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

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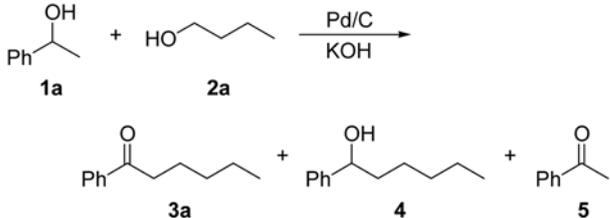[*]*E-mail: scshim@knu.ac.kr*

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)[2,6,7] or coupled secondary alcohols **D** (Scheme 1, route b)[3] 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]H$_2$ 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.

Given the controlled reaction conditions, various secondary alcohols **1** and primary alcohols **2** were employed to investigate the reaction scope. The representative results are summarized in Table 2. The reactions of **1a** with various straight and branched primary alcohols **2a-i** gave the corresponding oxidative alkylated ketones **3a-i** in the range of 43-83% yields with the concomitant formation of a considerable amount of acetophenone on GLC analysis. The reaction yield and rate were increased with the increase of the straight alkyl chain length in **2**. The reaction proceeds likewise with aryl(methyl) carbinols **1b-d** to afford the corresponding coupled ketones **3j-l**. On the other hand, with cyclic carbinol 1-tetralol (**1e**), which has methylene reaction

Table 1. Optimization of conditions for the reaction of **1a** with **2a**[a]

Run	[2a]/[1a]	Additive	Conv. (%)[b] of 1a	Yield (%)		
				3a	**4**	**5**[b]
1	2	–	21	2	3	3
2	2	1-decene	99	60-62[c]	2-4[c]	26-32[c]
3	1	1-decene	100	23	1	56
4	3	1-decene	95	41	19	23
5[d]	2	1-decene	95	29	5	50
6[e]	2	1-decene	98	47	3	24

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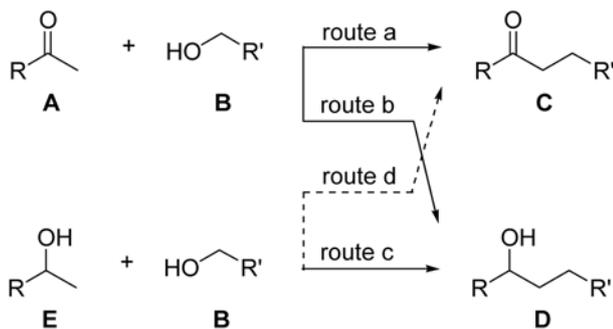
Scheme 1

Table 2. Pd/C-catalyzed oxidative alkylation of **1** with **2**[a]

Secondary alcohol **1**	Primary alcohol **2**	Coupled ketone **3**	Yield (%)
1a Ar = Ph	**2a** R = Pr	**3a**	62
	2b R = Bu	**3b**	66
	2c R = pentyl	**3c**	72
	2d R = undecyl	**3d**	83
	2e R = phenethyl	**3e**	45
	2f R = 3-pentyl	**3f**	71
	2g R = *i*Bu	**3g**	81
	2h R = *i*Pr	**3h**	43
	2i R = *s*Bu	**3i**	77
1b Ar = 4-MeC$_6$H$_4$	**2a**	**3j**	39
1c Ar = 4-MeOC$_6$H$_4$	**2a**	**3k**	55
1d Ar = 2-naphthyl	**2a**	**3l**	61
1e	**2a**	**3m**	52
1f	**2a**	**3n**	3[b]
1g	**2g**	**3o**	46

[a]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. [b]GLC yield.

site, coupled carbinol 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) carbinol **1f**, neither coupled ketone nor coupled carbinol were satisfactorily formed. In the reaction of 1-ferrocenylethanol (**1g**), the oxidative alkylation occurred under the employed conditions to give coupled ketone along with acetylferrocene (46% yield).

In summary, it has been shown that aryl(methyl) carbinols 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

^{1}H and ^{13}C 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-S25-050 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 GF$_{254}$, 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 (0.168 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-l**, and **3o**.[2,5,6]

1-Phenylheptan-1-one (3b).[12] Oil; ^{1}H NMR (CDCl$_3$) δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.31-1.40 (m, 6H), 1.69-1.77 (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); ^{13}C NMR (CDCl$_3$) δ 14.4, 22.9, 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 53-53.5 °C (lit.[13] 52.5 °C); ^{1}H NMR (CDCl$_3$) δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.26-1.40 (m, 20H), 1.70-1.77 (m, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 7.43-7.47 (m, 2H), 7.52-7.57 (m, 1H), 7.94-7.97 (m, 2H); ^{13}C NMR (CDCl$_3$) 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, 128.44, 128.91, 133.21, 137.51, 200.97.

4-Ethyl-1-phenylhexan-1-one (3f).[14] Oil; ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) 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; ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) 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-Methoxyphenyl)hexan-1-one (3k).[15] Solid (hexane); mp 32-35 °C; ^{1}H NMR (CDCl$_3$) 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); ^{13}C NMR (CDCl$_3$) δ 14.0, 22.6, 24.3, 31.6, 38.3, 55.4, 113.7, 130.2, 130.3, 163.3, 199.3.

1-(2-Naphthalenyl)hexan-1-one (3l).[16] Solid (hexane); mp 67-68 °C; ^{1}H NMR (CDCl$_3$) δ 0.93 (t, *J* = 7.0 Hz, 3H),

Notes

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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$_3$) δ 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-Ferrocenyl-5-methylhexan-1-one (3o). Brown oil; ^{1}H NMR (CDCl$_3$) δ 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$_3$) δ 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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