoxophenyl)hexan-1-one (3k).16 Solid (hexane); mp 32-35 °C; 1H NMR (CDCl3) δ 0.91 (t, J = 7.0 Hz, 3H), 1.34-1.38 (m, 4H), 1.69-1.76 (m, 2H), 2.90 (t, J = 7.5 Hz, 2H), 3.87 (s, 3H), 6.93 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H); 13C NMR (CDCl3) δ 14.0, 22.6, 24.3, 31.6, 38.3, 55.4, 113.7, 130.2, 163.3, 199.3.

1-(2-Naphthyl)hexan-1-one (3l). Solid (hexane); mp 67-68 °C; 1H NMR (CDCl3) δ 0.93 (t, J = 7.0 Hz, 3H),
1.37-1.42 (m, 4H), 1.76-1.84 (m, 2H), 3.09 (t, $J = 7.5$ Hz, 2H), 7.52-7.60 (m, 2H), 7.88 (t, $J = 7.8$ Hz, 2H), 7.96 (d, $J = 8.0$ Hz, 1H), 8.03 (dd, $J = 8.5$ and 1.5 Hz, 1H), 8.46 (s, 1H);

$^{13}$C NMR (CDCl$_3$) $\delta$ 14.4, 23.0, 24.6, 32.0, 39.1, 124.4, 127.1, 128.1, 128.7, 128.8, 129.9, 130.0, 133.0, 134.8, 135.9, 201.0.

1-Ferr ocenyl-5-methylhexan-1-one (3o). Brown oil; $^1$H NMR (CDCl$_3$) $\delta$ 0.91 (d, $J = 6.5$ Hz, 6H), 1.23-1.29 (m, 2H), 1.55-1.63 (m, 1H), 1.67-1.75 (m, 2H), 2.68 (t, $J = 7.5$ Hz, 2H), 4.19 (s, 5H), 4.48 (t, $J = 2.0$ Hz, 2H), 4.78 (t, $J = 2.0$ Hz, 2H); $^{13}$C NMR (CDCl$_3$) $\delta$ 22.89, 22.95, 28.35, 39.20, 40.37, 69.71, 70.11, 72.48, 79.58, 205.14. Anal. Calcd for C$_{17}$H$_{22}$FeO: C, 68.47; H, 7.44. Found: C, 68.11; H, 7.63.

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References


11. The oxidative alkylation of secondary alcohol conventionally can be performed via two step-by-step unit transformations such as oxidation of secondary alcohol to ketone and an appropriate alkylation.


