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Catalyst-Controlled Diastereoselection in the Hydrogenation of Heterocycloalkyl Ketones

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Abstract: α-Substituted chiral ketones that have small steric and electronic differences around the reaction sites are difficult substrates to reduce with high diastereoselectivity. Metal hydride reduction of 2-(4-benzoylmorpholinyl) phenyl ketone and 3-(1-*tert*-butoxycarbonylpiperidinyl) phenyl ketone using sodium borohydride, zinc borohydride, and potassium tri-*sec*-butylborohydride as reducing agents affords the *syn*- and *anti*-alcohols in a lower than 80:20 ratio. Hydrogenation of these ketones with a catalyst system of $RuCl_2$(BIPHEP)(DMEN) and potassium *tert*-butoxide in 2-propanol results in the *syn*-alcohols with $\geq$ 99:1 selectivity [BIPHEP = 2,2′-bis(diphenylphosphino)biphenyl, DMEN = *N*,*N*-dimethylethylenediamine]. The marked difference in the diastereoselectivity suggests that the stereoselection in this hydrogenation is primarily regulated by the structure of the catalyst's reaction field ("catalyst-controlled diastereoselection") but not the internal stereocontrol of the substrates. This chemistry is applied to the asymmetric hydrogenation through dynamic kinetic resolution with a $RuCl_2$[(*S*)-BINAP][(*R*)-DMAPEN]/potassium *tert*-butoxide catalyst [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, DMAPEN = 2-dimethylamino-1-phenylethylamine]. A series of aryl heterocycloalkyl ketones has been converted to the alcohols in excellent diastereo- and enantioselectivities. The modes of catalyst-controlled diastereoselection and enantioselection are interpreted by using transition-state molecular models. (*S*,*S*)-Reboxetine, a selective norepinephrine uptake inhibitor, was synthesized from one of product alcohols.

Keywords: diastereoselectivity; enantioselectivity; hydrogenation; ketones; reboxetine; ruthenium

Diastereoselective reduction of α-substituted chiral ketones to the 1,2-*syn*- or 1,2-*anti*-alcohols is a fundamental and indispensable reaction in modern organic synthesis.[1] Metal hydride reducing agents have made notable contributions to advance this important class of chemistry. The stereoselective outcome has been explained by using transition-state molecular models, such as the Felkin–Anh model and the chelation-controlled model (Figure 1).[1–3] In both cases the metal hydride reagent is recognized as just a hydride, and it reacts within the region of the substrate molecules. Therefore, the intramolecular stereoinduction principally depends on the substrate structure (substrate control), but not the shape of the metal hydrides (reagent control).[4] High diastereoselectivity in this reaction is achieved only when the substrates have α-substituents (L, M, S, and X) with marked differences in size and/or electronic properties. Thus, we thought that a new conceptual approach is required to develop a general method for the diastereoselective reduction of α-substituted ketones.

We selected heterocycloalkyl ketones **1a** and **1c** as substrates to examine the diastereoselective ability of reducing agents [Eq. (1)]. The small electronic and

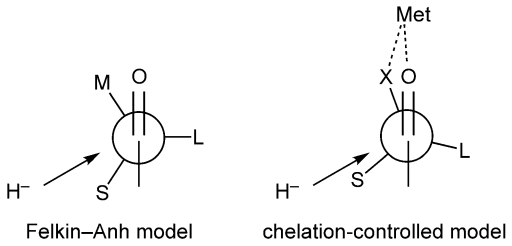
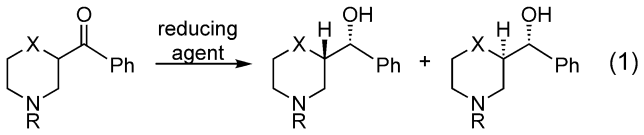


Figure 1. Typical transition-state models in the diastereoselective hydride reduction of α-substituted chiral ketones. L, M, and S = large-, medium-, and small-sized substituents, respectively. X = a group able to coordinate to metal. Met = metal.

Table 1. Diastereoselective metal hydride reduction of ketones **1**.[a]



a: X = O, R = Bz; **c**: X = CH_2, R = Boc

Entry	**1**	Reagent[b]	Conditions	Yield [%][c]	**2**:**3**[d]
1	**a**	$NaBH_4$ (1.0)	MeOH, 0 °C, 2 h	99	60:40
2	**a**	$Zn(BH_4)_2$ (1.2)	THF, −78 °C, 3 h	93	80:20
3	**a**	$KB(s\text{-}Bu)_3H$ (1.2)	THF, −78 °C, 3 h	79	70:30
4	**c**	$NaBH_4$ (1.0)	MeOH, 0 °C, 3 h	99	53:47
5	**c**	$Zn(BH_4)_2$ (1.2)	THF, −78 °C, 3 h	29	59:41
6	**c**	$KB(s\text{-}Bu)_3H$ (1.2)	THF, −78 °C, 3 h	92	49:51

[a] Reactions using 1 mmol of **1**.
[b] The molar equivalent of reagents to **1** is shown in the parentheses.
[c] Isolated yield.
[d] Determined by HPLC analysis.

steric differences between the −X(β)CH_2(γ)− (X = O, CH_2) and −CH_2(β)NR(γ)− (R = Bz, Boc) moieties of the heterocycles makes it difficult to achieve high stereoselectivity. Table 1 lists the results of reduction of **1a** and **1c** with the typical metal hydride reagents, $NaBH_4$,[5] $Zn(BH_4)_2$,[6] and $KB(sec\text{-}C_4H_9)_3H$.[7] In the reduction of **1a**, a **2a** (*syn*)/**3a** (*anti*) mixture in a ratio ranging from 60:40 to 80:20 was obtained (entries 1–3). The relatively high selectivity of 80:20 observed in the reaction with $Zn(BH_4)_2$ may have been caused by the formation of the chelate intermediate. 3-Piperidinyl ketone **1c** was reduced to give an almost 1:1 mixture of **2c** and **3c** (entries 4–6).

We have reported the asymmetric hydrogenation of ketones catalyzed by chiral diphosphine/diamine-Ru complexes.[8] A range of aromatic, hetero-aromatic, cyclic, and unsaturated ketones as well as some kinds of aliphatic ketones is hydrogenated with high reactivity and enantioselectivity. Our recent mechanistic studies on the hydrogenation of ketones revealed that the RuH_2(diphosphine)(diamine) is the active species.[8–10] As shown in Figure 2, this hydrogenation is

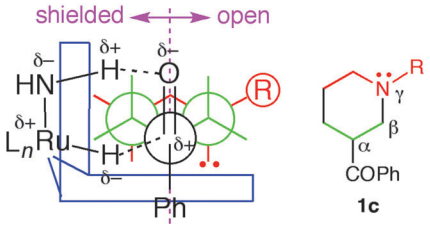
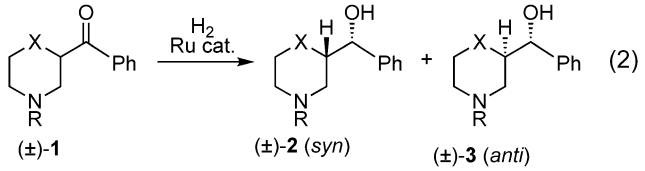


Figure 2. A transition state image in the diastereoselective hydrogenation of **1c** with diphosphine/diamine-Ru(II) catalysts. The diastereotopic environment constructed by the ligands of the catalyst is illustrated with blue lines. R = Boc.

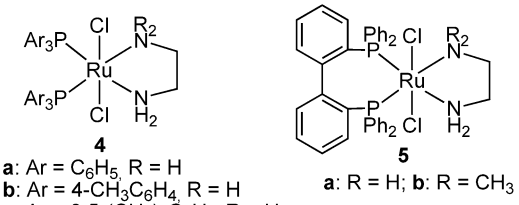
considered to proceed through the transition state (TS), in which the $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H^{\delta+}$ quadrupole of the Ru catalyst interacts with the $C^{\delta+}$=$O^{\delta-}$ dipole of the ketone (the metal-ligand cooperative TS). The carbonyl moiety is placed with a definite direction. The reaction site is surrounded by the phosphine-ligand skeleton, which is schematically illustrated as a blue wedge in this figure. By contrast with the metal hydride reduction, the ketonic substrate is hydrogenated within the field of the catalyst. We assumed that the reaction field could appropriately fix the conformation of **1**, and then the two diastereomeric faces of the carbonyl group are differentiated by the bulkiness around the β and γ positions, but not the α position close to the reaction site. In the hydrogenation of **1c**, the γ nitrogen atom with a bulky substituent (R) is predominantly placed at the position facing the "open" side of the reaction field to afford the *syn*-alcohol **2c** selectively. This is because the other side of the reaction field is "shielded" by the walls of the phosphine ligands. The hydrogenation of **1a** was expected to give **2a** in a same manner.

We selected the hydrogenation of **1a** in order to optimize the catalyst structure so that it would exhibit excellent diastereoselectivity (Table 2).[11] The reaction with $RuCl_2[P(C_6H_5)_3]_2$(EN) (**4a**) at a substrate-to-catalyst molar ratio (S/C) of 100 in $t\text{-}C_4H_9OK$ (30 mM) containing 2-propanol under 10 atm of H_2 at 25 °C afforded **2a** and **3a** in a 94:6 ratio (entry 1). A much higher *syn*-selectivity than that observed in the metal hydride reductions shown in Table 1 was obtained. When the phosphine ligand $P(C_6H_5)_3$ of the Ru complex was replaced with $P(4\text{-}CH_3C_6H_4)_3$ (electron rich; **4b**) or $P[3,5\text{-}(CH_3)_2C_6H_3]_3$ (sterically hindered; **4c**), the stereoselectivity was somewhat de-

Table 2. Diastereoselective hydrogenation of ketones **1**.[a]



a: X = O, R = Bz; **c**: X = CH_2, R = Boc



a: Ar = C_6H_5, R = H
b: Ar = 4-$CH_3C_6H_4$, R = H
c: Ar = 3,5-$(CH_3)_2C_6H_3$, R = H
d: Ar = C_6H_5, R = CH_3

a: R = H; **b**: R = CH_3

Entry	**1**	Ru cat.	S/C[b]	H_2 [atm]	Yield [%][c]	**2**:**3**[d]
1	**a**	**4a**	100	10	97	94:6
2	**a**	**4b**	100	10	96	88:12
3	**a**	**4c**	100	10	96	90:10
4	**a**	**4d**	100	10	94	72:28
5	**a**	**5a**	100	10	96	96:4
6[e]	**a**	**5b**	1000	10	97	>99:1
7[f,g]	**a**	**5b**	5000	50	96	99:1
8[e]	**c**	**5b**	1000	10	100	>99:1
9[f]	**c**	**5b**	5000	50	96	>99:1

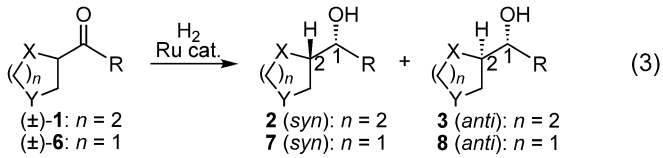
[a] Unless otherwise stated, reactions were conducted at 25 °C using **1** (1.0 mmol, 1.0 M) in 2-propanol containing a Ru complex and *t*-C_4H_9OK (30 mM) for 20 h. Complete conversion was observed in all cases.
[b] Substrate-to-catalyst molar ratio.
[c] Isolated yield.
[d] Determined by HPLC analysis.
[e] 4 mmol of **1** was used.
[f] 15 mmol of **1** was used.
[g] 0.5 M solution of **1** was used.

creased (entries 2 and 3). The combination of $P(C_6H_5)_3$ with *N*,*N*-dimethylethylenediamine (DMEN) instead of the unsubstituted ethylenediamine (EN) significantly decreased the diastereoselectivity to 72:28 (**4d**; entry 4). The higher selectivity of 96:4 was obtained when the biphenyl diphosphine ligand 2,2′-bis(diphenylphosphino)biphenyl (BIPHEP) was coupled with EN (**5a**; entry 5). Finally, the $RuCl_2$(BIPHEP)(DMEN) (**5b**)/*t*-C_4H_9OK catalyst system achieved an excellent *syn*-selectivity of ≥99:1 (entries 6 and 7). The hydrogenations with an S/C of 1000 under 10 atm H_2 and with an S/C of 5000 under 50 atm H_2 were completed within 20 h. The 3-piperidinyl ketone **1c** was also hydrogenated with the **5b**/*t*-C_4H_9OK catalyst to give the *syn*-alcohol **2c** predominantly (entries 8 and 9). Thus, the optimized catalyst system can precisely differentiate the $-CH_2(\beta)NBoc(\gamma)-$ moiety from the $-CH_2(\beta)CH_2(\gamma)-$ as well as the $-O(\beta)CH_2(\gamma)-$ groups of ketones **1**. The marked contrast in stereoselectivity between metal hydride reductions (Table 1) and the hydrogenation catalyzed by the **5b**/*t*-C_4H_9OK system (Table 2, entries 6–9) suggests that the diastereoface selection in this hydrogenation is primarily regulated by the structure around the reaction site of the catalyst ("catalyst-controlled diastereoselection").

We next applied this chemistry to the asymmetric hydrogenation of aryl heterocycloalkyl ketones **1** and **6** through dynamic kinetic resolution (Table 3).[11,12] $RuCl_2$[(*S*)-BINAP][(*R*)-DMAPEN] [(*S*,*R*)-**11**], a chiral analogue of the Ru complex **5b**, was selected as the pre-catalyst.[13,14] When (±)-**1a** (4.45 g, 15 mmol) was hydrogenated with (*S*,*R*)-**11** (S/C = 5000) in *t*-C_4H_9OK containing 2-propanol under 50 atm of H_2 for 20 h, the *syn*-alcohol (1*R*,2*S*)-**2a** (**2a**/**3a** = >99:1) was obtained in 99% *ee* quantitatively (entry 1). Both the diastereoface and enantioface selections of **1a** were successfully performed by the (*S*,*R*)-**11**/*t*-C_4H_9OK catalyst with a rapid stereomutation at the α chiral center of **1a**. Almost perfect stereoselection was achieved in the reaction of **1c** (S/C = 10 000, 10 atm H_2, 20 h). The complete conversion of this reaction with an S/C of 20 000 was achieved under an H_2 pressure of 50 atm without loss of stereoselectivity (entry 3). The reactions of a 3-chlorophenyl ketone **1e** and a thienyl ketone **1f** predominantly afforded the *syn*-alcohols (1*S*,2*S*)-**2e** and (1*S*,2*S*)-**2f**, respectively (entries 4 and 5). The 2-(1-*tert*-butoxycarbonylpiperidinyl) ketone **1g** was hydrogenated with the (*S*,*R*)-**11**/*t*-C_4H_9OK catalyst followed by cyclization to furnish the *anti*-product (1*R*,2*R*)-**10** (**9**/**10** = 1:>99) in 97% *ee* (entry 6). The high level of *anti*-selectivity suggests that the $-NBoc(\beta)CH_2(\gamma)-$ group of **1g** is precisely recognized by this catalyst system in a manner similar to the $-CH_2(\beta)NBoc(\gamma)-$ moiety of **1c**. The *N*-benzoyl analogue **1h** was also converted to the *anti*-alcohol (1*R*,2*R*)-**3h** (**2h**/**3h** = 1:>99) in 96% *ee* without cyclization (entry 7). Interestingly, the hydrogenation of 2-tetrahydrofuranyl ketone **6b** with the (*S*,*R*)-**11**/*t*-C_4H_9OK catalyst exhibited high *syn*- and enantioselectivity, revealing that the catalyst can efficiently discriminate between $-O(\beta)CH_2(\gamma)-$ and $-CH_2(\beta)CH_2(\gamma)-$ groups of the tetrahydrofuran ring (entry 8). In contrast, the reaction of 2-(1-benzoylpyrrolidinyl) ketone **6h** gave the *anti*-alcohol (1*R*,2*R*)-**8h** (**7h**/**8h** = 2:98) in 94% *ee* (entry 10). A 3-pyrrolidinyl ketone **6d** was hydrogenated to afford selectively (1*S*,2*S*)-**7d** (*syn*/*anti* = 75:25) in 98% *ee* (entry 9).

As we described above, the hydrogenation of ketones with the BINAP/diamine-Ru(II) catalyst has revealed that the *trans*-RuH_2(BINAP)(diamine) is the active species in the catalytic cycle.[8–10] Figure 3 illustrates molecular models of *trans*-RuH_2[(*S*)-BINAP]-[(*R*)-DMAPEN] based on an X-ray structure of the $RuCl_2$ precursor (*S*,*R*)-**11** that was previously reported by our group.[14c] The skewed five-membered chelate

Table 3. Stereoselective hydrogenation of ketones *via* dynamic kinetic resolution.[a]



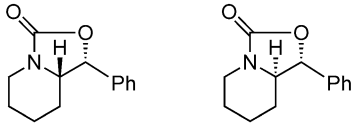
(3)

(±)-**1**: *n* = 2
(±)-**6**: *n* = 1

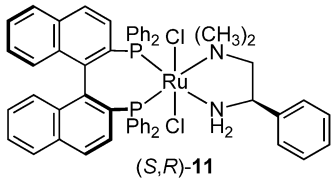
2 (*syn*): *n* = 2
7 (*syn*): *n* = 1

3 (*anti*): *n* = 2
8 (*anti*): *n* = 1

a: X = O, Y = NBz, R = C_6H_5
b: X = O, Y = CH_2, R = C_6H_5
c: X = CH_2, Y = NBoc, R = C_6H_5
d: X = CH_2, Y = NBz, R = C_6H_5
e: X = CH_2, Y = NBoc, R = 3-ClC_6H_4
f: X = CH_2, Y = NBoc, R = 2-thienyl
g: X = NBoc, Y = CH_2, R = C_6H_5
h: X = NBz, Y = CH_2, R = C_6H_5



9 (*syn*) **10** (*anti*)



(*S*,*R*)-**11**

Entry	Ketone	S/C[b]	Yield [%][c]	*syn*:*anti*[d]	*ee* [%][e]
1[f,g]	**1a**	5000	99	>99:1	99
2[h]	**1c**	10000	99	>99:1	>99
3[f,i]	**1c**	20000	97	>99:1	>99
4[g]	**1e**	5000	99	>99:1	99
5[j]	**1f**	500	95	>99:1	99
6	**1g**	1000	100[k]	1:>99[l]	97
7[j,m]	**1h**	200	95	1:>99	96
8	**6b**	500	97	95:5	99[n]
9	**6d**	1000	100	75:25	98[n]
10[j,o]	**6h**	200	100	2:98	94

[a] Unless otherwise stated, reactions were conducted under 10 atm of H_2 at 25 °C using ketone (3–4 mmol, 1.0 M) in 2-propanol containing (*S*,*R*)-**11** and *t*-C_4H_9OK (30 mM) for 20 h. Complete conversion was observed in all cases.
[b] Substrate-to-catalyst molar ratio.
[c] Isolated yield.
[d] Determined by HPLC analysis.
[e] Data of the major diastereomer. Determined by chiral GC or HPLC analysis.
[f] Under 50 atm of H_2.
[g] 15 mmol of **1** was used.
[h] 30 mmol of **1c** was used.
[i] 40 mmol of **1c** was used.
[j] 0.5 M solution of ketone was used.
[k] Yield of cyclized products **9** and **10**.
[l] Ratio of **9** and **10**.
[m] Reaction in 2-propanol:CH_2Cl_2 = 5:1.
[n] The *ee* values of **8b** and **8d** (*anti*-isomers) were both 88%.
[o] Reaction in 2-propanol:CH_2Cl_2 = 6:1.

ring with the (*R*)-DMAPEN has two diastereotopic amino protons, H_{ax} and H_{eq}. The torsion angle of the $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H_{ax}{}^{\delta+}$ structure is much smaller than that of the $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H_{eq}{}^{\delta+}$ moiety. The hydrogenation of ketone **1a** proceeds *via* six-membered TS, $\mathbf{TS_A}$, $\mathbf{TS_B}$, or $\mathbf{TS_C}$, in which the $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H_{ax}{}^{\delta+}$ quadrupole of the catalyst interacts with the ketonic $C^{\delta+}$=$O^{\delta-}$ dipole (see also Figure 2). The *C*-benzoyl and *N*-benzoyl groups are placed at the equatorial positions of the morpholine ring with a chair conformation. $\mathbf{TS_A}$, which affords (1*R*,2*S*)-**2a** (*syn*), has the most preferable structure, in which the *N*-benzoylmorpholine group fits well with the "V-shape channel" of BINAP's Ph_{ax}–P–Ph_{eq} moiety, and the planar phenyl ring of **1a** is faced on the amino Me_{eq} group. The *N*-benzoyl group is directed to the outside of the reaction field and has little influence on the formation of this TS. On the other hand, $\mathbf{TS_B}$, which yields (1*R*,2*R*)-**3a** (*anti*), suffers significant steric repulsion between the "wall" of the P–Ph_{ax} and the bulky *N*-benzoyl group directed to inside of the reaction field. $\mathbf{TS_C}$, which gives (1*S*,2*R*)-**2a** or (1*S*,2*S*)-**3a**, is also unfavorable due to destabilization by the notable nonbonded repulsion between the narrow BINAP's V-shape channel and the widely spread phenyl ring of **1a**. Thus, the reaction environment can precisely select the diastereoface of **1a**, **1c**, **1e**, and **1f** just by recognizing the γ-substituent, which is impossible for the metal hydride reductions. Furthermore, the enantioface selection is nearly perfect. The diastereoselection in the reaction of the 2-piperidinyl ketones, **1g** and **1h**, is controlled by recognition of the β-substituent, resulting in the *anti*-products, **3g** and **3h**, exclusively. The mode of enantioselection is the same as that of **1a**.[10] The stereoselective outcome of the hydrogenation of ketones with five-membered heterocyclic rings, **6b**, **6d**, and, **6h**, is rationalized in the same manner as described above. The hydrogenation of **6b** (X = O, Y = CH_2) afforded **7b** (*syn*) and **8b** (*anti*) in a 95:5 ratio, while the reaction of **6h** (X = NBz, Y = CH_2) furnished a 2:98 mixture of **7h** and **8h** (see Table 3, entries 8 and 10). These results suggest that the catalyst can strictly differentiate the size of the X group as NBz > CH_2 > O. The 75:25 diastereomeric ratio for the hydrogenation of **6d** means that discrimination between the β-NBoc moiety and the β-CH_2 group of the 3-pyrrolidinyl ring is possible in the catalytic system (see Table 3, entry 9).

The isolated hydrogenation product (1*R*,2*S*)-**2a** (>99% *ee*) was readily converted to (*S*,*S*)-reboxetine succinate [(1*S*,2*S*)-**13**] (>99% *ee*) in four steps through stereoinversion of the C-1 position (Scheme 1).[15] (*S*,*S*)-Reboxetine is the active enantiomer of racemic reboxetine, a selective norepinephrine uptake inhibitor.[16] The stereoselective hydrogenation of **1a** provides one of the most efficient and practical procedures for the synthesis of this important compound. (1*R*,2*R*)-**2e** is also a useful synthetic intermediate of a potent anti-hypertensive agent.[17]

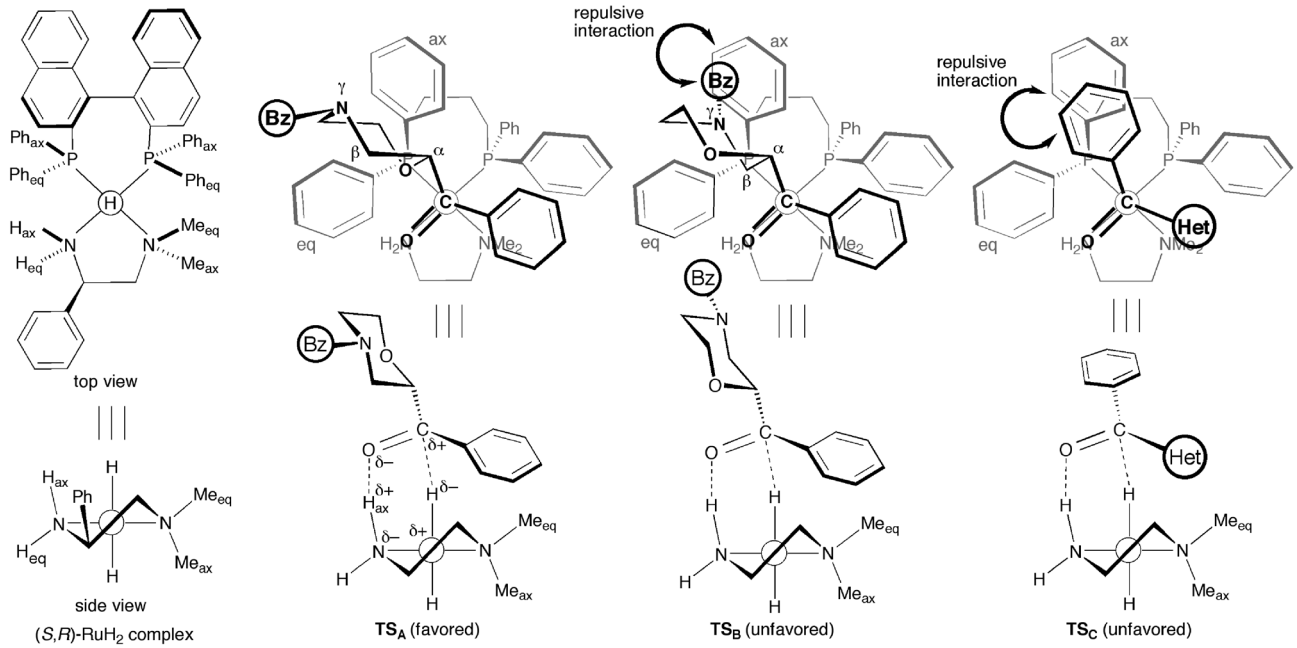
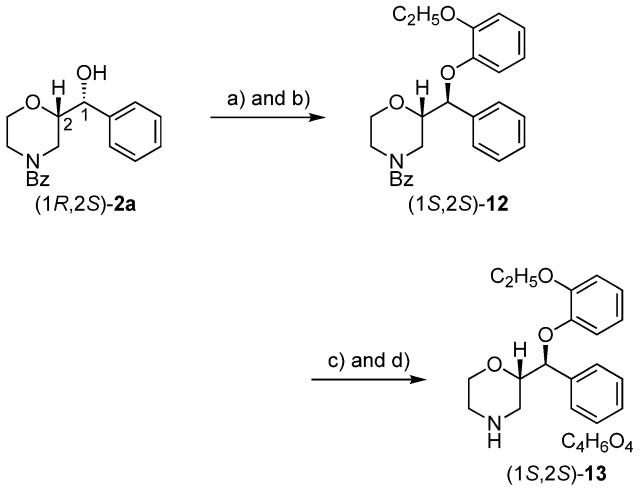


Figure 3. Molecular models of the (*S*,*R*)-RuH_2 complex (○ = Ru) derived from **11** and diastereomeric TSs in the hydrogenation of (±)-**1a** through dynamic kinetic resolution. The structures are simplified for clarity. Het = 2-(4-benzoylmorpholinyl).

In summary, the $RuCl_2$(BIPHEP)(DMEN) (**5b**)/*t*-C_4H_9OK catalyst system hydrogenates heterocycloalkyl phenyl ketones **1a** and **1c** in ≥99:1 diastereoselectivity. Reduction of these ketones with typical metal hydrides results in an 80:20 diastereoselectivity in the best case. The contrasting results suggest that the stereoselection in this hydrogenation is primarily regulated by the structure of the catalyst's reaction field ("catalyst-controlled diastereoselection"). This chemistry is applied to the asymmetric hydrogenation *via* dynamic kinetic resolution by using the (*S*)-BINAP/(*R*)-DMAPEN-Ru(II) catalyst. A series of aryl heterocycloalkyl ketones **1** and **6** is converted to the alcohols in excellent diastereo- and enantioselectivities. The modes of catalyst-controlled diastereoselection as well as enantioselection are interpreted by using transition-state molecular models. (*S*,*S*)-Reboxetine, a selective norepinephrine uptake inhibitor, is readily synthesized from the product alcohol (1*R*,2*S*)-**2a**.



Scheme 1. Preparation of (*S*,*S*)-reboxetine succinate [(1*S*,2*S*)-**13**]. *Conditions:* a) CH_3SO_2Cl, $(C_2H_5)_3N$, CH_2Cl_2, 0 °C; b) 2-ethoxyphenol, Cs_2CO_3, dioxane, reflux (83% in two steps); c) DIBAL, toluene, −78 °C; d) succinic acid, 2-propanol, reflux (74% in two steps).

Experimental Section

Typical Procedure for the Asymmetric Hydrogenation of 1c with (*S*,*R*)-11

Ru complex (*S*,*R*)-**11** (1.9 mg, 2 μmol),[14] ketone **1c** (11.57 g, 40 mmol), and 2-propanol (38.8 mL) were placed in a 200-mL SUS autoclave with a stirring propeller. A solution of *t*-C_4H_9OK in 2-propanol (1 M, 1.2 mL, 1.2 mmol) was added to the autoclave, and the contents in the autoclave were degassed. The vessel was pressurized with hydrogen to 50 atm, and the reaction mixture was stirred at 25 °C for 20 h. After carefully venting the hydrogen gas, the solvent was removed under reduced pressure. The diastereomeric ratio was determined to be >99:1 by HPLC analysis of the reaction mixture: GL Science Inertsil ODS-3 column (4.5×250 mm), 40 °C, CH_3CN:H_2O:10% H_3PO_4 = 600 mL:400 mL:1 mL, 1.0 mL min^{-1}, 215 nm, retention time (t_R) of **3c**: 9.6 min, t_R of **2c**: 11.0 min. The residue was purified by silica-gel column chromatography (hexane:ethyl acetate = 2:1 to 1:1) giving

(*S*,*S*)-**2c**; yield: 11.2 g (97%, >99% *ee*). The *ee* value of **2c** was determined by HPLC analysis (CHIRALPAK AD-H column (4.6×250 mm), 20 °C, hexane:EtOH:*i*-PrOH = 97:2:1, 1.0 mL min^{-1}, 215 nm): t_R of (*R*,*R*)-**2c**: 17.3 min (<0.5%), t_R of (*S*,*S*)-**2c**: 24.4 min (>99.5%); $[\alpha]_D^{28}$: −30.0 (*c* = 1.04, methanol). ^{1}H NMR (300 MHz, DMSO-d_6, 140 °C): δ = 1.16–1.46 (m, 3H, including s, 9H at 1.37), 1.54–1.68 (m, 2H), 2.59–2.71 (m, 2H), 3.75–3.84 (m, 1H), 4.01–4.10 (m, 1H), 4.33 (dd, 1H, *J* = 6.7, 4.6 Hz), 4.66 (d, 1H, *J* = 4.6 Hz), 7.18–7.31 (m, 5H). The procedure and physical data of products are described in detail in the Supporting Information.

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