HOKKAIDO UNIVERSITY

Title	Isomerization-Asymmetric Hydrogenation Sequence Converting Racemic beta-Ylidenecycloalkanols into Stereocontrolled beta-Substituted Cycloalkanols Using a Ru Catalytic System with Dual Roles
Author(s)	Arai, Noriyoshi; Okabe, Yuki; Ohkuma, Takeshi
Citation	Advanced synthesis & catalysis, 361(24), 5540-5547 https://doi.org/10.1002/adsc.201901269
Issue Date	2019-12-17
Doc URL	https://hdl.handle.net/2115/79985
Rights	"This is the peer reviewed version of the following article: N. Arai, Y. Okabe, T. Ohkuma, Adv. Synth. Catal. 2019, 361, 5540, which has been published in final form at https://doi.org/10.1002/adsc.201901269. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving."
Type	journal article
File Information	Text(Communication).pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Isomerization–Asymmetric Hydrogenation Sequence Converting Racemic β-Ylidenecycloalkanols into Stereocontrolled β-Substituted Cycloalkanols Using a Ru Catalytic System with Dual Roles

Noriyoshi Arai,[a] Yuki Okabe,[b] and Takeshi Ohkuma[a,]*

[a] Division of Applied Chemistry and Frontier Chemistry Center, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan
Phone: (+81)-11-706-6599; Fax: (+81)-11-706-6598
E-mail: ohkuma@eng.hokudai.ac.jp
[b] Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo, Hokkaido 060-8628, Japan

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

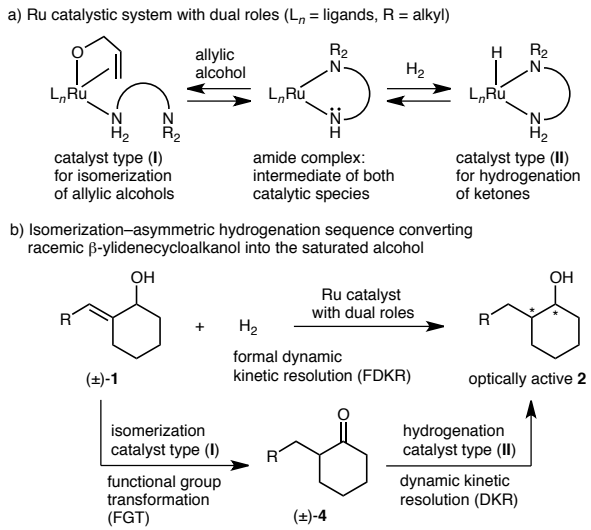
Abstract. Racemic β-ylidenecycloalkanols were transformed into the *cis*-β-substituted cycloalkanols with high enantio- and diastereoselectivities through an isomerization–asymmetric hydrogenation sequence with the (4,4'-bi-1,3-benzodioxole)-5,5'-diylbis[di(3,5-xylyl)phosphine (DM-Segphos)/2-dimethylamino-1-phenylethylamine (DMAPEN)–ruthenium(II) catalyst; such transformation hardly proceeded by single-step asymmetric hydrogenation. The reaction was usually carried out with a substrate-to-catalyst molar ratio of 500 under 4 to 10 atm of H_2 to afford the products in *cis*/*trans* ratio up to 99:1 and 98% ee. Mechanistic experiments suggested that this catalytic system reversibly formed two reactive species, types (I) and (II), through a ruthenacyclic amide intermediate. The amide complex and allylic alcohol reacted to afford the allylic alkoxide complex with partial or full removal of diamine (type (I)), and this type (I) complex catalyzed isomerization of the allylic alcohols into the racemic α-substituted ketones. The RuH_2 complex with chelation of diamine (type (II)) formed by reaction of the amide complex and hydrogen promoted asymmetric hydrogenation of racemic α-substituted ketone into the stereocontrolled β-substituted cycloalkanols through dynamic kinetic resolution.

Keywords: allylic alcohols; asymmetric catalysis; dynamic kinetic resolution; hydrogenation; isomerization; ruthenium; sequential reaction

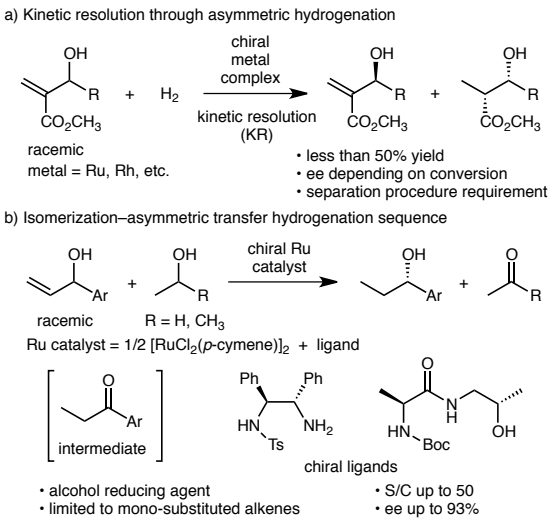
Optically active metal complexes have made a remarkable contribution to the progress of asymmetric catalytic reactions.[1] Usually, these complexes are appropriately designed as (pre)catalysts for specifically targeted reactions. The chemical features of the substrates are also significant factors in such design. Therefore, development of a catalyst that can efficiently promote multi-step reactions is difficult. We expected that a sequential two-step transformation could be realized by using a catalytic system that reversibly forms two active species. In support of this idea, we recently reported double asymmetric hydrogenation of β,β-disubstituted α,β-unsaturated ketones into the γ-substituted secondary alcohols in high enantio- and diastereoselectivities using a Ru catalytic system with dual roles.[2] Each of the two transformations, namely, carbonyl hydrogenation of the enones into the allylic alcohols and subsequent alkene hydrogenation into the saturated alcohols, was promoted by the different catalytic species reversibly forming with each other.

This successful result prompted us to investigate a Ru catalytic system that promotes two sequential reactions. The concept of this catalytic system is shown in Scheme 1a. Both catalyst type (I) and type (II) are reversibly formed via the ruthenacyclic amide complex. The reaction of the amide complex with an allylic alcohol provides the allylic alkoxide complex (catalyst type (I)) through removal of the dialkylamino group. Several Ru allylic alkoxides are known to function as catalytic species in the isomerization of allylic alcohols through a 1,3-hydrogen shift.[3] On the other hand, when the amide complex reacts with H_2, the hydride complex (catalyst type (II)) is obtained. We and other groups have reported the hydrogenation of ketones catalyzed by this type of Ru complexes.[4,5]

Then we targeted to achieve a transformation of racemic allylic alcohols (±)-**1** into the chiral β-substituted alcohols **2** with high enantio- and diastereoselectivities through an isomerization–asymmetric hydrogenation sequence as shown in Scheme 1b. The isomerization of (±)-**1** into the racemic α-substituted ketones (±)-**4** could be promoted by the catalyst type (I), and then



Scheme 1. Isomerization–Asymmetric Hydrogenation Sequence from Racemic Secondary Allylic Alcohols to the Optically Active Saturated Alcohols Using a Ru Catalyst with Dual Roles.



Scheme 2. Previous Works on the Formation of Optically Active Saturated Alcohols through Asymmetric (Transfer) Hydrogenation of Racemic Allylic Alcohols.

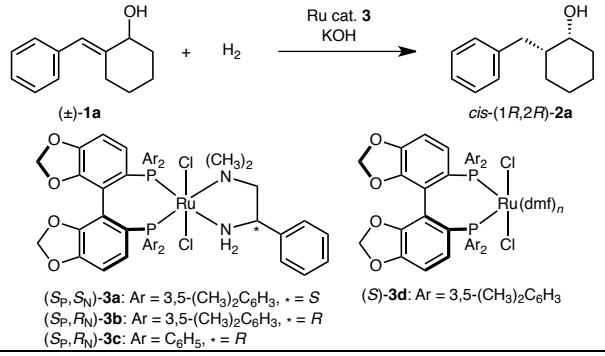
asymmetric hydrogenation of (±)-**4** into the optically active alcohols **2** could be catalyzed by the species (II). The first reaction is regarded as a functional group transformation (FGT) from a C=C bond to a C=O bond without stereocontrol. The second step controls both enantio- and diastereoselection through the dynamic kinetic resolution (DKR).[6,7] This two-step sequential reaction could realize asymmetric hydrogenation of racemic allylic alcohol into the saturated alcohol with formal dynamic kinetic resolution (FDKR), which is hardly achieved by the single-step transformation.

Usually asymmetric hydrogenation of racemic secondary allylic alcohol is conducted through (static) kinetic resolution (KR) to give the enantiomerically enriched saturated alcohol and the unreacted allylic alcohol (Scheme 2a).[8] The yield of the desired optically pure product or the substrate is at most 50% in principle. The enantiomeric purity of the compounds depends on the conversion of the reaction; therefore, the hydrogenation should be stopped at the appropriate conversion, and then the target compound should be separated from the resulting mixture.

The sequential reactions of isomerization of racemic secondary allylic alcohol followed by asymmetric transfer hydrogenation of the resulting ketone with chiral Ru catalysts have been reported (Scheme 2b).[9] The racemic allylic alcohol was converted to the saturated alcohol in up to 93% ee with the use of EtOH or *i*PrOH as a reducing agent. More than 2 mol% of catalyst (substrate-to-catalyst molar ratio (S/C) of 50) was employed to advance the reaction at a reasonable rate. The reaction was applicable only to aryl vinyl carbinol, a mono-substituted alkene, because the isomerization of the multi-substituted alkenyl compounds was sluggish.[10]

We commenced screening the reaction conditions for the isomerization–asymmetric hydrogenation sequence using racemic (*E*)-2-benzylidenecyclohexanol ((±)-**1a**) as a typical substrate (Table 1). $RuCl_2$[(*S*)-dm-segphos][(*S*)-dmapen] ((*S*$_P$,*S*$_N$)-**3a**) was the first choice for a catalyst precursor because it showed excellent efficiency for the double asymmetric hydrogenation of β,β-disubstituted α,β-unsaturated ketones into the γ-substituted secondary alcohols in the presence of a base.[2,11] When the reaction of (±)-**1a** was conducted with (*S*$_P$,*S*$_N$)-**3a** at an S/C of 300 in a base (KOH)-containing *i*PrOH under 20 atm of H_2 in 24 h, the desired (1*R*,2*R*)-2-benzylcyclohexanol ((1*R*,2*R*)-**2a**) was quantitatively obtained in 82% ee with a *cis*/*trans* ratio of 21:1 (Table 1, entry 1). It is noteworthy that the complete conversion was achieved using a less reactive trisubstituted alkenyl compound.[10] Replacement of *i*PrOH with *t*BuOH as a solvent and reduction of H_2 pressure from 20 atm to 8 atm increased both the enantioselectivity and the *cis*/*trans* ratio of **2a** (entries 2 and 3). Interestingly, use of the diastereomeric (*S*)-DM-Segphos/(*R*)-DMAPEN–Ru(II) complex ((*S*$_P$,*R*$_N$)-**3b**) gave an even better result (entry 4). The stereoselectivity was also increased in a 4:1 *t*BuOH–Et_3N mixed solvent (entry 5). The high catalytic activity of a (*S*$_P$,*R*$_N$)-**3b**–KOH system completed the transformation in 2 h under 4 atm of H_2 (entry 6). The reaction with an S/C of 500 in 4 h quantitatively afforded **2a** in 97% ee with a *cis*/*trans* ratio of 63:1 (entry 7). Complete conversion of this transformation with an S/C of 1000 was achieved by prolongation of the reaction time to 24 h with maintenance of high stereoselectivity (entry 8). The Segphos/DMAPEN–Ru(II) complex ((*S*$_P$,*R*$_N$)-**3c**) with a less bulky diphosphine ligand was much less active for this reaction (entry 9). Interestingly, $RuCl_2$[(*S*)-dm-segphos](dmf)$_n$ ((*S*)-**3d**) without a diamine ligand feebly promoted even the

Table 1. Isomerization–Asymmetric Hydrogenation Sequence from (±)-**1a**[a]



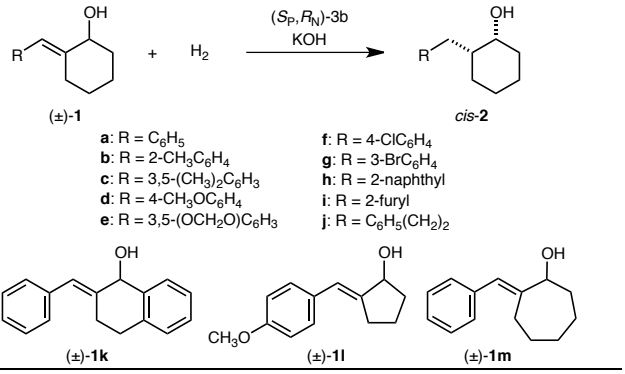
Entry	**3**[b]	S/C[c]	H_2 [atm]	Solvent	Time [h]	dr[d]	ee[e] [%]
1[f]	**3a**	300	20	*i*PrOH	24	21:1	82
2	**3a**	300	20	*t*BuOH	24	25:1	90
3	**3a**	300	8	*t*BuOH	24	32:1	92
4	**3b**	300	8	*t*BuOH	24	82:1	95
5	**3b**	300	8	A[g]	24	90:1	96
6	**3b**	300	4	A[g]	2	53:1	97
7	**3b**	500	4	A[g]	4	63:1	97
8	**3b**	1000	20	A[g]	24	47:1	96
9[h]	**3c**	300	4	A[g]	2	nd	nd
10[i]	**3d**	300	4	A[g]	2	nd	nd

[a] Unless otherwise stated, reactions were conducted at 30 °C with allylic alcohol **1a** in solvent containing Ru complex **3** and KOH. **2a** was obtained in >99% yield in entries 1–8. nd: not determined. [b] **3a**: (S_P,S_N)-**3a**. **3b**: (S_P,R_N)-**3b**. **3c**: (S_P,R_N)-**3c**. **3d**: (*S*)-**3d**. [c] Substrate/catalyst (**3**) molar ratio. [d] *cis*-**2a**/*trans*-**2a** ratio determined by GC analysis. [e] Data for *cis*-**2a** determined by HPLC analysis on a chiral stationary phase. [f] Reaction at 25 °C. [g] A: Reaction in a 4:1 mixture of *t*BuOH and Et_3N. [h] **2a** (8%) and **4a** (17%) were obtained. [i] **2a** (2%) and **4a** (7%) were obtained.

isomerization of **1a** under the reaction conditions (entry 10).

A series of racemic (*E*)-2-benzylidenecyclohexanol derivatives, **1a**–**1g**, was applied to the transformation catalyzed by the (S_P,R_N)-**3b**–KOH system with an S/C of 500 under 4–10 atm of H_2 (Table 2, entries 1–7). The reaction of 2'-methyl- and 3',5'-dimethylphenyl derivatives, **1b** and **1c**, under 4 atm of H_2 quantitatively afforded the saturated alcohols, **2b** and **2c**, in even higher enantiomeric purity (97%–98%) with a higher *cis*/*trans* ratio (77:1–99:1) than observed in the reaction of **1a** (entries 1–3). The benzylidene alcohols with electron-donating methoxy and methylenedioxy moieties, **1d** and **1e**, were converted with comparably high stereoselectivity (entries 4 and 5). Substitution of electron-withdrawing chloro and bromo groups (**1f** and **1g**) was allowed in this transformation (entries 6 and 7). It took 32 h for complete conversion of 2'-naphthylmethylidene compound **1h** even under 10 atm of H_2, but the stereoselective outcome was excellent (entry 8). The furylmethylidene substrate **1i**

Table 2. Isomerization–Asymmetric Hydrogenation Sequence from (±)-**1**[a]

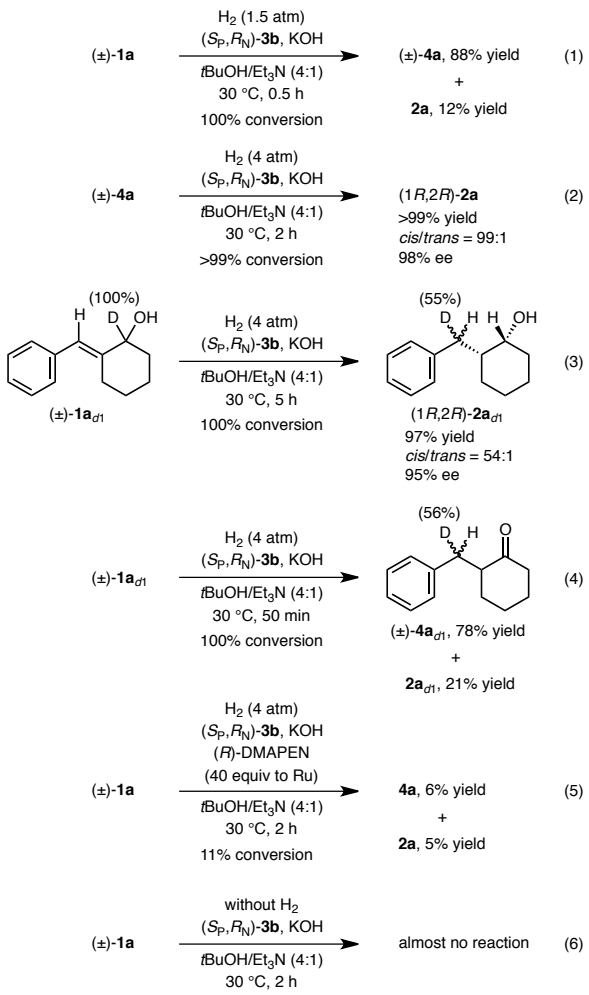


Entry	**1**	S/C[b]	H_2 [atm]	Time [h]	Yield [%][c]	dr[d]	ee[e] [%]
1	**1a**	500	4	4	>99(96)	63:1	97
2	**1b**	500	4	4	>99(95)	77:1	98
3	**1c**	500	4	7	>99(97)	99:1	97
4	**1d**	500	4	4	>99(97)	54:1	97
5	**1e**	500	10	4	99(92)	55:1	95
6	**1f**	500	4	9	>99(95)	57:1	96
7	**1g**	500	10	4	98(82)	16:1	94
8	**1h**	500	10	32	>99(96)	77:1	95
9[f]	**1i**	500	10	8	89(79)	17:1	95
10	**1j**	500	10	20	99(96)	77:1	95
11	**1k**	400	10	17	94(78)	14:1	76
12	**1l**	300	20	12	99(92)	24:1	81
13	**1m**	500	4	12	>99(94)	38:1	88

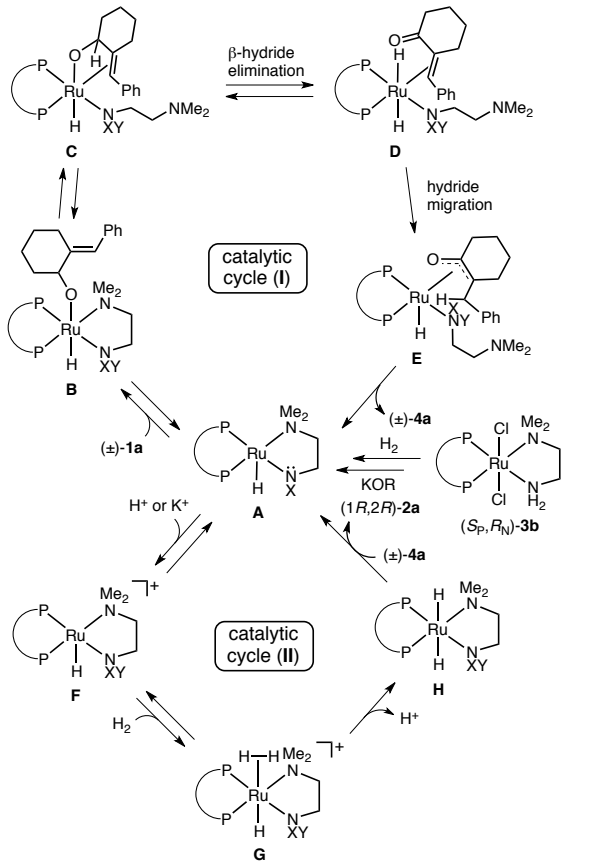
[a] Unless otherwise stated, reactions were conducted at 30 °C with allylic alcohol **1** in a 4:1 mixture of *t*BuOH and Et_3N containing (S_P,R_N)-**3b** and KOH. [b] Substrate (**1**)/catalyst (**3b**) molar ratio. [c] Yield of **2** determined by ^1H NMR analysis. The yield of the isolated *cis* product is given in parenthesis. [d] *cis*-**2**/*trans*-**2** ratio determined by ^1H NMR analysis. [e] Data for *cis*-**2** determined by HPLC analysis on a chiral stationary phase. [f] Undefined compounds were observed.

was also suitable for this reaction (entry 9). Notably, an alkylidene compound **1j** was successfully converted to the desired product **2j** (entry 10). The benzylidenecyclohexanol with a fused benzene ring **1k** was a difficult substrate to convert with high enantioselectivity, and thus the saturated alcohol **2k** was obtained in 76% ee, although the *cis*-selectivity was still high (entry 11). The ring size of the substrate affected the reaction rate and/or the enantioselectivity. The reaction of the benzylidenecyclopenatanol derivative **1l** required 20 atm of H_2 with an S/C of 300 to afford *cis*-**2l** in 81% ee (entry 12). The cycloheptanol analogue **1m** was smoothly converted to *cis*-**2m** in 88% ee under 4 atm of H_2 with an S/C of 500 (entry 13).

When the reaction of (±)-**1a** was carried out with the (S_P,R_N)-**3b**–KOH catalyst (S/C = 300) under 1.5 atm of H_2 for 0.5 h, the racemic α-substituted ketone (±)-**4a** was obtained as the major product in 88% yield (Scheme 3, equation 1). The isomerization of hindered tri-substituted alkene (±)-**1a** was sufficiently



Scheme 3. Experiments for Mechanistic Consideration (S/C = 300).



Scheme 4. Plausible Mechanism of the Isomerization–Hydrogenation Sequential Reaction of (±)-**1a** by a Ru catalytic system with Dual Roles. P—P = (*S*)-DM-SEGPHOS; X, Y = H or K; NH_2—NMe_2 = (*R*)-DMAPEN.

faster than the hydrogenation of ketone (±)-**4a** under these conditions. The racemic ketone (±)-**4a** was hydrogenated under the regular conditions (4 atm H_2) to quantitatively afford (1*R*,2*R*)-**2a** in almost the same enantio- and diastereoselectivities through DKR (equation 2). These results suggest that the transformation of (±)-**1a** into (1*R*,2*R*)-**2a** consisted of two-step sequential reactions of isomerization and asymmetric hydrogenation as we expected. When the reaction was carried out by using the deuterated substrate at the C1 position (±)-**1a**$_{d1}$ under the regular conditions, the 55% deuterated product at the benzylic position (1*R*,2*R*)-**2a**$_{d1}$ was quantitatively obtained with comparably high stereoselectivity (equation 3). A separate investigation revealed that the ketonic intermediate (±)-**4a**$_{d1}$ was deuterated in 56% at the benzylic position (equation 4). These results suggested that the H–D scrambling pathway exists at the isomerization (1,3-H shift) step of **1a** into **4a**.

The reaction using **3b** with an addition of 40 equiv of DMAPEN to Ru remarkably decreased the reaction rate (equation 5). As shown in Table 1, both the sterically less hindered Segphos/DMAPEN–Ru(II) complex **3c** (leading to the more stable coordination of DMAPEN) and the DM-Segphos–Ru(II) complex **3d** without a diamine ligand were much less reactive than **3b** (entries 9 and 10). These observations suggested that the DMAPEN ligand was required to form the catalytic species even for the isomerization of the allylic alcohol. However, liberation of the NMe_2 group of DMAPEN providing a vacant coordination site was necessary to promote the isomerization. Notably, no isomerization was observed without pressure of H_2, suggesting that the isomerization catalyst has a RuH partial structure (equation 6).

A plausible mechanism for the isomerization–asymmetric hydrogenation sequence is shown in Scheme 4. The Ru complex (*S*$_P$,*R*$_N$)-**3b** with a potassium base is converted to the RuH amide complex **A** in the presence of H_2, and it acts as a common species for catalytic cycles (I) and (II). The amine proton can be reversibly replaced with a potassium cation. Catalytic cycle (I) for isomerization of the allylic alcohol: The amide complex **A** reacts with the racemic allylic alcohol (±)-**1a** to give the alkoxide complex **B**, which reversibly forms an olefin-coordinated species **C** with partial or full removal of diamine DMAPEN.[2,12,13] The coordination stability of the diamine depends on the steric hindrance around the NMe_2 moiety.[14]

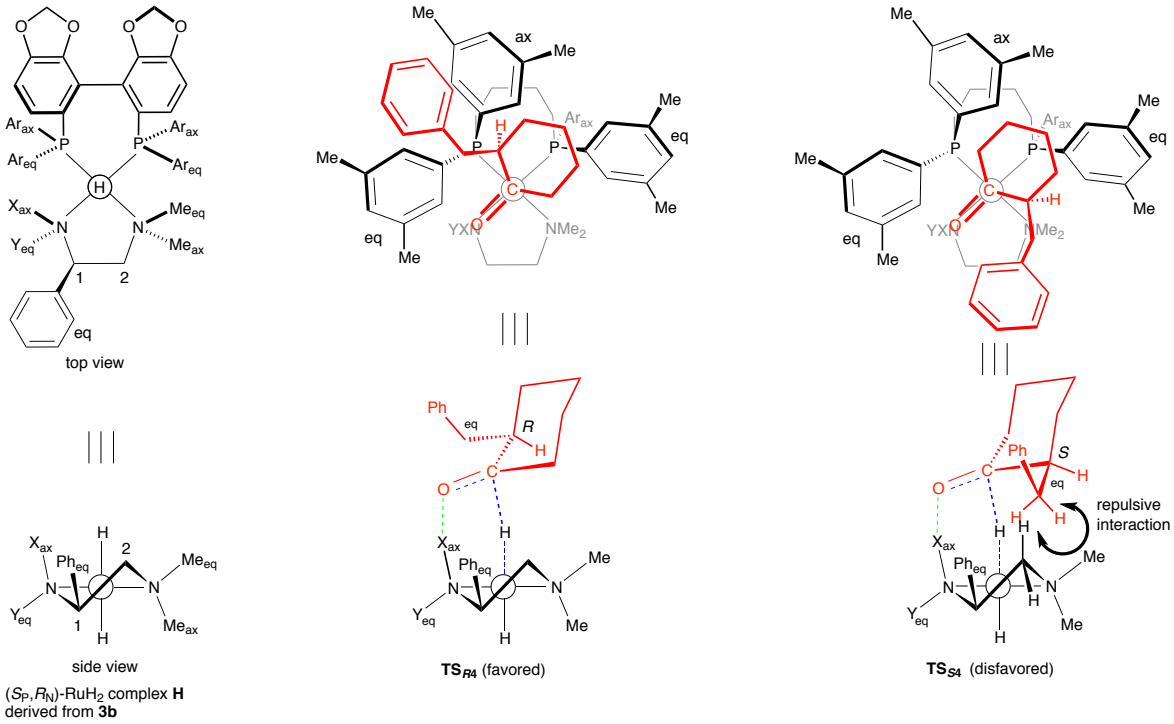


Figure 1. Structure of RuH_2 species **H** derived from (S_P,R_N)-**3b** and diastereomeric TS-models in the hydrogenation of (±)-**4a** through DKR (catalytic cycle (II)). Some aromatic groups and substituents in the TSs are omitted for clarity. X, Y = H or K. Ar = 3,5-$(CH_3)_2C_6H_3$.

β-Hydride elimination in species **C** gives a RuH_2 complex **D** coordinated with an unsaturated ketone. The η^3-oxaallyl complex **E** is formed through hydride migration from the Ru center to the β-carbon of the enone. H–D scrambling at the benzylic position as observed by using a deuterated substrate **1a**$_{d1}$ (equations 3 and 4) occurs during this process, because the two hydrides on Ru are respectively derived from the α-position of the alcohol **1a** and gaseous H_2.[15] Removal of the saturated ketone (±)-**4a** through keto–enol tautomerization, and reform of the chelate structure of DMAPEN regenerates **A**. Catalytic cycle (II) for hydrogenation of the saturated ketone based on the previous mechanistic investigations:[5,16] The amide complex **A** with H^+ or K^+ reversibly forms the cationic species **F**, which is known to be detectable in alcoholic solvent.[16b,17] **F** and H_2 reversibly afford **G**, and the following deprotonation with a base gives active (*S*)-DM-Segphos/(*R*)-DMAPEN–RuH_2 complex **H**. The racemic ketone (±)-**4a** is reduced by **H** through DKR, affording the alcoholic product (1*R*,2*R*)-**2a** with reformation of amide complex **A**. These species were suggested to interact with the alkoxide produced by the hydrogenation of acetophenone (an arimatic ketone) in 2-propanol catalyzed by a related diphosphine/diamine–Ru(II) complex.[16f,g]

Two enantiomers of an α-substituted cyclohexanone **4a** are reversibly formed with each other in the presence of an alkaline base (Supporting Information, Scheme SI(1)).[6] The (S_P,R_N)-**3b**–KOH catalyst kinetically selects (*R*)-**4a** with the stable chair conformer possessing an equatorial benzyl group (see below), and the carbonyl hydrogenation by the bulky RuH_2 species **H** shown in Scheme 4 occurs from the equatorial direction.[18] The less reactive (*S*)-**4a** was hydrogenated after conversion to the *R* isomer. Therefore, *cis*-(1*R*,2*R*)-**2a** is selectively obtained among four possible stereoisomers from (±)-**4a** through DKR.

Figure 1 illustrates the molecular models of the active RuH_2 complex **H** derived from an (S_P,R_N)-**3b**–KOH catalytic system and plausible diastereomeric transition states (TSs) **TS**$_{R4}$ and **TS**$_{S4}$ in the hydrogenation of (±)-**4a** with an equatorial conformation based on the previous related studies.[5,16,19] (*R*)-DMAPEN forms a λ-chelate structure due to the preferential equatorial placement of the phenyl substituent. The reaction proceeds through the cyclic TS, **TS**$_{R4}$ or **TS**$_{S4}$ in which the carbonyl hydride reduction with the RuH (blue broken lines) is promoted by interaction with the axially oriented proton or K^+ on the diamine (green broken line).[16f,g] The **TS**$_{S4}$ suffers steric repulsion between the equatorial-oriented benzyl group of (*S*)-**4a** and the skewed chelate ring of the DMAPEN in the catalyst. In contrast, **TS**$_{R4}$ avoids such significant repulsion because the benzyl moiety of (*R*)-**4a** enters the channel formed by the Ar_{ax}–P–Ar_{eq} (Ar = 3,5-$(CH_3)_2C_6H_3$) structure of DM-Segphos. Thus, (*R*)-**4a** is preferably hydrogenated over the *S* isomer.

In conclusion, we have reported herein the transformation of racemic β-ylidenecycloalkanols into the saturated *cis*-β-substituted cycloalkanols with high enantio- and diastereoselectivities through an isomerization–asymmetric hydrogenation sequence

by using a catalytic system of the DM-Segphos/DMAPEN–Ru(II) complex with KOH, which is hardly achieved by traditional single-step asymmetric hydrogenation. In most cases the reaction with an S/C of 500 under 4 to 10 atm of H_2 smoothly proceeded to yield the products in *cis*/*trans* ratio of 14:1 to 99:1 and 76% to 98% ee. The mechanistic experiments suggested that this system reversibly forms two catalytic species, **C** (type (I)) and **H** (type (II)), via a common intermediate of ruthenacyclic amide complex **A** shown in Scheme 4. Namely, the amide complex **A** reacts with an allylic alcohol to form the allylic alkoxide complex **C** through partial or full removal of the diamine DMAPEN, which promotes isomerization (1,3-H shift) of the allylic alcohol into the racemic α-substituted ketone (catalytic cycle (I)). Reaction of **A** with H_2 affords the RuH_2 complex **H** with chelation of DMAPEN, which catalyzes asymmetric hydrogenation of racemic α-substituted ketone into the stereoregulated β-substituted cycloalkanol through DKR (catalytic cycle (II)). The mode of stereoselection in the hydrogenation of (±)-**4a** into (1*R*,2*R*)-**2a** is also proposed.

Experimental Section

Typical Procedure for the Isomerization–Asymmetric Hydrogenation Sequence of 1a with (S_P,R_N)-3b

The ruthenium complex (S_P,R_N)-**3b** (1.3 mg, 1.2 μmol), allylic alcohol **1a** (117.4 mg, 0.624 mmol), and a Teflon-coated stirring bar were placed in a 100 mL glass autoclave that had been filled with argon. A mixture of 0.25 M KOH in *t*BuOH (0.10 mL), *t*BuOH (2.4 mL), and Et_3N (0.60 mL) that had been degassed by three freeze-thaw cycles was transferred into the autoclave through a Teflon cannula. The autoclave was then pressurized with H_2 gas (4 atm), and the solution was stirred vigorously at 30 °C for 4 h. After careful release of the hydrogen, the diastereomeric ratio of **2a** was determined by GC analysis. Column, SUPELCOWAX (0.25 mm × 30 m, DF = 0.25 μm); carrier, He (100 kPa); oven temp, 80 °C, held for 2 min, heated to 240 °C at a rate of 10 °C min^{-1}, held for 7 min; t_R of *cis*-**2a**, 19.87 min (98.5%); t_R of *trans*-**2a**, 20.16 min (1.5%). After concentration of the solution, purification by silica gel column chromatography (hexane:ethyl acetate = 9:1) gave (1*R*,2*R*)-2-benzylcyclohexan-1-ol (**2a**) (114.2 mg, 0.600 mmol, 96%). The enantiomeric excess of **2a** was determined by HPLC analysis. Column, CHIRALCEL OD-H (4.6 × 250 mm); eluent, hexane:2-PrOH = 95:5; flow, 1.0 $mLmin^{-1}$; detector : UV 254 nm; column temp, 30 °C; t_R of (1*R*,2*R*)-**2a**, 6.26 min (98.5%); t_R of (1*S*,2*S*)-**2a**, 8.19 min (1.5%), 97% ee. The procedures and chemical properties of products in detail are described in the Supporting Information.

Acknowledgements

This work was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 19H02706).

References

[1] See for example: a) *Science of Synthesis: Stereoselective Synthesis, Vols. 1 to 3* (Eds.; J. G. de Vries, G. A. Molander, P. A. Evans), Thieme, Stuttgart, **2011**; b) *Comprehensive Chirality, Vols. 4 and 5* (Eds.: E. M. Carreira, H. Yamamoto, M. Shibasaki, K. Maruoka), Elsevier, Amsterdam, **2012**.

[2] N. Arai, H. Satoh, R. Komatsu, T. Ohkuma, *Chem. Eur. J.* **2017**, *23*, 8806–8809.

[3] Reviews for isomerization of allylic alcohols: a) R. C. van der Drift, E. Bouwman, E. Drent, *J. Organomet. Chem*. **2002**, *650*, 1–24; b) R. Uma, C. Crévisy, R. Grée, *Chem. Rev*. **2003**, *103*, 27–51; c) G. C. Fu in *Modern Rhodium-Catalyzed Organic Reactions* (Ed.: P. A. Evans), Wiley-VCH, Weinheim, **2005**, pp 79–91; d) V. Cadierno, P. Crochet, J. Gimeno, *Synlett* **2008**, 1105–1124; e) L. Mantilli, C. Mazet, *Chem. Lett*. **2011**, *40*, 341–344; f) N. Ahlsten, A. Bartoszewicz, B. Martín-Matute, *Dalton Trans*. **2012**, *41*, 1660–1670; g) P. Lorenzo-Luis, A. Romerosa, M. Serrano-Ruiz, *ACS Catal*. **2012**, *2*, 1079–1086; h) D. Cahard, S. Gaillard, J.-L. Renaud, *Tetrahedron Lett*. **2015**, *56*, 6159–6169.

[4] Selected reviews: a) T. Ohkuma, R. Noyori in *The Handbook of Homogeneous Hydrogenation, Vol. 3* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, pp. 1105–1163; b) N. Arai, T. Ohkuma in *Science of Synthesis: Stereoselective Synthesis 2; Stereoselective Reactions of Carbonyl and Imino Groups* (Ed.: G. A. Molander), Thieme, Stuttgart, **2010**, pp. 9–57; c) T. Ohkuma and N. Arai in *Comprehensive Chirality, Vol. 5* (Eds.: E. M. Carreira, H. Yamamoto, K. Maruoka), Elsevier, Amsterdam, **2012**, pp. 270–300; d) J.-H. Xie, D.-H. Bao, Q.-L. Zhou, *Synthesis* **2015**, *47*, 460–471.

[5] Accounts: a) T. Ohkuma, N. Arai, *Chem. Rec*. **2016**, *16,* 2801–2819; b) T. Ohkuma, N. Kurono, N. Arai, *Bull. Chem. Soc. Jpn.* **2019**, *92*, 475–504.

[6] For asymmetric hydrogenation of α-alkyl and α-aryl cycloalkanones with diphosphine/diamine–Ru(II) catalysts through DKR, see: a) T. Ohkuma, H. Ooka, M. Yamakawa, T. Ikariya, R. Noyori, *J. Org. Chem*. **1996**, *61*, 4872–4873; b) T. Ohkuma, J. Li, R. Noyori, *Synlett* **2004**, 1383–1386; c) J.-H. Xie, S. Liu, X.-H. Huo, X. Cheng, H.-F. Duan, B. M. Fan, L.-X. Wang, Q.-L. Zhou, *J. Org. Chem*. **2005**, *70*, 2967–2973.

[7] For stereoselective synthesis through DKR, see: R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn*. **1995**, *68*, 36–56.

[8] a) J. M. Brown, Angew. Chem. **1987**, *99*, 169–182; *Angew. Chem. Int. Ed. Engl*. **1987**, *26*, 190–203; b) M. Kitamura, I. Kasahara, K. Manabe, R. Noyori, H. Takaya, *J. Org. Chem*. **1988**, *53*, 708–710; c) J. Holz, B. Schäffner, O. Zayas, A. Spannenberg, A. Börner, *Adv. Synth. Catal*. **2008**, *350*, 2533–2543.

[9] a) H. C. Maytum, J. Francos, D. J. Whatrup, J. M. J. Williams, *Chem. Asian J*. **2010**, *5*, 538–542; b) T. Slagbrand, H. Lundberg, H. Adolfsson, *Chem. Eur. J*. **2014**, *20*, 16102–16106; c) C. O. Shoola, T. DelMastro,

R. Wu, J. R. Sowa, Jr., *Eur. J. Org. Chem*. **2015**, 1670–1673.

[10] Isomerization of secondary allylic alcohols with a trisubstituted alkenyl moiety was conducted with at least 1 mol% of catalyst. See: a) H. Cherkaoui, M. Soufiaoui, R. Grée, *Tetrahedron* **2001**, *57*, 2379–2383; b) B. Ganchegui, S. Bouquillon, F. Hénin, J. Muzart, *J. Mol. Catal. A: Chemical* **2004**, *214*, 65–69; c) M. Ito, S. Kitahara, T. Ikariya, *J. Am. Chem. Soc*. **2005**, *127*, 6172–6173; d) M. T. Reetz, H. Guo, *Synlett* **2006**, 2127–2129; e) P. Crochet, M. A. Fernández-Zúmal, J. Gimeno, M. Scheele, *Organometallics* **2006**, *25*, 4846–4849; f) P. N. Liu, K. D. Ju, C. P. Lau, *Adv. Synth. Catal*. **2011**, *353*, 275–280; g) A. J. A. Watson, B. N. Atkinson, A. C. Maxwell, J. M. J. Williams, *Adv. Synth. Catal*. **2013**, *355*, 734–740; h) T.-L. Liu, T. W. Ng, Y. Zhao, *J. Am. Chem. Soc*. **2017**, *139*, 3643–3646.

[11] DMAPEN = 2-dimethylamino-1-phenylethylamine; DM-SEGPHOS = (4,4'-bi-1,3-benzodioxole)-5,5'-diylbis[di(3,5-xylyl)phosphane].

[12] For the mechanism via a ruthenium allylic alkoxide complex, see: a) B. M. Trost, R. J. Kulawiec, *Tetrahedron Lett*. **1991**, *32*, 3039–3042; b) B. M. Trost, R. J. Kulawiec, *J. Am. Chem. Soc*. **1993**, *115*, 2027–2036; c) J.-E. Bäckvall, U. Andreasson, *Tetrahedron Lett*. **1993**, *34*, 5459–5462; d) C. Slugovc, E. Rüba, R. Schmid, K. Kirchner, *Organometallics* **1999**, *18*, 4230–4233; e) I. E. Markó, A. Gautier, M. Tsukazaki, A. Llobet, E. Plantalech-Mir, C. J. Urch, S. M. Brown, *Angew. Chem*. **1999**, *111*, 2126–2128; *Angew. Chem. Int. Ed*. **1999**, *38*, 1960–1962; f) R. C. van der Drift, M. Vailati, E. Bouwman, E. Drent, *J. Mol. Catal. A: Chemical* **2000**, *159*, 163–177; g) R. C. van der Drift, J. W. Sprengers, E. Bouwman, W. P. Mul, H. Kooijman, A. L. Spwk, E. Drent, *Eur. J. Inorg. Chem*. **2002**, 2147–2155; h) H. Suzuki, T. Takao in *Ruthenium in Organic Synthesis* (Ed.: S. Murahashi), Wiley-VCH, Weinheim, **2004**, pp 309–331; i) B. Marín-Matute, K. Bogár, M. Edin, F. B. Kaynak, J.-E. Bäckvall, *Chem. Eur. J*. **2005**, *11*, 5832–5842; j) V. Cadierno, S. E. Garcia-Garrido, J. Gimeno, A. Varela-Álvarez, J. A. Sordo, *J. Am. Chem. Soc*. **2006**, *128*, 1360–1370; k) A. Bouziane, B. Carboni, C. Bruneau, F. Carreaux, J.-L. Renaud, *Tetrahedron* **2008**, *64*, 11745–11750; l) A. Varela-Álvarez, J. A. Sordo, E. Piedra, N. Nebra, V. Cadierno, J. Gimeno, *Chem. Eur. J*. **2011**, *17*, 10583–10599; m) S. Manzini, A. Poater, D. J. Nelson, L. Cavallo, S. P. Nolan, *Chem. Sci*. **2014**, *5*, 180–188.

[13] For asymmetric isomerization of primary allylic alcohols catalyzed by an optically active diphosphine/diamine–Ru(II) complex, see: N. Arai, K. Sato, K. Azuma, T. Ohkuma, *Angew. Chem*. **2013**, *125*, 7648–7652; *Angew. Chem. Int. Ed*. **2013**, *52*, 7500–7504.

[14] For hemilabile ligands, see: a) A. Bader, E. Lindner, *Coord. Chem. Rev*. **1991**, *108*, 27–110; b) C. S. Slone, D. A. Weinberger, C. A. Mirkin, *Prog. Inorg. Chem*. **1999**, *48*, 233–350; c) P. Braunstein, F. Naud, *Angew. Chem*. **2001**, *113*, 702–722; *Angew. Chem. Int. Ed*. **2001**, *40*, 680–699.

[15] See, for example: J.-E. Bäckvall, *J. Organomet. Chem*. **2002**, *652*, 105–111.

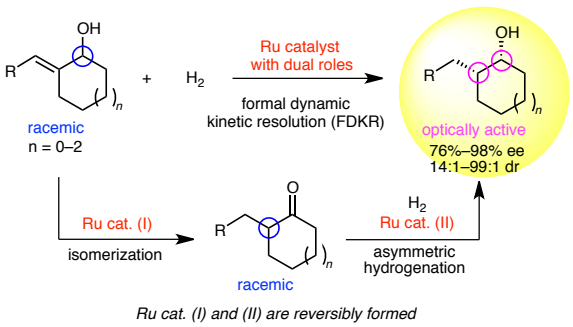
[16] For selected mechanistic studies, see: a) K. Abdur-Rashid, S. E. Clapham, A. Hadzovic, J. N. Harvey, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc*. **2002**, *124*, 15104–15118; b) C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc*. **2003**, *125*, 13490–13503; c) R. J. Hamilton, S. H. Bergens, *J. Am. Chem. Soc*. **2006**, *128*, 13700–13701; d) S. A. French, D. Di Tommaso, A. Zanotti-Gerosa, F. Hancock, C. R. A. Catlow, *Chem. Commun*. **2007**, 2381–2383; e) S. Takebayashi, N. Dabral, M. Miskolzie, S. H. Bergens, *J. Am. Chem. Soc.* **2011**, *133*, 9666–9669; f) P. A. Dub, N. J. Henson, R. L. Martin, J. C. Gordon, *J. Am. Chem. Soc*. **2014**, *136*, 3505–3521; g) P. A. Dub, J. C. Gordon, *Nat. Rev. Chem*. **2018**, *2*, 396–408.

[17] K. Matsumura, N. Arai, K. Hori, T. Saito, N. Sayo, T. Ohkuma, *J. Am. Chem. Soc*. **2011**, *133*, 10696–10699.

[18] See for example: a) A. P. Davis in *Methods of Organic Chemistry (Houben-Weyl)*, *4th ed., Vol. E21d* (Eds.; G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, pp 3988–4048; b) M. Hudlicky in *Reductions in Organic Chemistry*, *2nd ed*., American Chemical Society, Washington, DC, **1996**, pp 149–190.

[19] a) N. Arai, K. Azuma, N. Nii, T. Ohkuma, *Angew. Chem*. **2008**, *120*, 7567–7570; *Angew. Chem. Int. Ed*. **2008**, *47*, 7457–7460; b) H. Ooka, N. Arai, K. Azuma, N. Kurono, T. Ohkuma, *J. Org, Chem*. **2008**, *73*, 9084–9093; c) M. Akashi, N. Arai, T. Inoue, T. Ohkuma, *Adv. Synth. Catal*. **2011**, *353*, 1955–1960.

Isomerization–Asymmetric Hydrogenation Sequence Converting Racemic β-Ylidenecycloalkanols into Stereocontrolled β-Substituted Cycloalkanols Using a Ru Catalytic System with Dual Roles

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Noriyoshi Arai, Yuki Okabe, and Takeshi Ohkuma*