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Rhodium-Catalyzed Alkylation of Ketones and Alcohols with Alcohols[1]

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Abstract—An efficient method for direct alkylation of ketones and alcohols through the borrowing hydrogen strategy in the presence of rhodium complexes as catalyst was developed. This transformation is tolerant to various functional substrates and is efficient in C–C coupling of primary and secondary alcohols, which provides an alternative method of the synthesis of functional ketones from simple and commercially available materials.

Keywords: rhodium, alkylation, alcohols, ketones, borrowing hydrogen

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INTRODUCTION

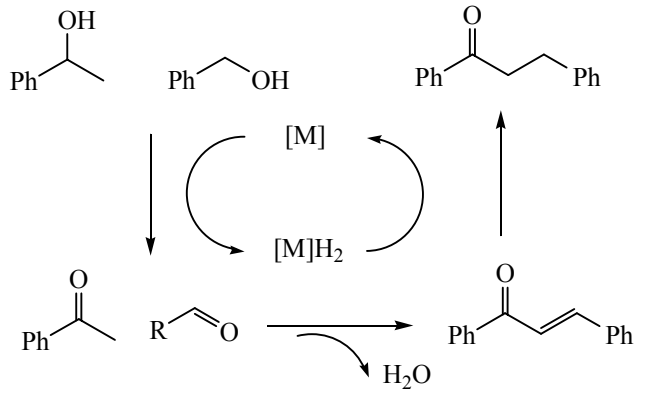
The borrowing hydrogen reaction is considered to be one of the most valuable achievements of chemistry during the past ten decades, providing an efficient method for synthesizing numerous functional amines and ketones [1–8]. In some cases, the above amines and ketones are very difficult to synthesize by the traditional method. Therefore, the borrowing hydrogen reaction becomes an irreplaceable transformation for these compounds. Generally, the borrowing hydrogen strategy has been carried out in the presence of Ru and Ir complexes as catalyst [9-15]. The catalytic activity of Ru and Ir catalysts is much better than that of rhodium catalyst. Although some progress in this area is achieved, the above reactions commonly proceed at high temperatures and under harsh conditions. Therefore, Rh-catalyzed borrowing hydrogen reaction is still a scientific and challenging issue. In 2014, Donohoe et al. reported rhodium-catalyzed ketone methylation using methanol as the alkylating agent and the hydrogen-borrowing method [16].

Compared to coupling of amines with alcohols, coupling of alcohols with ketones, and self-coupling of alcohols in particular, through the borrowing hydrogen strategy is more difficult reaction (Scheme 1). Iridium-catalyzed reactions of C–N and C–C coupling with moderate to good yield were carried out using the borrowing hydrogen method in our previous studies [17–20]. In this study, the borrowing hydrogen strategy is used for rhodium-catalyzed direct alkylation of primary and secondary alcohols (Scheme 2).

RESULTS AND DISCUSSION

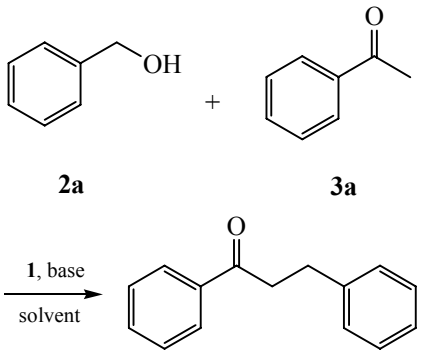
Recently, Cowie et al. have synthesized a series of mono- and binuclear rhodium(I) complexes bearing ortho-phosphinoanilido and ortho-phosphinoaniline ligands [21], which were tested as catalysts for styrene silylation. Here, we found that the rhodium complex [(P,P-dppe)(P,N-Ph_2PAr)Rh] (**1**) could catalyze the reaction of alcohols with ketones (Scheme 2). Although the reaction proceeded with a low yield, it

Scheme 1. C–C bond formation through the borrowing hydrogen strategy.



[1] The text was submitted by the authors in English.

Table 1. Screening of the reaction condition[a]



4a

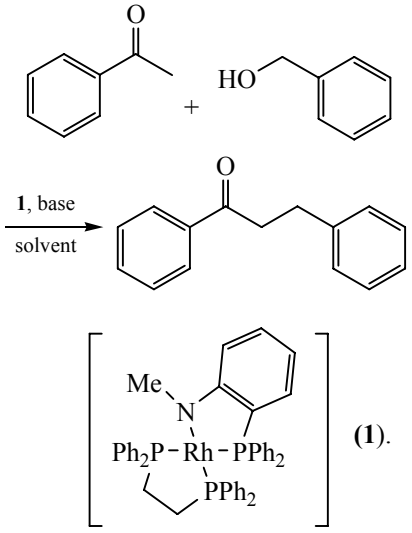
Run no.	Base	Solvent	Yield, %[b]
1	Na_2CO_3	Dioxane	32
2	Na_2CO_3	CH_3CN	68
3	Na_2CO_3	DMF	64
4	Na_2CO_3	Toluene	71
5	Na_2CO_3	Xylene	76
6	Na_2CO_3	THF	58
7	–	Xylene	28
8	NaOH	Xylene	63
9	KOH	Xylene	57
10	K_2CO_3	Xylene	68
11	Cs_2CO_3	Xylene	91
12	*t*-BuONa	Xylene	85
13	*t*-BuOK	Xylene	82
14	NEt_3	Xylene	48
15	Cs_2CO_3	Xylene	84[c]

[a] Conditions: **2a** (1.2 mmol), **3a** (1 mmol), cat. **1** (2 mol %), base (1.5 mmol), solvent (3 mL), 150°C or reflux, 24 h, N_2. [b] Isolated yield. [c] **1** (1 mol%).

was found that this rhodium complex is suitable catalyst for the reaction (Table 1, run no. 1). To increase the reaction yield, xylene was chosen as superior solvent (see Table 1, run nos. 1–6) and Cs_2CO_3 as the best base (see Table 1, run nos. 6–12).

After screening the reaction conditions, we studied a series of aryl halides under the optimal conditions of the reaction. The results are summarized in Table 2. As seen, all secondary alcohols in a nitrogen atmosphere are converted into the corresponding carbonyl

Scheme 2. Rh-catalyzed ketone alkylation.



(1).

compounds in high yields. Electron deficient substrates were found to be applicable in all cases. For substrates with an electron withdrawing group, slightly lower yields were obtained. In general, the yields were mostly from good to excellent (Table 2).

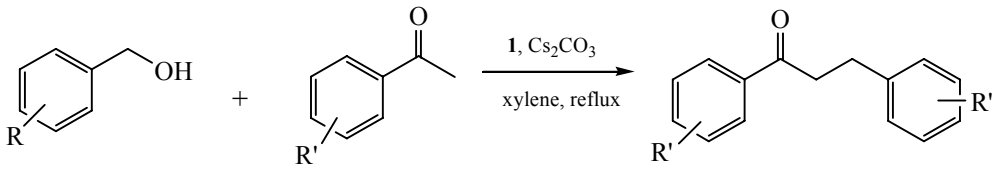
Furthermore, we found that this complex is effective for self-coupling of alcohols. The results are summarized in Table 3. Generally, the products were also separated in moderate to good yields (Table 3).

EXPERIMENTAL

General experiments. ^{1}H NMR spectra were measured on a Bruker Avance-400 and Bruker Avance-300 spectrometers. Chemical shifts (δ, ppm) are downfield relative to tetramethylsilane. Proton coupling patterns have peaks due to singlet (s), doublet (d), triplet (t), and multiplet (m). Thin layer chromatography (TLC) was performed with commercial 100-400 mesh silica gel plates GF_{254} and the separated components were visualized at the wavelength 254 nm. All reagents were purchased from commercial suppliers and used without further purification.

Typical procedure for the synthesis of 4a. A solution of catalyst **1** (2 mol %, 0.01 mmol), acetophenone (1.0 mmol), benzyl alcohol (1.2 mmol), cesium carbonate (1.5 mmol), and xylene (3 mL) were stirred in a Schlenk tube in N_2 atmosphere. The mixture was heated under reflux for 24 h and then cooled to room temperature. The resulting solution was directly purified by column chromatography with

Table 2. Ketone alkylation with alcohols[a]



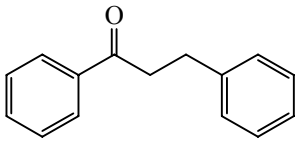
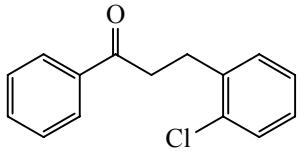
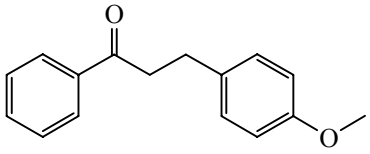
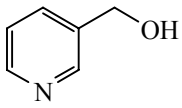
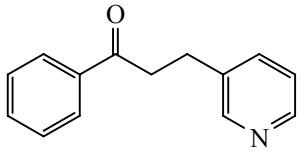
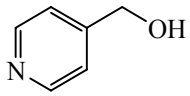
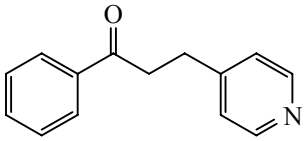
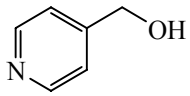
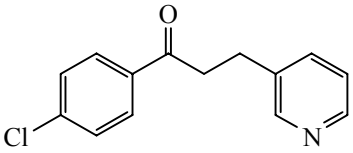
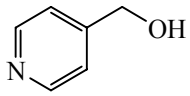
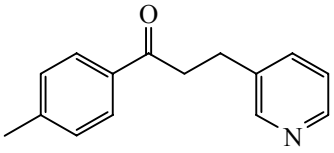
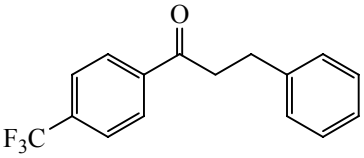
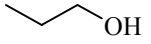
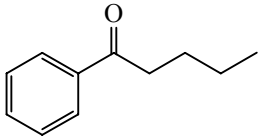
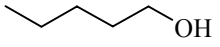
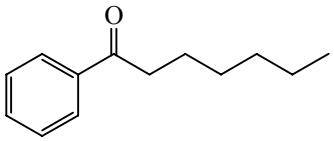
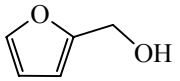
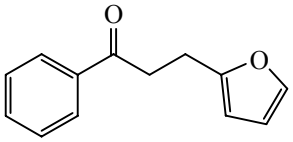
Run no.	R (alcohol)	R' (ketone)	Product	Yield, %[b]
1	H	H		91 (**4a**)
2	H	2-Cl		86 (**4b**)
3	H	4-OMe		83 (**4c**)
4		H		78 (**4d**)
5		H		86 (**4e**)
6		4-Cl		80 (**4f**)
7		4-Me		86 (**4g**)
8	H	4-CF_3		86 (**4h**)
9		H		48 (**4i**)[c]

Table 2. (Contd.)

Run no.	R (alcohol)	R' (ketone)	Product	Yield, %[b]
10		H		57 (**4j**)[c]
11		H		68 (**4k**)

[a] Conditions: **2** (1.2 mmol), **3** (1 mmol), cat. **1** (2 mol %), base (1.5 mmol), xylene (3 mL), reflux, 24 h, N_2. [b] Isolated yield. [c] Primary alcohol **2** (20 mmol, 20 equiv.).

petroleum ether/ethyl acetate (10 : 1) as eluent to give the desired product.

1,3-Diphenylpropan-1-one (4a). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 7.88 d (*J* = 7.6 Hz, 2H), 7.49 t (*J* = 7.7 Hz, 1H), 7.39 t (*J* = 7.6 Hz, 2H), 7.27–7.17 m (4H), 7.14 t (*J* = 7.1 Hz, 1H), 3.24 t (*J* = 5.6 Hz, 2H), 3.01 t (*J* = 5.6 Hz, 2H).

3-(2-Chlorophenyl)-1-phenylpropan-1-one (4b). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.04–7.96 m (2H), 7.62–7.57 m (1H), 7.49 t (*J* = 7.8 Hz, 2H), 7.38 d.d (*J* = 7.6, 1.7 Hz, 1H), 7.35 d.d (*J* = 7.4, 1.9 Hz, 1H), 7.21 d.d (*J* = 7.6, 1.7 Hz, 2H), 3.39–3.32 m (2H), 3.26–3.16 m (2H).

3-(4-Methoxyphenyl)-1-phenylpropan-1-one (4c). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.05–7.93 m (2H), 7.59 t (*J* = 7.4 Hz, 1H), 7.47 t (*J* = 7.6 Hz, 2H), 7.21 d (*J* = 8.2 Hz, 2H), 6.91–6.85 m (2H), 3.81 s (3H), 3.35–3.26 m (2H), 3.11–2.99 m (2H).

1-Phenyl-3-(pyridin-3-yl)propan-1-one (4d). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.55 s (1H), 8.46 d (*J* = 3.8 Hz, 1H), 8.01–7.92 m (2H), 7.63–7.54 m (2H), 7.48 t (*J* = 7.5 Hz, 2H), 7.23 d.d (*J* = 7.6, 4.9 Hz, 1H), 3.34 d.d (*J* =7.4 Hz, 2H), 3.08 t (*J* = 7.5 Hz, 2H).

1-Phenyl-3-(pyridin-4-yl)propan-1-one (4e). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.43 s (2H), 7.86 d.d (*J* = 5.4, 3.4 Hz, 2H), 7.53–7.47 m (1H), 7.39 d (*J* = 8.6 Hz, 2H), 7.11 t (*J* = 7.0 Hz, 2H), 3.31–3.20 m (2H), 3.01 t (*J* = 7.4 Hz, 2H).

1-(4-Chlorophenyl)-3-(pyridin-3-yl)propan-1-one (4f). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.45 d (*J* = 1.8 Hz, 1H), 8.41–8.35 m (1H), 7.86–7.77 m (2H), 7.51–7.46 m (1H), 7.38–7.31 m (2H), 7.15–7.10 m (1H), 3.21 t (*J* = 7.4 Hz, 2H), 3.01 t (*J* = 7.4 Hz, 2H).

3-(Pyridin-3-yl)-1-(*p*-tolyl)propan-1-one (4g). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.54 d (*J* = 1.8 Hz, 1H), 8.43 d.d (*J* = 5.0, 1.4 Hz, 1H), 7.84 d (*J* = 8.2 Hz, 2H), 7.62–7.55 m (1H), 7.24–7.21 m (3H), 3.29 t (*J* = 7.5, 2H), 3.07 t (*J* = 7.5 Hz, 2H), 2.42 s (3H).

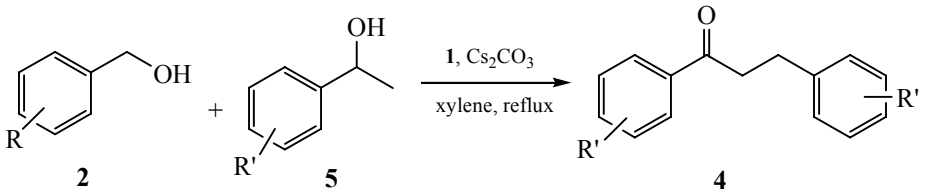
3-Phenyl-1-[4-(trifluoromethyl)phenyl]propan-1-one (4h) ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.08 d (*J* = 8.2 Hz, 2H), 7.75 t (*J* = 7.1 Hz, 2H), 7.37–7.28 m (4H), 7.27 s (1H), 3.39–3.33 m (2H), 3.11 t (*J* = 7.6 Hz, 2H).

1-Phenylpentan-1-one (4i). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.03–7.97 m (2H), 7.61–7.54 m (1H), 7.53–7.44 m (2H), 3.01 t (*J* = 7.4 Hz, 2H), 1.83–1.68 m (2H), 0.98–0.84 m (5H).

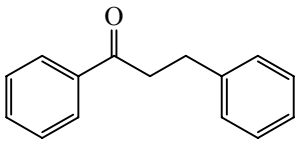
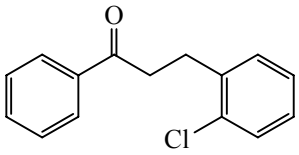
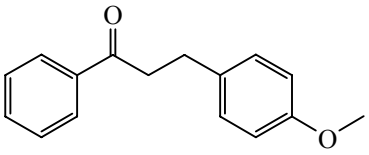
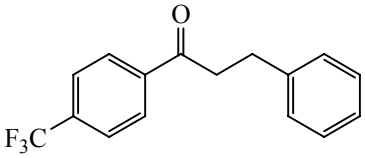
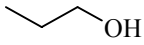
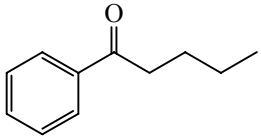
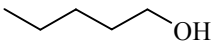
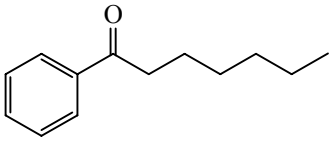
1-Phenylheptan-1-one (4j). Yield 62%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.02–7.96 m (2H), 7.57 t (*J* = 7.5 Hz, 1H), 7.49 t (*J* = 7.6 Hz, 2H), 2.99 t (*J* = 7.4 Hz, 2H), 1.80–1.70 m (2H), 1.41–1.27 m (4H), 0.97–0.86 m (5H).

3-(Furan-2-yl)-1-phenylpropan-1-one (4k). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.05–7.98 m (2H), 7.59 t (*J* = 7.4 Hz, 1H), 7.49 t (*J* = 7.6 Hz, 2H),

Table 3. The coupling reaction of primary and secondary alcohols[a]



2 **5** **4**

Run no.	R (compound **2**)	R' (compound **5**)	Product	Yield, %[b]
1	H	H		83
2	H	2-Cl		76
3	H	4-OMe		78
4	H	4-CF_3		72
5		H		42[c]
6		H		46[c]

[a] Conditions: **2** (1.2 mmol), **5** (1 mmol), cat. **1** (2 mol %), Cs_2CO_3 (1.5 mmol), xylene (5 mL), reflux, 24 h, N_2. [b] Isolated yield. [c] Primary alcohol **2** (20 mmol, 20 equiv.).

7.33 m (1H), 6.33–6.28 m (1H), 6.09 d (J = 3.1 Hz, 1H), 3.35 d.d (J = 9.0, 5.8 Hz, 2H), 3.17–3.11 m (2H).

CONCLUSIONS

In summary, we developed a method of direct alkylation of ketones with alcohols, primary and secondary alcohols in particular. This reaction was carried out through a borrowing hydrogen strategy in the presence of the rhodium complex as catalyst. Importantly, the reaction proceeds in good to excellent yields and is tolerant to various functional substrates.

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