Asymmetric Hydrogenation

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Highly Enantioselective Hydrogenation of Aryl Vinyl Ketones to Allylic Alcohols Catalyzed by the Tol-Binap/Dmapen Ruthenium(II) Complex**

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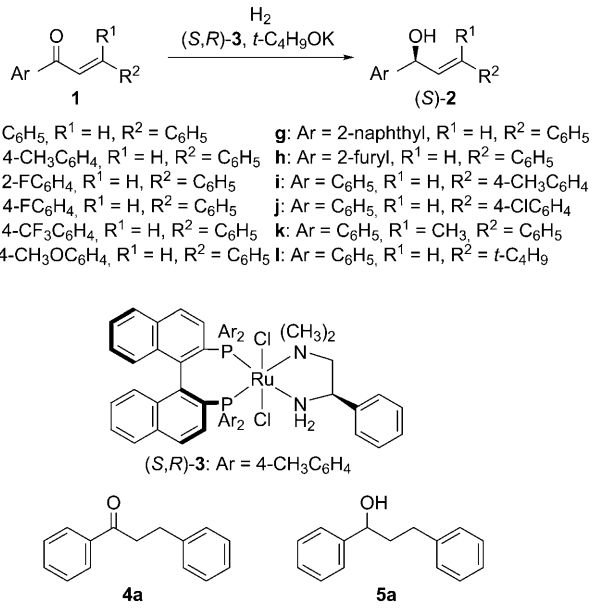
Enantioselective hydrogenation of prochiral ketones (R^1COR^2, $R^1 \neq R^2$) requires distinction between two substituents, R^1 and R^2, connected to the carbonyl group. In the reaction of functionalized ketones, α, β, or γ-hetero-substituted alkyl moieties are accurately discriminated from simple alkyl groups by means of chirally modified transition-metal catalysts.[1] The synthesis of the xyl-binap/daipen Ru^{II} catalyst,[2,3] has made possible the precise differentiation of sp^2-carbon groups (sp^2-CG, including aryl, hetero-aryl, and vinyl groups), from sp^3-carbon groups (sp^3-CG, primary and secondary alkyl groups) in the hydrogenation of simple, unfunctionalized ketones.[4] Tol-binap/α-picolylamine Ru^{II} catalyst[2] effectively discriminates tertiary alkyl groups (sp^3-CG) from both *n*-alkyl (sp^3-CG) and aryl (sp^2-CG) groups.[5] Differentiation of *ortho*-substituted benzene rings (sp^2-CG) from phenyl (sp^2-CG) groups has also been achieved with the xyl-binap/daipen Ru^{II} catalyst.[6] However, accurate distinction between aryl (sp^2-CG) and vinyl (sp^2-CG) groups has to date been a difficult and unrealized target in asymmetric catalysis. In fact, asymmetric hydrogenation of (*E*)-chalcone (**1a**) catalyzed by the xyl-binap/daipen Ru^{II} complex afforded the allylic alcohol in only 45% *ee*.[3,7] Borane reduction catalyzed by chiral oxazaborolidine gave a 66% *ee*.[8,9] The best *ee* value of 75% in the reduction of **1a** was achieved by the use of catecholborane with a chiral gallium catalyst.[10] To our knowledge, even enzymatic reduction has not succeeded in this discrimination.[11] Herein we describe for the first time highly enantioselective hydrogenation of aryl vinyl ketones to chiral allylic alcohols, catalyzed by the tol-binap/dmapen Ru^{II} complex.[2,12]

First, we chose (*E*)-chalcone (**1a**) as a standard substrate. Hydrogenation of **1a** (225.2 mg, 1.1 mmol) in 2-propanol (2.5 mL) with [$RuCl_2$\{(*S*)-tol-binap\}\{(*R*)-dmapen\}] ((*S*,*R*)-**3**; 1.1 mg, 1.1 μmol, substrate/catalyst ratio (S/C) = 1000)[12] and *t*-C_4H_9OK (10 mmol dm^{-3} in 2-propanol, 0.50 mL, 5.0 μmol) at 0 °C under 8 atm of H_2 was completed in 5 h to afford (*S*)-1,3-diphenyl-2-propen-1-ol ((*S*)-**2a**) in 97% *ee* and 99% yield accompanied by 1% of 1,3-diphenyl-1-propanone (**4a**) (Scheme 1 and Table 1, entry 1). No saturated alcohol, 1,3-diphenyl-1-propanol (**5a**), was detected. To our knowledge, this example is the first reduction of **1a** with high carbonyl- and enantioselectivity.[13] When the hydrogenation was conducted at 30 °C, **4a** and **5a** were obtained in 8% and 9% yield, respectively, although the reaction was completed in 1 h (Table 1, entry 2). Interestingly, the separate experiment shown in Scheme 2 revealed that the saturated ketone **4a** was produced by an isomerization of (*S*)-**2a** under hydrogenation conditions (see Supporting Information). The catalytic activity of (*S*,*R*)-**3** with a base is fairly high. Thus, the reaction of **1a** with a substrate:catalyst molar ratio (S/C) of 10000 at 0 °C under 40 atm of H_2 was completed in 3 h to afford (*S*)-**2a** in 97% *ee* and in 99% yield (Table 1, entry 3).



Scheme 1. Asymmetric hydrogenation of aryl vinyl ketones with [$RuCl_2$\{(*S*)-tol-binap\}\{(*R*)-dmapen\}] ((*S*,*R*)-**3**).

Scheme 2 and Table 1, entry 1). No saturated alcohol, 1,3-

The hydrogenation of a series of aryl vinyl ketones (**1**) to the aromatic allylic alcohols (**2**) was achieved in high enantiomeric excess using the chiral ruthenium complex **3** (Scheme 1). The results are summarized in Table 1. The chalcone **1b**, methyl-substituted at the 4′ position (Ar in Scheme 1), was hydrogenated (S/C = 1000, 0 °C, 8 atm H_2) with 98% *ee* (Table 1, entry 4). Hydrogenation of 2′-F-

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[**] This work was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 18350046). Tol-binap = 2,2′-bis(di-4-tolylphosphanyl)-1,1′-binaphthyl. Dmapen = 2-dimethylamino-1-phenylethylamine.

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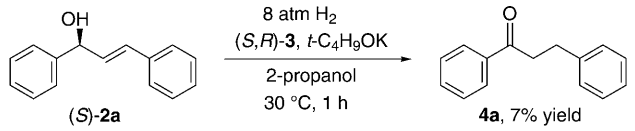
Table 1: Asymmetric hydrogenation of aryl vinyl ketones with [$RuCl_2${(*S*)-tol-binap}{(*R*)-dmapen}] (see Scheme 1).[a]

Entry	**1**	S/C[b] ((*S*,*R*)-**3**)	H_2 [atm]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	**1a**	1000	8	5	99 (1)	97
2[e]	**1a**	1000	8	1	91[f] (8)	96
3	**1a**[g]	10000	40	3	99 (1)	97
4	**1b**	1000	8	4	100 (1)	98
5	**1c**	1000[h]	8	15.5	95 (<1)	97
6	**1d**	1000	8	3	96 (1)	96
7[i]	**1e**	1000	8	2	94 (2)	92
8[j]	**1f**	1000	8	3	96 (2)	95
9[i]	**1g**	1000	8	5	96 (1)	95
10[i]	**1h**	1000[h]	8	8	98 (<1)	92
11	**1i**	1000	8	13	93 (1)	97
12	**1j**	1000	8	5	99 (<1)	97
13	**1k**	1000	50	43	97 (<1)	89
14	**1l**	1000	8	8	86 (<1)[k]	97

[a] Unless otherwise stated, reactions were conducted at 0 °C using 0.5–1.0 mmol of ketone (0.16–0.33 M) in 2-propanol containing (*S*,*R*)-**3** (0.037–0.37 mM) and *t*-C_4H_9OK (1.7 mM). [b] Substrate/catalyst molar ratio. [c] Yield of isolated (*S*)-**2**. Yield of the saturated ketone is stated in parentheses. [d] Data for (*S*)-**2** determined by chiral HPLC analysis or comparison with the literature. [e] Reaction at 30 °C. [f] Contaminated by **5a** (9%). [g] Reaction using 10.8 mmol (2.3 g) of **1a**. [h] One equiv of $P(C_6H_5)_3$ to **3** was added. [i] Reaction in a 2:1 mixture of 2-propanol and DMF. [j] Reaction in a 1:1 mixture of 2-propanol and DMF. [k] 13% of **1l** was recovered.



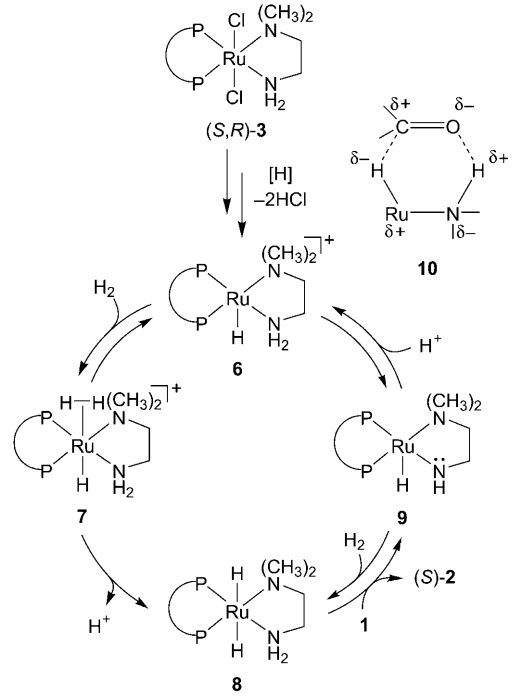
Scheme 2. Isomerization of (*S*)-**2a** to **4a**.

substituted ketone **1c** was relatively slow under the standard conditions (0 °C, 8 atm H_2), and the saturated ketone **4c** and the saturated alcohol **5c** were obtained in 3% and 5% yield, respectively. This problem was solved by an addition of triphenylphosphine (1 equiv to **3**) to the reaction system. The desired (*S*)-**2c** was obtained in 97% *ee* and 95% yield without detectable amounts of the by-products (Table 1, entry 5). Triphenylphosphine is believed to inhibit the coordination of the allylic alcohols **2** to the ruthenium center responsible for the isomerization to ketones **4** depicted in Scheme 2, thus lessening the formation of saturated by-products.

Substrates with electron-withdrawing F and CF_3 at the 4′ position, **1d** and **1e**, were hydrogenated to give the allylic alcohols **2d** in 96% *ee* (96% yield) and **2e** in 92% *ee* (94% yield), respectively (Table 1, entries 6 and 7). The reaction of **1e** was conducted in a 2:1 mixture of 2-propanol and DMF as **1e** has low solubility in 2-propanol. An electron-donating methoxy group at the 4′ position (**1f**) did not affect the reactivity and enantioselectivity, affording **2f** in 95% *ee* and 96% yield (Table 1, entry 8). The 2′-naphthyl enone, **1g**, is also a good substrate for this reaction, affording **2g** in 95% *ee* and 96% yield (Table 1, entry 9). The hydrogenation of 2′-furyl enone, **1h**, resembles that of the 2′-fluorophenyl substrate, **1c**. The allylic alcohol product **2h** was selectively obtained in 92% *ee* and 98% yield in the presence of triphenylphosphine (Table 1, entry 10), whereas, without the additive the reaction also afforded saturated ketone and alcohol side-products in 2% and 5% yields, respectively.[14]

Substituents on the β-phenyl group (R^2 in Scheme 1) had little effect on the reactivity of the enone and the enantioselectivity of the hydrogenation. The reaction of **1i** (R^2 = 4-$CH_3C_6H_4$) and **1j** (R^2 = 4-ClC_6H_4) under the regular conditions gave the allylic alcohols **2i** (97% *ee*, 93% yield) and **2j** (97% *ee*, 99% yield), respectively (Table 1, entries 11 and 12). The β,β-disubstituted enone, **1k**, was a difficult substrate to hydrogenate because of steric hindrance at the β-position. Complete conversion with an S/C of 1000 was achieved after 43 h under 50 atm of H_2, affording **2k** in 89% *ee* (Table 1, entry 13). The *tert*-butyl-substituted enone **1l** was also hydrogenated with an excellent enantioselectivity, while the reactivity was relatively lower (Table 1, entry 14). The reaction of 1-phenyl-2-buten-1-one gave a complex mixture as deprotonation occurs at the allylic position.

A mechanism for the hydrogenation of **1** using (*S*,*R*)-**3** in basified 2-propanol (based on our previous mechanistic study of the hydrogenation of alkyl aryl ketones catalyzed by a tol-binap/dpen Ru^{II} complex)[2,15,16] is proposed in Scheme 3. In this mechanism, the {$RuCl_2$} complex **3** is first converted to a cationic {RuH} species **6** with 2 equivalents of base and a hydride source, hydrogen. Complex **6** coordinates to H_2 to form cationic **7** and subsequent deprotonation with a base affords the active {RuH_2} complex **8**. The ketone **1** is readily reduced by **8**, giving the alcoholic product **2** and the amide complex **9**. Protonation of **9** by the alcoholic solvent regenerates **6**, whereas reaction of **9** with H_2 partially regenerates **8**. The reaction of **8** with **1** proceeds through a pericyclic six-membered transition state (TS) **10**, in which the



Scheme 3. Proposed mechanism of hydrogenation of **1** by (*S*,*R*)-**3** in basified 2-propanol. $\widehat{PP}$ = (*S*)-tol-binap[2]; $\widehat{NH_2N}(CH_3)_2$ = (*R*)-dmapen.[2]

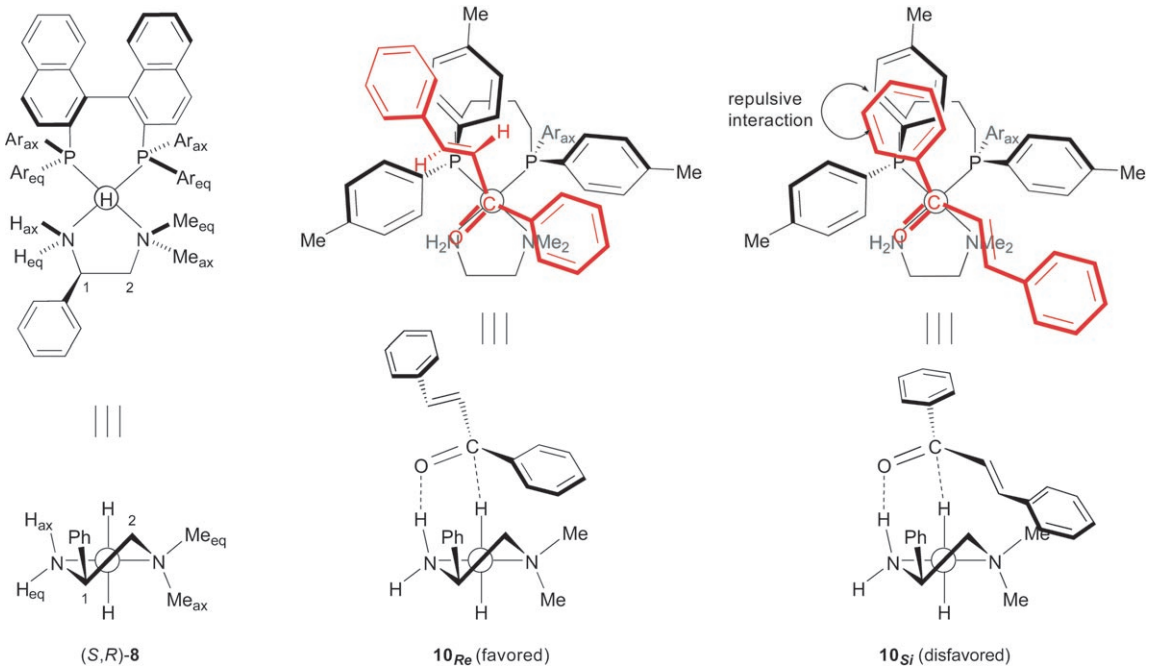


Figure 1. Structure of {RuH_2} species (*S*,*R*)-**8** and diastereomeric transition states in the hydrogenation of **1a**. In the transition states $\mathbf{10}_{Re}$ and $\mathbf{10}_{Si}$, some aromatic groups in the tol-binap and dmapen ligands are omitted for clarity. Ar = 4-$CH_3C_6H_4$; ○ = Ru^{II}.

catalyst $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H^{\delta+}$ quadrupole coordinates to the carbonyl $C^{\delta+}$=$O^{\delta-}$ dipole (see Scheme 3).[15]

Complex (*S*,*R*)-**8** is expected to have a *trans*-RuH_2 geometry owing to the strong *trans* σ-donating property of the hydride (Figure 1).[17,18] The skewed five-membered chelate ring formed by dmapen has two diastereotopic amino protons adjacent to C1. The axially oriented hydrogen (H_{ax}) is more reactive than the equatorial one (H_{eq}), because the smaller dihedral angle of the $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H_{ax}^{\delta+}$ moiety suitably stabilizes TS **10**. Ketone **1a** approaches the catalyst reaction site with the *Re* face (to form TS $\mathbf{10}_{Re}$) or *Si* face (to form TS $\mathbf{10}_{Si}$). TS $\mathbf{10}_{Re}$, which affords the allylic alcohol (*S*)-**2a**, is more favored than $\mathbf{10}_{Si}$ (which forms (*R*)-**2a**), as the "sickle-shape" vinylic group of **1a** fits well with the channel formed by the Ar_{ax}–P–Ar_{eq} (Ar = 4-$CH_3C_6H_4$) structure of tol-binap in $\mathbf{10}_{Re}$, whereas the formation of $\mathbf{10}_{Si}$ leads to a nonbonded repulsive interaction between the phenyl group of **1a** and the Ar_{ax}–P–Ar_{eq} channel.[19] Thus, the chiral environment of the tol-binap/dmapen Ru^{II} catalyst differentiates between aromatic and vinylic groups.

In conclusion, we report herein the first example of highly enantioselective hydrogenation of aryl vinyl ketones to allylic alcohols. Unlike other methods (including enzymatic reductions), the chiral environment of the tol-binap/dmapen Ru^{II} catalyst achieves accurate discrimination between aromatic and vinylic groups by their shape.

Experimental Section

The general procedure for hydrogenation of aryl vinyl ketones is as follows: hydrogenation of **1a** illustrates the typical reaction procedure using standard Schlenk techniques. For full reaction conditions and spectroscopic data, see the Supporting Information.

2a: Ruthenium complex (*S*,*R*)-**3** (1.1 mg, 1.1 μmol) and **1a** (225.2 mg, 1.1 mmol) were placed in a 100 mL glass autoclave equipped with a Teflon-coated magnetic stirring bar. A solution in 2-propanol (3.0 mL) of *t*-C_4H_9OK (1.7 mM, 0.56 mg, 5.0 μmol), which had been degassed by four freeze-thaw cycles, was added to the precooled (ice-bath) autoclave. Hydrogen was introduced into the autoclave at a pressure of 8 atm, and the reaction mixture was vigorously stirred at 0 °C for 5 h. After carefully venting the hydrogen gas, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, giving (*S*)-**2a** (colorless oil, 225.2 mg, 99 % yield, 97 % *ee*), accompanied by **4a** (2.5 mg, 1 % yield). The enantiomeric excess of **2a** and the absolute configuration of the major isomer were determined by HPLC analysis. Column, CHIRALCEL OD-H; eluent, hexane:2-propanol = 9:1; flow, 1.0 mL min^{-1}; column temp, 40 °C; detection, UV 254 nm; t_R ((*S*)-**2a**) 12.8 min (98.5 %); t_R ((*R*)-**2a**) 15.8 min (1.5 %), compare with literature values: t_R = 13.41 min for (*S*)-**2a**, t_R = 17.40 min for (*R*)-**2a**.[20] ^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.01 (br s, 1H, OH), 5.40 (br m, 1H, C*H*OH), 6.39 (dd, 1H, *J* = 15.9, 6.5 Hz, CH(OH)C*H*=CH), 6.70 (d, 1H, *J* = 15.9 Hz, CH(OH)CH=C*H*), 7.21–7.45 ppm (m, 10H, aromatics).

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