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# Asymmetric Deactivation of Racemic BINAP-Ru(II) Catalysts through Complete Enantiomer Discrimination by Dimethylbinaphthylamine: Highly Enantioselective Hydrogenation of Olefin and β-Keto Ester

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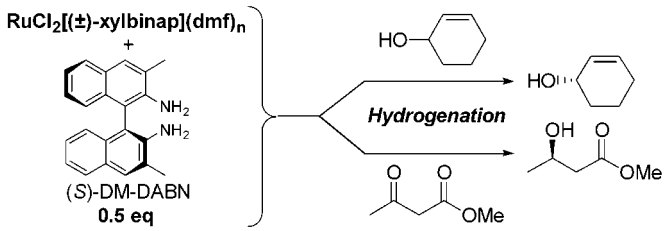
## ABSTRACT




**3,3′-Dimethyl-2,2′-diamino-1,1′-binaphthyl (DM-DABN) is designed as a "chiral poison" (deactivator) for complete enantiomer resolution of racemic BINAP-Ru(II) catalysts in a highly enantioselective hydrogenation of β-keto ester and kinetic resolution of racemic 2-cyclohexen-1-ol.**

The use of racemic catalysts in catalytic asymmetric synthesis has been reported in different manners.[1] We have reported the selective activation of one enantiomer of a racemic catalyst by a "chiral activator" (asymmetric activation).[2] In contrast, the selective deactivation[3] or "chiral poisoning"[4] of a racemic catalyst has been reported by Brown, Yamamoto-Maruoka, and Faller. However, the chiral poisoning approach is useful when a chiral poison completely discriminates between the two enantiomers of a racemic catalyst, because asymmetric catalysis is performed by the noncomplexed and remaining catalyst enantiomer (Figure 1a).

Selective complexation of one enantiomer of racemic catalysts with chiral poisons has been reported to be a difficult task[3c,4] (Figure 1b), using easily available natural products and their derivatives. In fact, the chiral poisons must be used in larger amounts[5] than the catalyst enantiomers

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(4) (a) Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804−805. (b) Faller, J. W.; Tokunaga, M. *Tetrahedron Lett.* **1993**, *34*, 7359−7362. (c) Faller, J. W.; Liu Sams, X. *J. Am. Chem. Soc.* **1996**, *118*, 1217−1218. (d) Sablong, R.; Osborn, J. A.; Faller, J. W. *J. Organomet. Chem.* **1997**, *527*, 65−70.

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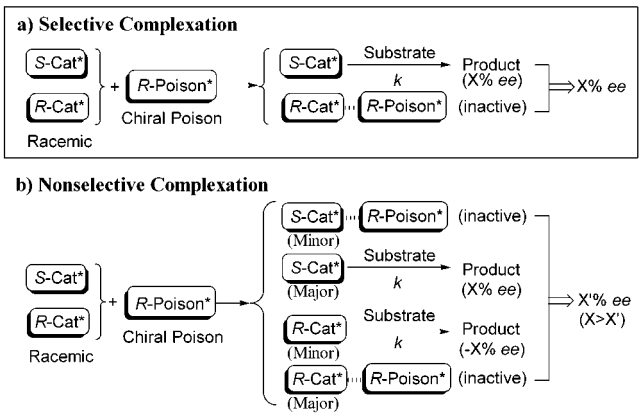


**Figure 1.** Chiral poisoning of racemic catalysts.

because of ineffective discrimination thereof, and high enantioselectivities equal to those by enantiopure catalysts have not been attained (Figure 1b). Herein, we report asymmetric deactivation of racemic BINAP-Ru(II) catalysts through complete enantiomer discrimination by a designed deactivator (Figure 1a), 3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl (DM-DABN) in a highly enantioselective hydrogenation of $\beta$-keto ester and kinetic resolution[6] of racemic 2-cyclohexen-1-ol, using just 1.0 molar amount with respect to the BINAP-Ru(II) catalyst enantiomer.

The highly effective resolving agent DM-DABN[7] with sterically demanding methyl substituents at 3,3′-positions in diaminobinaphthyl (DABN)[8] was thus employed to clarify whether the remaining BINAP-Ru enantiomer shows a high level of enantioselectivity in olefin hydrogenation. XylBINAP-$RuCl_2$[9,10] (BINAP-Ru(II), **1**) with DM-DABN (**2**) gave the stable *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-dmdabn] (**1**/**2**) complex as expected by the CAChe molecular modeling study (Figure 2).[7] Indeed, (*S*)-**2** in (*S*)-**1**/(*S*)-**2** did not exchange at all with another diamine such as DPEN even after 24 h at ambient temperature.

Complete resolution and asymmetric deactivation of the racemic XylBINAP-Ru(II) (**1**) by DM-DABN (**2**) was found to be effective for kinetic resolution[6] of racemic 2-cyclohexen-1-ol (**3**) through olefin hydrogenation[4b] (Table 1). To

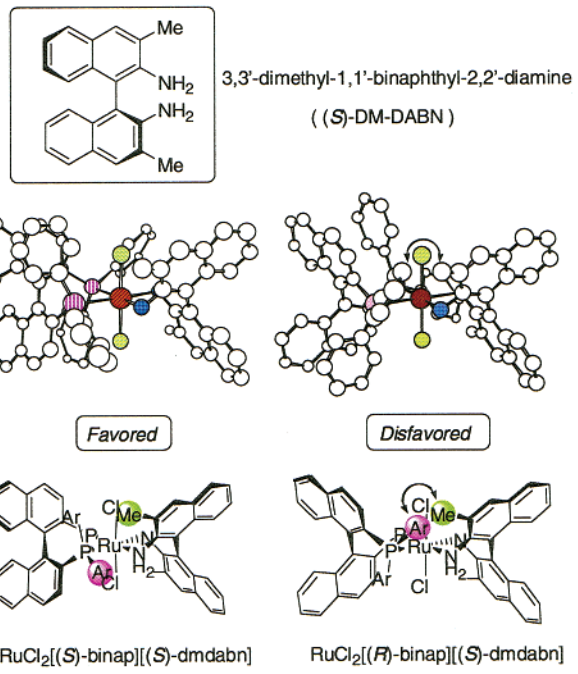


**Figure 2.** CAChe modeling study of a chiral deactivator for enantiomer discrimination of racemic BINAP-Ru(II) complexes.

**Table 1.** Kinetic Resolution of Racemic 2-Cyclohexen-1-ol (**3**) by Racemic XylBINAP-Ru(II) Catalyst through Asymmetric Deactivation


| run | cat. | (*S*)-**2** | % conv[a] | % ee of **3**[b] | $k_f/k_s$[c] |
|---|---|---|---|---|---|
| 1[d] | (±) | none | 100 | | |
| 2[d] | (±) | 0.5 equiv | **53** | 100 (*S*) | |
| 3[e] | (*R*) | none | 53 | 100 (*S*) | |
| 4[d,f] | (±) | 0.5 equiv | 48 | 88 (*S*) | 102 |

[a] Determined by GC analysis (TC-1701). [b] Determined by chiral GC analysis (CP-Chirasil-Dex CB). [c] Relative rate is calculated by the following equation: $\ln[(1-\text{conv.})(1-\text{ee}_{sub})]/\ln[(1-\text{conv.})(1+\text{ee}_{sub})]$ (conv. = 0.482, $\text{ee}_{sub}$ = 0.879). [d] *S*/*C* (substrate to catalyst molar ratio) = 250. [e] *S*/*C* = 500. [f] $H_2$ = 1 atm.

the mixture of $RuCl_2$[(±)-xylbinap](dmf)$_n$ complex (**1**) and (*S*)-DM-DABN (**2**) (0.5 equiv) in an autoclave was added $CH_2Cl_2$ under argon atmosphere. After stirring for 1 h at room temperature, $CH_2Cl_2$ was removed under reduced pressure. Racemic 2-cyclohexen-1-ol (**3**), MeOH, and $H_2$ were subsequently introduced. Hydrogenation of (±)-2-cyclohexen-1-ol (**3**) by (±)-**1** was done in MeOH at room temperature for 5 min under $H_2$ (2 atm). The racemic XylBINAP-Ru(II) (**1**) without DM-DABN (**2**) led to cyclohexanol (**4**) quantitatively with no remaining cyclohexenol

(5) Amounts of chiral poisons: 2.0 equiv for Al (ref 3c); 1.4 equiv for Rh (ref 4a); 20 equiv for Ru (ref 4b); 3.0 equiv for Ti (ref 4c); 2.0 equiv for Ir (ref 4d).

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(7) Mikami, K.; Korenaga, T.; Ohkuma, T.; Noyori, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3707−3710.

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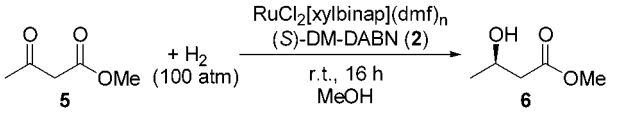
(run 1). However, the use of 0.5 equiv of (*S*)-**2** to (±)-**1** gave enantiopure (*S*)-**3** (run 2). Racemic 2-cyclohexen-1-ol (**3**) was kinetically resolved in the same (53%) conversion as enantiopure (*R*)-**1** (run 2 vs 3). Indeed, the relative rate of hydrogenation of (*R*)- vs (*S*)-**3** in the presence of just a 0.5 molar amount of (*S*)-**2** to (±)-**1** was found to be large ($k_f/k_s$ = 102).[11]

Racemic BINAP-Ru(II) (**1**) was also effective for the enantioselective hydrogenation of β-keto esters[12] using enantiopure DM-DABN (**2**) (Table 2). Methyl 3-oxobutanoate (**5**), MeOH, and $H_2$ were introduced after removal of $CH_2Cl_2$ (vide supra). Methyl (*R*)-3-hydroxybutanoate (**6**) was thus obtained in virtually enantiopure (99.3% ee) form in quantitative yield (run 1). The enantioselectivity (99.3% ee) was equally high as that (99.9% ee) actually obtained by the enantiopure (*R*)-**1** catalyst (run 1 vs 2).

**Table 2.** Hydrogenation of Methyl 3-Oxobutanoate (**5**) by Racemic Catalyst XylBINAP-Ru(II) through Asymmetric Deactivation




| run | cat. | (*S*)-**2** | % ee of **6**[a] | % yield of **6**[b] |
|---|---|---|---|---|
| 1[c] | (±) | 0.5 equiv | **99.3** (*R*) | quant |
| 2[d] | (*R*) | none | 99.9 (*R*) | quant |

[a] Determined by chiral HPLC analysis (CHIRALCEL OB-H) after conversion to methyl 3-benzoyloxybutanoate. [b] Determined by GC analysis (TC-1701). [c] *S*/*C* (substrate to catalyst molar ratio) = 750. [d] *S*/*C* = 1500. [e] See ref 11a.

In conclusion, the racemic BINAP-Ru(II) (**1**) can be completely resolved with 0.5 equiv of the enantiopure DM-DABN (**2**) and used as a catalyst equally effective to the enantiopure **1** for asymmetric hydrogenation. The success with DM-DABN will provide a guiding principle for rational design of a chiral deactivator for enantiomeric catalysts discrimination and asymmetric catalysis therewith.

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(11) **Typical Experimental Procedure. Kinetic Resolution of Racemic 2-Cyclohexen-1-ol by Racemic XylBINAP-Ru(II) catalyst (1) with DM-DABN (2).** To the mixture of $RuCl_2$[(±)-xylbinap](dmf)$_n$ catalyst (**1**) (5.2 mg, 0.005 mmol) and (*S*)-DM-DABN (**2**) (0.8 mg, 0.0025 mmol) in a 100-mL autoclave was added dichloromethane (2.0 mL) under argon atmosphere. After 1 h of stirring at room temperature, dichloromethane was removed under reduced pressure. After replacement with argon, methanol (1.0 mL) and racemic 2-cyclohexen-1-ol (1.23 mL, 1.25 mmol) was added to the autoclave under a stream of argon. Hydrogen was introduced at a pressure of 2 atm. The solution was stirred for 5 min at room temperature. After concentration under reduced pressure, the residue was filtered through a short column on silica gel to give the mixture of 100% ee of (*S*)-2-cyclohexen-1-ol and cyclohexanol. Conversion and % ee of (*S*)-2-cyclohexen-1-ol was calculated by GC analysis. GC analysis for conversion to cyclohexanol: column, OV-1701; i.d. 0.25 mm × 25 m; carrier gas, nitrogen (75 kPa); column temp, 60 °C; injection temp, 90 °C; split ratio, 100:1, $t_R$ of cyclohexanol, 15.8 min (53.4%); $t_R$ of 2-cyclohexen-1-ol 16.9 min (46.6%). GC analysis for % ee of 2-cyclohexen-1-ol: column, CP-Chirasil-Dex-CB; i.d. 0.25 mm × 25 m, CHROMPACK.; carrier gas, nitrogen (75 kPa); column temp, 75 °C; injection temp, 105 °C; split ratio, 100:1, $t_R$ of *S*-isomer, 17.2 min (100%); $t_R$ of *R*-isomer, 18.7 min (0%).

(12) Hydrogenation of β-keto esters by enantiopure $RuCl_2$(binap): (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858. (b) Review: Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327−3355 and references therein.