Asymmetric Activation/ Deactivation of Racemic Ru Catalysts for Highly Enantioselective Hydrogenation of Ketonic Substrates**

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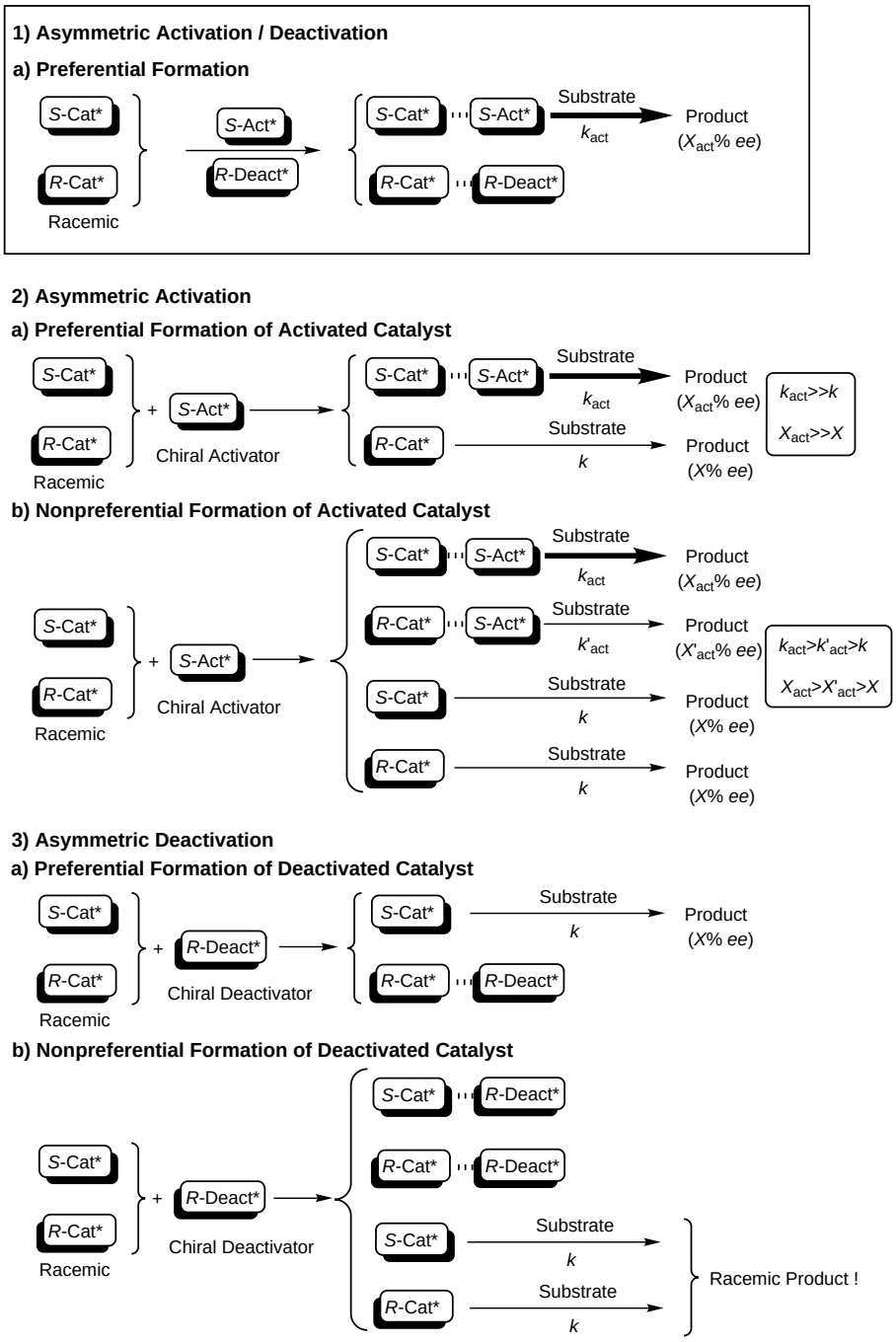
In asymmetric catalytic reactions[1] racemic catalysts give only racemic products, whereas nonracemic catalysts generate nonracemic products. Recently, an enantiomer-selective deactivation strategy for racemic catalysis was reported to provide a level of asymmetric induction that does not exceed that attained by enantiopure catalysts. In this system, the selective complexation and deactivation with a "chiral poison" is indispensable (Scheme 1; 3a versus 3b).[2] In contrast, a "chiral activator" may selectively complex but activate rather than deactivate one enantiomer of a racemic catalyst; an enantioselectivity higher than that achieved with enantiopure catalysts ($x_{act} \gg x$), as well as a higher level of catalyst efficiency ($k_{act} \gg k$; Scheme 1; 2a), can be obtained.[3] Asymmetric activation can also be achieved by nonpreferential complexation (Scheme 1; 2b), which utilizes the difference in the turnover frequencies (catalytic activities) between the activated diastereomers ($k_{act} > k'_{act}$); these differences depend on the substrates employed.[3d] We report here an asymmetric activation/deactivation protocol for achieving higher enantioselectivity irrespective of the substrates employed (Scheme 1; 1) by maximizing the difference in the catalytic activity between the catalyst enantiomers.



Scheme 1. Asymmetric activation/deactivation.

The preferential complexation of [$RuCl_2$((*R*)-binap)] (BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl)[4] with (*R*)-3,3′-dimethyl-1,1′-binaphthyl-2,2′-diamine (DM-DABN)[5] was readily explained from a modeling study (Figure 1a). As expected, the addition of a racemic [$RuCl_2$(binap)] species to 0.5 molar equivalents of (*R*)-DM-DABN resulted in a preferential complexation to form the single diastereomeric complex [$RuCl_2$((*R*)-dm-dabn)((*R*)-binap)]. Only the [$RuCl_2$((*R*)-dm-

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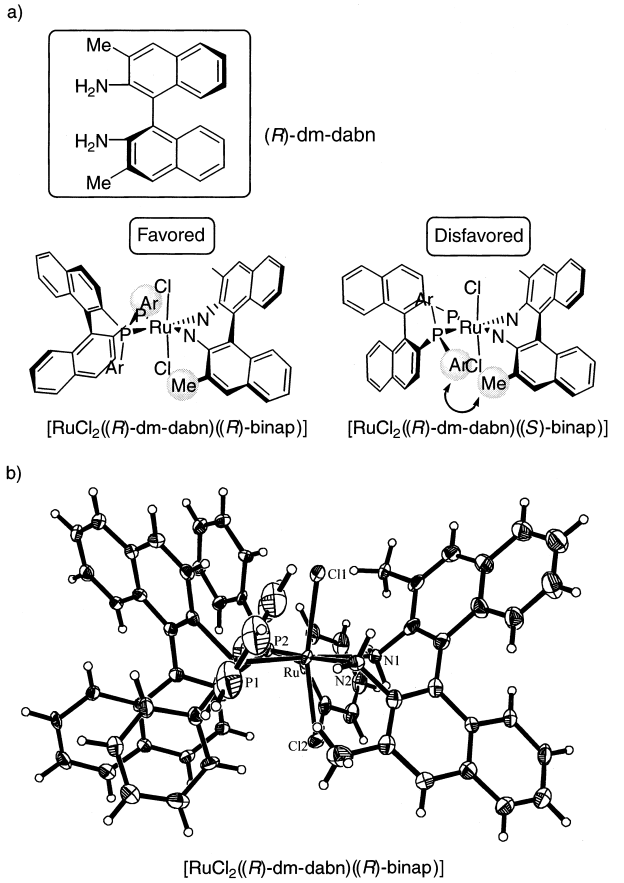
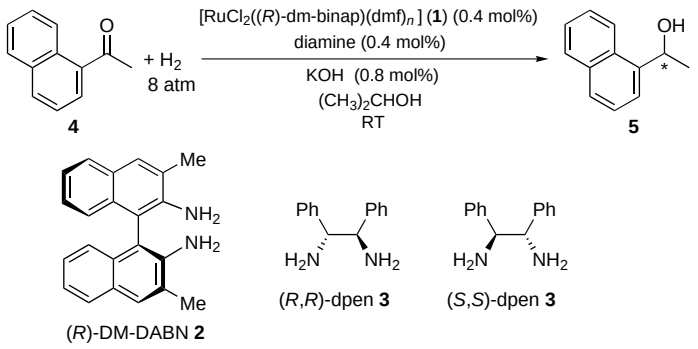


Figure 1. a) Model study of the [$RuCl_2$(dm-dabn)((*R*)-binap)] complex. b) X-ray analysis of [$RuCl_2$((*R*)-dm-dabn)((*R*)-binap)]. Selective bond lengths [Å] and bond angles [°]: Ru-Cl1 2.418(4), Ru-Cl2 2.401(3), Ru-P1 2.273(3), Ru-P2 2.270(4), Ru-N1 2.228(9), Ru-N2 2.263(10); Cl1-Ru-Cl2 165.34(11), P1-Ru-P2 89.80(12), N1-Ru-N2 80.1(4).

dabn)((*R*)-binap)] complex formed even when a racemic complex of [$RuCl_2$(binap)] was treated with an excess of (*R*)-DM-DABN in $CDCl_3$ at room temperature. No [$RuCl_2$((*R*)-dm-dabn)((*S*)-binap)] complex was evident in the ^{1}H NMR ($CDCl_3$) spectrum, which showed only one set of amino protons corresponding to the [$RuCl_2$((*R*)-dm-dabn)((*R*)-binap)] complex ($\delta = 3.80, 4.69$). The (*R*)/(*R*) configuration of the [$RuCl_2$(dm-dabn)(binap)] diastereomer was confirmed by X-ray analysis[6] of the single crystal obtained from a mixture of dichloromethane/diethyl ether/hexane (Figure 1b). This structure showed that the reason why no complex was formed from a mixture of [$RuCl_2$((*S*)-binap)] and (*R*)-DM-DABN was because of the severe steric repulsion that would result between the aryl group of (*S*)-binap and the methyl group of (*R*)-DM-DABN, as exemplified in the modeling study (Figure 1a). However, the [$RuCl_2$((*S*)-binap)] complex gave a different complex with enantiopure (*S*,*S*)- or (*R*,*R*)-diphenylethylenediamine (DPEN).[7, 8] The two different dichlororuthenium complexes formed with DM-DABN and DPEN may be further converted into mono- or dihydridoruthenium species under hydrogenation conditions,[9, 10] although the dm-dabn complex is far less catalytically active under such conditions (Table 1).

Table 1. Hydrogenation of 1′-acetonaphthone **4** by [$RuCl_2$((*R*)-dm-binap)] with diamines.



Diamines	Time [h]	*ee* [%] of **5**	Yield [%] of **5**
none	14	4 (*R*)	4
(*R*)-DM-DABN (**2**)	14	7 (*R*)	6
(*R*,*R*)-DPEN (**3**)	4	> 99 (*S*)[a]	> 99
(*S*,*S*)-DPEN (**3**)	4	56 (*S*)	> 99

[a] The enantiomeric pair (*S*)-**1**/(*S*,*S*)-**3** afforded the enantiomeric product of (*R*)-**5**.

Thus, a racemic [Ru(dm-binap)][9f, 11] catalyst achieves higher enantioselectivity in carbonyl hydrogenation after activation/deactivation by the sequential addition of two different types of chiral diamines than that attained by simple activation.[3d] The mixture of [$RuCl_2$((±)-dm-binap)$(dmf)_n$] and 0.6 molar equivalents of (*R*)-DM-DABN was stirred for 30 minutes at room temperature in dichloromethane. After removal of the dichloromethane under reduced pressure, 0.5 molar equivalents of (*S*,*S*)-DPEN in 2-propanol was added to give [$RuCl_2$((*R*)-dm-dabn)((*R*)-dm-binap)] and [$RuCl_2$((*S*,*S*)-dpen)((*S*)-dm-binap)], selectively. Enantioselective hydrogenation was performed after the addition of KOH and ketones **4**, and **6**–**8** to a mixture of [$RuCl_2$(dm-binap)$(dmf)_n$] (**1**), (*R*)-DM-DABN (**2**), and (*S*,*S*)-DPEN (**3**). The efficiency of this asymmetric activation/deactivation protocol was reflected in the higher enantioselectivity in the hydrogenation irrespective of the ketonic substrates was used relative to the enantioselectivity obtained using the [$RuCl_2$((*S*,*S*)-dpen)((±)-dm-binap)] complex at the same temperature and pressure (Table 2). Thus, (*R*)-1-(1-naphthyl)-ethanol[12] (**5**) was obtained with 96% *ee* in quantitative yield. 2,4,4-Trimethyl-2-cyclohexenone[3d, 9d, 13] (**9**) was also hydrogenated in high enantioselectivity by changing the chirality of DPEN from *S* to *R*.

In summary, we have developed an "asymmetric activation/deactivation" strategy for highly enantioselective hydrogenation irrespective of the ketonic substrates used by maximizing the difference in the catalytic activity between the enantiomeric catalysts. Thus, the present "asymmetric activation/deactivation protocol" can be regarded as a paradigm shift in racemic catalysis.

Experimental Section

5: [$RuCl_2$((±)-dm-binap)$(dmf)_n$] (**1**; 10.5 mg, 10 μmol) and (*R*)-DM-DABN (**2**; 1.9 mg, 6 μmol) were placed in an autoclave, and the air replaced with argon. Dichloromethane (3.3 mL) was added to the autoclave under a

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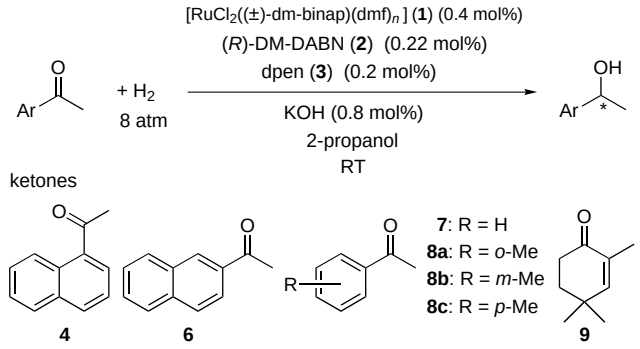
Table 2. Hydrogenation of ketones by the racemic [$RuCl_2$(dm-binap)] complex through asymmetric activation/deactivation.



Ketones	(*R*)-**2**[a]	**3**	Time [h]	*ee* [%]	Yield [%]
4	++	(*S*,*S*)	4	96 (*R*)	> 99
4	–	(*S*,*S*)	4	80 (*R*)	> 99
6	++	(*S*,*S*)	4	91 (*R*)	> 99
6	–	(*S*,*S*)	4	45 (*R*)	> 99
7	++	(*S*,*S*)	4	95 (*R*)	> 99
7	–	(*S*,*S*)	4	70 (*R*)	> 99
8a	++	(*S*,*S*)	4	95 (*R*)	> 99
8a	–	(*S*,*S*)	4	82 (*R*)	> 99
8b	++	(*S*,*S*)	6	95 (*R*)	> 99
8b	–	(*S*,*S*)	4	60 (*R*)	> 99
8c	++	(*S*,*S*)	4	93 (*R*)	> 99
8c	–	(*S*,*S*)	4	60 (*R*)	> 99
9	++	(*R*,*R*)	4	92 (*R*)	> 99[b]
9	–	(*R*,*R*)	4	84 (*R*)	> 99[b]

[a] ++ denotes the presence of (*R*)-**2**. [b] Racemic [$RuCl_2$(Tol-binap)] was used; Tol-BINAP = (2,2′-bis(di-4-tolylphosphanyl)-1,1′-binaphthyl).

stream of argon. After the mixture had been stirred at room temperature for 30 min, the dichloromethane was removed under reduced pressure. The autoclave was again purged with argon after the addition of (*S*,*S*)-DPEN (**3**; 1.0 mg, 4.5 μmol). 2-Propanol (2.8 mL) was added to the autoclave under a stream of argon, followed by the addition of KOH/2-propanol (0.5 M, 40 μL, 20 μmol) with stirring at room temperature for 30 min. 1′-Acetonaphthone (**4**; 0.38 mL , 2.5 mmol) was added to the autoclave at room temperature under a stream of argon, and then hydrogen was introduced at a pressure of 8 atm. After vigorously stirring the mixture for 4 h at room temperature, the solvent was removed under reduced pressure. The residue was filtered through a short column of silica gel. The chemical yield and enantiomeric ratio of 1-(1-naphthyl)ethanol (**5**) were calculated by gas chromatography on a column with a chiral stationary phase (> 99 %, 96 % *ee* (*R*)). The product could also be isolated by column chromatography on silica gel (eluent, hexane/EtOAc 5/1) to give 426 mg (99 %) of **5**. $[\alpha]_D^{28} = +75.5$ ($c = 1.0$, $CHCl_3$) (Ref. [12] $[\alpha]_D^{25} = +78.9$ ($c = 1$, $CHCl_3$), *R* isomer); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.59$ (d, $J = 6.6$ Hz, 3H, CH_3), 1.90 (d, $J = 3.6$ Hz, 1H, OH), 5.59 (dq, $J = 3.6$, 6.6 Hz, 1H, CH), 7.37 – 7.51 (m, 3H, aromatic CH), 7.60 (d, $J = 6.6$ Hz, 1H, aromatic CH), 7.70 (d, $J = 8.1$ Hz, 1H, aromatic CH), 7.78 – 7.81 (m, 1H, aromatic CH), 8.02 – 8.05 (m, 1H, aromatic CH); GC (column CP-Cyclodextrin-β-2,3,6-M-19, i.d. 0.25 mm × 25 m, CHROMPACK; carrier gas, nitrogen (75 KPa); column temp. 160 °C; injection temp. 190 °C; split ratio 100/1), retention time (t_R); (*R*)-(+)-**5**: 32.7 min (98.1 %), (*S*)-(−)-**5**: 31.6 min (1.9 %), **4**: 21.3 min (0 %).

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[6] The single crystal was grown from a dichloromethane/diethyl ether/hexane mixed solvent at room temperature. X-ray crystallographic analysis was performed with a Bruker SMART 1000 diffractometer (graphite monochromator, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å). Crystal data for [$RuCl_2$((*R*)-dm-dabn)((*R*)-binap)]: $C_{66}H_{52}Cl_2N_2P_2Ru$, reddish-orange, crystal dimensions $0.07 \times 0.17 \times 0.22$ mm, orthorhombic, space group $P2_12_12$ (No. 18), $a = 20.822(3)$, $b = 22.130(3)$, $c = 13.1320(18)$ Å, $V = 6051.2(14)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.215$ gcm^{-3}, $\mu(Mo_{K\alpha}) = 1.43$ cm^{-1}, $T = 103$ K, 10304 reflections were independent and unique, and 6256 with $I > 2\sigma(I)$ (2θmax = 24.7°) were used. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. $R = 0.095$, w$R2 = 0.2116$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-144099. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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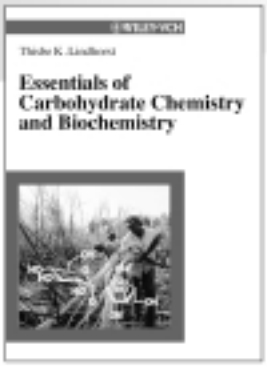

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