Ruthenium-catalyzed reductive coupling between ketones and primary alcohols in the presence of ethylenediamine

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Abstract

Ketones are reductively coupled with an array of primary alcohols in dioxane at 80 °C in the presence of a catalytic amount of a ruthenium catalyst along with KOH and ethylenediamine to give the corresponding carbon–carbon coupled secondary alcohols in moderate to good yields.
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1. Introduction

Transition metal-catalyzed carbon–carbon and carbon–heteroatom bond forming reactions have been widely explored and used as an easy synthetic access tool for compounds which play an important role as an intermediate for the synthesis of pharmaceuticals and organic materials [1]. As part of our ongoing studies on ruthenium catalysis, as shown in Scheme 1, we recently found ruthenium-catalyzed carbon–carbon bond forming reactions between ketones **1** (or secondary alcohols **5**) and primary alcohols **2**. The coupling of ketones **1** with primary alcohols **2** gives rise to preferential formation of coupled ketones **3** (α-alkylation of **1** with **2**) (Scheme 1, route a) [2] or coupled secondary alcohols **4** (Scheme 1, route b) [3] according to the molar ratio of primary alcohols **2** to ketones **1**. Furthermore, it was also disclosed that secondary alcohols **5** were found to be coupled with primary alcohols **2** in the presence of a ruthenium catalyst along with sacrificial hydrogen acceptor to give coupled secondary alcohols **4** (β-alkylation of **5** with **2**) (Scheme 1, route c) [4]. Several other transition metal precursors have also been used for such couplings [5–10] and this coupling protocol could be applied to modified Friedländer quinoline synthesis [11–17]. In connection with this report, it is

reported that ruthenium-catalyzed transfer hydrogenation from 2-propanol to the carbonyl group of a simple aromatic ketone is remarkably enhanced by the addition of ethylenediamine [18]. Under these circumstances, compared to route b of Scheme 1, which needs the molar ratio of [**2**]/[**1**] = 3 for the preferential formation of **4**, the present report describes an effective atom economical reductive coupling between **1** and **2** leading to **4** under the molar ratio of [**2**]/[**1**] = 1–1.2 by the addition of ethylenediamine.

2. Experimental

2.1. General

^{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. 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 (silica gel 60 GF$_{254}$, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification and dioxane was purchased from Junsei (extra pure grade).

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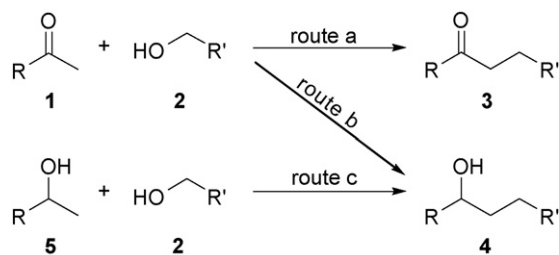
Scheme 1.

2.2. General experimental procedure for ruthenium-catalyzed reductive coupling between ketones and primary alcohols in the presence of ethylenediamine

A mixture of ketone (1 mmol), primary alcohol (1.2 mmol), $RuCl_2(PPh_3)_3$ (0.024 g, 0.025 mmol), KOH (0.056 g, 1 mmol) and ethylenediamine (0.072 g, 1.2 mmol) in dioxane (3 mL) was placed in a 5 mL screw-capped vial and allowed to react at 80 °C for 40 h. The reaction mixture was passed through a short silica gel column (ethyl acetate–hexane mixture) 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 coupled secondary alcohols. Except for **4f–4i** and **4k**, which were characterized spectroscopically as shown below, all coupled secondary alcohols prepared by the above procedure were characterized by GLC and spectroscopic comparison with authentic samples synthesized by our recent reports [3,4].

3-Phenyl-1-(2-thienyl)propan-1-ol (**4f**) [19]: oil; ^{1}H NMR (400 MHz, CDCl3): δ 03–2.27 (m, 3H), 2.67–2.82 (m, 2H), 4.70 (dd, J = 8.0 and 5.5 Hz, 1H), 5.99–6.00 (m, 1H), 6.27–6.28 (m, 1H), 7.26–7.31 (m, 2H), 7.34–7.36 (m, 4H); ^{13}C NMR (100 MHz, CDCl3) δ 24.4, 37.1, 73.7, 105.0, 110.1, 125.9, 127.7, 128.5, 140.9, 144.3, 155.5.

3-(4-Methylphenyl)-1-phenylpropan-1-ol (**4g**) [7]: solid; mp 56–57 °C (hexane–chloroform); ^{1}H NMR (400 MHz, CDCl3): δ 1.94–2.14 (m, 3H), 2.30 (s, 3H), 2.56–2.71 (m, 2H), 4.63 (dd, J = 7.5 and 5.5 Hz, 1H), 7.04–7.09 (m, 4H), 7.23–7.34 (m, 5H); ^{13}C NMR (100 MHz, CDCl3) δ 21.4, 32.0, 41.0, 74.3, 126.4, 128.0, 128.7, 128.9, 129.5, 135.7, 139.1, 145.1.

3-(4-Methoxyphenyl)-1-phenylpropan-1-ol (**4h**) [7]: solid; mp 67–68 °C (hexane–chloroform); ^{1}H NMR (400 MHz, CDCl3): δ 1.90–2.10 (m, 2H), 2.34 (s, 1H), 2.52–2.68 (m, 2H), 3.73 (s, 3H), 4.60 (dd, J = 7.5 and 5.5 Hz, 1H), 6.77–6.81 (m, 2H), 7.06 (d, J = 8.6 Hz, 2H), 7.21–7.33 (m, 5H); ^{13}C NMR (100 MHz, CDCl3) δ 31.6, 41.1, 55.7, 74.2, 114.3, 126.4, 128.0, 128.9, 129.8, 134.3, 145.1, 158.2.

3-(3-Chlorophenyl)-1-phenylpropan-1-ol (**4i**): oil; ^{1}H NMR (400 MHz, CDCl3): δ 1.92–2.12 (m, 2H), 2.15 (s, 1H), 2.57–2.73 (m, 2H), 4.62 (dd, J = 7.8 and 5.3 Hz, 1H), 7.02–7.04 (m, 1H), 7.12–7.19 (m, 3H), 7.24-7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl3) δ 32.1, 40.6, 74.1, 126.3, 126.3, 126.5, 127.1, 128.1, 128.9, 129.0, 130.0, 134.5, 144.3, 144.8.

3-(2-Furyl)-1-phenylpropan-1-ol (**4k**) [20]: oil; ^{1}H NMR (400 MHz, CDCl3): δ 2.01–2.17 (m, 3H), 2.68–2.75 (m, 2H), 4.91–4.94 (m, 1H), 6.95–6.98 (m, 2H), 7.17–7.30 (m, 6H); ^{13}C NMR (100 MHz, CDCl3) δ 29.7, 40.7, 69.5, 123.9, 124.7, 125.9, 126.6, 128.4, 128.5, 141.4, 148.5.

3. Results and discussion

The results of several attempted reactions between acetophenone (**1a**) and benzyl alcohol (**2a**) are listed in Table 1. As has been observed in our recent report [2], treatment of equimolar amounts of **1a** and **2a** in dioxane at 80 °C for 20 h in the presence of a catalytic amount of $RuCl_2(PPh_3)_3$ (2 mol%) along with KOH afforded 1,3-diphenylpropan-1-one (**3a**) as a major coupled ketone product with concomitant formation of further hydrogenated 1,3-diphenylpropan-1-ol (**4a**) (run 1). The product yield and distribution were not nearly changed with a longer reaction time and a more amount of the ruthenium catalyst under similar conditions (run 2). However, interestingly, when one equivalent of ethylenediamine was further added, **4a** was obtained as a major product in preference to **3a** without significant change of total yield (run 3). These results clearly indicate that ethylenediamine plays a decisive role in the carbonyl reduction of **3a** to **4a**. To account for the odd statistical result for hydrogen between reactants and products under redox shuttle in run 3, solvent dioxane may be considered as an additional source of hydrogen. It is known that dioxane has been used as a hydrogen donor in transition metal-catalyzed transfer hydrogenation [21–23]. Actually, we recently reported on ruthenium-catalyzed α-alkylation of ketones with aldehydes, the product being formed by transfer hydrogenation from dioxane [24]. The product selectivity was considerably affected by the amount of ethylenediamine under the employed conditions, decreasing with the decrease in the relative amount of ethylenediamine (run 4). Considering the molar ratio of ethylenediamine to ruthenium catalyst and the selectivity between **3a** and **4a**, ethylenediamine seems to act as not only a ligand of the ruthenium catalyst but also a hydrogen donor [25]. The best result in terms of both overall yield and the selectivity of **4a** to **3a** is best accomplished by the molar ratio [**2a**]/[**1a**] = 1.2 and a slight increased amount of ethylenediamine (run 5).

Having reaction conditions being established, various ketones **1** were subjected to the reaction with **2** in order to investigate the reaction scope and several representative results are summarized in Table 2. The reaction of aryl methyl ketones (**1b–1d**) with **2a** also proceeds to give the corresponding coupled secondary alcohols (**4b–4d**) in the range of 66–75% yields with predominant selectivity to the coupled alcohols. The product yield and selectivity were not significantly affected by the electronic nature of the substituent on the aromatic ring of aryl methyl ketones. 2′-Acetonaphthone (**1e**) was also coupled with **2a** to give the corresponding coupled secondary alcohol **4e** with similar yield and selectivity. The reaction proceeds likewise with heteroaryl methyl ketone **1f**, however, the yield of coupled secondary alcohol **4f** was lower than when aryl methyl ketones were used. From the reactions between **1a** and various activated primary alcohols (**2b–2f**), the corresponding coupled secondary alcohols (**4g–4k**) were also produced in moderate to good yields along with coupled ketones (5–19%). In the reaction of **1a** with ferrocenemethanol (**2g**), the corresponding coupled secondary

Table 1
Optimization of conditions for the reaction of **1a** with **2a**
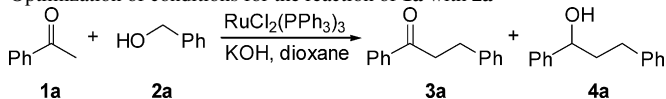
Run	[**2a**]/[**1a**]	RuCl$_2$(PPh$_3$)$_3$ (mol%)[a]	Ethylenediamine (mmol)	Time (h)	Yield[a] (%)	
					3a	**4a**
1	1	2	–	20	70	14
2	1	5	–	40	70	13
3	1	2.5	1	40	16	60
4	1	2.5	0.2	40	25	35
5	1.2	2.5	1.2	40	11	72

Reaction conditions: **1a** (1 mmol), KOH (1 mmol), dioxane (3 mL), 80 °C.
[a] Isolated yield based on **1a**.

Table 2
Ruthenium-catalyzed reductive coupling between **1** and **2**

Ketones **1**	Primary alcohols **2**	Products	Yield (%)
R = Ph (**1a**)	R = Ph (**2a**)	**4a**	72
R = 4-MeC$_6$H$_4$ (**1b**)	**2a**	**4b**	75
R = 4-MeOC$_6$H$_4$ (**1c**)	**2a**	**4c**	69
R = 4-FC$_6$H$_4$ (**1d**)	**2a**	**4d**	66
R = 2-naphthyl (**1e**)	**2a**	**4e**	69
R = 2-thienyl (**1f**)	**2a**	**4f**	47
1a	R′ = 4-MeC$_6$H$_4$ (**2b**)	**4g**	81
1a	R′ = 4-MeOC$_6$H$_4$ (**2c**)	**4h**	74
1a	R′ = 3-ClC$_6$H$_4$ (**2d**)	**4i**	64
1a	R′ = 1-naphthyl (**2e**)	**4j**	55
1a	R′ = 2-furyl (**2f**)	**4k**	66
1a	R′ = ferrocenyl (**2g**)	**4l**	57
1g	**2a**	**4m**	62[a]
1e	**2h**	**4n**	63[b]

Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), RuCl$_2$(PPh$_3$)$_3$ (0.025 mmol), ethylenediamine (1.2 mmol), KOH (1 mmol), dioxane (3 mL), 80 °C, 40 h.
[a] Diastereoisomeric mixture.
[b] Step-by-step procedure.

alcohol **4l** was obtained in 57% yield with a considerable amount of coupled ketone (35% yield). Benzo-fused cyclic ketone 1-tetralone (**1g**) also reacted with **2a** to give 2-benzyl-1,2,3,4-tetrahydronaphthalen-1-ol (**4m**) as a diastereoisomeric mixture. However, in contrast to the reductive coupling with activated primary alcohols, similar treatment of **1e** with non-activated primary alcohol butanol (**2h**) afforded 1-(2-naphthyl)ethanol (42% yield) as a major identifiable product by direct transfer hydrogenation from **2h** to **1e**, rather than the desirable coupled secondary alcohol **4n** (25% yield) [18,26–29]. Neither prolonged reaction time (60 h) nor the amount of RuCl$_2$(PPh$_3$)$_3$ (5 mol%) significantly affected the yield of coupled secondary alcohols and the product distribution. However, step-by-step

procedure, an initial treatment of **1e** and **2h** in the presence of RuCl$_2$(PPh$_3$)$_3$ and KOH in dioxane at 80 °C for 10 h and subsequent addition of ethylenediamine to the mixture followed by stirring for 30 h resulted in an increased yield of **4n** (63%) along with coupled ketone (16%) and 1-(2-naphthyl)ethanol (20%).

4. Conclusion

In summary, we have demonstrated that ketones reacts with an array of primary alcohols in the RuCl$_2$(PPh$_3$)$_3$/ethylenediamine/KOH/dioxane system at 80 °C to afford coupled secondary alcohols in moderate to good yields. The present reaction provides an efficient atom economical procedure for

the synthesis of secondary alcohols from ketones and primary alcohols compared with known procedures.

Acknowledgement

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