Cobalt-catalyzed Oxidative Kinetic Resolution of Secondary Benzylic Alcohols with Molecular Oxygen

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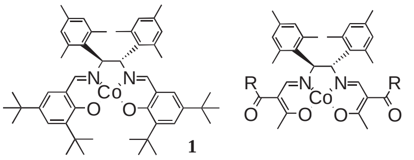
The oxidative kinetic resolution of secondary alcohols using molecular oxygen and olefins was catalyzed by the optically active ketoiminatocobalt(II) complexes. The various secondary benzylic alcohols were subjected to the aerobic oxidative reaction to afford optically active alcohols of high ee along with the corresponding ketones in high yield. The oxidation of the deuterated alcohols revealed that the accompanying olefin mediated the oxidation for conversion to the corresponding α-deuterated ketones.

Molecular oxygen is an abundant and ubiquitous oxidant on the earth as well as a clean, safe, and easily handled oxidant compared to peroxides or heavy-metal oxidants, although stereoselective oxidation by molecular oxygen remains one of the most challenging research targets because of its high radical-like reactivity and consequent side reactions. Much effort has been performed to develop reliable complex catalysts containing various transition metals that would provide efficient and stereoselective aerobic oxidation systems.[1] For example, the oxidative kinetic resolution of racemic alcohols with molecular oxygen[2] was reported to establish one of the most efficient methods to obtain enantiomerically enriched secondary alcohols.[3] Two catalyst systems using palladium(II) complexes[4,5] were independently reported. The (nitroso)(salen)ruthenium(II)[6] complexes have been developed to perform the highly selective oxidative kinetic resolution of the allyl and 2-propynyl alcohols using molecular oxygen as the oxidant. Very recently, it was reported that a ruthenium or iridium complex with a chiral bifunctional amido ligand effectively catalyzed the aerobic oxidative kinetic resolution of benzylic secondary alcohols.[7]

It has been noted that Schiff-base cobalt(II) complexes can capture and activate molecular oxygen,[8] and various aerobic oxidation reactions have been examined in the presence of these cobalt complexes.[9] By using the bis(1,3-diketonato)cobalt(II) complexes as catalysts, various alkenes were converted into the corresponding alcohols with molecular oxygen in a secondary alcohol solvent (oxidation–reduction hydration).[10] The catalytic enantioselective version was reported, but the highest enantioselectivity reached 38% ee using the optically active salen–cobalt(II) complex catalyst.[11] During the course of our continuous studies on the catalytic enantioselective versions,[12] we found out that the oxidative kinetic resolution of racemic secondary alcohols with the combined use of molecular oxygen and olefinic compounds was catalyzed by the optically active ketoiminatocobalt(II) complexes to afford the corresponding secondary alcohols in high optical purity, while the olefinic compounds were employed as the oxygen acceptor to be converted into the corresponding ketones.

A racemic mixture of 1-(2-naphthyl)ethanol (**4a**) was subjected to oxidative kinetic resolution (OKR) in the presence of 5 mol % of various cobalt(II) complexes (Figure 1) and 0.65 equivalent of styrene under atmospheric pressure of oxygen at 50 °C (Scheme 1). The oxidation reaction proceeded to afford the corresponding ketone along with the unreacted alcohol. Material balance of this reaction (ketone plus the recovered alcohol) is almost quantitative. The selectivity was evaluated by the k_{rel} value[13] calculated from the yield[14] and the optical purity[15] of the recovered alcohol. As shown in Table 1, although the salen–cobalt(II) complex **1** did not catalyze the reaction at all, the ketoiminatocobalt(II) complexes smoothly converted the 1-(2-naphthyl)ethanol into the corresponding ketone with kinetic resolution. The cobalt(II) complexes with the acyl side chain **2a** and **2b** afforded the optically active alcohol in 60% and 45% yields with 45% ee and 44% ee, and the k_{rel} values were calculated to be 7.6 and 3.2, respectively (Entries 2 and 3). The ketoiminatocobalt(II) complex possessing an ester side chain **3a**



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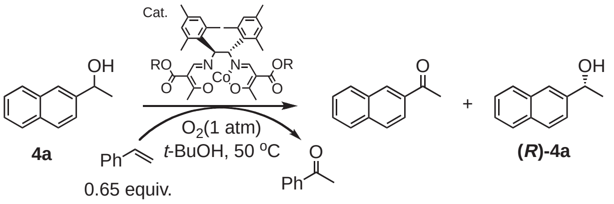
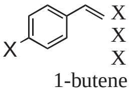
2a : R = Me
2b : R = Mesityl
3a : R = OEt
3b : R = O^{c}Hex
3c : R = O-2-Adamantyl

Figure 1. Optically active cobalt(II) complexes.



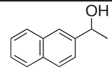
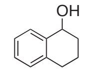
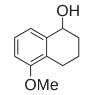
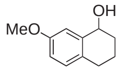
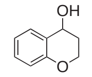
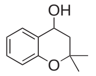
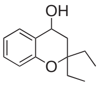
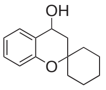
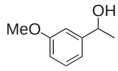
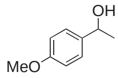
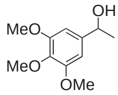
Scheme 1. Oxidative kinetic resolution of secondary alcohol.

Table 1. Examination of various catalysts and olefins[a]

Entry	Catalyst	Olefin	Yield/%[b]	ee/%[c]	k_{rel}
1[d]	**1**	styrene	No reaction		
2[d]	**2a**		60	45	7.6
3[d]	**2b**		45	44	3.2
4[d]	**3a**		43	70	6.7
5[d]	**3b**		52	60	8.8
6			43	96	22.3
7		 X = CF3	45	86	14.6
8		X = F	33	83	10.2
9		X = Cl	39	96	16.1
10[e]		1-butene	76	19	4.6
11[e]		isobutene	23	97	6.3

[a]The reaction was carried out in 1.5 mL of *t*-BuOH using 10 mol % Co^{II} complex, 0.25 mmol substrate, and 0.65 equiv of olefin at 50 °C under atmospheric O$_2$ pressure. [b]Recoverd alcohol; determined by GC using naphthalene as the internal standard. [c]Determined by HPLC using Chiralpak IA. [d]5 mol % Co^{II} complex was employed in *m*-xylene solvent. [e]Under the mixed gas of O$_2$ and olefin.

Table 2. Various secondary benzylic alcohols in aerobic OKR[a]

Entry	Alcohol		Yield/%[b]	ee/%[d]	$k_{\rm rel}$
1[f]		**4a**	54.5	79.9	>100
2[e]		**4b**	45.2	68.5	7.2
3[f]		**4c**	49.7	73.6	14
4[f]		**4d**	46.4[c]	74.6	12
5[e,f]		**4e**	51.2[c]	76.4	21
6[e,f,g]		**4f**	47.3	76.6	12
7[e,g]		**4g**	48.5	86.1	26
8[e,g]		**4h**	54.2	67.5	18
9[e,f]		**4i**	55.8	55.9	10
10		**4j**	49.0	66.1	8.7
11[e,f]		**4k**	51.4	71.2	15

[a]The reaction was carried out in 3.0 mL of *t*-BuOH with 10 mol % Co^{II} complex **3b**, 0.5 mmol substrate, and 0.65 equiv of styrene at 50 °C under atmospheric O_2 pressure. [b]Recoverd alcohols; determined by GC using naphthalene as the internal standard. [c]Isolated yield. [d]Determined by HPLC.[16] [e]Catalyst **3c** was employed. [f]*p*-Chlorostyrene was used. [g]In *t*-butylbenzene at 65 °C.

improved the selectivity to 6.7 (Entry 4). From the reaction catalyzed by the cobalt(II) complex with the cyclohexyl ester side chain **3b**, the selectivity was slightly improved to 8.8 (Entry 5). When the reaction was carried out in a *tert*-butyl alcohol solvent, the alcohol **4a** was recovered in 43% yield with 96% ee, and the selectivity was improved to 22 (Entry 6). Since the combined olefinic compounds would be essential in accepting an oxygen atom in the present oxidation, the reactivity of the styrene derivatives would also influence the reaction and the enantioselectivity of the secondary alcohol (Entries 7–9). When *p*-chlorostyrene was employed, the $k_{\rm rel}$ was calculated to be 16 (Entry 9). Olefinic compounds other than the styrenes were examined; for example, in the presence of 1-butene and isobutene, kinetic resolution during the oxidation was observed though their selectivities were lower than that of the styrene derivatives (Entries 10 and 11).

Various secondary benzylic alcohols were then successfully used for the aerobic oxidative kinetic resolution (Table 2). Based on the oxidative kinetic resolution of **4a**, the optically active alcohol of 79.9% ee was obtained in 54.5% yield and the selectivity was calculated to be >100 (Entry 1). The tetralol **4b** was subjected to the oxidative kinetic resolution to afford the optically active alcohol and the selectivity was calculated to be 7.2 (Entry 2). The tetralols substituted by methoxy group at the 5- and 7-positions were good substrates for the present oxidation system (Entries 3 and 4). For the oxidative kinetic resolution of the chromanol derivatives, *tert*-butylbenzene was found to be a suitable solvent. Also, the cobalt(II) complex with a steric-demanding side chain, such as the 2-adamantyl ester **3c**, improved the selectivity (**4f** $k_{\rm rel}$ 12, Entry 6). The chromanol derivatives with the 2,2-diethyl **4g** (Entry 7) and spiro-cyclohexyl groups **4h** (Entry 8) were smoothly converted into the corresponding ketones along with recovery of the optically active alcohols in 48.5% yield with 86.1% ee and 54.2% yield with 67.5% ee, and the $k_{\rm rel}$ values reached 26 and 18, respectively. This oxidation system was also applicable for acyclic benzyl alcohols. For the reaction of (3-methoxyphenyl)-1-ethanol (**4i**), the $k_{\rm rel}$ value reached 10 (Entry 9). The oxidation of (4-methoxyphenyl)-1-ethanol (**4j**) smoothly proceeded with $k_{\rm rel}$ values of 8.7 (Entry 10). The combination with *p*-chlorostyrene effectively improved the selectivity during the oxidation of [3,4,5-tri(methoxy)phenyl]-1-ethanol (**4k**), and the $k_{\rm rel}$ value was calculated to be 15 (Entry 11).

In the presence of the cobalt complex catalyst **3b,** 1-deuterio-5-methoxy-1-tetralol was subjected to the oxidative kinetic resolution with *p*-chlorostyrene under atmospheric oxygen pressure and converted into the corresponding ketone and the optically active recovered alcohol along with the α-deuterated *p*-chloroacetophenone as the sole product. Further investigation of this mechanism is currently underway.

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