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NH/π Attraction: A Role in Asymmetric Hydrogenation of Aromatic Ketones with Binap/1,2-Diamine-Ruthenium(II) Complexes

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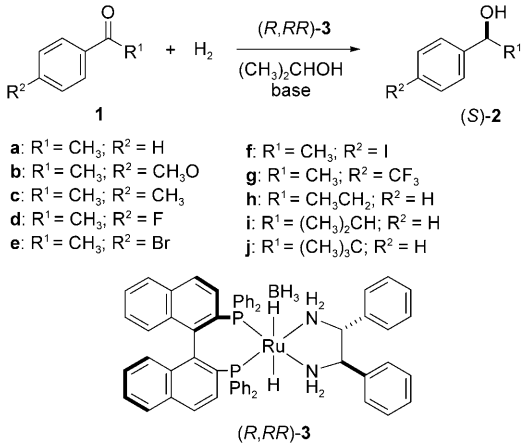
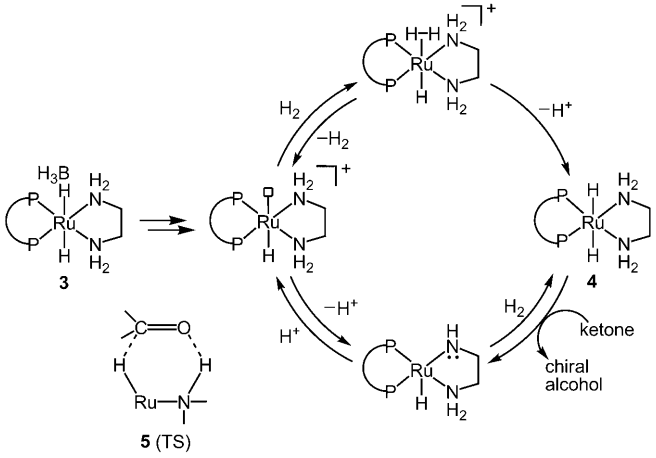
Chiral [RuX_2(diphosphine)(1,2-diamine)] complexes (X = Cl or other anionic ligands) are excellent precatalysts for asymmetric hydrogenation (AH) of simple ketones which lack heteroatom groups capable of interacting with a transition-metal center.[1,2] The presence of NH_2 moieties in the diamine ligand are crucial for obtaining high catalytic activity and enantioselectivity. This method allows for rapid, productive, and C=O-selective AH of a range of aromatic, heteroaromatic, and olefinic ketones in strongly basic to near-neutral 2-propanol.

Acetophenone (**1a**) is hydrogenated to (*S*)-1-phenylethanol [(*S*)-**2a**] in 80% *ee* in 2-propanol containing *trans*-[RuH(BH_4){(*R*)-binap}{(*R,R*)-dpen}] [(*R,RR*)-**3**] (binap = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl; dpen = 1,2-diphenylethylenediamine) with or without base (Scheme 1).[3] As outlined in Scheme 2, the AH reaction proceeds via a metal–ligand bifunctional mechanism[4–6] involving coordinatively saturated *trans*-[RuH_2\{(*R*)-binap\}\{(*R,R*)-dpen\}] [(*R,RR*)-**4**] as a reducing species, in which H/N,N ligands on Ru have a *fac* relationship. Thus reduction of **1a** occurs via the six-membered pericyclic TS **5** using the outer sphere of **4** without C=O/Ru interaction. As illustrated in Scheme 3, each nitrogen atom in the λ-skewed dpen ligand of (*R,RR*)-**4** has axially oriented H_{ax} and equatorially directed H_{eq} atoms that possess different functions. The TS **5** utilizes NH_{ax}/O=C hydrogen bonding. Furthermore, we proposed[4a] that, as shown in favored structure $\mathbf{5}_S$, the enantioselection leading



Scheme 1. Asymmetric hydrogenation of aromatic ketones.



Scheme 2. Metal–ligand bifunctional mechanism for the asymmetric hydrogenation of aromatic ketones catalyzed by binap/dpen-Ru^{II} complex **3**. The structures of binap and dpen are simplified.

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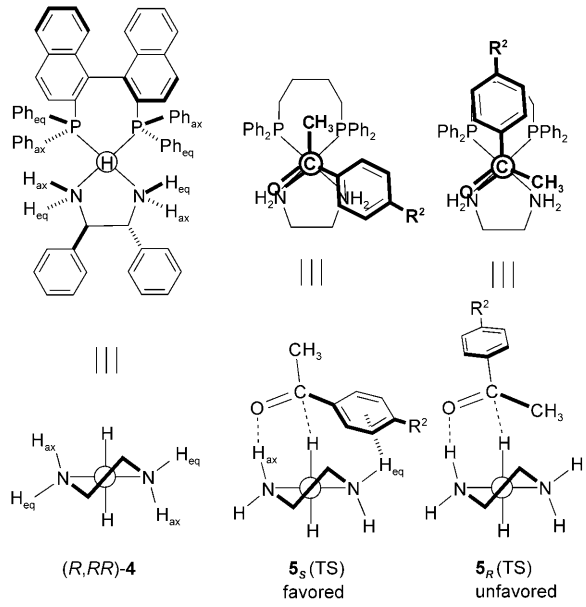
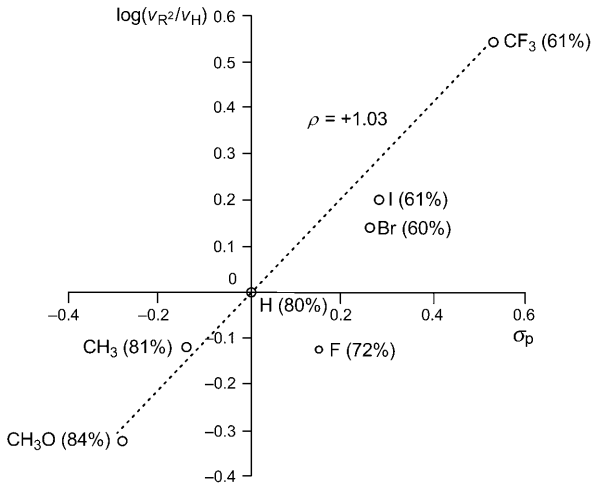


Scheme 3. The RuH_2 species (*R,RR*)-**4** and the diastereomeric transition states **5** (top and side views). The naphthyl rings in binap and the equatorially oriented phenyl substitutents in dpen are omitted for **5**.



Scheme 4. Relative rates and enantioselectivity (% *ee* of alcohols) in the asymmetric hydrogenation of *p*-substituted acetophenones.

to (*S*)-**2a** arises from electrostatic NH_{eq}/π attraction between the other NH_2 unit and the ketone phenyl substituent, in addition to nonbonding repulsion between a *P*-phenyl group in binap and the phenyl or methyl group in **1a**, consistent with the recent theoretical studies.[7] This unique effect is due to the high NH_2 acidity caused by the nitrogen coordination to the Ru center.[4c] Acidic NH_{eq} interacts with certain electron-rich carbon atoms of the phenyl ring in $\mathbf{5}_S$. Herein we present systematic experimental data which support this postulate.

The aromatic ketone **1a** and various *para*-substituted derivatives **1b–g** were subjected to AH catalyzed by (*R,RR*)-**3** with a substrate/catalyst molar ratio (S/C) of 1000 at 4 atm of H_2 in a basic 2-propanol solution (Scheme 1). In order to compare the relative reaction rates under identical conditions, the AH was performed by the use of an equimolar mixture of **1a** and its derivative **1b–g** ([**1a**]=[**1b–g**]=0.4 M each, [(*R,RR*)-**3**]=0.04 mM, [KO-*t*-C_4H_9]=25 mM, V=6 mL, T=30–32 °C). Aliquots were analyzed by chiral GC after 90 min reaction. The results are given in a Hammett plot form against σ_p constants in Scheme 4.[8,9] An increase in hydrogen pressure enhanced the AH rates but did not affect the relative reactivities of the ketones to any great extent.

First, the hydrogenation rate was enhanced by the presence of an electron-accepting group at the *para* position and was decreased by an electron donor. In comparison to *p*-methoxy ketone **1b**, the *p*-trifluoromethyl derivative **1g** was hydrogenated five times faster under the same conditions. This electronic effect is in accord with the nature of TS **5**, through which a hydride is delivered from Ru to the carbonyl carbon atom.[4] The ρ value, +1.03, is much less than the value of +3.06 for the $NaBH_4$ reduction.[10] The pericyclic character of TS **5** involving the $NH_{ax}/O=C$ hydrogen bond reduces the extent of negative-charge development in the ketonic substrate. Since the *S*-generating TS $\mathbf{5}_S$ is further stabilized by NH_{eq}/π interaction, the observed ρ value includes this additional substituent effect. The *p*-fluoro derivative **1d** showed a significant deviation from the Hammett linear relationship. The marked low reactivity would be due to the decreased NH_{eq}/π attraction caused by the electron deficiency at the carbon atom *meta*[7] to the highly electronegative fluorine atom.

The substituent effect on the product *ee* value is to be particularly noted. AH of standard **1a** produced (*S*)-**2a** in 80 % *ee*. In comparison, the *p*-methoxy ketone **1b** afforded a somewhat higher value, (*S*)-**2b** with 84 % *ee*, while **1e–g** possessing an electron-withdrawing substituent and *p*-fluoro derivative **1d** gave much lower *S* selectivity, 60–72 % *ee*. The difference is small but consistent. The tendency in Scheme 4 well reflects the presence of an NH/π attraction that stabilizes TS $\mathbf{5}_S$. Otherwise, an equal level of enantioselectivity would be obtained for **1a–g**, because the *para*-substituted phenyl groups suffer from a similar nonbonding repulsion with nearby atomic assemblies in $\mathbf{5}_S$ and $\mathbf{5}_R$.

Consistent with this view, the binap/1,2-diamine-Ru complexes catalyze highly selective AH of relatively uncongested olefinic alkyl (but not dialkyl) ketones with the same sense of asymmetric induction,[11] where the C=C linkage flanking C=O would favorably interact with NH_{eq} during the reduction. Such reasoning is also in accord with the poor performance of binap-Ru complexes with α-picolylamine (an unsymmetrical NH_2/pyridine hybrid ligand) instead of bis-NH_2 ligands like dpen in the AH of **1a**.[4d,12] Thus, the difference in steric bulk between phenyl and methyl is not sufficient to well differentiate the enantiofaces of **1a** during this AH. This TS stabilizing effect is reminiscent of the AH and asymmetric transfer hydrogenation (ATH) of aromatic ketones catalyzed by a chiral [(η^6-arene)RuX(Ts-dpen)] complex [X=Cl or TfO; Ts-dpen=(*R,R*)- or (*S,S*)-TsNCH-(C_6H_5)CH(C_6H_5)NH_2], in which the enantioface discrimina-

tion results from CH/π interaction between the η^6-arene ligand of the RuH intermediate and the aromatic substituent of the ketones.[13,14] Thus, secondary electrostatic attraction plays an important role in efficient asymmetric reactions.

For reference, we examined steric effects in the AH of phenyl alkyl ketones **1h–j** catalyzed by (*R,RR*)-**3**. As expected, competition experiments using an equimolar mixture of **1a** and these ketones ($[\mathbf{1a}]=[\mathbf{1h–j}]=0.4$ M, $[\mathbf{3}]=0.4$ mM, $[KO\text{-}t\text{-}C_4H_9]=25$ mM, V(2-propanol)$=3$ mL, $P(H_2)=4$ atm, $T=30\,^\circ$C, 40 min) showed a sharp decrease in relative reactivity as a function of the bulkiness of R^1: **1a** (1), **1h** (0.5), **1i** (0.1), and **1j** (0.01). This tendency is in accord with the above argument. However, this result is to be handled with caution, because the *ee* values (>95% conversion) were not straightforward; (*S*)-**2a** in 80% *ee*, (*S*)-**2h** in 87% *ee*, (*S*)-**2i** in 77% *ee*, and (*S*)-**2j** in 77% *ee*.[15]

Experimental Section

Competitive hydrogenation: Equimolar mixtures of acetophenone (**1a**) and a *p*-substituted substrate **1b–g** were used. Hydrogenations were conducted in a glass autoclave equipped with a sampling needle connected to a three-way stop valve as previously described.[4a] Accurately measured masses of (*R,RR*)-**3** and KO-*t*-C_4H_9 were placed into a predried (120 °C) glass autoclave containing a magnetic stirring bar, and this mixture was maintained under high vacuum for at least 5 min prior to purging with argon. Into a predried Schlenk tube were placed accurately measured amounts of **1a** and **1b–g** and 2-propanol solvent such that: $[(R,RR)\text{-}\mathbf{3}]=0.4$ mM; $[\mathbf{1a}]=[\mathbf{1b\text{-}g}]=0.4$ M; $[KO\text{-}t\text{-}C_4H_9]=25$ mM; S/C for both **1a** and **1b–g** $=1000$; $V_T=6$ mL of 2-propanol. The reaction mixture was degassed by three freeze–thaw cycles and was added under Ar to the autoclave. H_2 was introduced under 7 atm pressure with several quick release–fill cycles before being set to 4 atm. Stirring and timing ($t=0$ min) were immediately commenced at 30–32 °C (oil bath). Reaction samples were obtained at specified time intervals, and the extent of substrate consumption and *ee* values of both alcoholic products **2a** and **2b–g** were determined by GC. Correlations between a substrate, log (v_R/v_H) where v is the conversion after 90 min, and σ_p constant of R^2 are given in Scheme 4.

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Keywords: asymmetric catalysis · homogeneous catalysis · hydrogenation · reaction mechanisms · ruthenium

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[3] Enantioselectivity of 80% does not meet with the current standard of organic synthesis. AH of **1a** using a suitably modified binap/diamine-Ru complex with an S/C value of 100000 gives (*S*)-**2a** with > 99% *ee*.[2b]

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[8] The enantiomeric excess (*ee*) values were obtained from a seperate hydrogenation using only **1b–g** (S/C = 2000) under the same conditions (>95% conv.).

[9] Similar results were obtained by the use of *trans*-[$RuCl_2${(*R*)-binap}-{(*R,R*)-dpen}] and KO-*t*-C_4H_9 in 2-propanol.

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[12] [$RuCl_2$(binap)(α-picolylamine)] is an excellent precatalyst for the AH of *tert*-alkyl ketones, where the enantiofaces are differentiated by the difference in steric bulk between the substituents; see: a) T. Ohkuma, C. A. Sandoval, R. Srinivasan, Q. Lin, Y. Wei, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **2005**, *127*, 8288–8289; b) N. Arai, K. Suzuki, S. Sugizaki, H. Sorimachi, T. Ohkuma, *Angew. Chem.* **2008**, *120*, 1794–1797; *Angew. Chem. Int. Ed.* **2008**, *47*, 1770–1773.

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[14] Similar substituent effects on rates and enantioselectivity have been observed in the asymmetric transfer hydrogenation of *para*-substituted benzaldehydes; see: I. Yamada, R. Noyori, *Org. Lett.* **2000**, *2*, 3425–3427.

[15] For **1a**, the methyl group possessing a certain degree of π character might exert a competitive electronic effect in TS **5**. A similar trend,

a lower enantioselectivity for **1a** in comparison to **1h** and other *n*-alkyl phenyl ketones, was seen in binal-H asymmetric reduction. See: R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6709–6716. In addition, unlike for the AH of **1a**, which is known to proceed via **4**, the kinetically active species in other cases remains unidentified. The RuH intermediates formed under AH conditions undergo stereomutation via pentacoordinate species, and the equilibrium ratio of the existing RuH species is variable according to the reaction conditions and even the *substrates*, particularly bulky ones.[4d]

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