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Highly Selective Aldol Reaction of Dibenzoylmethanes with Formaldehyde Catalyzed by Cobalt Schiff Base Complex under Neutral Conditions

Kazushige Maruyama,* Katsunobu Kubo, Yukinobu Toda, Kazuhiko Kawase, Takahiro Mashino, and Akira Nishinaga*

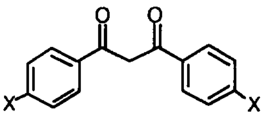
Department of Applied Chemistry, Osaka Institute of Technology,
Ohmiya 5, Asahi-ku, Osaka 535, Japan

Abstract: Coordinatively saturated hydroxocobalt(III) Schiff base complexes catalyze highly selective aldol reaction of dibenzoylmethanes with formaldehyde in methanol to give 1,3-dibenzoylpropanes, resulting from retro-Claisen reaction of 1,1,3,3-tetrabenzoylpropanes, which are obtained quantitatively in dichloromethane. Coordinatively saturated cobalt(III) Schiff base complexes ligating a substrate anion as a monodentate ligand is found to be the reactive species.

It has been shown that the interesting catalytic activity of cobalt(II) Schiff base complexes in model dioxygenase reactions is attributed to the function as a base of hydroxocobalt(III) species produced in initial step of the reactions.[1] Examples of such basic function of a coordinatively saturated hydroxocobalt(III) complex Co^{III}(salpr)(OH)[H_2salpr = 1,11-bis-(2-hydroxyphenyl)-2,6,10-triazaundeca-1,10-diene] [Co(L^1)] have been demonstrated in the reversible interconversion between 2'-hydroxychalcones and flavanones in methanol,[2] in the retro-Claisen reaction of *o*-hydroxydibenzoylmethanes in methanol,[3] and in the highly selective synthesis of chromones.[4] As a series of studies on the basic function of hydroxocobalt(III) species, we find now another new interesting example: highly selective aldol reaction of 1,3-dibenzoylmethanes with formaldehyde catalyzed by Co(L^1) under neutral conditions, where 1,3-dibenzoylpropanes and 1,1,3,3-tetrabenzoylpropanes are obtained quantitatively in methanol and in dichloromethane, respectively, providing a model for the aldolase reaction. Little has been known about this type of metal complex catalyzed aldol condensation reaction.

When a mixture of dibenzoylmethane (**1c**) (1mmol) and paraformaldehyde (0.5 mmol) in methanol (25 ml) containing Co(L^1)[5] (0.2 mmol) was warmed at 60 °C for 3 h, the substrate was consumed completely with appearance of two products as monitored by TLC. Separation of the resulting mixture by preparative TLC (silica gel) gave methyl benzoate (**2c**) (92%) and 1,3-dibenzoylpropane (**4c**) (96%). Interestingly, however, when the reaction was carried out in dichloromethane in place of methanol at room temperature, 1,1,3,3-tetrabenzoylpropane (**5c**) was obtained quantitatively. In order to examine the generality of these reactions, we have investigated the reactions of substituted dibenzoylmethanes (**1**) with formaldehyde in the presence of hydroxocobalt(III) Schiff base complex, Co(L^n)[5] in methanol as well as in dichloromethane. The results are summarized in Table 1.

As seen from Table 1, no reaction takes place without the cobalt catalyst (Run 1). The catalytic activity is observed only with coordinatively saturated complexes Co(L^1) and Co(L^3) (Runs 11 and 15), but not with



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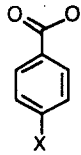

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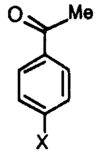

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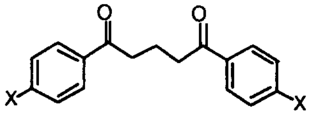

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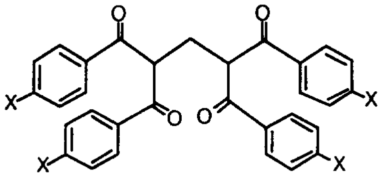
a; X = NO$_2$
b; X = Cl
c; X = H
d; X = Me
e; X = MeO



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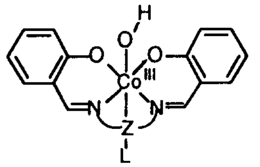


Co(L^1): Z, L = (CH$_2$)$_3$NH(CH$_2$)$_3$
Co(L^2): Z = (CH$_2$)$_2$; L = none
Co(L^3): Z = (CH$_2$)$_2$; L = 1-MeIm

Table 1. Co(L^n) catalysed reaction of ArCOCH$_2$COAr (**1**) with CH$_2$O[a]

Run	1	Co(L^n)	[1]/[Co]	Solvent	Reaction temp(°C)	Reaction time(h)	Conversion (%)	Product yield (%)[b] 2	3	4	5
1	**1c**	-	-	MeOH	60	0.5	0	-	-	-	-
2	**1a**	Co(L^1)	1	MeOH	60	0.5	100	81	19	58	-
3	**1b**	Co(L^1)	1	MeOH	60	0.7	100	92	3.4	76	-
4	**1c**	Co(L^1)	1	MeOH	60	1.5	100	92	-	96	-
5	**1c**	Co(L^1)	5	MeOH	60	3	100	92	-	96	
6	**1d**	Co(L^1)	1	MeOH	60	4	100	89	-	86	-
7	**1e**	Co(L^1)	1	MeOH	60	10	100	complex mixture			
8	**1a**	Co(L^1)	20	*t*-BuOH	60	1	100	-	-	-	85
9	**1a**	Co(L^1)	20	CH$_2$Cl$_2$	25	0.5	100	-	-	-	98
10	**1b**	Co(L^1)	20	CH$_2$Cl$_2$	25	0.2	100	-	-	-	96
11	**1c**	Co(L^1)	20	CH$_2$Cl$_2$	25	0.3	100	-	-	-	98
12	**1d**	Co(L^1)	20	(CH$_2$Cl)$_2$	60	23	100	-	-	-	94
13	**1e**	Co(L^1)	20	(CH$_2$Cl)$_2$	60	48	100	-	-	-	96
14	**1c**	Co(L^2)	1	CH$_2$Cl$_2$	25	1	0	-	-	-	-
15	**1c**	Co(L^3)	1	CH$_2$Cl$_2$	25	24	100	-	-	-	94

[a] Reaction conditions: 1 (1 mmol), CH$_2$O (0.5 mmol), solvent (25 ml). [b] Isolated yield.

coordinatively unsaturated complex Co(L^2) (Run 14). These results suggest that the cobalt(III) catalyst functions as a base but not as a Lewis acid. Compounds **1a** and **1b**, which have an electron-withdrawing group at 4-position, gave acetophenone derivatives **3a** and **3b** (Runs 2 and 3), because the carbonyl group in these substrates is activated by the electron-withdrawing group to undego significantly the retro-Claisen reaction.[3] In the reaction in dichloromethane at room temperature, on the other hand, 1,1,3,3-tetrabenzoylpropanes (**5**) were obtained quantitatively regardless of the substituent X, although **1d** and **1e** (X = electron-releasing group)

Table 2. Analytical and ^{1}H NMR of 5 ($CDCl_3$) δ (ppm)

5	m.p. (°C)[a]	^{1}H NMR of 5 ($CDCl_3$) d (ppm)			
		-CO-CH-CO-	$-CH_2-$	X	Ar
5a	193.0-194.5	5.71[b]	2.77[b]	-	8.3 - 8.4[g]
5b	190.0-192.0	5.56[c]	2.68[c]	-	7.4 - 8.1[g]
5c	179.0-180.5	5.76[d]	2.77[d]	-	7.3 - 8.3[h]
5d	195.5-197.0	5.67[e]	2.70[e]	2.39[f]	7.2 - 8.1[g]
5e	165.7-167.0	5.60[e]	2.70[e]	3.84[f]	7.0 - 8.2[g]

[a] Elemental analysis: C, ± 0.05%; H, ± 0.05%.

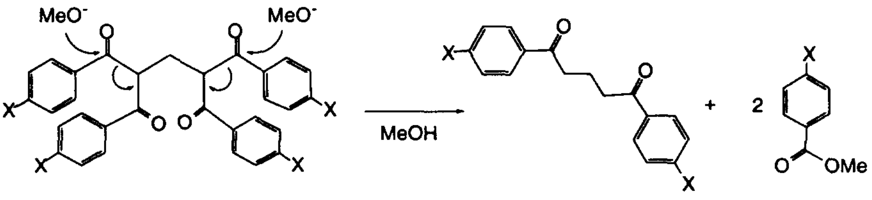
[b] t, 2H, J = 6.6 Hz [c] t, 2H, J = 6.9 Hz [d] t, 2H, J = 6.8 Hz

[e] t, 2H, J = 7.1 Hz [f] s, 12H [g] m, 8H [h] m, 10H.

requires somewhat higher temperature (Runs 12 and 13). Compounds 5 except 5a are new products, whose analytical and ^{1}H NMR data are in good agreement with the structures (Table 2).

Heating a solution of 5 at 60 °C in methanol in the presence of a catalytic amount of Co(L^1) (0.1 eq.) gave the corresponding known compounds 2 and 4 quantitatively. The conversion time depended on the para substituent X: the more electron-releasing the longer reaction time (5a, 1.3 h; 5b, 2.5 h; 5c, 3.5 h; 5d, 15 h; and 5e, 24 h). The conversion of 5 to 4 may be rationalized by assuming the attack of a methoxide anion on the carbonyl groups in 5 (Scheme 1).[2]

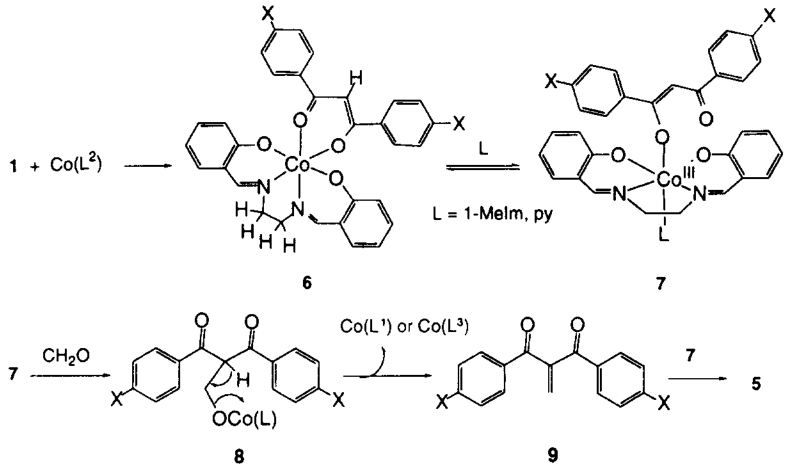
$$\mathrm{Co^{III}(salpr)(OH) + MeOH \rightleftharpoons [Co^{III}(salpr)]^+ + MeO^- + H_2O}$$



5 4 2

Scheme 1

The reaction of 1 with Co(L^2) in dichloromethane gave complex 6, whose analytical and ^{1}H NMR data are in good agreement with the structure.[6] The multiplet ^{1}H NMR signals (δ 3.6 - 4.4) assigned to the ethylene group in the salen ligand is due to a twisted conformation of the salen ligand[7] resulting from coordination of 1 as a bidentate ligand. Upon addition of a coordinative ligand such as pyridine or 1-methylimidazole, the multiplet signals lead to a singlet (δ around 4.5), indicating that the coordination of the substrate anion in 7 was changed to a monodentate state. Complexes 6 were not reactive. Only 7 reacted with formaldehyde to give 5, indicating that coordination of the substrate 1 as a monodentate ligand is a requisite of the reactivity. The slower reaction with Co(L^3) compared to Co(L^1) must be attributed to lower concentratin of 7 brought by an equilibrium (Scheme 2). No such association-dissociation equilibrium is attained with the reactive species derived from 1 and Co(L^1). Since the formation of 1,3-dibenzoyl-2-hydroxymethylmethane was detected at a low temperature (TLC and ^{1}H NMR), the mechanism should involve intermediates **8** and **9** (Scheme 2).



Scheme 2

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6. **6** (**R = H**): ^{1}H NMR ($CDCl_3$) δ, 3.64 (m, 1H), 3.93 (m, 1H), 4.08 (m, 1H), 4.42 (m, 1H), 6.57 (t, 1H, J = Hz), 6.70 (t, 1H, J = Hz), 6.77 (s, 1H), 7.09 - 7.92 (m, 18H). Anal. Calcd for $C_{31}H_{25}N_2O_4Co$: C, 67.88; H, 4.56; N, 5.11%. Found: C, 67.54; H, 4.62; N, 5.16%. **6** (**R = MeO**): ^{1}H NMR ($CDCl_3$) δ, 3.54 (m, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.91 (m, 1H), 4.01 (m, 1H), 4.35 (m, 1H), 6.51 (t, 1H, J = Hz), 6.60 (s, 1H), 6.65 - 7.95 (m, 17H). Anal. Calcd for $C_{33}H_{29}N_2O_6Co$: C, 65.02; H, 4.93; N, 4.60%. Found: C, 64.09; H, 5.18; N, 4.42%. **6** (**R = Me**): ^{1}H NMR ($CDCl_3$) δ, 2.32 (s, 3H), 2.43 (s, 3H), 3.56 (m, 1H), 3.99 (m, 2H), 4.37 (m, 1H), 6.51 (t, 1H, J = Hz), 6.67 (m, 2H), 6.81 - 7.93 (m, 16H). Anal. Calcd for $C_{33}H_{29}N_2O_4Co$: C, 68.63; H, 4.20; N, 4.85%. Found: C, 67.49; H, 5.04; N, 4.84%. **6** (**R = Cl**): ^{1}H NMR ($CDCl_3$) δ, 3.63 (m, 1H), 3.95 (m, 2H), 4.34 (m, 1H), 6.53 (t, 1H, J = Hz), 6.59 (s, 1H), 6.72 (t, 1H), 6.72 - 7.15 (m, 16H). Anal. Calcd for $C_{31}H_{23}Cl_2N_2O_4Co$: C, 60.31; H, 3.75; N, 4.54%. Found: C, 60.04; H, 3.78; N, 4.45%.
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