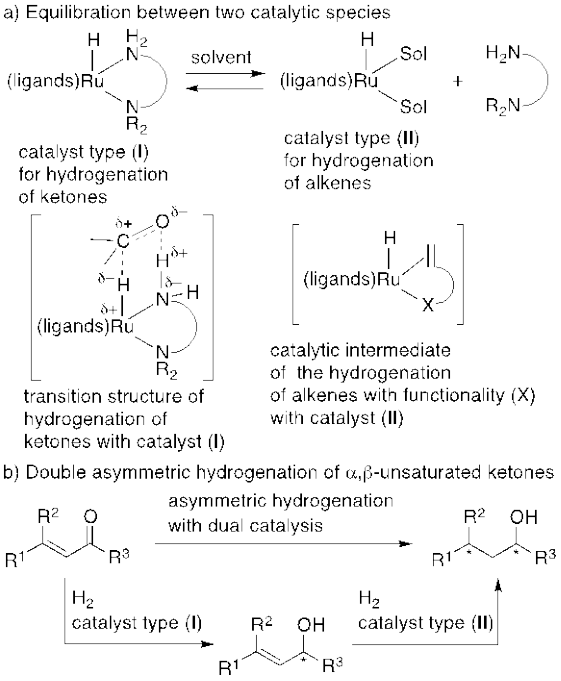
Double Asymmetric Hydrogenation of Linear β,β-Disubstituted α,β-Unsaturated Ketones into γ-Substituted Secondary Alcohols with Dual Catalytic Systems

Noriyoshi Arai, Hironori Satoh, Ryo Komatsu, and Takeshi Ohkuma*

Abstract: Double asymmetric hydrogenation of linear β,β-disubstituted α,β-unsaturated ketones catalyzed by the DM-SEGPHOS/DMAPEN/Ru(II) complex with *t*-C_4H_9OK afforded the γ-substituted secondary alcohols in high diastereo- and enantioselectivities. Some mechanistic experiments suggested that two different reactive species, type (I) and (II), were reversibly formed in this catalytic system: Type (I) with the diamine ligand DMAPEN enantioselectively hydrogenated the enones into the chiral allylic alcohols, and type (II) without the diamine ligand diastereoselectively hydrogenated the allylic alcohols into the γ-substituted secondary alcohols. This dual catalysis protocol was successfully applied to the reaction of a variety of aliphatic- and aromatic-substituted enone substrates.

Asymmetric hydrogenation of unsaturated compounds into the optically active saturated products has contributed greatly to a range of research fields, including organic synthesis, medicinal science, and functional materials.[1] Generally, chiral catalysts for this transformation are appropriately designed according to the chemical features of substrates. We have reported asymmetric hydrogenation of ketones catalyzed by chiral Ru complexes.[2,3] The catalytic species (type (**I**)) is a Ru hydride coordinated by a diamine derivative which has at least one NH_2 group (Scheme 1-a)). The catalyst type (**I**) smoothly hydrogenates C=O groups through a six-membered transition structure in which the $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H^{\delta+}$ quadrupole fits with the $C^{\delta+}$=$O^{\delta-}$ dipole.[2–5] The less polar C=C groups are hardly reduced by this catalytic system. On the other hand, catalyst type (**II**) with vacant coordination sites (solvents occupy them in this scheme) is appropriate for the hydrogenation of C=C moieties through coordination with the π-orbital. The presence of another coordinative functionality (X) in the molecule promotes the alkene hydrogenation with formation of a stable chelate intermediate.[6] In general, the σ-coordinative C=O groups are much more slowly reduced with the catalyst (**II**).[2] We expected that when these two species, type (**I**) and (**II**), were reversibly formed as shown in Scheme 1-a), both polar C=O and less polar C=C groups would be smoothly hydrogenated via *the dual catalysis*. According to this protocol, we designed double asymmetric hydrogenation of linear β,β-disubstituted α,β-unsaturated ketones into the γ-substituted secondary alcohols in high diastereo- and enantioselectivities (Scheme 1-b)). The carbonyl hydrogenation of the enone into the allylic alcohol is catalyzed by the species (**I**),[7,8] and then the alkene hydrogenation into the saturated alcohol is promoted by the



Scheme 1. Primary concept for the double asymmetric hydrogenation of α,β-unsaturated ketones using a dual catalytic system.

catalyst type (**II**).[9] No efficient catalyst for this double asymmetric hydrogenation has been reported to our knowledge.

We selected (*E*)-4-phenyl-3-penten-2-one (**1a**) as a standard substrate to investigate the catalyst structure and reaction conditions (Table 1). $[RuCl_2\{(S)\text{-tolbinap}\}\{(R)\text{-dmapen}\}]$ ((S_P,R_N)-**4a**) with *t*-C_4H_9OK was the first choice for a catalyst system showing excellent catalytic performance in the asymmetric hydrogenation of alkenyl aryl ketones into the secondary allylic alcohols.[7b,10] When enone **1a** (0.77 mmol) was hydrogenated in 2-propanol (4.5 mL) with (S_P,R_N)-**4a** and *t*-C_4H_9OK in a substrate/catalyst/base molar ratio (S/C/B) of 500:1:5 under 50 atm of H_2 at 0°C (ice bath) in 6 h and then 25°C (ambient temperature) in 34 h, *anti*-(2*R*,4*S*)-4-phenyl-2-pentanol (*anti*-(2*R*,4*S*)-**2a**) (4% yield, 46% *ee*), *syn*-(2*S*,4*S*)-**2a** (6% yield, 82% *ee*), and (*R*)-4-phenyl-3-penten-2-ol ((*R*)-**3a**) (90% yield, 30% *ee*) were obtained (Table 1, entry 1). The saturated ketone, 4-phenyl-2-pentanone, was not detected. The hydrogenation of allylic alcohol **3a** was slow, but this result suggested that our dual catalysis concept was reasonable. The increase in bulkiness close to the Ru center of catalysts **4b** and **4c** resulted in a higher conversion of **3a** into **2a** (entries 2 and 3). The bulkiness seems to assist in full or partial elimination of the diamine ligand, increasing the amount of the type(II) species (see Scheme 1-a)). Use of the (*S*)-DM-SEGPHOS/(*R*)-DEAPEN/Ru(II) complex (S_P,R_N)-**5** increased the yield of **2a** (*anti*/*syn* = 2.5:1) to 99% (entry 4).[10] To our delight, *anti*-**2a**

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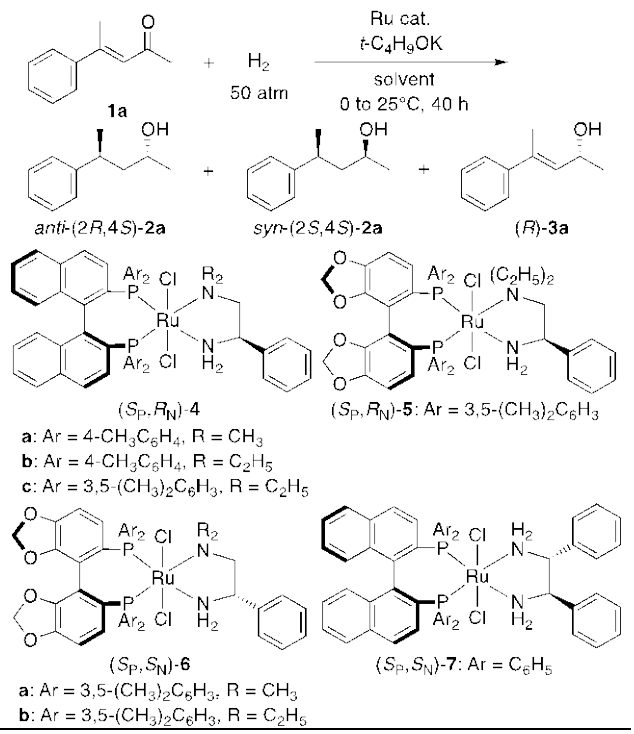
Table 1. Double asymmetric hydrogenation of enone **1a** into the saturated alcohol **2a** with chiral Ru catalysts.[a]



Entry	Ru cat.	Solvent	Conv [%][b]	Yield [%],[b] *ee* [%][c] *anti*-**2a**	*syn*-**2a**	**3a**
1	(S_P,R_N)-**4a**	2-PrOH	100	4, 46	6, 82	90, 30
2	(S_P,R_N)-**4b**	2-PrOH	93[d]	6, 26	12, 83	73, 40
3	(S_P,R_N)-**4c**	2-PrOH	100	56, 85	37, 90	7, 93
4	(S_P,R_N)-**5**	2-PrOH	100	71, 89	28, 79	1, nd
5	(S_P,S_N)-**6a**	2-PrOH	100	74, 98	5, 40	20,[e] 58
6	(S_P,S_N)-**6b**	2-PrOH	99	73, 95	19, 86	7, 28
7	(S_P,S_N)-**7**	2-PrOH	100	0	0	100, 86
8	(S_P,S_N)-**6a**	*t*-BuOH	100[f]	23, 94	4, 61	57,[e] 77
9	(S_P,S_N)-**6a**	IP/TB[g]	100	87, 98	8, 52	4,[e] 42
10	(S_P,S_N)-**6a**[h]	IP/TB[g]	100	87, 98	8, 45	<1, nd
11	(S_P,S_N)-**6a**[h,i]	IP/TB[g]	23[j]	0	0	17, 69

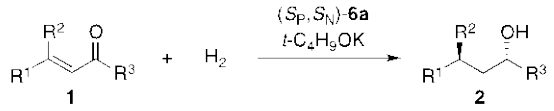
[a] Unless otherwise stated, reactions were conducted at 0°C (6 h) and then 25°C (34 h) under 50 atm of H_2 using 0.63–1.06 mmol of enone **1a** (0.13–0.21 M) in solvent containing a Ru complex and *t*-C_4H_9OK. **1a**/Ru/*t*-C_4H_9OK = 500:1:5. [b] Determined by ^1H NMR analysis. 100% conversion means enone **1a** was not detected. 0% yield means the corresponding peaks were not observed. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 4-Phenyl-2-pentanone in 2% was detected. [e] The *Z* isomer in 1% was detected. [f] Unidentified compounds were observed. [g] IP/TB = 2-PrOH/*t*-BuOH (3:1). [h] **1a**/Ru = 300:1. [i] (*S*)-DMAPEN (7 equiv. to **6a**) was added. [j] The *Z* isomer of **1a** in 6% was detected.

was obtained in an excellent *ee* of 98% with high diastereoselectivity (*anti*/*syn* = 15:1) by using a [$RuCl_2${(*S*)-dm-segphos}][(*S*)-dmapen] ((S_P,S_N)-**6a**)/*t*-C_4H_9OK system, although the mono-hydrogenation product **3a** remained (entry 5). The diastereo- and enantioselectivity were somewhat decreased in the reaction with the (*S*)-DM-SEGPHOS/(*S*)-DEAPEN/Ru(II) complex (S_P,S_N)-**6b** (entry 6). The mono-hydrogenation product **3a** was obtained quantitatively with the complex (S_P,S_N)-**7** bearing the strongly binding diamine DPEN (entry 7).[2,10] Double hydrogenation of **1a** was observed in *tert*-butyl alcohol, but the yield and stereoselectivity of **2a** were lower than those in 2-propanol (entry 8). Interestingly, higher conversion of the **3a** hydrogenation was achieved in a 3:1 mixture of 2-propanol and *tert*-butyl alcohol (entry 9). Allylic alcohol **3a** was almost completely reduced with an S/C/B of 300:1:5 to afford *anti*-**2a** (*anti*/*syn* = 11:1) in 98% *ee* (entry 10).[11] The reaction was retarded with excess amount of (*S*)-DMAPEN (entry 11).

A variety of linear β,β-disubstituted enones **1** were converted to the γ-substituted secondary alcohols **2** in high diastereo- and enantioselectivities in the double hydrogenation with the (S_P,S_N)-**6a**/*t*-C_4H_9OK catalyst system (Table 2). The reactions of 4-phenyl-3-penten-2-ones (R^1 = C_6H_5, R^3 = CH_3) with a methyl- and an ethyl-β-substituent, **1a** (R^2 = CH_3) and **1b** (R^2 = C_2H_5), gave similar results (entries 1 and 2). The *anti*-γ-isopropyl alcohol, *anti*-**2c**, was also obtained in an excellent *ee* of 99%, although the diastereoselectivity was lowered (entry 3). The enone substrates with the *para*-substituents on the β-phenyl ring, **1d**–**1g**, were hydrogenated to afford the desired γ-aryl alcohols, **2d**–**2g**, in 95–98% *ee* (*anti*/*syn* = 8:1–14:1) (entries 4–6, and 8). The reaction of **1f** was carried out with an S/C of 1000 for 50 h to afford **2f** in 83% yield (entry 7). The ethyl ketone **1h** (R^3 = C_2H_5) was converted to the alcohol **2h** in 98% *ee* with a remarkably high *anti*/*syn* selectivity of 23:1 (entry 9). The reaction rate was slowed in the reaction of the bulky isopropyl ketone **1i**, but the *anti*-product **2i** was obtained with high stereoselectivity (entry 10). The alkenyl phenyl ketone **1j** was converted to a 1:1 mixture of *anti* (84% *ee*) and *syn* (83% *ee*) isomers (entry 11). The *anti*-**2j** in 96% *ee* (*anti*/*syn* = 3:1) was obtained when the diastereomeric complex (S_P,R_N)-**6a** was used instead of (S_P,S_N)-**6a** (entry 12). The β,β-dialkyl enones, **1k** (R^1 = *n*-C_4H_9, R^2 = CH_3) and **1l** (R^1 = *cyclo*-C_6H_{11}, R^2 = CH_3), were quantitatively converted to the γ-branched saturated alcohols, **2k** and **2l**, in 92% *ee* (*anti*/*syn* = 2:1) and 94% *ee* (*anti*/*syn* = 3:1), respectively, under the regular conditions (entries 13 and 14).

Allylic alcohol (*R*)-**3a** in 91% *ee* was the major product with a small amount of *anti*-**2a** at the early stage of the hydrogenation of **1a** with the Ru complex (S_P,S_N)-**6a** (Scheme 2, equation (1)). The isolated (*R*)-**3a** in 86% *ee* was hydrogenated by the (S_P,S_N)-**6a**/*t*-C_4H_9OK catalyst system to afford *anti*-(2*R*,4*S*)-**2a** in high diastereo- and enantioselectivities comparable to those in the double hydrogenation of **1a** (equation (2)). The reaction using [$RuCl_2${(*S*)-dm-segphos}$(dmf)_n$] ((*S*)-**8**) without a diamine ligand gave almost the same result. These data suggest that the double hydrogenation proceeds through enone **1a** → allylic alcohol **3a** → saturated alcohol **2a**, as shown in Scheme 1-b). The diamine ligand DMAPEN is not necessary in the second hydrogenation of **3a** into **2a**. Either of two reaction pathways may account for the transformation of **3a** to **2a**: 1) hydrogenation

Table 2. Double asymmetric hydrogenation of enones **1** into the saturated alcohols **2**.[a]

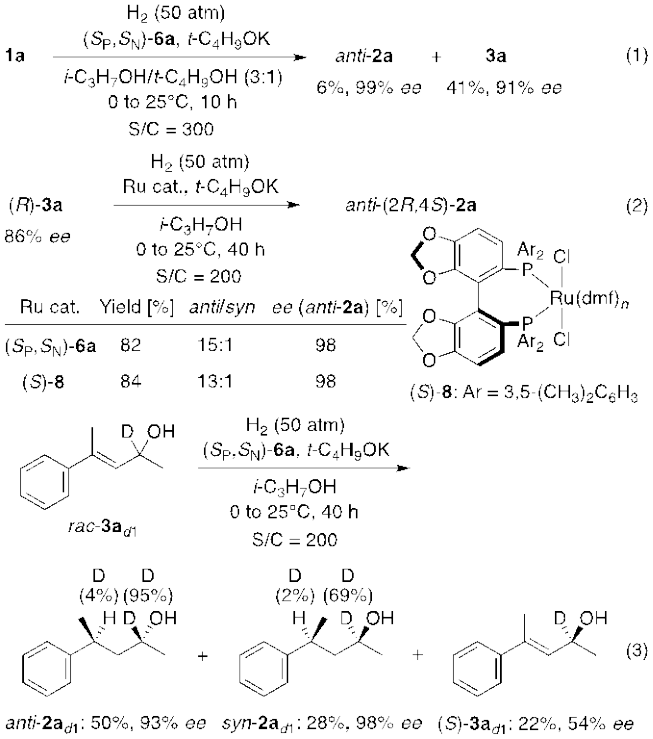


a: $R^1 = C_6H_5$, $R^2 = R^3 = CH_3$ **g**: $R^1 = 4\text{-}ClC_6H_4$, $R^2 = R^3 = CH_3$
b: $R^1 = C_6H_5$, $R^2 = C_2H_5$, $R^3 = CH_3$ **h**: $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = C_2H_5$
c: $R^1 = C_6H_5$, $R^2 = i\text{-}C_3H_7$, $R^3 = CH_3$ **i**: $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = i\text{-}C_3H_7$
d: $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = R^3 = CH_3$ **j**: $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = C_6H_5$
e: $R^1 = 4\text{-}C_6H_5C_6H_4$, $R^2 = R^3 = CH_3$ **k**: $R^1 = n\text{-}C_4H_9$, $R^2 = R^3 = CH_3$
f: $R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = R^3 = CH_3$ **l**: $R^1 = c\text{-}C_6H_{11}$, $R^2 = R^3 = CH_3$

				2		
Entry	**1**	S/C[b]	Conv [%][c]	Yield [%][c]	*anti*/*syn*[c]	*ee* [%][d]
1	**1a**	300	100	95 (95)	11:1	98
2	**1b**	300	100	98 (81)	12:1	99
3	**1c**	300	100	91 (87)	4:1	99
4	**1d**	300	100	90 (80)	11:1	97
5	**1e**	300	100	91 (77)	8:1	95
6	**1f**	300	100	96 (85)	14:1[e]	98
7	**1f**	1000	100	83 (78)[f]	13:1[e]	98
8	**1g**	300	100	98 (93)	12:1	98
9	**1h**	300	100	92 (89)	23:1	98
10	**1i**	300	86	70 (63)	22:1	94
11	**1j**	300	96	92	1:1	84[g]
12[h]	**1j**	300	100	>99 (85)	3:1	96
13	**1k**	300	100	98 (93)	2:1[i]	92[i]
14	**1l**	300	100	99 (95)	3:1[e]	94[i]

[a] Unless otherwise stated, reactions were conducted at 0°C (6 h) and then 25°C (34–42 h) under 50 atm of H_2 using 0.50–1.60 mmol of enone **1** (0.10–0.31 M) in a 3:1 mixture of 2-propanol and *tert*-butyl alcohol containing Ru complex (S_P,S_N)-**6a** and *t*-C_4H_9OK. Ru/*t*-C_4H_9OK = 1:5. [b] Substrate/catalyst molar ratio. [c] Determined by ^1H NMR analysis. 100% conversion means enone **1** was not detected. The yield of the isolated product is given in parenthesis. The unreacted allylic alcohols were obtained as byproducts. [d] Data for *anti*-**2** determined by GC or HPLC analysis on a chiral stationary phase. [e] Determined by GC analysis. [f] Reaction at 0°C (6 h) and then 25°C (44 h). [g] The *ee* value of *syn*-**2j** was 83%. [h] (S_P,R_N)-**6a** was used instead of (S_P,S_N)-**6a**. [i] Determined after conversion to the phenylcarbamate.

of the C=C bond of **3a**, or 2) isomerization of **3a** into 4-phenyl-2-pentanone through 1,3-hydrogen migration from the C2-position to the C4-position followed by carbonyl hydrogenation of this ketone. Next, therefore, we examined the hydrogenation of racemic 2-deuterated allylic alcohol *rac*-**3a**$_{d1}$ with the (S_P,S_N)-**6a**/*t*-C_4H_9OK catalyst system to determine the reaction pathway (equation (3)). The deuterium content at the C4-position of the saturated alcohols, *anti*- and *syn*-**2a**$_{d1}$, was very low, revealing that **3a** was exclusively converted to **2a** by the alkene hydrogenation.[12] Interestingly, no reaction of the methyl ether of the allylic alcohol **3a** was observed under the standard

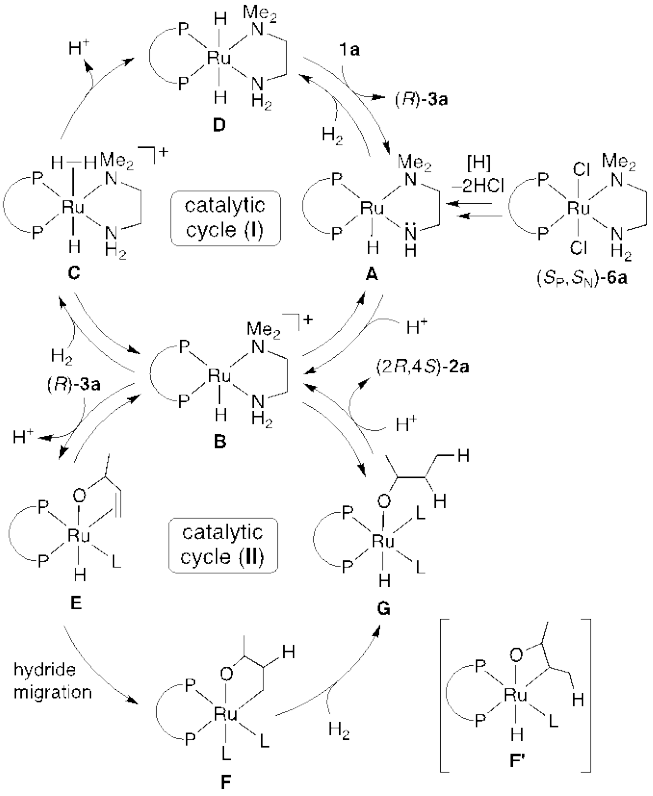


Scheme 2. Experiments for mechanistic consideration.

hydrogenation conditions. This suggested that the hydrogenation of **3a** occurred via formation of ruthenium alkoxide of the allylic alcohol.

A plausible mechanism for the double hydrogenation of α,β-unsaturated ketone **1a** with the (S_P,S_N)-**6a**/*t*-C_4H_9OK catalyst system consisting of dual catalytic cycles (**I**) and (**II**) is shown in Scheme 3. The catalytic cycle (**I**) hydrogenates α,β-unsaturated ketone **1a** to the allylic alcohol (*R*)-**3a**,[2,7] and the cycle (**II**) converts (*R*)-**3a** into the saturated alcohol (2*R*,4*S*)-**2a**. Catalytic cycle (**I**): (S_P,S_N)-**6a** is converted to the catalytic cycle species with the hydride source, H_2, in a base containing alcoholic solvent. The (RuH) amide complex **A** is reversibly converted to the cationic species **B** in the alcoholic media. The species **B** and H_2 form **C**, followed by deprotonation with the base to afford the (RuH_2) complex **D**. The active complex **D** readily hydrogenates **1a** to (*R*)-**3a** with regeneration of the amide complex **A** in equilibrium with **B**. Catalytic cycle (**II**): The allylic alcohol (*R*)-**3a** reversibly reacts with the cationic species **B** to form the allylic alkoxide complex **E** under a basic condition in which the diamine ligand DMAPEN is fully or partly removed from the Ru center to provide coordination sites for the alkene moiety of **3a**. The $N(CH_3)_2$ group confers the diamine ligand with the appropriate binding ability. Hydride migration from the Ru center to the β- or γ-position of the alkoxide affords the ruthenacyclic complex **F** or **F'**. Hydrogenolysis of the Ru–C bond of **F** or **F'** to convert these complexes to **G** followed by release of (2*R*,4*S*)-**2a** reproduces the cationic species **B**.

In summary, we report herein the first successful example of the double asymmetric hydrogenation of linear β,β-disubstituted



Scheme 3. Plausible mechanism of the double hydrogenation of enone **1a** through a dual catalytic system. P—P = (*S*)-DM-SEGPHOS; NMe_2—NH_2 = (*S*)-DMAPEN; L = DMAPEN or a weakly bonding compound.

α,β-unsaturated ketones, which we achieved by using a novel dual catalytic system of the DM-SEGPHOS/DMAPEN/Ru(II) complex with *t*-C_4H_9OK. This system is designed to reversibly form two hydrogenation catalysts, a catalyst type (I) and (II), where type (I) bears a diamine ligand DMAPEN and selectively hydrogenates the enone substrates to the chiral allylic alcohols, and type (II) lacks the diamine ligand and preferentially reduces the alkenyl groups of the allylic alcohols. Using this system, the γ-substituted secondary alcohols are obtained with high diastereo- and enantioselectivities in a one-pot reaction.

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Keywords: asymmetric catalysis • chiral alcohols • hydrogenation • ruthenium • unsaturated ketones

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[9] For hydrogenation of optically active or racemic secondary allylic alcohols with chiral catalysts, see the following. For Ru catalysts: a) M. Kitamura, I. Kasahara, K. Manabe, R. Noyori, H. Takaya, *J. Org. Chem*. **1988**, *53*, 708–710; b) Q. Chen, F.-L. Qing, *Tetrahedron* **2007**, *63*, 11965–11972. For Rh catalysts: c) J. M. Brown, I. Cutting, *J. Chem. Soc. Chem. Commun*. **1985**, 578–579; d) J. M. Brown, *Angew. Chem*. **1987**, *99*, 169–182; *Angew. Chem. Int. Ed. Engl*. **1987**, *26*, 190–203; e) J. Holz, B. Schäffner, O. Zayas, A. Spannenberg, A. Börner, *Adv. Synth. Catal.* **2008**, *350*, 2533–2543. For Ir catalysts: f) Y. Zhu, K. Burgess, *J. Am. Chem. Soc*. **2008**, *130*, 8894–8895.

[10] DEAPEN = 2-diethylamino-1-phenylethylamine; DMAPEN = 2-dimethylamino-1-phenylethylamine; DM-SEGPHOS = (4,4'-bi-1,3-benzodioxole)-5,5'-diylbis[di(3,5-xylyl)phosphane]; DPEN = 1,2-diphenylethylenediamine; TolBINAP = 2,2'-bis(di-4-tolylphosphanyl)-1,1'-binaphthyl; XylBINAP = 2,2'-bis(di-3,5-xylylphosphanyl)-1,1'-binaphthyl.

[11] Hydrogenation of enone **1a** with Ir catalysts bearing chiral sulfoximine-derived P,N-ligands (S/C = 100, 60 atm H_2, rt) gave the saturated ketone, 4-phenyl-2-pentanone, in 65–75% yield and in 79–81% *ee* accompanied by the saturated alcohol **2a** (diastereomeric structure was not mentioned) in 57–66% *ee* as a byproduct. See: S.-M. Lu, C. Bolm, *Chem. Eur. J.* **2008**, *14*, 7513–7516.

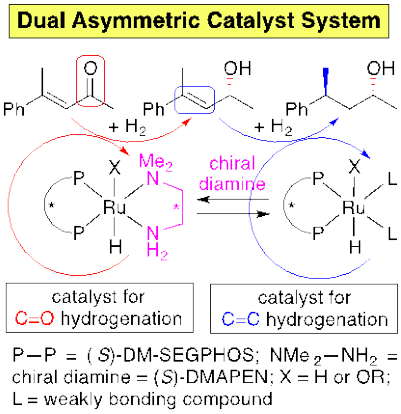
[12] The reason for a low deuterium content of 69% at the C2-position of the minor *syn*-$\mathbf{2a}_{d1}$ is not clear.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

A dual asymmetric catalyst system realizes double hydrogenation of linear β,β-disubstituted α,β-unsaturated ketones into the γ-substituted secondary alcohols with high diastereo- and enantioselectivities. The Ru catalyst with a diamine ligand hydrogenates the enones to the allylic alcohols exclusively, and then the reversibly formed catalyst without diamine selectively reduces the allylic alcohols to the saturated alcohols.



P—P = (*S*)-DM-SEGPHOS; NMe_2—NH_2 = chiral diamine = (*S*)-DMAPEN; X = H or OR; L = weakly bonding compound

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Double Asymmetric Hydrogenation of Linear β,β-Disubstituted α,β-Unsaturated Ketones into γ-Substituted Secondary Alcohols with Dual Catalytic Systems