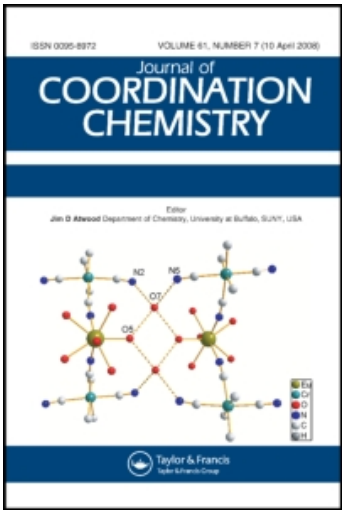

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ENANTIOSELECTIVE DEHYDROGENATION OF RACEMIC 1-PHENYLETHANOL BY RHODIUM(I) CHIRAL PHOSPHINE COMPLEXES

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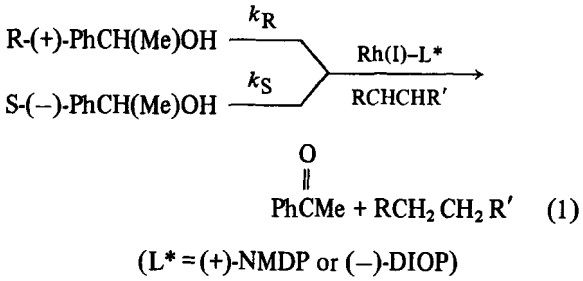
The enantioselective dehydrogenation of 1-phenylethanol by *in situ* prepared RhCl ((+)-NMDP)$_3$ or RhCl ((−)-DIOP) (NMDP = neomenthyldiphenylphosphine and DIOP = 2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane) was investigated with and without unsaturated additives. The selectivity was dependent on (a) the concentrations of the chiral phosphine and unsaturated additive, (b) the product distribution, (c) the basicity of the reaction system, (d) the structure of the unsaturated additive, and (e) the reaction temperature. The last two factors, respectively, play a predominant role in the introduction of molecular asymmetry to the Rh(I) complex and in the enhancement of the enantioselective interaction at lower temperature.

KEY WORDS: Asymmetric dehydrogenation by Chiral Rh(I) complexes.

INTRODUCTION

The enantio-differentiating reaction with chiral phosphine complexes of transition metals, especially those of rhodium(I), have recently received considerable attention in the asymmetric hydrogenation[1–3] or hydroformilation[4] of prochiral olefins and in the asymmetric hydrosilylation of ketones.[5,6] Indeed, rhodium(I) complexes possessing such chiral phosphine ligands as o-anisylcyclohexylmethylphosphine and 2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane (DIOP) are efficient catalysts for the above reactions of asymmetric synthesis.[2,3] However, transition-metal chiral phosphine complexes have hitherto been the objects of only limited investigation in terms of their utilization for the kinetic resolution of organic or inorganic racemates. In our laboratory, *in situ* prepared rhodium(I)-(−)-DIOP or rhodium(I)-(+)-NMDP (NMDP = neomenthyldiphenylphosphine) was found to catalyze the kinetic resolution of (±)-1-phenylethanol during the transfer hydrogenation of unsaturated species (RCHCHR′) such as benzylideneacetone by the alcohol.



(1)

(L* = (+)-NMDP or (−)-DIOP)

where k_R and k_S denote the pseudo-first-order rate constants.

The present authors report, here, the enantioselective dehydrogenation of (±)-l-phenylethanol by *in situ* prepared RhCl((+)-NMDP)$_3$ or RhCl((−)-DIOP) in the presence or absence of unsaturated additives. The enantioselective ability of the chiral Rh(I) complexes was found to be dependent on the reaction conditions, so that we noticed how the enantioselectivity was influenced by the concentration or structure of the chiral phosphine and of unsaturated additives, and by the reaction temperature.

EXPERIMENTAL

Complexes and Reaction Procedure

The (+)-NMDP and (−)-DIOP were prepared according to the usual methods described pre-

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viously.[7,8] The asymmetric dehydrogenation of freshly distilled (±)-1-phenylethanol was carried out at 160–190°C in a N_2 atmosphere with RhCl((+)-NMDP)$_3$ or RhCl((−)-DIOP) prepared *in situ* from the chiral phosphine ((+)-NMDP or (−)-DIOP) and $(RhCl(C_2H_4)_2)_2$.[9,10] The mole ratio of (+)-NMDP/$(RhCl(C_2H_4)_2)_2$ or (−)-DIOP/$(RhCl(C_2H_4)_2)_2$ was 6 or 3 respectively with some exceptions noticed in this paper. The unreacted 1-phenylethanol was obtained by fractional distillation from the reaction mixture and its optical rotation was measured with a UNION PM–101 polarimeter. The above distilled 1-phenylethanol was confirmed to include no optically active contaminants; the dehydrogenation of optically inactive alcohols such as benzyl alcohol with the present chiral Rh(I) complexes under the same conditions resulted in no optically active contaminants in the distilled alcohol recovered from the reaction mixture. The product distributions were followed by gas chromatographic analysis to determine the conversion of the alcohol.

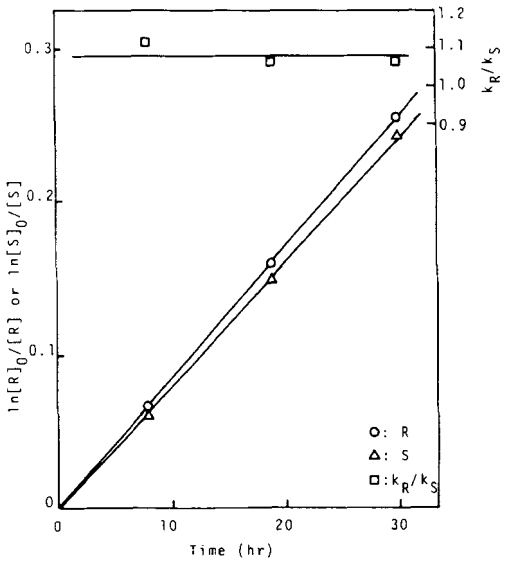


FIGURE 1 Pseudo-first-order relationship of the present reaction (reaction conditions are shown in Table I).

RESULTS AND DISCUSSION

Concentration Effect of Ligands and Additives on Enantioselectivity

When the asymmetric dehydrogenation of (±)-1-phenylethanol (I) catalyzed by RhCl((+)-NMDP)$_3$ or RhCl((−)-DIOP) was carried out at 160–190°C with or without unsaturated additives, the optical purity (O.P.) of unreacted I enriched in the S-(−) enantiomer increased monotonically with increasing conversion (Conv.); A typical example is the dehydrogenation of I by RhCl((+)-NMDP)$_3$ in the presence of benzylideneacetone (Table I). The reaction obeys a pseudo-first-order rate law, reflected in almost constant k_R and k_S values which can be evaluated as:

$$k_R = \ln([R]_0/[R])/t = \{\ln(10^4/(100\text{-Conv.})(100-\text{O.P.}))\}/t \quad (2a)$$

$$k_S = \ln([S]_0/[S])/t = \{\ln(10^4/(100\text{-Conv.})(100+\text{O.P.}))\}/t \quad (2b)$$

where $[R]_0$ and $[S]_0$ = respective initial concentrations of R-(+) and S-(−) enantiomers of I; Conv./100 = 1-([R] + [S])/($[R]_0$ + $[S]_0$); O.P./100 = ([S] − [R])/([R] + [S]); t = reaction time.

The dehydrogenation products of the present reaction mainly consisted of acetophenone (AP) and racemic or meso bis(1-phenylethyl) ether (PEE: ^{1}H NMR($CDCl_3$) δ 1.46(d, 6H, J = 6.4 Hz), 4.25(q, 2H,

TABLE I
Optical purity and product distribution in the dehydrogenation of I (83.5 mmol) by RhCl((+)-NMDP)$_3$ (5 mM) with benzylideneacetone (68.5 mmol) at 180°C[a]

Time (hr)	Conv. (%)	$-[\alpha]_D^{23}$[b] (deg.)	O.P. (%)	$10^6 k_R$ (sec^{-1})	$10^6 k_S$ (sec^{-1})	k_R/k_S	Products (mol %)[c] AP	PEE	ST	EB
8	6.14	0.188	0.358	2.32	2.08	1.11	75.6	16.8	6.0	1.6
19	14.3	0.224	0.427	2.32	2.19	1.06	64.5	30.0	3.2	2.3
30	21.6	0.363	0.691	2.31	2.18	1.06	79.8	17.6	1.4	1.2
36	25.2	0.516	0.983	2.32	2.17	1.07	79.9	17.9	1.9	0.3

[a] RhCl((+)-NMDP)$_3$ was prepared *in situ* from $(RhCl(C_2H_4)_2)_2$ = 5 mM and (+)-NMDP = 30 mM.
[b] $[\alpha]_D^{23}$ −52.5° (c 2.27, CH_2Cl_2).[18]
[c] AP = acetophenone; PEE = bis(1-phenylethyl) ether; ST = styrene; EB = ethylbenzene.

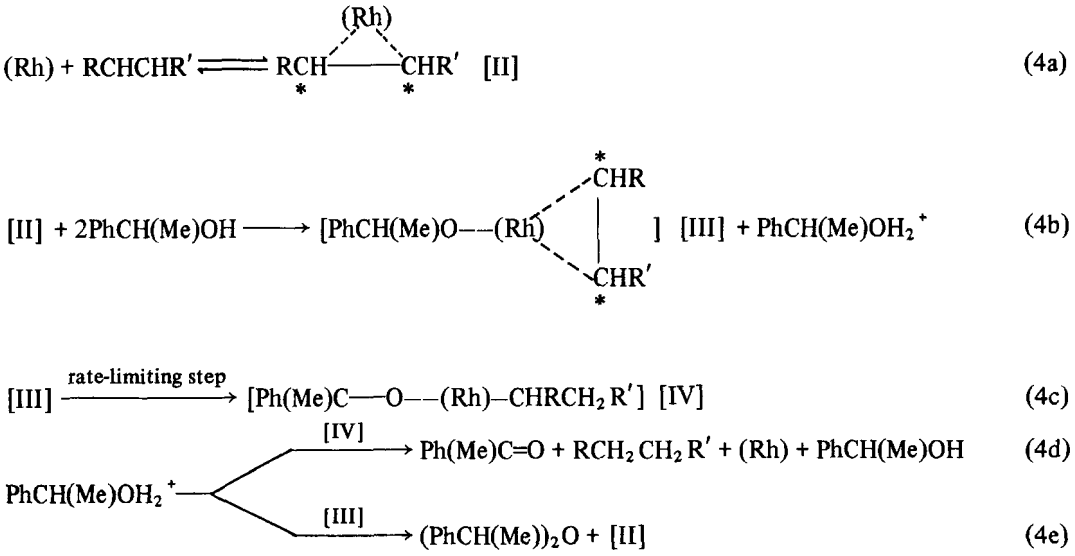
J = 6.4 Hz), 7.29(s, 10H) and δ 1.40(d, 6H, J = 6.4 Hz), 4.25(q, 2H, J = 6.4 Hz), 7.31(s, 10H); small amounts of a dehydrogenation product (styrene) and hydrogenation product of styrene (ethylbenzene) were also detected.

The enantioselective ability (defined by k_R/k_S) of the present *in situ* prepared chiral Rh(I) complexes, which was very low but reproducible, was found to be dependent on the concentration of the chiral phosphine or the unsaturated additive. Figure 2 indicates the concentration effect of (+)-NMDP on the selectivity of RhCl((+)-NMDP)$_3$ in the dehydrogenation of I with benzylideneacetone at 180°C. The selectivity increased monotonically up to [(+)-NMDP]/[(RhCl(C$_2$H$_4$)$_2$)$_2$] ≅ 6 and, thereafter, decreased gradually with increasing (+)-NMDP concentration. The maximum selectivity found around [(+)-NMDP]/[(RhCl(C$_2$H$_4$)$_2$)$_2$] = 6 may be related to the formation of an active chlorine-bridged dimer of (RhCl((+)-NMDP)$_2$)$_2$[11] probably *via* the following equilibrium:

$$(RhCl(C_2H_4)_2)_2 + 4(+)\text{-NMDP} \longrightarrow (RhCl((+)\text{-NMDP})_2)_2 + 2(+)\text{-NMDP} \rightleftharpoons 2RhCl((+)\text{-NMDP})_3 \quad (3)$$

The increase of (+)-NMDP with respect to (RhCl(C$_2$H$_4$)$_2$)$_2$ elevated the enantioselectivity through the formation of (RhCl((+)-NMDP)$_2$)$_2$ which, on the contrary, resulted in a lower dehydrogenation rate because of its less activity than (RhCl(C$_2$H$_4$)$_2$)$_2$ *per se*. However, the excess concentration of (+)-NMDP ([(+)-NMDP]/(RhCl(C$_2$H$_4$)$_2$)$_2$] > 6), which promotes the formation of five-coordinated RhCl((+)-NMDP)$_3$, depressed the selectivity appreciably.

The selectivity was also dependent on the product distribution and decreased with the increase of the side reaction products with respect to the main product of AP. Such a product distribution, which is reflected in [AP]/[PEE], was appreciably affected by the concentration of unsaturated additive (RCHCHR′) with respect to that of I (Figure 3); In the absence of RCHCHR′, the PEE formation was accelerated, and the enantioselection of I became lower through the consumption of I without direct enantioselection. Although RCHCHR′ suspends the PEE formation through hydrogen transfer from I to RCHCHR′, the PEE formation still occurred even in an excess concentration of RCHCHR′, so that the present reaction includes the competitive processes of AP and PEE formations, as shown in the speculative mechanism in Scheme I where (Rh) denotes the active chiral Rh(I) complex. The intermediates of [II] and [III], which possess a newly formed asymmetric field when R≠H and R′≠H, contributes to an enhancement of the enantioselection of I during Reaction (4B). The deprotonation and protonation processes (Reactions (4b) and (4d) respectively) have been confirmed in the transfer hydrogenation of benzylideneacetophenone by deuterated I with RuCl$_2$(PPh$_3$)$_3$,[12] where the abstraction of the α-carbon-bound hydrogen by the complex in Reaction (4c) is the rate-limiting step.[12]



SCHEME I

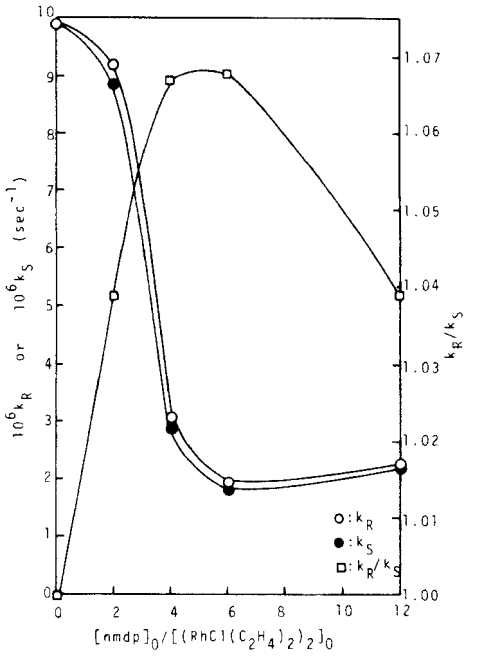


FIGURE 2 Effect of nmdp concentration on the selectivity ([(RhCl(C$_2$H$_4$)$_2$)$_2$]$_0$ = 5 mM; [benzylideneacetone]$_0$/[I]$_0$ = 0.84; Temp. = 180°C).

Asymmetry Formed by Unsaturated Additives

Unsaturated additives (RCHCHR′) as hydrogen acceptors play an important role in the enhancement of the selectivity by changing the product distribution and by the introduction of an asymmetric field through their coordination to the chiral Rh(I) complex in Reaction (4a). In fact, changing the structures of RCHCHR′ results in a variation in the magnitude of the selectivity without affecting the product distribution ([AP]/]PEE]). The effect of RCHCHR′ tested on the selectivity augment follows the order, benzylideneacetophenone>benzylideneacetone>*trans*-stilbene>ethyl cinnamate>hexyl methacrylate (Table II). Such an order of the additive effect on the selectivity elevation was just the same as in the RuCl$_2$((+)-NMDP)$_3$-catalyzed dehydrogenation of I in the presence of the same additives.[13] The bulky substituents (R and R′ in RCHCHR′) seem to be more effective for selectivity elevation, and it is also taken into consideration that the remarkable effect of the unsaturated ketones on the selectivity is due to the formation of a bulky chiral ligand of phosphobetaine ($R'_3\overset{+}{P}CH(Ph)CH{=}C(R)\bar{O}$) from the ketone and the chiral ligand (R'_3P).[14] The phosphobetaine is capable of behaving as an optically effective ligand instead of (+)-NMDP.

Basicity Effect on Enantioselectivity

Inorganic bases accelerate hydrogen transfer from alcohols to unsaturated species,[15] and this basicity effect has already been recognized in the transfer hydrogenation of benzylideneacetophenone by PhCH(Me)O$^-$Na$^+$ with RuCl$_2$(PPh$_3$)$_3$.[12] In the present study, the effect of 2,5-xylidine on the enantioselectivity of I in the presence of RhCl((+)-NMDP)$_3$ (or RhCl((−)-DIOP)) and benzylideneacetone was investigated. 2,5-Xylidine caused AP to dominate PEE completely, changing the reaction rate and the selectivity (Table III). However, the dehydrogenation rate and the selectivity did not vary consistently with the 2,5-xylidine concentration, so that, such a basicity effect is not simple; The base is capable of participating in both protonation and deprotonation steps, and in changing the catalytic activity fo the chiral Rh(I) complex. At any rate, the basicity effect was observed in the present asymmetric catalysis of the chiral Rh(I) complexes.

TABLE II
Effect of unsaturated additives (RCHCHR′) on the enantioselectivity in the dehydrogenation of I catalyzed by RhCl((+)-NMDP)$_3$ at 180°C for 30 hr[a]

RCHCHR′	Conv. (%)	$-[\alpha]_D^{23}$ (deg.)	O.P. (%)	$10^6 k_R$ (sec^{-1})	$10^6 k_S$ (sec^{-1})	k_R/k_S	AP (mmol)	PEE (mmol)
none	29.4	0.025	0.048	4.02_7	4.01_6	1.00_3	6.17	7.50
PhCHCHCOMe	18.4	0.354	0.675	1.95_0	1.82_5	1.06_8	7.82	3.43
PhCHCHCOPh	12.4	0.331	0.631	1.28_7	1.17_0	1.10_0	7.82	0.56
trans-PhCHCHPh	6.4	0.077	0.147	0.62_3	0.59_6	1.04_5	3.87	0.73
PhCHCHCOOMe	11.0	0.035	0.066	1.08_7	1.07_5	1.01_1	8.52	trace
HCHC(Me)COOC$_6$H$_{13}$	23.2	0.031	0.059	2.45_4	2.44_3	1.00_5	16.78	1.37

[a] Reaction conditions were the same as in Table I.

TABLE III
Basicity effect of 2,5-xylidine on the enantioselectivity in the dehydrogenation of I by RhCl((+)-NMDP)$_3$ or RhCl((−)-DIOP) at 180°C for 30 hr[a]

Complex	2,5-xylidine (mM)	Conv. (%)	O.P. (%)	$10^6 k_R$ (sec^{-1})	$10^6 k_S$ (sec^{-1})	k_R/k_S	AP (mmol)	PEE (mmol)
RhCl((+)-NMDP)$_3$	0	18.4	0.67_5	1.95_0	1.82_5	1.06_8	7.82	3.43
	50	40.7	0.67_2	4.89_6	4.77_2	1.02_6	32.9	trace
RhCl((−)-DIOP)	0	73.3	0.05_5	12.2_3	12.2_2	1.00_1	26.1	32.2
	25	36.0	0.04_7	4.13_7	4.13_8	1.00_2	29.5	trace
	50	48.7	0.69_9	6.23_6	6.10_7	1.02_1	35.8	3.79
	100	39.4	0.26_1	4.65_6	4.60_9	1.01_0	32.0	trace

[a]The reaction conditions were the same as in Table I, and RhCl((−)-DIOP) was prepared *in situ* from $(RhCl(C_2H_4)_2)_2$ = 5 mM and (−)-DIOP = 15 mM. Benzylideneacetone was used as an unsaturated additive.

Temperature Effect on Enantioselectivity

The temperature effect on the selectivity will be discussed by taking notice of the dehydrogenation of I by the *in situ* prepared RhCl((+)-NMDP)$_3$ with or without benzylideneacetone. As can be seen from Table IV, the selectivity (k_R/k_S) substantially decreased with elevating temperature in spite of an increase in the conversion of I without any considerable change in the product distribution, even though such a conversion-increase results in the enhancement of the optical purity of I (see Table I). Presumably, the higher temperature lowers the magnitude of the induced asymmetry of benzylideneacetone by the epimerization or mutarotation[16,17] and makes the interaction between the catalyst and the reactants less rigid so as to diminish the selectivity.

It is noteworthy that each rate constant (k_R or k_S) satisfies the Arrhenius relationship (Figure 4) and that the activation-energy difference of 0.87 kcal/mol

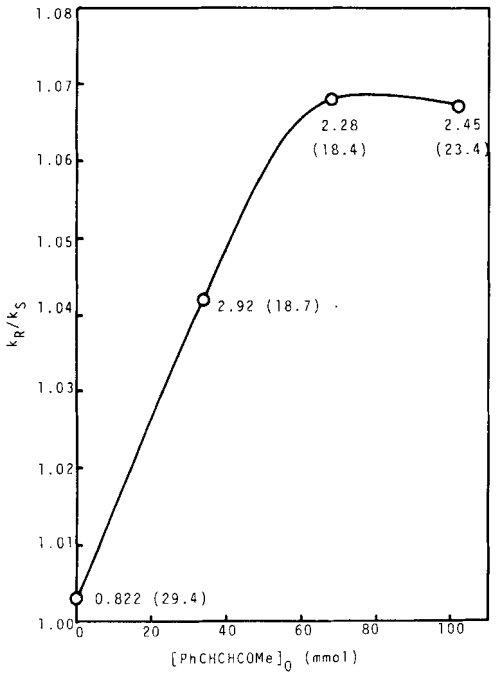


FIGURE 3 Concentration effect of an unsaturated additive (PhCHCHCOMe) on the selectivity ([nmdp]$_0$/[(RhCl-$(C_2H_4)_2)_2$]$_0$ = 6; [I] = 83.5 mM; Temp. = 180°C; Time = 30 hr. Values and those in parentheses are [AP]/[PEE] and Conv. (%) respectively).

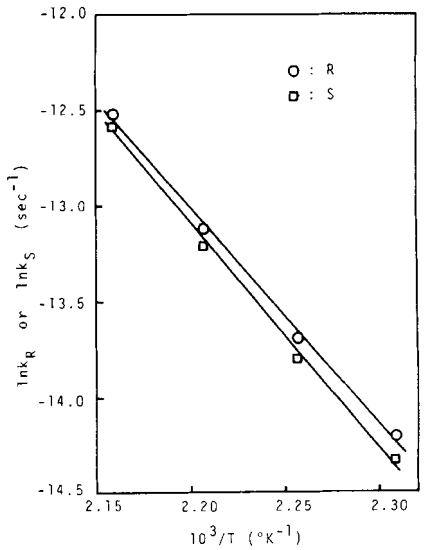


FIGURE 4 Arrhenius dependence of k_R and k_S (rate-constant values are specified in Table IV).

TABLE IV
Temperature effect on the enantioselectivity in the dehydrogenation of I by $RhCl((+)\text{-NMDP})_3$ with or without benzylideneacetone[a]

Run[b]	Temp. (°C)	Time (hr)	Conv. (%)	O.P. (%)	$10^6 k_R$ (sec^{-1})	$10^6 k_S$ (sec^{-1})	k_R/k_S	AP (mmol)	PEE (mmol)
1	170	30	12.1	0.13_3	1.21_0	1.18_5	1.02_1	4.01	2.44
2	190	22	45.1	0.09_1	7.57_1	7.54_8	1.00_3	6.39	10.14
3	160	36	7.9	0.51_2	0.67_7	0.59_7	1.13_5	2.17	0.67
4	170	30	10.9	0.61_3	1.13_0	1.01_6	1.11_2	6.10	1.29
5	180	30	18.5	0.74_3	1.96_1	1.82_3	1.07_6	9.74	2.52
6	190	20	22.5	0.82_7	3.64_8	3.41_9	1.06_7	13.13	2.38

[a] Reaction conditions were the same as in Table I except $(RhCl(C_2H_4)_2)_2$ = 10 mM in Runs 3–6.
[b] Runs 1–2 exclude benzylideneacetone, and Runs 3–6 include benzylideneacetone.

(22.38 kcal/mol for R-(+)-I and 23.25 kcal/mol for S-(−)-I) in the presence of benzylideneacetone is undoubtedly larger than that (0.36 kcal/mol) in the absence of the unsaturated ketone (37.39 kcal/mol for R-(+)-I and 37.75 kcal/mol for S-(−)-I). Thus, the unsaturated additive substantially contributes to the separation of the activation barriers in the present reaction. The activation-energy difference is probably caused by the difference in the coordination of each enantiomer of I to the chiral complex. This is reflected in the difference of $\Delta S^{\neq}$ (−37.99 e.u. for R-(+)-I and −36.23 e.u. for S-(−)-I) and/or $\Delta H^{\neq}$ (21.49 kcal/mol for R-(+)-I and 22.36 kcal/mol for S-(−)-I).

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