An Efficient Direct Synthesis of β-Ferrocenylketones Catalyzed by Ruthenium

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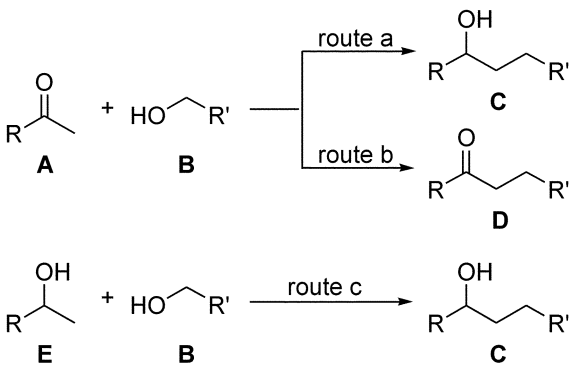
Transition metal-catalyzed carbon-carbon bond forming reaction has been widely used as a fundamental synthetic tool in organic synthesis.[1] During the course of our ongoing studies on ruthenium-catalyzed organic syntheses and transformations, we recently found an unusual type of ruthenium-catalyzed transfer hydrogenation[2,3] of ketones by primary alcohols accompanied by C-C coupling.[4,5] The preferential formation of coupled secondary alcohols **C** to coupled ketones **D** was attributed to the use of an excess amount of alcohols **B** to ketones **A** ([**B**]/[**A**] = 3) (Scheme 1, route a).[4] Thus, when equimolar amounts of both substrates ([**B**]/[**A**] = 1) were used under similar ruthenium catalyst system, α-alkylated ketones **D** were preferentially formed (Scheme 1, route b).[5-7] In addition, we recently disclosed an unprecedented ruthenium-catalyzed coupling between secondary alcohols **E** and primary alcohols **B** which leads to secondary alcohols **C** (Scheme 1, route c).[8] Prompted by these findings,[9] we have directed our attention to the extension of this alkylation (Scheme 1, route b). Herein we report a ruthenium-catalyzed efficient direct synthesis of β-ferrocenylketones from ferrocenemethanol and ketones.[10]

The results of several attempted couplings between ferrocenemethanol (**1**) and acetophenone (**2a**) are listed in Table 1. Treatment of equimolar amounts of **1** and **2a** in dioxane in the presence of $RuCl_2(PPh_3)_3$ (5 mol%) and KOH (3 equiv) at 80 °C for 24 h afforded 3-ferrocenyl-1-phenylpropan-1-one (**3a**) in 58% isolated yield with concomitant formation of 3-ferrocenyl-1-phenylpropenone (**4**, 14%) (entry 1).[11] When the reaction was carried out at room temperature, **3a** was obtained in only 30% yield even for a longer reaction time (43 h) (entry 2). The slight increase of molar ratio of **1** to **2a** ([**1**]/[**2a**] = 1.2) resulted in an increased yield of **3a**, but further increase of the molar ratio ([**1**]/[**2a**] = 1.4) showed no significant change (entries 3 and 4). We previously reported that a hydrogen acceptor triggers the increase of reactivity and selectivity in the ruthenium-catalyzed coupling between ketones (or secondary alcohols) and primary alcohols.[5,8] However, as can be seen from entry 5, the selectivity of **3a**/**4** was not affected by the presence of the hydrogen acceptor and the yield of **4** showed no significant change.

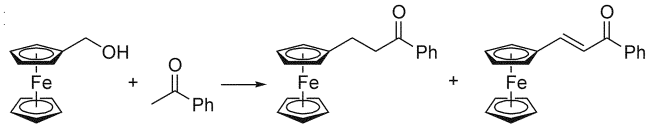


Scheme 1

Given these results, the reactions between **1** and various ketones **2** were screened in order to synthesize a wide range of β-ferrocenylketones **3** (Table 2). Alkyl aryl ketones (**2a**-**2j**) were readily reacted with **1** to give the corresponding β-ferrocenylketones (**3a**-**3j**) in the range of 20-77% yields. The yield of **3** was affected by the position and electronic nature of the substituent on the aromatic ring of the ketones **2a**-**2j**. With *meta*- and *para*-substituted ketones, the product yield was higher than that with *ortho*-substituted ketones (**2b**, **2e** and **2g**). With ketones (**2h** and **2i**) having electron-withdrawing substituents such as 4-fluoro and 3-trifluoromethyl, the product yield was lower than that when ketones having electron-donating substituents such as methyl and methoxy were employed. In cases of dialkyl ketones (**2k**-**2m**), the alkylation took place exclusively at the less-hindered methyl position over α-methylene and methine. Similar regioselectivity was observed by others[12] and in our recent reports.[4,5,8,13]

A possible reaction pathway based on our recent reports,[4,8]

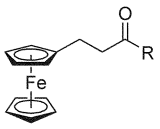
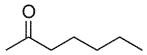
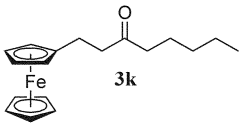
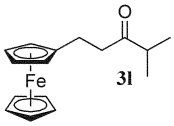
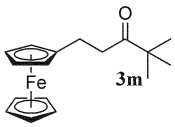
Table 1. Ruthenium-catalyzed coupling between **1** and **2a**[a]



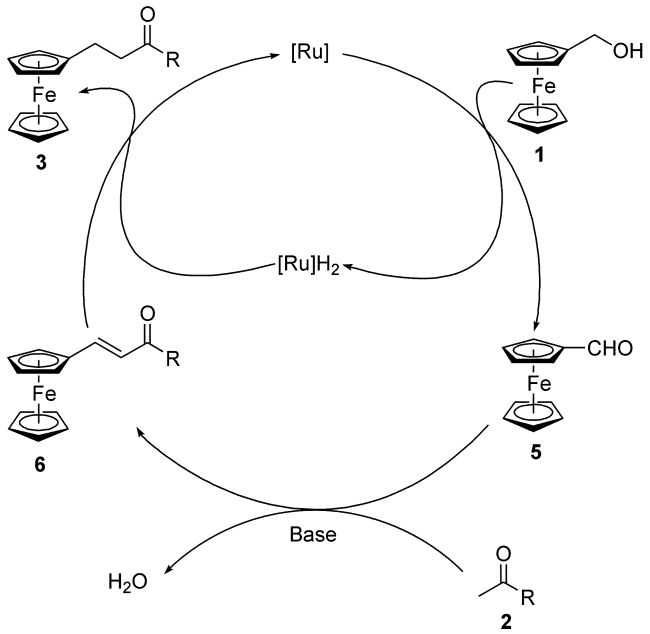
Entry	**1**/**2a**	Temp (°C)	Time (h)	Yield (%) of **3a**/**4**
1	1	80	24	58/14
2	1	25	43	30/10
3	1.2	80	24	71/10
4	1.4	80	24	69/9
5[b]	1.2	80	24	60/12

[a]Reaction conditions: **2a** (0.5 mmol), $RuCl_2(PPh_3)_3$ (0.025 mmol), KOH (1.5 mmol), dioxane (3 mL), under Ar. [b]In the presence of 1-dodecene (0.6 mmol).

Table 2. Ruthenium-catalyzed synthesis of β-ferrocenylketones[a]

Ketones **2**	β-Ferrocenylketones **3**	Yield (%)
		
2a R = Ph	**3a** R = Ph	71
2b R = 2-MeC_6H_4	**3b** R = 2-MeC_6H_4	39
2c R = 3-MeC_6H_4	**3c** R = 3-MeC_6H_4	75
2d R = 4-MeC_6H_4	**3d** R = 4-MeC_6H_4	75
2e R = 2-MeOC_6H_4	**3e** R = 2-MeOC_6H_4	32
2f R = 4-MeOC_6H_4	**3f** R = 4-MeOC_6H_4	77
2g R = 2-HOC_6H_4	**3g** R = 2-HOC_6H_4	20
2h R = 4-FC_6H_4	**3h** R = 4-FC_6H_4	51
2i R = 3-$CF_3C_6H_4$	**3i** R = 3-$CF_3C_6H_4$	46
2j R = 2-naphthyl	**3j** R = 2-naphthyl	54
 **2k**	 **3k**	53
 **2l**	 **3l**	60
 **2m**	 **3m**	61

[a]Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), $RuCl_2(PPh_3)_3$ (0.025 mmol), KOH (1.5 mmol), dioxane (3 mL), 80 °C, 24 h, under Ar.



Scheme 2

consistent with the products formed, is shown in Scheme 2. Initial oxidation of **1** to ferrocenecarboxaldehyde (**5**) followed by cross aldol reaction between **2** and **5** produces β-ferrocenyl-α,β-unsatureted ketone **6**. Subsequent hydrogenation of **6** by a dihydridoruthenium generated in the initial oxidation of **1** to **5** gives β-ferrocenylketone **3**. We separated the intermediate **5** in 6% yield from the experiment shown in entry 4 of Table 1.

In summary, we have demonstrated that ferrocenemethanol is coupled with an array of ketones in the presence of a ruthenium catalyst and a base to give β-ferrocenylketones. The present reaction is a straightforward synthetic approach for β-ferrocenylketones.

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. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The isolation of pure products was carried out *via* thin layer chromatography (silica gel 60 GF_{254}, Merck). Commercially available organic compounds were used without further purification. $RuCl_2(PPh_3)_3$ was prepared by the reported method.[14]

General procedure. A mixture of ferrocenemethanol (**1**) (0.130 g, 0.6 mmol), ketone **2** (0.5 mmol), $RuCl_2(PPh_3)_3$ (0.024 g, 0.025 mmol) and KOH (0.084 g, 1.5 mmol) in dioxane (3 mL) was placed in a 5 mL screw-capped vial. The system was flushed with argon and allowed to react at 80 °C for 24 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thin layer chromatography (silica gel, ethyl acetate/hexane mixture) to give β-ferrocenylketones. The compounds prepared by the above procedure were characterized spectroscopically as shown below.

3-Ferrocenyl-1-phenylpropan-1-one (3a). Yellow solid, mp 94-96 °C (from hexane-ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.78 (t, J = 7.5 Hz, 2H), 3.19 (t, J = 7.5 Hz, 2H), 4.07-4.12 (m, 9H), 7.43-7.47 (m, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.95 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.0, 40.3, 67.3, 68.1, 68.5, 88.0, 128.0, 128.5, 133.0, 136.8, 199. Anal. Calcd for $C_{19}H_{18}FeO$: C, 71.72; H, 5.70. Found: C, 71.91; H, 5.91.

3-Ferrocenyl-1-(2-methylphenyl)propan-1-one (3b). Yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.74 (t, J = 7.5 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 4.06-4.12 (m, 9H), 7.23-7.26 (m, 2H), 7.33-7.38 (m, 1H), 7.59-7.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 24.7, 43.6, 67.8, 68.6, 69.0, 88.4, 126.1, 128.8, 131.6, 132.4, 138.3, 138.5, 204.1.

3-Ferrocenyl-1-(3-methylphenyl)propan-1-one (3c). Yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.76 (t, J = 7.5 Hz, 2H), 3.16 (t, J = 7.5 Hz, 2H), 4.05-4.12 (m, 9H), 7.31-7.36 (m, 2H), 7.73-7.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.8, 24.5, 40.8, 67.8, 68.6, 69.0, 88.5, 125.7, 128.9, 129.0, 134.2, 137.4, 138.8, 200.1.

3-Ferrocenyl-1-(4-methylphenyl)propan-1-one (3d). Yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H), 2.75 (t, J = 7.5 Hz, 2H), 3.14 (t, J = 7.5 Hz, 2H), 4.05-4.11 (m, 9H), 7.23 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$)

δ 22.1, 24.6, 40.6, 67.8, 68.6, 69.0, 88.6, 128.6, 129.7, 134.8, 144.2, 199.6.

3-Ferrocenyl-1-(2-methoxyphenyl)propan-1-one (3e). Yellow solid, mp 66-68 °C (from hexane-ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.71 (t, J = 7.5 Hz, 2H), 3.23 (t, J = 7.5 Hz, 2H), 3.90 (s, 3H), 4.05-4.12 (m, 9H), 6.95-7.02 (m, 2H), 7.43-7.47 (m, 1H), 7.68 (dd, J = 7.5 and 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.5, 45.7, 55.9, 67.6, 68.5, 69.0, 89.0, 111.9, 121.1, 128.9, 130.7, 133.7, 158.9, 202.5. Anal. Calcd for $C_{20}H_{20}FeO_2$: C, 68.98; H, 5.79. Found: C, 68.99; H, 5.92.

3-Ferrocenyl-1-(4-methoxyphenyl)propan-1-one (3f). Yellow solid, mp 82-84 °C (from hexane-ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.76 (t, J = 7.5 Hz, 2H), 3.13 (t, J = 7.5 Hz, 2H), 3.84 (s, 3H), 4.05-4.11 (m, 9H), 6.92 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.7, 40.4, 55.9, 67.8, 68.6, 69.0, 88.6, 114.1, 130.4, 130.7, 163.8, 198.5. Anal. Calcd for $C_{20}H_{20}FeO_2$: C, 68.98; H, 5.79. Found: C, 68.72; H, 5.79.

3-Ferrocenyl-1-(2-hydroxyphenyl)propan-1-one (3g). Yellow solid, mp 94-96 °C (from hexane-ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 2.79 (t, J = 7.5 Hz, 2H), 3.22 (t, J = 7.5 Hz, 2H), 4.07-4.13 (m, 9H), 6.87-6.91 (m, 1H), 6.99 (dd, J = 8.5 and 1.0 Hz, 1H), 7.45-7.49 (m, 1H), 7.75 (dd, J = 8.0 and 1.5 Hz, 1H), 12.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6, 40.4, 67.9, 68.5, 69.0, 87.9, 119.0, 119.3, 119.7, 130.3, 136.7, 162.9, 206.1. Anal. Calcd for $C_{19}H_{18}FeO_2$: C, 68.29; H, 5.43. Found: C, 68.09; H, 5.67.

3-Ferrocenyl-1-(4-fluorophenyl)propan-1-one (3h). Brown solid, mp 79-81 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 2.77 (t, J = 7.5 Hz, 2H), 3.15 (t, J = 7.5 Hz, 2H), 4.06-4.12 (m, 9H), 7.09-7.14 (m, 2H), 7.95-8.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.5, 40.7, 67.8, 68.6, 69.0, 88.3, 116.1 (d, J = 22.2 Hz), 131.3 (d, J = 8.7 Hz), 133.7 (d, J = 2.9 Hz), 166.1 (d, J = 252.1 Hz). Anal. Calcd for $C_{19}H_{17}FFeO$: C, 67.88; H, 5.10. Found: C, 67.59; H, 5.24.

3-Ferrocenyl-1-(3-trifluoromethylphenyl)propan-1-one (3i). Brown oil; ^{1}H NMR ($CDCl_3$) δ 2.80 (t, J = 7.5 Hz, 2H), 3.19 (t, J = 7.5 Hz, 2H), 4.04-4.13 (m, 9H), 7.59 (t, J = 7.5 Hz, 2H), 7.80 (d, J = 7.5 Hz, 2H), 8.11 (d, J = 7.5 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.4, 41.0, 67.9, 68.6, 69.0, 88.0, 124.1 (q, J = 270.5 Hz), 125.3 (q, J = 3.9 Hz), 129.7, 129.8 (q, J = 3.9 Hz), 131.5, 131.6 (q, J = 32.8 Hz), 137.8, 198.5.

3-Ferrocenyl-1-(2-naphthyl)propan-1-one (3j). Yellow solid, mp 95-97 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 2.82 (t, J = 7.3 Hz, 2H), 3.28 (t, J = 7.3 Hz, 2H), 4.06-4.12 (m, 9H), 7.51-7.58 (m, 2H), 7.83-7.87 (m, 2H), 7.91 (d, J = 7.5 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.7, 40.9, 67.9, 68.7, 69.1, 88.5, 124.3, 127.2, 128.2, 128.9, 130.0, 130.1, 132.9, 134.6, 136.0, 199.9. Anal. Calcd for $C_{23}H_{20}FeO$: C, 75.02; H, 5.47. Found: C, 74.95; H, 5.31.

1-Ferrocenyloctan-3-one (3k). Yellow solid, mp 58-59 °C (determined as isolated because of the difficulty of recrystallization); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.23-1.33 (m, 4H), 1.53-1.60 (m, 2H), 2.38 (t, J = 7.3 Hz, 2H), 2.57-2.61 (m, 4H), 4.09-4.14 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.4, 22.9, 23.9, 24.1, 31.8, 43.4, 44.6, 67.7, 68.4, 68.9, 88.3, 211.1.

1-Ferrocenyl-4-methylpentan-3-one (3l). Viscous yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.07 (d, J = 7.0 Hz, 6H), 2.51-2.67 (m, 5H), 4.04-4.10 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 18.1, 23.6, 40.8, 41.8, 67.2, 67.9, 68.4, 87.9, 214.0.

1-Ferrocenyl-4,4-dimethylpentan-3-one (3m). Yellow solid, mp 64-66 °C (from hexane-ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 9H), 2.56-2.60 (m, 2H), 2.65-2.70 (m, 2H), 4.04-4.10 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 24.4, 26.8, 38.8, 44.5, 67.7, 68.5, 68.9, 88.6, 215.6. Anal. Calcd for $C_{17}H_{22}FeO$: C, 68.47; H, 7.44. Found: C, 68.08; H, 7.56.

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