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Asymmetric Hydrogenation of Aromatic Ketones Catalyzed by the TolBINAP/DMAPEN−Ruthenium(II) Complex: A Significant Effect of *N*-Substituents of Chiral 1,2-Diamine Ligands on Enantioselectivity

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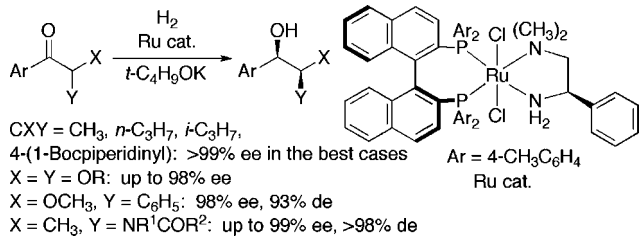

Asymmetric hydrogenation of acetophenone in the presence of Ru(II) catalysts coordinated by TolBINAP and a series of chiral 1,2-diamines was studied. The sense and degree of enantioselectivity were highly dependent on the *N*-substituents of the diamine ligands. The *N*-substituent effect was discussed in detail. Among these catalysts, the (*S*)-TolBINAP/(*R*)-DMAPEN−Ru(II) complex showed the highest enantioselectivity. The mode of enantioface selection was interpreted by using transition state models based on the X-ray structure of the catalyst precursor. The chiral catalyst effected the hydrogenation of alkyl aryl ketones and arylglyoxal dialkyl acetals to afford the chiral alcohol in >99% ee in the best cases. Hydrogenation of racemic benzoin methyl ether with the chiral catalyst through dynamic kinetic resolution gave the *anti*-alcohol (syn:anti = 3:97) in 98% ee, while the reaction of α-amidopropiophenones resulted in the *syn*-alcohols (syn:anti = 96:4 to >99:1) in >98% ee.

Introduction

Asymmetric hydrogenation of ketones is a key technology providing synthetically useful chiral secondary alcohols.[1] We have reported highly reactive and enantioselective hydrogenation of simple ketones catalyzed by Ru complexes bearing a chiral diphosphine and a nitrogen-based bidentate ligand.[2] These two ligands coordinating to the Ru center cooperatively accelerate the reaction rate and also control the enantioface selectivity. For example, a Ru complex coordinated by (*S*)-2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl [(*S*)-TolBINAP] and (*S*,*S*)-1,2-diphenylethylenediamine [(*S*,*S*)-DPEN] catalyzed hydrogenation of acetophenone in a base-containing 2-propanol with a substrate-to-catalyst molar ratio (S/C) of 2 400 000 under 45 atm of H_2 to afford (*R*)-1-phenylethanol in 80−82% ee quantitatively (Scheme 1).[3,4] The use of an (*S*)-XylBINAP/(*S*)-DAIPEN−Ru(II) catalyst achieves excellent enantioselectivity in the reaction of a series of acyclic aromatic, heteroaromatic, amino, and α,β-unsaturated ketones.[5−7] The ee value of >99%

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(2) (a) Ohkuma, T. *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 1070–1080. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.

(3) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675–2676.

(4) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703–1707.

(5) XylBINAP = 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl. DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine.

(6) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530.

(7) Ohkuma, T.; Koizumi, M.; Muñiz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508–6509.

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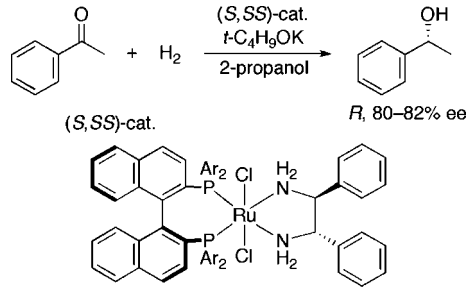
SCHEME 1. Asymmetric Hydrogenation of Acetophenone Catalyzed by the (*S*)-TolBINAP/(*S*,*S*)-DPEN−Ru Complex[a]



[a] Ar = 4-$CH_3C_6H_4$.

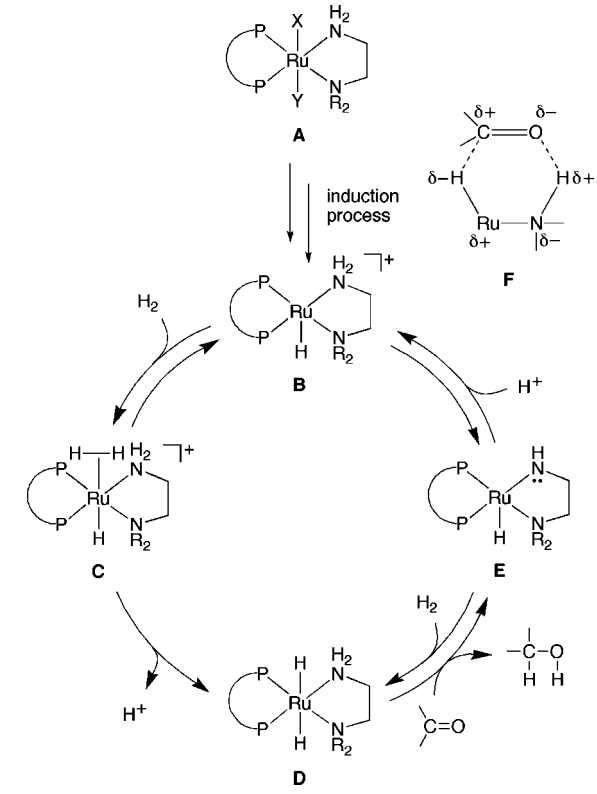
is obtained. Although 1-tetralones, a kind of cyclic aromatic ketones, are difficult substrates to hydrogenate with the chiral diphosphine/1,2-diamine−Ru(II) catalysts, these ketones are smoothly converted to the desired alcohols in up to 99% ee by using the TolBINAP or XylBINAP/1,4-diamine−Ru(II) catalyst.[8] The TolBINAP/picolyl amine−Ru(II) catalyst effects asymmetric hydrogenation of sterically hindered *tert*-alkyl ketones and acylsilanes.[9,10] Thus, the combination of two different ligands on the Ru center is the origin of the electronic and structural diversity of the catalyst, which results in the unique catalytic performance.

Scheme 2 illustrates a proposed catalytic cycle of hydrogenation of acetophenone with an (*S*)-TolBINAP/(*S*,*S*)-DPEN−Ru(II) complex (R = H).[11,12] The catalyst precursor RuXY(tolbinap)(dpen) (**A**: X, Y = Cl, Cl or η^1-BH_4, H) is converted to $[RuH(tolbinap)(dpen)]^+$ (**B**) in 2-propanol with or without an alkaline base. **B** and H_2 reversibly form a cationic complex **C**, followed by deprotonation resulting in the active RuH_2 species **D**. A ketone is readily reduced by **D** to afford the alcohol and a 16-electron amide complex **E**. The prompt protonation of **E** by an alcoholic solvent regenerates species **B**, while **E** partially returns to **D** by the reaction with H_2.

The ketone-reduction step (**D** → **E**) is expected to proceed through a transition state (TS) schematically shown by **F**.[2,11] The catalyst quadropole ($H^{\delta-}-Ru^{\delta+}-N^{\delta-}-H^{\delta+}$) fits with a carbonyl dipole ($C^{\delta+}=O^{\delta-}$) of the substrate to form the six-membered pericyclic TS. Both hydride on the Ru and the amino proton smoothly transfer onto the carbonyl moiety in a pericyclic manner, affording the alcoholic product. This mechanism is now recognized as the "metal−ligand cooperative mechanism". Therefore, at least one "NH" part, preferably an "NH_2" group for steric reasons, is required on the diamine ligands.

We can clarify the mode of enantioface selection in the hydrogenation of acetophenone through the use of molecular models, as shown in Figure 1.[11] The (*S*)-TolBINAP/(*S*,*S*)-DPEN−RuH_2 species (*S*,*SS*)-**D** (see also Scheme 2: R = H)

SCHEME 2. Proposed Catalytic Cycle for TolBINAP/1,2-Diamine−Ru-Catalyzed Hydrogenation of Simple Ketones[a]



[a] X, Y = Cl, Cl or η^1-BH_4, H. P−P = (*S*)-TolBINAP. NH_2-NR_2 = 1,2-diamine: R = H {(*S*,*S*)-DPEN}, CH_3 {(*R*)-DMAPEN}.

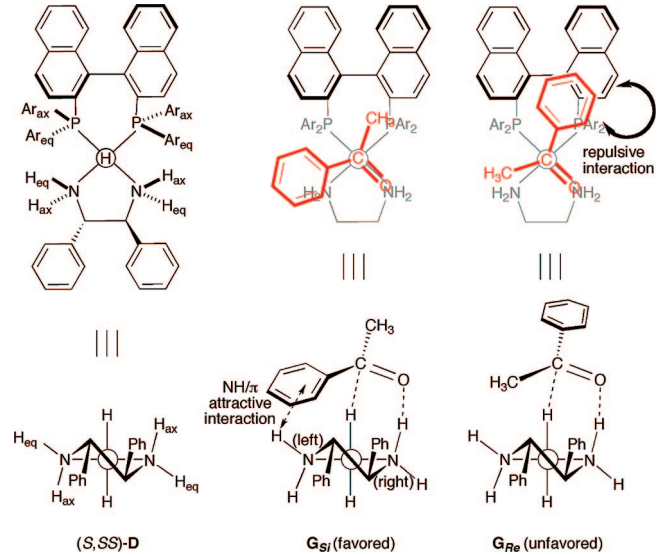


FIGURE 1. Structure of RuH_2 species (*S*,*SS*)-**D** (Scheme 2; R = H) and diastereomeric transition states in the hydrogenation of acetophenone (Ar = 4-$CH_3C_6H_4$).

forms a C_2-symmetric chiral environment. The skewed DPEN chelate ring determines the positions of the axial and equatorial amino protons, H_{ax} and H_{eq}. The reduction of ketone occurs at the H−Ru−N−H_{ax} moiety with a smaller dihedral angle. Acetophenone approaches the reaction site with the *re*-race or *si*-face. The TS $\mathbf{G}_{Re}$ suffers nonbonding repulsion between the aromatic groups of the (*S*)-TolBINAP[13] and the phenyl ring of acetophenone, so that (*R*)-1-phenylethanol is selectively obtained

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(10) Arai, N.; Suzuki, K.; Sugizaki, S.; Sorimachi, H.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1770–1773.
(11) (a) Sandoval, C. A.; Ohkuma, T.; Muñiz, K.; Noyori, R. *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503. (b) Noyori, R.; Sandoval, C. A.; Muñiz, K.; Ohkuma, T. *Phil. Trans. R. Soc. A* **2005**, *363*, 901–912.
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through the favored TS $\mathbf{G}_{Si}$. An attractive NH/π interaction is suggested to contribute to the enantioface selection.[11,12e,14−16]

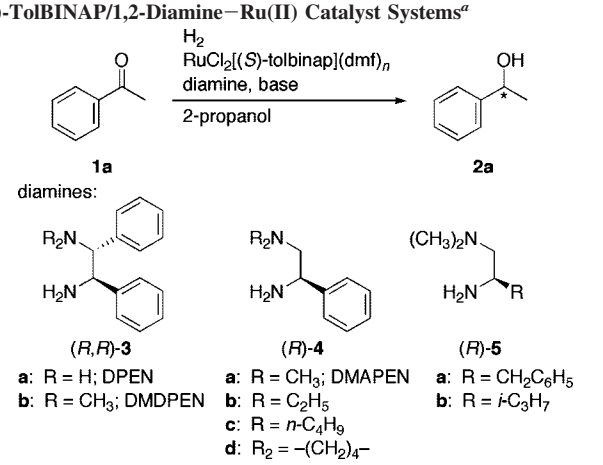
This scenario for enantioselection is completely changed by the use of *N*,*N*-disubstituted ethylenediamine ligands instead of DPEN bearing no *N*-substituent. We wish to describe here asymmetric hydrogenation of aromatic ketones catalyzed by the (*S*)-TolBINAP/(*R*)-2-dimethylamino-1-phenylethylamine [(*R*)-DMAPEN]−Ru(II) complex.[17] We will also discuss the effects of the *N*-substituents of chiral ethylenediamine ligands on the enantioselectivity in the reaction with TolBINAP/chiral 1,2-diamine−Ru(II) catalysts.

Results and Discussion

The Structure of Chiral 1,2-Diamines and Its Influence on Catalyst Performance. We selected acetophenone (**1a**) as a standard substrate to examine the performance of catalysts which were prepared in situ from $RuCl_2$[(*S*)-tolbinap](dmf)$_n$ (oligomeric form)[18] and chiral diamines **3**−**5** in a base (KOH or *t*-C_4H_9OK) containing 2-propanol. As we have already reported, when **1a** (5.0 mmol, 1.0 M) was hydrogenated with the (*S*)-TolBINAP−Ru(II) complex (10 μmol, S/C = 500), (*S*,*S*)-DPEN [(*S*,*S*)-**3a**] (10 μmol), and a base (200 μmol) at 23 °C under 8 atm of H_2 for 1 h, (*R*)-1-phenylethanol [(*R*)-**2a**] in 82% ee was obtained quantitatively (Table 1, entry 1).[3,4] The combination of (*S*)-TolBINAP and (*S*,*S*)-*N*,*N*-dimethyl-1,2-diphenylethylenediamine [(*S*,*S*)-DMDPEN] [(*S*,*S*)-**3b**] afforded (*R*)-**2a** in 22% ee (entry 2), whereas the reaction with the *S*/*R*,*R* catalyst resulted in the *S* alcohol in 79% ee (entry 3). Replacement of an NH_2 moiety of **3a** by the $N(CH_3)_2$ group changed the matching ligand-combination from (*S*)-TolBINAP/(*S*,*S*)-**3a** to (*S*)-TolBINAP/(*R*,*R*)-**3b**, and also reversed the absolute configuration of product from *R* to *S*.

A single chiral center is sufficient for the 1,2-diamine ligand to achieve high catalytic efficiency. In fact, hydrogenation of **1a** with the combined catalyst of (*S*)-TolBINAP and (*R*)-DMAPEN [(*R*)-**4a**] afforded (*S*)-**2a** in 91% ee (Table 1, entry 5). It is worth noting that the (*S*)-TolBINAP/(*R*)-**4a** catalyst achieved a higher degree of enantioselectivity than the originally used (*S*)-TolBINAP/(*S*,*S*)-**2a** catalyst (91% ee vs 82% ee). The (*S*)-TolBINAP/(*S*)-**4a** combination gave (*S*)-**2a** in 43% ee (entry 4). Interestingly, use of the bulkier diethylamino and dibutylamino ligands, (*R*)-**4b** and (*R*)-**4c**, instead of (*R*)-**4a** coupled with (*S*)-TolBINAP resulted in much lower reactivity and enantioselectivity with the reverse asymmetric sense (entries 6 and 7). The relatively smaller pyrrolidinyl ligand **4d** directed the same enantiomeric sense as that with **4a** (entry 8).

TABLE 1. Asymmetric Hydrogenation of Acetophenone (1a) with (*S*)-TolBINAP/1,2-Diamine−Ru(II) Catalyst Systems[a]



entry	diamine	yield (%)[b]	ee (%)[b]	config[c]
1	(*S*,*S*)-**3a**	>99	82	*R*
2	(*S*,*S*)-**3b**	>99	22	*R*
3	(*R*,*R*)-**3b**	>99	79	*S*
4	(*S*)-**4a**	79	43	*S*
5	(*R*)-**4a**	>99	91	*S*
6	(*R*)-**4b**	77[d]	31	*R*
7	(*R*)-**4c**	21	26	*R*
8	(*R*)-**4d**	80	84	*S*
9	(*S*)-**5a**	25	40	*S*
10	(*R*)-**5a**	>99	84	*S*
11	(*R*)-**5b**	>99	82	*S*

[a] Reactions were conducted at 20−25 °C under 8 atm of H_2 for 1 h, using a 1.0 M solution of **1a** (5.0 mmol) in 2-propanol containing the (*S*)-TolBINAP−Ru(II) complex (10 μmol, S/C = 500), diamine (10 μmol), and KOH or *t*-C_4H_9OK (200 μmol). For the sake of formal consistency, the table lists results obtained with an (*S*)-TolBINAP−Ru(II) complex, although some experiments were actually performed with the *R* complex, in which the configuration of the amine was also opposite to that shown in the table. [b] Determined by chiral GC analysis. [c] Determined by comparison of the chiral GC behavior with that of the reference sample. [d] Reaction for 4 h.

The substituents (R) connected to the chiral center of diamine ligands had little effect on the stereoselectivity. The hydrogenation of **1a** with the (*S*)-TolBINAP/(*R*)-**5a** (R = $CH_2C_6H_5$) and (*S*)-TolBINAP/(*R*)-**5b** (R = *i*-C_3H_7) catalysts afforded (*S*)-**2a** in 84% and 82% ee, respectively (Table 1, entries 10 and 11). The combination of (*S*)-TolBINAP and (*S*)-**5a** gave poor reactivity and enantioselectivity (entry 9) as observed in the reaction with the (*S*)-TolBINAP/(*S*)-**4a** catalyst (entry 4).

Preparation and Structure Determination of the (*S*)-TolBINAP/(*R*)-DMAPEN−Ru(II) Complex. $RuCl_2$[(*S*)-tolbinap](dmf)$_n$ and (*R*)-DMAPEN [(*R*)-**4a**] were readily reacted in DMF at 25 °C to form *trans*-$RuCl_2$[(*S*)-tolbinap][(*R*)-dmapen] [(*S*,*R*)-**6**] in 86% yield (see the Experimental Section). Single-crystal X-ray analysis revealed that (*S*,*R*)-**6** has a Ru center with a distorted octahedral geometry, in which two Cl atoms possess both apical positions [Cl(1)−Ru–Cl(2) = 166.05(4)°] (Figure 2). The (*S*)-TolBINAP coordinates to Ru with a δ seven-membered chelate structure, while (*R*)-**4a** forms a λ five-membered chelate ring.[19] The skewed chelate structure of ligands arranges the positions of four 4-$CH_3C_6H_4$ groups on P atoms and two amino hydrogen. The small Cl(1)−Ru−N(1)−H(1) torsion angle (15°) results in the relatively short Cl(1)−H(1)

(13) For the (*S*)-TolBINAP–Ru chelate structure, see the ORTEP drawing in Figure 2. See also ref 4.

(14) (a) Oki, M.; Mutai, K. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 784–789. (b) Oki, M.; Mutai, K. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 387–392. (c) Oki, M.; Mutai, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 809–813.

(15) For ammonium/π(aryl) interaction, see: (a) Meot-Ner, M.; Deakyne, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 469–474. (b) Singh, J.; Thornton, J. M. *J. Mol. Biol.* **1990**, *211*, 595–615. (c) Dougherty, D. A.; Stauffer, D. A. *Science* **1990**, *250*, 1558–1560. (d) Garel, L.; Lozach, B.; Dutasta, J.-P.; Collet, A. *J. Am. Chem. Soc.* **1993**, *115*, 11652–11653. (e) Koh, K. N.; Araki, K.; Ikeda, A.; Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 755–758. (f) Roelens, S.; Torriti, R. *J. Am. Chem. Soc.* **1998**, *120*, 12443–12452. (g) Gallivan, J. P.; Dougherty, D. A. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9459–9464.

(16) DFT calculations of transition states in asymmetric hydrogenation of **1a** with the TolBINAP/DPEN−Ru(II) catalyst also suggested the presence of an NH/π interaction, see: (a) French, S. A.; Di Tommaso, D.; Zanotti-Gerosa, A.; Hancock, F.; Catlow, C. R. A. *Chem. Commun.* **2007**, 2381–2388. (b) Di Tommaso, D.; French, S. A.; Zanotti-Gerosa, A.; Hancock, F.; Palin, E. J.; Catlow, C. R. A. *Inorg. Chem.* **2008**, *47*, 2674–2687.

(17) A preliminary communication, see: Arai, N.; Ooka, H.; Azuma, K.; Yabuuchi, T.; Kurono, N.; Inoue, T.; Ohkuma, T. *Org. Lett.* **2007**, *9*, 939–941.

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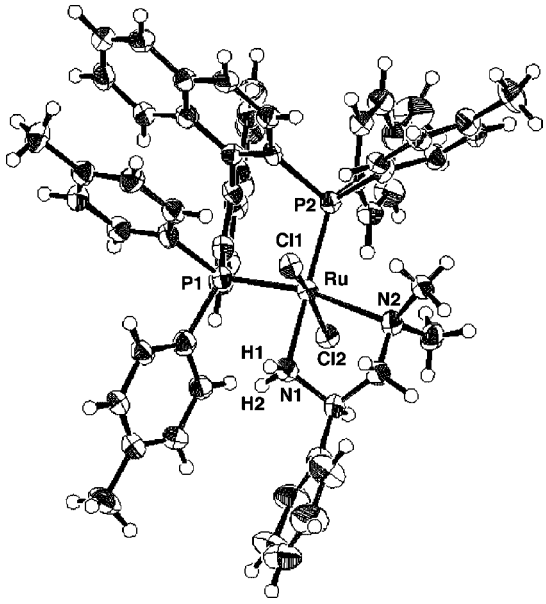


FIGURE 2. ORTEP Drawing of (*S*,*R*)-**6**. Selected distances (Å) and bond angles (deg): Ru−Cl1 2.4082(13), Ru−Cl2 2.4153(12), Ru−P1 2.2714(13), Ru−P2 2.3075(13), Ru−N1 2.147(4), Ru−N2 2.373(4), Cl1−H1 2.63, Cl2−H2 3.00; Cl1−Ru−Cl2 166.05(4), P1−Ru−P2 89.97(4), and N1−Ru−N2 77.65(16).

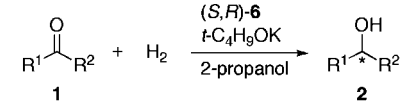
distance of 2.63 Å (expected van der Waals separation, 3.0 Å). The $^{31}P\{^1H\}$ NMR measurement in $CDCl_3$ indicated a set of doublet signals at 36.6 and 51.4 ppm with J_{P-P} = 38.5 Hz, suggesting that (*S*,*R*)-**6** exists as a sole diastereomeric compound in the solution phase.

Hydrogenation of Alkyl Aryl Ketones with the (*S*)-TolBINAP/(*R*)-DMAPEN−Ru(II) Catalyst. We next focused our attention on efficiency of the (*S*)-TolBINAP/(*R*)-DMAPEN [(*R*)-**4a**]−Ru(II) catalyst in asymmetric hydrogenation of simple ketones by using a preformed complex (*S*,*R*)-**6** in basic 2-propanol. Acetophenone (**1a**) was hydrogenated with (*S*,*R*)-**6** at an S/C of 500 in *t*-C_4H_9OK containing 2-propanol under 8 atm of H_2 to afford (*S*)-1-phenylethanol [(*S*)-**2a**] in 92% ee (Table 2). The degree and sense of enantioselectivity were the same as those obtained with the ternary catalyst system of $RuCl_2$[(*S*)-tolbinap](dmf)$_n$, (*R*)-**4a**, and a base (Table 1, entry 5), suggesting that both reactions were mediated by the same catalytic species. Hydrogenation of acetophenones bearing an electron-attracting or -donating function at the 4′ position, **1b** and **1c**, gave the *S* alcohols in 84% and 81% ee, respectively. The electronic properties of substrates did not influence the reactivity. The slight decrease of enantioselectivity may be caused by a steric factor. Interestingly, (*S*,*R*)-**6** showed excellent enantioselectivity for hydrogenation of butyrophenone (**1d**) and isobutyrophenone (**1e**), affording the *S* alcohols in 95% ee. A heterocyclic aromatic ketone **1f** was hydrogenated with perfect stereoselectivity. The resulting alcohol, (*S*)-**2f**, is an intermediate for the synthesis of a non-narcotic analgestic and muscle relaxant agent.[20] The reaction of cyclohexyl methyl ketone (**1g**), a simple secondary aliphatic ketone, with (*S*,*R*)-**6** gave (*R*)-**2g** in 47% ee. These results reveal that (*S*,*R*)-**6** effectively differentiates primary and secondary alkyl groups from aromatic rings.

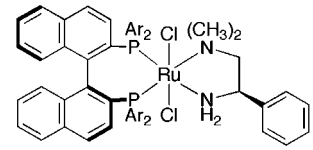
(19) $RuCl_2$[(*S*)-tolbinap][(*S*,*S*)-dpen] has two δ-chelate structures with both ligands. See ref 4.

(20) Nieduzak, T. R.; Margolin, A. L. *Tetrahedron: Asymmetry* **1991**, *2*, 113–122.

TABLE 2. Asymmetric Hydrogenation of Alkyl Aryl Ketones 1 with (*S*)-TolBINAP/(*R*)-DMAPEN−Ru(II) Complex [(*S*,*R*)-6][a]



a: R^1 = C_6H_5, R^2 = CH_3 **e**: R^1 = C_6H_5, R^2 = *i*-C_3H_7
b: R^1 = 4-$CF_3C_6H_4$, R^2 = CH_3 **f**: R^1 = 4-FC_6H_4,
c: R^1 = 4-$CH_3OC_6H_4$, R^2 = CH_3 R^2 = 4-(1-Bocpiperidinyl)
d: R^1 = C_6H_5, R^2 = *n*-C_3H_7 **g**: R^1 = *cyclo*-C_6H_{11}, R^2 = CH_3



(*S*,*R*)-**6**: Ar = 4-$CH_3C_6H_4$

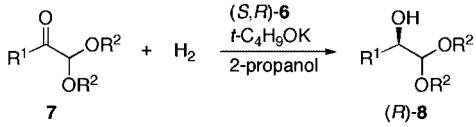
ketone	S/C[b]	time (h)	yield (%)	ee (%)[c]	config[d]
1a	500	3	89	92	*S*
1b	500	3	91	84	*S*
1c	500	3	96	81	*S*
1d	500	3	96	95	*S*
1e	2000	10	94	95	*S*
1f	400	7	98	>99[e]	*S*[f]
1g	500	7	85	47	*R*

[a] Unless otherwise stated, reactions were conducted at 20−25 °C under 8 atm of H_2 with a 0.3−0.7 M solution of **1** (1.0−3.6 mmol) in 2-propanol containing (*S*,*R*)-**6** (0.3−1.2 μM) and *t*-C_4H_9OK (20 μM). Conversion was >95% in all cases. [b] Substrate/catalyst molar ratio. [c] Determined by the chiral GC or HPLC analysis. [d] Determined by the sign of rotation. [e] Determined by ^1H and ^{19}F NMR integration of the corresponding MTPA ester. [f] See the Supporting Information.

Hydrogenation of Arylglyoxal Dialkyl Acetals. The (*S*)-TolBINAP/(*R*)-DMAPEN−Ru(II) complex, (*S*,*R*)-**6**, was applied to the asymmetric hydrogenation of arylglyoxal dialkyl acetals **7**, a kind of functionalized aromatic ketones. We expected that an α-branched structure similar to **1e** and **1f** would be preferable to achieve high enantioselectivity. In fact, phenylglyoxal diethylacetal (**7a**) (580 mg, 0.7 M) was hydrogenated with (*S*,*R*)-**6** (1.4 mg, S/C = 2000) and *t*-C_4H_9OK (13.0 mg) in 2-propanol under 8 atm of H_2 to afford the α-hydroxy acetal (*R*)-**8a** in 96% ee and 95% yield (Table 3). The reaction (1.5 M of **7a**) with an S/C of 5000 proceeded smoothly under 50 atm of H_2 without loss of enantioselectivity. Complete conversion was attained under 1.5 atm of H_2 with an S/C of 500 in 9 h. The ketonic substrate bearing a cyclic acetal **7b** was also reduced with high enantioselectivity. Hydrogenation of the 2′- and 4′-methyl-substituted ketones, **7c** and **7d**, gave the *R* alcohols in 92% and 96% ee, respectively. Substitution of an electron-donating CH_3O group at the 4′ position (**7e**) increased the enantioselectivity to 98%, while the optical yield of the reaction with the ketone substituted by an electron-withdrawing Cl **7f** was slightly reduced to 92%. The 2-naphthyl ketone **7g** was hydrogenated to give (*R*)-**8g** in 97% ee with the same sense of enantioface selection. The reaction of pyruvic aldehyde dimethylacetal (**7h**), the simplest aliphatic substrate, yielded (*R*)-**8h** in only 40% ee. To our knowledge, the (*S*)-TolBINAP/(*R*)-DMAPEN−Ru(II) complex is the only catalyst system to achieve >95% optical yield in hydrogenation of arylglyoxal dialkyl acetals.[21]

Asymmetric Hydrogenation of Racemic α-Alkoxy and α-Amido Ketones via Dynamic Kinetic Resolution. Asymmetric hydrogenation of racemic α-substituted ketones through dynamic kinetic resolution is a reliable method to obtain optically active alcohols with two contiguous stereogenic

TABLE 3. Asymmetric Hydrogenation of Arylglyoxal Dialkyl Acetals 7 with (*S*,*R*)-6[a]



a: $R^1 = C_6H_5$, $R^2 = C_2H_5$ **e**: $R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = C_2H_5$
b: $R^1 = C_6H_5$, R^2–$R^2 = -(CH_2)_3-$ **f**: $R^1 = 4\text{-}ClC_6H_4$, $R^2 = C_2H_5$
c: $R^1 = 2\text{-}CH_3C_6H_4$, $R^2 = C_2H_5$ **g**: $R^1 = 2$-naphthyl, $R^2 = C_2H_5$
d: $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = C_2H_5$ **h**: $R^1 = CH_3$, $R^2 = CH_3$

ketone	S/C[b]	H_2 (atm)	time (h)	yield (%)	ee (%)[c]
7a	2000	8	18	95	96
7a[d]	5000	50	22	98	96
7a	500	1.5	9	94	96
7b	1000	8	24	97	93
7c	1000	8	18	96	92
7d	1000	8	4	95	96
7e	1000	8	5	96	98
7f	1000	8	4	95	92
7g	1000	8	24	91	97
7h	1200	8	5.5	99	40

[a] Unless otherwise stated, reactions were conducted at 25−30 °C with a 0.3−1.4 M solution of **7** (0.9−2.8 mmol) in 2-propanol containing (*S*,*R*)-**6** (0.25−0.73 μM) and *t*-C_4H_9OK (20 μM) to give (*R*)-**8**. Conversions were >95% in all cases. [b] Substrate/catalyst molar ratio. [c] Determined by the chiral GC or HPLC analysis. [d] Reaction with 2.21 g of **7a** (1.5 M).

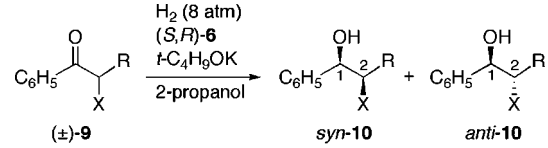
centers.[22,23] In situ mutation at the α position enables us to attain a single stereoisomer among four possible enantiomeric and diastereomeric compounds. When racemic benzoin methyl ether [(±)-**9a**] (268.2 mg, 0.40 M) was hydrogenated with (*S*,*R*)-**6** (1.6 mg, S/C = 750) and *t*-C_4H_9OK (11.3 mg, 34 mM) in 2-propanol under 8 atm of H_2, (1*R*,2*S*)-**10a**(syn:anti = 3:97) was quantitatively obtained in 98% ee (Table 4). The slightly basic condition accelerated the stereomutation at the α position.[23] This is the first example of antiselective asymmetric hydrogenation of (±)-**9a** under dynamic kinetic discrimination.[24] Hydrogenation of racemic 2-methoxypropiophenone [(±)-**9b**] with (*S*,*R*)-**6** gave a mixture of (1*R*,2*R*)-**10b** (syn) and (1*R*,2*S*)-**10b** (anti) in a 57:34 ratio. 2-(Pivaloylamino)propiophenone [(±)-**9c**], an α-amido aromatic ketone, with (*S*,*R*)-**6** afforded *syn*-(1*R*,2*R*)-**10c** (syn:anti = 96:4) in 99% ee quantitatively (Table 4). In the same manner, racemic 2-(benzoylmethylamino)propiophenone [(±)-**9d**] was hydrogenated with (*S*,*R*)-**6** to give (1*R*,2*R*)-**10d** (syn:anti = >99:1) in 98% ee. Removal of a benzoyl group from (1*R*,2*R*)-**10e** (NaOH, C_2H_5OH aq, reflux, 12 h) gave (−)-pseudoephedrine, which is a widely used nasal decongestant as well as a useful chiral auxiliary in synthetic organic chemistry.[25,26]

Role of *N*-Substituents of Chiral 1,2-Diamine Ligands in the Enantioface Selection. We have already proposed a mechanism for hydrogenation of **1a** with the (*S*)-TolBINAP/(*S*,*S*)-**3a**−Ru(II) catalyst, as shown in Scheme 2.[11] The *trans*-RuH_2[(*S*)-tolbinap][(*S*,*S*)-**3a**] (**D**) is expected to be the active catalytic species due to the strong *trans* σ-donating property of the hydride.[27,28] The reaction with the new (*S*)-TolBINAP/(*R*)-DMAPEN [(*R*)-**4a**]−Ru(II) complex is thought to proceed through the same catalytic cycle, in which *trans*-RuH_2[(*S*)-tolbinap][(*R*)-**4a**] [**D** (R = CH_3) in Scheme 2] is a plausible active species according to the X-ray structure of the precatalyst (*S*,*R*)-**6** (see Figure 2). Figure 3 schematically illustrates the structure of *trans*-RuH_2[(*S*)-tolbinap][(*R*)-**4a**] [(*S*,*R*)-**11**] and two diastereomeric TSs, $\mathbf{12}_{Re}$ and $\mathbf{12}_{Si}$, in the hydrogenation of **1a**. These six-membered TSs are constructed with the $H_{ax}^{\delta+}-N^{\delta-}-Ru^{\delta+}-H^{\delta-}$ quadropole and carbonyl $C^{\delta+}=O^{\delta-}$ dipole, where H_{ax} is an axially oriented amino proton.[29] The *Re*-face selected TS $\mathbf{12}_{Re}$ places the CH_3 group of **1a** at the "V-shape channel" of TolBINAP's $Ar_{ax}-P-Ar_{eq}$ (Ar = 4-$CH_3C_6H_4$) structure, and the planar phenyl ring of **1a** is faced on the amino Me_{eq} group. On the other hand, the *Si*-face selected TS $\mathbf{12}_{Si}$ orients the widespread phenyl group of **1a** to the narrow TolBINAP's V-shape channel, resulting in the serious nonbonded repulsion between these components. Thus, the hydrogenation selectively proceeds via the TS $\mathbf{12}_{Re}$ to afford (*S*)-**2a**.

The (*S*)-TolBINAP/(*R*,*R*)-**3b**−Ru(II) catalyst shows the same sense of enantioselectivity as the (*S*)-TolBINAP/(*R*)-**4a** combination, but has a relatively lower degree of optical yield (79% vs 91%) (Table 1, entries 3 and 5). This suggests that **3b** acts in a manner similar to **4a**, as shown in the TS $\mathbf{13}_{Re}$ (Figure 4). Destabilization of the TS by a 1,2-repulsion between the C1-phenyl and the amino Me_{ax} in the five-membered chelate ring could cause this lower enantioselectivity.

The significant effect of the size of amino substituents on the enantioselectivity (Table 1, entries 5−8) is also explained

TABLE 4. Asymmetric Hydrogenation of α-Hetero-Substituted Ketones 9 with (*S*,*R*)-6[a]



a: $R = C_6H_5$, $X = OCH_3$ **c**: $R = CH_3$, $X = NHCO\text{-}t\text{-}C_4H_9$
b: $R = CH_3$, $X = OCH_3$ **d**: $R = CH_3$, $X = N(CH_3)COC_6H_5$

ketone	S/C[b]	time (h)	yield (%)	dr[c,d]	ee (%)[d]	config[e]
9a	750	18	95	3:97	98	1*R*,2*S*[f]
9b	800	20	72	57:43	79	1*R*,2*R*
9c	1000	64	92	96:4	99	1*R*,2*R*
9d	500	9	90	>99:1	98	1*R*,2*R*[g]

[a] Unless otherwise stated, reactions were conducted at 20−25 °C under 8 atm of H_2 with a 0.3−1.4 M solution of **9** (0.5−1.3 mmol) in 2-propanol containing (*S*,*R*)-**6** (0.25−0.73 μM) and *t*-C_4H_9OK (20 μM). Conversions were >95% in all cases. [b] Substrate/catalyst molar ratio. [c] *syn*-**10**:*anti*-**10** diastereomeric ratio. [d] Determined by the chiral HPLC analysis. [e] Determined by the sign of rotation. Data for *syn*-**10**. [f] Data for *anti*-**10**. [g] See the Supporting Information.

(21) Asymmetric hydrogenation of **7a** and phenylglyoxal dimethylacetal with Pt/Al_2O_3 catalysts modified by cinchonidine derivatives gave the alcohols in 81% and 89% ee, respectively, see: Studer, M.; Burkhardt, S.; Blaser, H.-U. *Chem. Commun.* **1999**, 1727–1728.

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(24) Asymmetric transfer hydrogenation of (±)-**9a** catalyzed by a chiral arene−Ru complex in a formic acid−$(C_2H_5)_3N$ mixture selectively gave the syn alcohol. See: Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119–1121.

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(29) A related theoretical study suggested that possibility to use H_{eq} instead of H_{ax} in the transition state, see ref 12e.

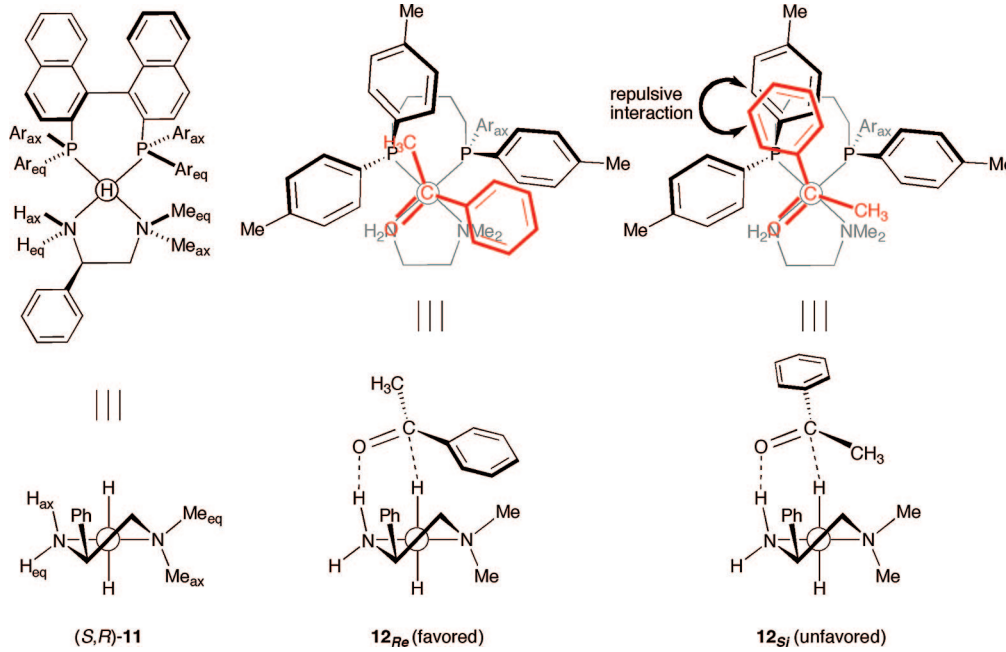


FIGURE 3. Structure of RuH_2 species (*S*,*R*)-**11** and diastereomeric transition states in the hydrogenation of acetophenone. In the TSs $\mathbf{12}_{Re}$ and $\mathbf{12}_{Si}$, some aromatic groups in the TolBINAP and DMAPEN are omitted for clarity. Ar = 4-$CH_3C_6H_4$.

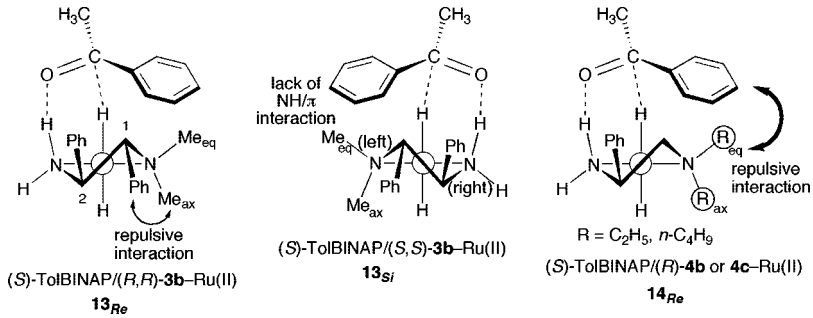


FIGURE 4. TS structures in asymmetric hydrogenation of **1a** with (*S*)-TolBINAP/(*R*,*R*)-**3b**−Ru(II) $\mathbf{13}_{Re}$, (*S*)-TolBINAP/(*S*,*S*)-**3b**−Ru(II) $\mathbf{13}_{Si}$, and (*S*)-TolBINAP/(*R*)-**4c** or **4d**−Ru(II) $\mathbf{14}_{Re}$. TolBINAP is omitted for clarity.

by the TS model $\mathbf{14}_{Re}$ in Figure 4. When (*R*)-**4b** (R = C_2H_5) or (*R*)-**4c** (R = *n*-C_4H_9) is used as a diamine ligand, the TS is destabilized by a steric repulsion between the phenyl ring of **1a** and the bulkier alkyl (R) group than CH_3. A diamine (*R*)-**4d** with a small pyrrolidinyl moiety performs the selectivity at a level comparable to that by (*R*)-**4a**.

The phenyl group of (*R*)-**4a** connected to the diamine backbone mainly contributes to fix the λ chelate conformation of TS $\mathbf{12}_{Re}$ (see Figure 3). Therefore, **5a** (R = $CH_2C_6H_5$) and **5b** (R = *i*-C_3H_7) basically show the same efficiency as **4a** in the hydrogenation of **1a** (see Table 1, scheme and entries 9−11).

Introduction of an $N(CH_3)_2$ group instead of an NH_2 moiety to the DPEN ligand dramatically changes the enantioselectivity in the hydrogenation of **1a**, as shown in Table 1. The reaction with the original (*S*)-TolBINAP/(*S*,*S*)-**3a**−Ru(II) catalyst gave (*R*)-**2a** in 82% ee, while the (*S*)-TolBINAP/(*S*,*S*)-**3b** combination afforded the *R* alcohol in only 22% ee (entries 1 and 2). $\mathbf{13}_{Si}$ in Figure 4 is the expected TS model of the reaction with the (*S*)-TolBINAP/(*S*,*S*)-**3b** system, in which two CH_3 groups are connected to the N(left) atom. The TS is not stabilized by the NH/π attractive interaction[11,14,15] observed in the TS $\mathbf{G}_{Si}$ (see Figure 1), resulting in the lower level of enantioselectivity. The steric repulsion between the Me_{eq} group on the N(left) atom and the phenyl group of **1a** should not be a significant effect, because the reaction with the (*S*)-TolBINAP/(*R*,*R*)-**3b** combination through TS $\mathbf{13}_{Re}$, which has a similar partial structure around the N atom, attains high enantioselectivity (Table 1, entry 3). Such a notable effect of NH/π interaction exceeds our expectations. But our previous observation that hydrogenation of electronic deficient 4′-trifluoromethylacetophenone with the (*S*)-TolBINAP/(*S*,*S*)-**3a**−Ru(II) catalyst gave the *R* alcohol in a relatively lower ee of 65% is consistent with the present discussion.[11,16] The reaction of 4′-methylacetophenone with the same catalyst resulted in 83% optical yield.

The (*S*)-TolBINAP/(*S*,*S*)-**3a**−Ru(II) catalyst and the (*S*)-TolBINAP/(*R*)-**4a**−Ru(II) catalyst show the opposite sense of enantioselectivity in the hydrogenation of **1a**, while both catalysts have the same enantiomer of the TolBINAP ligand (Table 1, entries 1 and 5). These results indicate that the chiral 1,2-diamine ligands, **3a** and **4a**, should play crucial roles in the enantioface recognition. Figure 5 illustrates the comparison of these TSs, $\mathbf{G}_{Si}$ (Figure 1) and $\mathbf{12}_{Re}$ (Figure 3). (*S*,*S*)-**3a** in $\mathbf{G}_{Si}$ forms a δ-five-membered chelate structure, so that the TS uses the H−Ru−N(right)−H_{ax} moiety, affording (*S*)-**2a** selectively. On the other hand, (*R*)-**4a** in $\mathbf{12}_{Re}$ coordinates to the Ru center in a λ fashion, in which the H−Ru−N(left)−H_{ax} part is available for reduction, resulting in (*R*)-**2a** predominantly. Thus, the TolBINAP/chiral

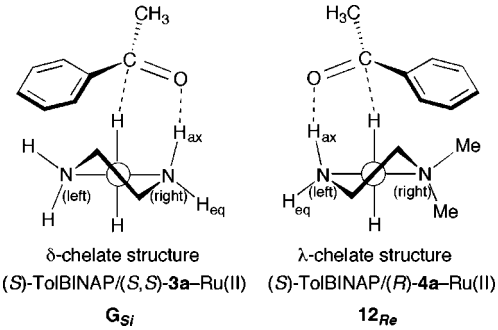


FIGURE 5. Comparison of TS structures in asymmetric hydrogenation of **1a** with (*S*)-TolBINAP/(*S*,*S*)-**3a**−Ru(II) ($\mathbf{G}_{Si}$ in Figure 1) and (*S*)-TolBINAP/(*R*)-**4a**−Ru(II) ($\mathbf{12}_{Re}$ in Figure 3). TolBINAP and phenyl rings of diamines are omitted for clarity.

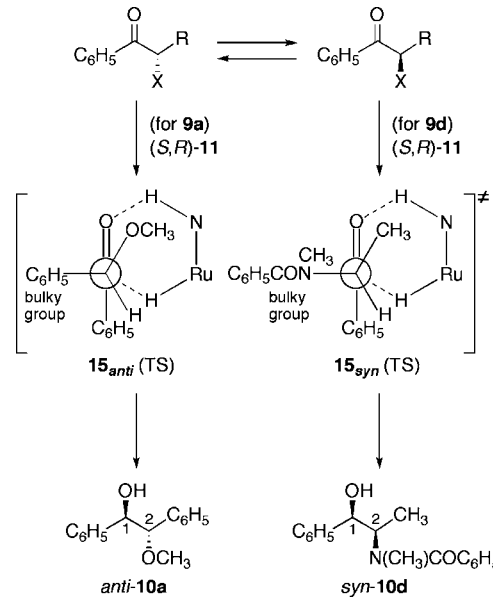
1,2-diamine−Ru(II) catalysts differentiate enantiofaces of **1a** mainly by using the chiral environment of TolBINAP, while *chiral 1,2-diamines determine the reaction site of the catalyst and the direction of the ketonic substrate.*

Scope of the Hydrogenation with the (*S*)-TolBINAP/(*R*)-DMAPEN−Ru(II) Catalyst. The (*S*)-TolBINAP/(*R*)-**4a**−Ru(II) complex (*S*,*R*)-**6** is applicable to asymmetric hydrogenation of a series of aromatic ketones **1** (Table 2). Aromatic rings are successfully differentiated from CH_3, *n*-C_3H_7, *i*-C_3H_7, and an even bulkier protected piperidinyl group with a consistent sense of enantioselection. The $Ar_{ax}-P-Ar_{eq}$ V-shape channel of TS $\mathbf{12}_{Re}$ accepts such primary and secondary alkyls, but does not fit widespread aromatics (see Figure 3). The N-Me_{eq} moiety does not block placement of the planar aromatic ring above it. But the bulkier alkyl groups could suffer some repulsion from the N-Me_{eq} moiety in the TS $\mathbf{12}_{Si}$, so that the enantioselectivity in the hydrogenation of **1d**−**f** was even higher than that in the reaction of **1a**. The electronic properties of phenyl rings had little effect on the enantioselectivity, because no NH/π interaction is available in this system. (*S*,*R*)-**6** is not appropriate for enantioselection of an aliphatic ketone **1g**. The catalyst is expected to *differentiate two carbonyl substituents mainly by their shape and less by their size.*

These features of (*S*,*R*)-**6** in enantioface selection enable asymmetric hydrogenation of arylglyoxal dialkyl acetals **7** (Table 3). Usually, **7** behaves as a kind of functionalized ketone due to the presence of two coordinatable α-oxygens. However, in the hydrogenation system, the acetal part of **7** could locate in the $Ar_{ax}-P-Ar_{eq}$ V-shape channel of TS $\mathbf{12}_{Re}$ (see Figure 3). The NMe_2 moiety may prevent the acetal approach to the Ru center in the TS $\mathbf{12}_{Si}$. Here, the acetal group behaves merely as a *sec*-alkyl group.

The chiral environment of (*S*,*R*)-**6** is also effective for hydrogenation of racemic α-monoheterosubstituted ketones [(±)-**9**] through dynamic kinetic resolution (see Table 4).[22,23] The sense of enantioface selectivity is consistent with that observed in the reaction of **1**. However, the diastereoselective manner is highly dependent on the α-substitution pattern of substrates **9**. The stereoselective outcome is interpreted by using the Felkin−Anh-type TS models (Scheme 3).[30] The chiral ketones **9** are in rapid equilibrium under the basic conditions. **9a** (R = C_6H_5, X = OCH_3) is reduced with the RuH_2 species (*S*,*R*)-**11** (see Figure 3) via the TS $\mathbf{15}_{anti}$, in which the bulkiest

SCHEME 3. Plausible Reaction Pathway for Diastereo- and Enantioselective Hydrogenation of Racemic Ketones 9 with (*S*,*R*)-11 through Dynamic Kinetic Resolution[a]



[a] **9a** (R = C_6H_5, X = OCH_3). **9d** (R = CH_3, X = $N(CH_3)COC_6H_5$). The catalyst structure is given in an abbreviated form.

C_6H_5 is placed antiperiplanar to the hydridic RuH, resulting in predominantly *anti*-**10a**.[31] The reaction of **9b** (R = CH_3, X = OCH_3) gave a 57:43 syn/anti mixture of **10b**, because the size difference between CH_3 (R) and OCH_3 (X) is small. These observations suggest that the electronegativity of the α-substituents of **9** is not significant for the diastereocontrol, which frequently regulates diastereoselectivity of carbonyl nucleophilic additions.[30,32] The hydrogenation of **9c** (R = CH_3, X = NHCO-*t*-C_4H_9) and **9d** (R = CH_3, X = $N(CH_3)COC_6H_5$) exclusively affords the syn alcohols (see Table 4), because the bulky amido groups (X) dominantly occupy the antiperiplanar position at the TS $\mathbf{15}_{syn}$.

Conclusions

The sense and degree of enantioselectivity in asymmetric hydrogenation of acetophenone catalyzed by (*S*)-TolBINAP/chiral 1,2-diamine−Ru(II) complexes is highly dependent on the *N*-substituents of diamine ligands. The hydrogenation promoted by a Ru catalyst bearing (*S*)-TolBINAP and (*S*,*S*)-DPEN without *N*-substituent affords (*R*)-1-phenylethanol in 82% ee, while the reaction with the catalyst coordinated by (*S*)-TolBINAP and *N*,*N*-dimethyl-substituted (*R*)-DMAPEN results in the *S* alcohol in 91% ee. The mode of enantioselection is interpreted by using transition state models based on the X-ray structure of the catalyst precursor—that is, the enantioface of ketone is differentiated by means of the chiral environment of TolBINAP, while chiral 1,2-diamine ligands determine the reaction site of the catalyst and the direction of the ketonic substrate.

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(31) Reduction of **9a** with potassium tri-*sec*-butylborohydride (K-Selectride), a bulky and nonchelation reducing agent, in ether at −78 °C predominantly afforded *anti*-**10a**. See: Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021–2024.

(32) See for example: Davis, A. P. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Shaumann, E., Eds.; Thieme: Stuttgart, Germany, 1995; Vol. E21d, pp 3988−4048.

The (*S*)-TolBINAP/(*R*)-DMAPEN−Ru(II) catalyst performs asymmetric hydrogenation of simple alkyl aryl ketones and arylglyoxal dialkyl acetals, a kind of functionalized ketones, to afford the chiral secondary alcohols in >99% ee in the best cases with a consistent sense of enantioselection. The reaction of the cyclohexyl methyl ketone, an aliphatic ketone, gives the alcohol in only 47% ee. These results suggest that the catalyst differentiates two carbonyl substituents mainly by their shape.

The (*S*)-TolBINAP/(*R*)-DMAPEN−Ru(II) catalyst is also effective for hydrogenation of racemic α-monoheterosubstituted ketones through dynamic kinetic resolution. Benzoin methyl ether is hydrogenated to give the *anti*-alcohol in 98% ee predominantly, while the reaction of α-amidopropiophenones affords the *syn*-alcohols in >98% ee exclusively. The stereoselective outcome is explained by using Felkin−Anh-type models, in which the bulkiest α-substituent locates the antiperiplanar position to the hydridic RuH. Electronegativity of the substituents is not the decisive factor.

Experimental Section

General Procedure for Hydrogenation of Acetophenone (1a) Catalyzed by the $RuCl_2$[(*S*)-tolbinap](dmf)$_n$-Chiral 1,2-Diamine−*t*-C_4H_9OK Combined System. Hydrogenation with the (*S*)-TolBINAP-(*R*)-DMAPEN [(*R*)-**4a**]−*t*-C_4H_9OK system is shown as a typical reaction procedure.[3] Solid $RuCl_2$[(*S*)-tolbinap](dmf)$_n$ (9.4 mg, 0.01 mmol)[18] and (*R*)-**4a** (2.1 mg, 0.01 mmol) were placed in a 100-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, a pressure gauge, and a gas inlet tube attached to a hydrogen source. Air present in the autoclave was replaced by argon. 2-Propanol (3 mL) and a 0.5 M *t*-C_4H_9OK solution in 2-propanol (40 μL, 0.02 mmol) were added to the autoclave under a stream of argon. The mixture was degassed by three cycles of vacuum-filling with argon. 2-Propanol (4 mL) and **1a** (691 mg, 5.0 mmol), which had been degassed by 3 freeze−thaw cycles, were added to the autoclave. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen. Hydrogen was initially introduced into the autoclave at a pressure of 4 atm, before being reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated ten times, the vessel was pressurized to 8 atm. The reaction mixture was vigorously stirred at 25 °C for 1 h. The yield and ee of (*S*)-1-phenylethanol [(*S*)-**2a**] determined by chiral GC analysis were >99% and 91%, respectively. Column, CHIRASIL DEX-CB, df = 0.25 μm, 0.32 mm i.d. × 25 m; carrier gas, helium (60 kPa); column temp, 110 °C, 14 min hold, heating to 180 °C at a rate of 10 deg min^{-1}; detection, FID; retention time (t_R) of (*S*)-**2a**, 12.99 min (95.5%); t_R of (*R*)-**2a**, 12.04 min (4.5%).

Preparation and Physical Data of $RuCl_2$[(*S*)-tolbinap][(*R*)-4a] [(*S,R*)-6]. [$RuCl_2(\eta^6$-benzene)]$_2$ (30.7 mg, 61.4 μmol) and (*S*)-TolBINAP (83.3 mg, 123 μmol) were placed in a 20-mL Schlenk flask equipped with a Teflon-coated magnetic stirring bar, and air present in the flask was replaced with argon. DMF (2 mL), which had been degassed by 3 freeze−thaw cycles, was added to the flask. The mixture was then heated at 100 °C for 20 min with stirring to give a reddish brown solution.[18] After the solution was cooled to 25 °C, a solution of (*R*)-**4a** (20.2 mg, 123 μmol) in DMF (2 mL) was added and the mixture was stirred for 3 h. DMF was removed under reduced pressure (1 mmHg) at 25 °C, and then at 40 °C. The residue was washed with hexane (1 mL), dissolved in degassed hexane−dichloromethane (20:1; approximately 10 mL), and filtered. This operation (dissolving−filtration) was repeated once more. The filtrate was concentrated under reduced pressure. The resulting orange-yellow powder was dried under reduced pressure to give (*S,R*)-**6** (107 mg, 86% yield). Decomposing point (dec) 174.1 °C. IR (KBr-disk) 3431, 2919, 2864, 1498, 1088, 805 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.78 (s, 3H), 1.8−1.9 (br m, 1H), 1.88 (s, 3H), 2.19 (s, 3H), 2.35 (s, 3H), 2.59 (s, 3H), 2.6−2.7 (br d, 1H), 2.95 (br t, 1H), 3.49 (br t, 1H), 4.44 (br t, 1H), 6.0−8.5 (m, 28H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 36.6 (d, J = 38.5 Hz), 51.4 (d, J = 38.5 Hz). HRMS (FD$^+$) m/z 1014.2328 (M$^+$), calcd for $C_{58}H_{56}{}^{35}Cl_2N_2P_2{}^{102}Ru$ 1014.2339. The data for the single-crystal X-ray analysis are listed in the Supporting Information (CIF file). Because (*S,R*)-**6** is fairly air- and moisture-stable, it can be stored in ordinary vials, preferably under an argon atmosphere.

General Procedure for Asymmetric Hydrogenation with the Preformed Complex (*S,R*)-6. The hydrogenation of phenylglyoxal diethylacetal (**7a**) (S/C = 2000) is described as a typical reaction procedure. Solid (*S,R*)-**6** (1.4 mg, 1.4 μmol) and *t*-C_4H_9OK (13.0 mg, 0.116 mmol) were placed in a 100-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, a pressure gauge, and a gas inlet tube attached to a hydrogen source. Air present in the autoclave was replaced by argon. A solution of **7a** (579.7 mg, 2.78 mmol) in 2-propanol (4 mL), which had been degassed by 3 freeze−thaw cycles, was added to the autoclave under a stream of argon. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen. Hydrogen was initially introduced into the autoclave at a pressure of 4 atm, before being reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated ten times, the vessel was pressurized to 8 atm. The reaction mixture was vigorously stirred at 30 °C. After 18 h of stirring and careful venting of the hydrogen gas, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography giving (*R*)-2,2-diethoxy-1-phenylethanol [(*R*)-**8a**] (colorless oil, 556.5 mg, 95% yield, 96% ee). The enantiomeric excess of **8a** was determined by HPLC analysis. Column, CHIRALCEL OD-H; eluent, hexane:2-propanol = 98:2; flow, 0.5 mL min^{-1}; column temp, 40 °C; retention time (t_R) of (*S*)-**8a**, 14.3 min (2%); t_R of (*R*)-**8a**, 15.5 min (98%). $[\alpha]^{25}_D$ −18.6 (*c* 1.09, $CHCl_3$) (lit.[33] $[\alpha]^{23}_D$ +19.2 (*c* 5.11, $CHCl_3$), 96% ee (*S*)). IR (KBr, neat) 3464, 2977, 2896, 1454, 1120, 1063, 762, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (distorted t, 3H, J = 7 Hz), 1.25 (distorted t, 3H, J = 7 Hz), 2.76 (d, 1H, J = 2.2 Hz), 3.19−3.27 (m, 1H), 3.51−3.63 (m, 2H), 3.78−3.85 (m, 1H), 4.38 (d, 1H, J = 6.6 Hz), 4.59 (br dd, 1H), 7.27−7.36 (m, 3H), 7.42−7.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 15.2, 63.5, 64.5, 74.6, 105.9, 127.1, 127.7, 128.0, 139.5. HRMS(ESI$^+$), m/z (M + Na$^+$) calcd 233.1154, obsd 233.1160. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.18; H, 8.57.

Reaction Conditions of Asymmetric Hydrogenation and Analytical Data of Products. Hydrogenation of 1-(*tert*-Butoxycarbonyl)-4-(4-fluorobenzoyl)piperidine (1f). Conditions: (*S,R*)-**6** (3.1 mg, 3.1 μmol), **1f** (401.8 mg, 1.31 mmol), *t*-C_4H_9OK (1 M in *t*-C_4H_9OH, 0.10 mL, 0.10 mmol), 2-propanol (5 mL), 8 atm H_2, 30 °C, 7 h. (*S*)-1-(*tert*-Butoxycarbonyl)-4-(4-fluorobenzylhydroxymethyl)piperidine [(*S*)-**2f**]: 396.3 mg, 98% yield, >99% ee. The enantiomeric excess of **2f** was determined after conversion to the MTPA ester (the minor isomer was not observed by ^{1}H and ^{19}F NMR). Mp 131−132 °C (hexane). $[\alpha]^{26}_D$ −5.8 (*c* 0.69, $CHCl_3$). IR (KBr-disk) 3426, 2985, 2950, 2858, 1658, 1432, 1214, 1161, 849 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.03−1.31 (m, 3H), 1.44 (s, 9H), 1.63−1.76 (m, 1H), 1.90−1.98 (br m, 2H), 2.53−2.70 (m, 2H), 4.03−4.17 (br m, 2H), 4.37 (dd, 1H, J = 7.3, 1.7 Hz), 7.00−7.06 (m, 2H), 7.24−7.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 28.3, 43−44 (br), 43.5, 77.6, 79.3, 115.1 (J_{C-F} = 21.5 Hz), 128.1 (J_{C-F} = 8.3 Hz), 138.8 (J_{C-F} = 3.3 Hz), 154.7, 162.1 (J_{C-F} = 245.6 Hz). HRMS(EI$^+$), m/z (M$^+$) calcd 309.1740, obsd 309.1736. Anal. Calcd for $C_{17}H_{24}FNO_3$: C, 66.00; H, 7.82; N, 4.53. Found: C, 65.86; H, 7.87; N, 4.53.

Hydrogenation of 2,2-Diethoxy-2′-methylacetophenone (7c). Conditions: (*S,R*)-**6** (1.7 mg, 1.7 μmol), **7c** (398.6 mg, 1.79 mmol), *t*-C_4H_9OK (10.6 mg, 0.0945 mmol), 2-propanol (4 mL), 8 atm H_2, 30 °C, 18 h. (*R*)-2,2-Diethoxy-1-(4-methylphenyl)ethanol [(*R*)-**8c**]:

(33) (a) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1994**, *5*, 1147–1150. (b) Cho, B. T.; Chun, Y. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2095–2100.

386.3 mg, 96% yield, 92% ee. The enantiomeric excess of **8c** was determined by HPLC analysis. Column, CHIRALCEL OB-H; eluent, hexane:2-propanol = 98:2; flow, 0.5 mL min^{-1}; column temp, 40 °C; t_R of (*R*)-**8c**, 11.3 min (96%); t_R of (*S*)-**8c**, 14.0 min (4%). $[\alpha]^{28}_D$ −38.3 (*c* 1.05, $CHCl_3$). IR (NaCl, neat) 3465, 2976, 2929, 1372, 1120, 1065, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, 3H, *J* = 7.0 Hz), 1.27 (t, 3H, *J* = 7.0 Hz), 2.39 (s, 3H), 2.70 (d, 1H, *J* = 2.2 Hz), 3.12−3.20 (m, 1H), 3.52−3.59 (m, 2H), 3.80−3.87 (m, 1H), 4.42 (d, 1H, *J* = 6.6 Hz), 4.89 (dd, 1H, *J* = 6.6, 2.2 Hz), 7.12−7.23 (m, 3H), 7.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 15.3, 19.7, 63.8, 65.2, 70.7, 106.9, 125.9, 126.5, 127.5, 130.1, 136.5, 137.9. HRMS(EI^+), *m*/*z* ($M + Na^+$) calcd 247.1310, obsd 247.1300. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.15; H, 9.34.

Hydrogenation of 2,2-Diethoxy-4′-methylacetophenone (7d). Conditions: (*S*,*R*)-**6** (1.6 mg, 1.6 μmol), **7d** (357.9 mg, 1.61 mmol), *t*-C_4H_9OK (10.4 mg, 0.0927 mmol), 2-propanol (4 mL), 8 atm H_2, 30 °C, 4 h. (*R*)-2,2-Diethoxy-1-(4-methylphenyl)ethanol [(*R*)-**8d**]: 343.7 mg, 95% yield, 96% ee. The enantiomeric excess of **8d** was determined by HPLC analysis. Column, CHIRALCEL OD-H; eluent, hexane:2-propanol = 98:2; flow, 0.5 mL min^{-1}; column temp, 40 °C; t_R of (*S*)-**8d**, 13.9 min (2%); t_R of (*R*)-**8d**, 14.9 min (98%). $[\alpha]^{28}_D$ −19.0 (*c* 0.922, $CHCl_3$). IR (NaCl, neat) 3454, 2976, 2890, 1517, 1120, 1065, 818 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 6.6 Hz), 2.34 (s, 3H), 2.71 (d, 1H, *J* = 2.2 Hz), 3.21−3.29 (m, 1H), 3.51−3.62 (m, 2H), 3.77−3.85 (m, 1H), 4.37 (d, 1H, *J* = 6.6 Hz), 4.56 (dd, 1H, *J* = 6.6, 2.2 Hz), 7.15 (d, 2H, *J* = 8.1 Hz), 7.31 (d, 2H, *J* = 8.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 15.2, 21.1, 63.5, 64.3, 74.4, 105.9, 127.0, 128.7 (overlapping), 136.5, 137.3. HRMS(EI^+), *m*/*z* (M^+) calcd 224.1412, obsd 224.1413. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.23; H, 9.12.

Hydrogenation of 2,2-Diethoxy-4′-methoxyacetophenone (7e). Conditions: (*S*,*R*)-**6** (2.2 mg, 2.2 μmol), **7e** (562.8 mg, 2.36 mmol), *t*-C_4H_9OK (11.5 mg, 0.102 mmol), 2-propanol (5 mL), 8 atm H_2, 30 °C, 5 h. (*R*)-2,2-Diethoxy-1-(4-methoxyphenyl)ethanol [(*R*)-**8e**]: 546.6 mg, 96% yield, 98% ee. The enantiomeric excess of **8e** was determined by HPLC analysis. Column, CHIRALCEL OD-H; eluent, hexane:2-propanol = 98:2; flow, 0.5 mL min^{-1}; column temp, 40 °C; t_R of (*S*)-**8e**, 21.1 min (1%); t_R of (*R*)-**8e**, 24.5 min (99%). $[\alpha]^{26}_D$ −16.9 (*c* 1.05, $CHCl_3$). IR (KBr, neat) 3475, 2976, 2898, 1614, 1515, 1250, 1119, 1065, 1034, 831 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (distorted t, 3H, *J* = 7 Hz), 1.26 (distorted t, 3H, *J* = 7 Hz), 2.73 (br s, 1H), 3.20−3.26 (m, 1H), 3.51−3.61 (m, 2H), 3.77−3.85 (m, 1H), 3.81 (s, 3H), 4.35 (d, 1H, *J* = 6.6 Hz), 4.53 (br d, 1H), 6.88 (m, 2H), 7.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 15.3, 55.1, 63.5, 64.4, 74.2, 106.0, 113.4, 128.3, 131.6, 159.1. HRMS(EI^+), *m*/*z* (M^+) calcd 240.1361, obsd 240.1379. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.96; H, 8.39. Found: C, 64.49; H, 8.07.

Hydrogenation of 4′-Chloro-2,2-diethoxyacetophenone (7f). Conditions: (*S*,*R*)-**6** (1.2 mg, 1.2 μmol), **7f** (323.0 mg, 1.33 mmol), *t*-C_4H_9OK (10.6 mg, 0.0945 mmol), 2-propanol (4 mL), 8 atm H_2, 30 °C, 4 h. (*R*)-1-(4-Chlorophenyl)-2,2-diethoxyethanol [(*R*)-**8f**]: 307.6 mg, 95% yield, 92% ee. The enantiomeric excess of **8f** was determined by HPLC analysis. Column, CHIRALCEL OB-H; eluent, hexane:2-propanol = 98:2; flow, 0.5 mL min^{-1}; column temp, 40 °C; t_R of (*R*)-**8f**, 12.3 min (96%); t_R of (*S*)-**8f**, 13.1 min (4%). $[\alpha]^{27}_D$ −9.7 (*c* 1.07, $CHCl_3$). IR (KBr, neat) 3460, 2977, 2896, 1492, 1120, 1065, 1014, 830 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 7.0 Hz), 2.77 (d, 1H, *J* = 2.2 Hz), 3.22−3.29 (m, 1H), 3.52−3.65 (m, 2H), 3.77−3.85 (m, 1H), 4.32 (d, 1H, *J* = 6.2 Hz), 4.56 (dd, 1H, *J* = 6.2, 2.2 Hz), 7.30−7.33 (m, 2H), 7.36−7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 15.3, 63.7, 64.7, 74.0, 105.8, 128.2, 128.5, 133.4, 138.0. HRMS(EI^+), *m*/*z* ($M + Na^+$ (^{35}Cl)) calcd 267.0763, obsd 267.0771. Anal. Calcd for $C_{12}H_{17}O_3Cl$: C, 58.90; H, 7.00. Found: C, 58.63; H, 6.76.

Hydrogenation of 2,2-Diethoxy-2′-acetonaphthone (7g). Conditions: (*S*,*R*)-**6** (1.0 mg, 1.0 μmol), **7g** (239.9 mg, 0.929 mmol), *t*-C_4H_9OK (4.4 mg, 0.039 mmol), 2-propanol (3 mL), 8 atm H_2, 30 °C, 24 h. (*R*)-2,2-Diethoxy-1-(2′-naphthyl)ethanol [(*R*)-**8g**]: 218.9 mg, 91% yield, 97% ee. The enantiomeric excess of **8g** was determined by HPLC analysis. Column, SUMICHIRAL OA-4400; eluent, hexane:2-propanol = 95:5; flow, 0.5 mL min^{-1}; column temp, 40 °C; t_R of (*R*)-**8g**, 23.4 min (98.7%); t_R of (*S*)-**8g**, 26.2 min (1.3%). $[\alpha]^{24}_D$ −209.8 (*c* 1.01, $CHCl_3$). IR (NaCl, neat) 3457, 2976, 2895, 1370, 1122, 1065, 1014, 820, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, 3H, *J* = 7.0 Hz), 1.28 (t, 3H, *J* = 7.0 Hz), 3.03 (br s, 1H), 3.19−3.27 (m, 1H), 3.54−3.64 (m, 2H), 3.80−3.88 (m, 1H), 4.49 (d, 1H, *J* = 6.4 Hz), 4.79 (br dd, 1H), 7.46−7.51 (m, 2H), 7.58 (dd, 1H, *J* = 8.5, 1.4 Hz), 7.83−7.87 (m, 3H), 7.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 15.2, 63.5, 64.5, 74.7, 105.9, 125.1, 125.7, 125.8, 126.0, 127.6, 128.0, 133.0, 133.1, 137.0. HRMS(EI^+), *m*/*z* (M^+) calcd 260.1412, obsd 260.1414. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.63; H, 7.78.

Hydrogenation of 2-Methoxy-1,2-diphenyl-1-ethanone (9a). Conditions: (*S*,*R*)-**6** (1.2 mg, 1.2 μmol), **9a** (268.2 mg, 1.19 mmol), *t*-C_4H_9OK (11.3 mg, 0.101 mmol), 2-propanol (3 mL), 8 atm H_2, 30 °C, 18 h. (1*R*,2*S*)-2-Methoxy-1,2-diphenylethanol [(1*R*,2*S*)-**10a**]: 257.7 mg, 95% yield (syn:anti = 97:3), 98% ee. The enantiomeric excess of (1*R**,2*S**)-**10a** (anti) was determined by HPLC analysis. Column, CHIRALCEL OD-H; eluent, hexane:2-propanol = 98:2; flow, 0.5 mL min^{-1}; column temp, 40 °C; t_R of (1*S*,2*R*)-**10a**, 27.0 min (1%); t_R of (1*R*,2*S*)-**10a**, 33.1 min (99%). $[\alpha]^{23}_D$ +17.9 (*c* 0.939, $CHCl_3$), (lit.[31] $[\alpha]_D$ +23.4 (*c* 1.6, $CHCl_3$), 1*R*,2*S* product). Analytical data are shown in the Supporting Information.

Hydrogenation of 2-Pivaloylamino-1-phenyl-1-propanone (9c). Conditions: (*S*,*R*)-**6** (1.3 mg, 1.3 μmol), **9c** (279.1 mg, 1.28 mmol), *t*-C_4H_9OK (11.3 mg, 0.101 mmol), 2-propanol (3 mL), 8 atm H_2, 30 °C, 64 h. (1*R*,2*R*)-2-Pivaloylamino-1-phenylethanol [(1*R*,2*R*)-**10c**]: 256.2 mg, 88% yield (syn:anti = 96:4), 99% ee. The enantiomeric excess of (1*R**,2*R**)-**10c** (syn) was determined by HPLC analysis. Column, CHIRALCEL OD-H; eluent, hexane:2-propanol = 90:10; flow, 0.5 mL min^{-1}; column temp, 40 °C; t_R of (1*S*,2*S*)-**10c**, 11.5 min (0.6%); t_R of (1*R*,2*R*)-**10c**, 14.0 min (99.4%). Mp 106−107 °C (hexane), $[\alpha]^{22}_D$ +12.3 (*c* 1.34, ethanol). IR (KBr-disk) 3422, 2973, 1615, 1450, 1211, 766, 701 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (s, 9H), 1.14 (d, 3H, *J* = 6.9 Hz), 3.82 (br s, 1H), 4.11−4.21 (m, 1H), 4.65 (distorted t, 1H, *J* = 5 Hz), 5.87 (br d, 1H), 7.22−7.36 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.4, 27.4, 38.6, 51.2, 77.3, 126.2, 127.6, 128.2, 141.8, 179.2. HRMS(EI^+), *m*/*z* ($M + H^+$) calcd 236.1650, obsd 236.1649. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.59; H, 9.15; N, 5.92.

Hydrogenation of 2-(*N*-Benzoylmethylamino)-1-phenyl-1-propanone (9d). Conditions: (*S*,*R*)-**6** (1.1 mg, 1.1 μmol), **9d** (144.4 mg, 0.542 mmol), *t*-C_4H_9OK (5.5 mg, 0.049 mmol), 2-propanol (1.5 mL), 8 atm H_2, 30 °C, 9 h. (1*R*,2*R*)-*N*-Benzoylpseudoephedrine [(1*R*,2*R*)-**10d**]: 124.6 mg, 90% yield (syn:anti = >99:1), 98% ee. The enantiomeric excess of (1*R**,2*R**)-**10d** (syn) was determined by HPLC analysis. Column, CHIRALCEL OJ-H; eluent, hexane:ethanol = 96:4; flow, 0.5 mL min^{-1}; column temp, 40 °C; t_R of (1*S*,2*S*)-**10d**, 37.8 min (1%); t_R of (1*R*,2*R*)-**10d**, 49.2 min (99%). Mp 140 °C (hexane−ethyl acetate), $[\alpha]^{19}_D$ −139.7 (*c* 1.22, $CHCl_3$). IR (KBr-disk) 3247, 2977, 1605, 1586, 774, 752, 698 cm^{-1}. ^1H NMR (270 MHz, DMSO-d_6 at 100 °C) δ 0.97 (d, 3H, *J* = 6.6 Hz), 2.89 (s, 3H), 4.58 (br s, 1H), 5.19 (d, 1H, *J* = 3.9 Hz), 7.23−7.39 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.9 (minor), 15.0 (major), 26.8 (major), 32.3 (minor), 53.8 (minor), 59.2 (major), 73.6 (major), 73.7 (minor), 126.5, 126.7, 126.8, 127.2, 127.4, 128.0, 128.1, 128.2, 128.6, 129.0, 137.6 (minor), 137.7 (major), 143.4 (major), 143.5 (minor), 170.6 (minor), 171.4 (major). The terms "major" and "minor" refer to the amide rotamers. Several signals are overlapping. HRMS(EI^+), *m*/*z* ($M + H^+$) calcd 270.1494, obsd 270.1498. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.60; H, 7.08; N, 5.16.

Asymmetric Hydrogenation of 7a under 50 atm of H_2 (S/C = 5000). Solid (*S*,*R*)-**6** (2.1 mg, 0.0021 mmol) and *t*-C_4H_9OK (17.9 mg, 0.160 mmol) were placed in a 50-mL SUS autoclave equipped with a glass inner vessel, a Teflon-coated magnetic stirring bar, a pressure gauge, and a gas inlet tube attached to a hydrogen source. Air present in the autoclave was replaced by argon. A solution of **7a** (2.21 g, 10.6 mmol) in 2-propanol (5 mL), which had been degassed by 3 freeze−thaw cycles, was added to the autoclave under a stream of argon. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen. Hydrogen was initially introduced into the autoclave at a pressure of 20 atm, before being reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated ten times, the vessel was pressurized to 52 atm. The reaction mixture was vigorously stirred at 30 °C. After 22 h of stirring and careful venting of the hydrogen gas, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography giving (*R*)-**8a** (2.20 g, 98% yield, 96% ee). Analytical data are described in the former section.

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Supporting Information Available: Analytical and physical data for alcoholic products **2a**−**e**, **2g**, **8b**, **8h**, **10a**, and **10b**, diamines **3b**, **4**, and **5**, and ketonic substrates **1f**, **7c**, **7d**, and **7g**, and absolute-configuration determinations for alcoholic products **2f**, **8c**−**g**, and **10b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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