VIP Asymmetric Catalysis

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Enantioselective Isomerization of Primary Allylic Alcohols into Chiral Aldehydes with the tol-binap/dbapen/Ruthenium(II) Catalyst**

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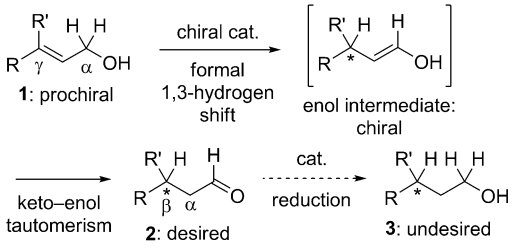
Asymmetric isomerization of primary allylic alcohols is a direct and simple transformation to afford optically active aldehydes (Scheme 1).[1] In the presence of an appropriate chiral catalyst, one of the α hydrogens of a prochiral allylic alcohol **1** is formally transposed to the γ position (1,3-hydrogen shift) with migration of the C–C double bond to give the chiral enol intermediate. The following keto–enol tautomerism produces the desired aldehyde **2** with a stereogenic center at the β position. Undesired reduction of **2** to afford the saturated alcohol **3** is a significant problem under reductive conditions. High reactivity (resulting in low catalyst loading), enantioselectivity, and chemoselectivity are major requirements to achieve an efficient isomerization, leading to highly productive environmentally benign reaction.



Scheme 1. Reaction pathway in the enantioselective isomerization of primary allylic alcohols.

Studies on this asymmetric reaction with Rh catalysts bearing planar chiral phospha ferrocene ligands were reported by Fu and co-workers.[2,3] The isomerization of **1** ($R = C_6H_5$, $R' = iC_3H_7$) with a substrate-to-catalyst molar ratio (S/C) of 100 in THF at 100 °C for 67 h gave the aldehyde **2** in 94 % yield and 90 % *ee*.[2] A range of *E*- and *Z*-configured aryl-substituted alcohols **1** (R or R′ = aryl group) and a non-aromatic substrate **1** (R = cyclohexyl, $R' = CH_3$) were reacted with an S/C of 20 to afford **2** with 57–92 % *ee*. Mazet and co-workers reported that the Ir complexes with chiral phosphane–oxazoline ligands activated by addition of H_2, catalyzed the transformation of *E*-configured aryl-substituted alcohols **1** with large alkyl groups (R = aryl, R′ = secondary or tertiary alkyl) at an S/C of 20 at 23 °C to give products **2** with > 98 % *ee*.[4,5] However, the *Z* isomers and aliphatic substrates reacted with moderate enantioselectivity. Andersson and co-workers modified the chiral ligand of this catalyst; the use of this modified catalyst resulted in high enantioselectivity for the reactions of the *Z* substrates.[6] However, the insufficient catalytic activity and limited substrate scope remain as unsolved problems. Recently, Sowa and co-workers reported asymmetric reduction of primary allylic alcohols **1** to saturated alcohols **3** through the tandem process of asymmetric isomerization of **1** into the aldehydes **2** with a subsequent transfer hydrogenation of **2** catalyzed by the $\{RuCl_2(cod)\}_n$–tol-binap system or [RuCl(*p*-cymene)(tol-binap)]Cl in a basic solution of 2-propanol at 83–100 °C with an S/C of 10–33.[7,8] Geraniol derivatives were reduced with high enantioselectivity, but this process could not selectively give the chiral aldehydes **2** as products because the RuH species, formed in situ, catalyzed both isomerization and reduction.[9,10]

We have studied the asymmetric hydrogenation of aryl vinyl ketones to the chiral allylic alcohols catalyzed by the $[RuCl_2(tol\text{-}binap)(dmapen)]$–$tC_4H_9OK$ system in 2-propanol.[11–13] The corresponding saturated ketone was obtained in a small amount as a by-product through isomerization (achiral in this case) of the allylic alcohol. This finding prompted us to investigate asymmetric isomerization of primary allylic alcohols into the chiral aldehydes with the tol-binap/1,2-diamine/Ru^{II} catalysts.

We primarily focused on the influence of the structure of diamine, the second ligand, on the reactivity and enantioselectivity of the isomerization. The use of 2-dibutylamino-1-phenylethylamine (dbapen), gave an excellent result in the isomerization of (*E*)-4-methyl-3-phenyl-2-penten-1-ol (**1a**; Table 1). Thus, the reaction of **1a** (3 mmol) in the presence of ($S_R R_N$)-**4a** (3 μmol, S/C = 1000) and KOH (15 μmol) in ethanol at 25 °C for 1 h afforded the *R* aldehyde **2a** in 90 % yield with > 99 % *ee* and a small amount of the saturated alcohol **3a** with > 99 % *ee* (Table 1, entry 1). The aldehyde product **2a** was oxidized, and converted into the ethyl ester in ethanol in < 2 %.[14] Owing to the significantly high catalytic activity a turnover number (TON) of about 1550 in 1 h was achieved without loss of enantioselectivity in the reaction with an S/C of 2000 (Table 1, entry 2). To our knowledge, this is the highest TON and also TOF (TON h^{-1}) for the asymmetric isomerization of primary allylic alcohols with a trisubstituted alkene moiety. Ethanol was the best solvent; the use of 2-propanol, methanol, or *tert*-butyl alcohol resulted

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dbapen = 2-dibutylamino-1-phenylethylamine, tol-binap = 2,2′-bis(di-4-tolylphosphanyl)-1,1′-binaphthyl.

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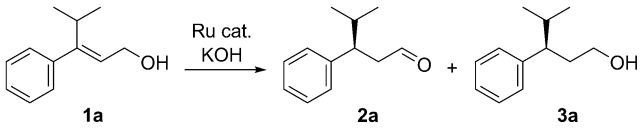
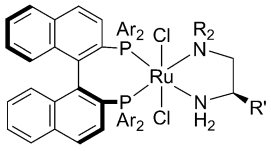
Table 1: Enantioselective isomerization of allylic alcohol **1a** into aldehyde **2a**.[a]



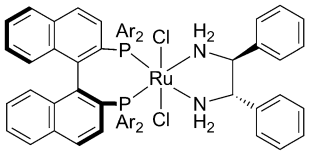
1a **2a** **3a**

Entry	Ru cat.	S/C[b]	Solvent	Conv. [%][c]	Yield [%][c]		*ee* [%][c]	
					2a[d]	**3a**	**2a**	**3a**
1	**4a**	1000	EtOH	99	90(80)[e]	7	>99	>99
2	**4a**	2000	EtOH	78	75	3	>99	>99
3	**4a**	1000	*i*PrOH	56	55	<1	>99	nd
4	**4a**	1000	MeOH	48	45	2	>99	>99
5	**4a**	900	*t*BuOH	25	23	<1	>99	nd
6	**4a**	1000	–[f]	79	79	<1	>99	nd
7	**4a**	1000	THF	7	6	1	93	94
8	**4a**	900	toluene	20	16	2	>99	nd
9	**4b**	1000	EtOH	99	84	12	>99	>99
10	**4c**	1000	EtOH	25	7	<1	nd	nd
11	**5**	1000	EtOH	1	<1	<1	nd	nd
12	**6**	1000	EtOH	91	79	9	>99	>99
13	**7**	1000	EtOH	48	45	2	>99	>99
14	**8**	1000	EtOH	88	77	11	>99	>99
15	**9**	1000	EtOH	<1	<1	<1	nd	nd
16	**10**	1000	EtOH	6	5	<1	>99	nd

[a] Reactions were carried out using 1–3 mmol of allylic alcohol **1a** in solvent containing the Ru catalyst and KOH (Ru/KOH = 1:5) at 25 °C for 1 h. [b] Substrate/catalyst molar ratio. [c] Determined by GC analysis on a chiral stationary phase. [d] Less than 2% of the ethyl ester was contained in some cases. [e] The yield of the isolated product is given in parentheses. [f] *t*BuOH/MeOH = 3:1. cod = 1,5-cyclooctadiene, *p*-cymene = 1-methyl-4-(1-methylethyl)benzene, nd = not determined.



(S_P,R_N)-**4**: Ar = 4-$CH_3C_6H_4$
a: R = nC_4H_9, R' = C_6H_5
b: R = nC_4H_9, R' = H
c: R = CH_3, R' = C_6H_5



(S_P,S_N)-**5**: Ar = 4-$CH_3C_6H_4$

[$RuCl_2${(*S*)-tol-binap}(dmf)$_n$
(*S*)-**6**

[RuCl{(*S*)-tol-binap}(*p*-cymene)]Cl
(*S*)-**7**

1/*n* {$RuCl_2$(cod)}$_n$–(*S*)-tol-binap
(*S*)-**9**

[$(C_2H_5)_2NH_2$][RuCl{(*S*)-tol-binap}$_2$(μ-Cl)$_3$]
(*S*)-**8**

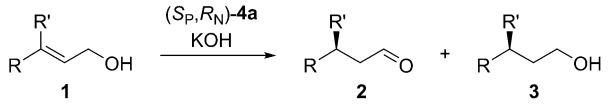
[$Ru(OCOCH_3)_2${(*S*)-tol-binap}]
(*S*)-**10**

in a slower reaction rate, although the almost perfect enantioselectivity was maintained (Table 1, entries 3–5). Interestingly, the use of a 3:1 mixture of *tert*-butyl alcohol and methanol gave a faster reaction rate than the use of either solvent alone, thus suggesting the importance of the hydrogen-bond network in the alcohol solvent for this reaction (Table 1, entry 6). Aprotic THF and toluene gave unsatisfactory results with regard to the rate (Table 1, entries 7 and 8).

The isomerization in the presence of complex **4b** with the achiral *N*,*N*-dibutyl diamine (R′ = H) afforded **2a** in >99% *ee*, but the saturated alcohol **3a** was formed in more than 10% yield (Table 1, entry 9). Notably, the size of the N substituent (R) of the diamine ligands had a major impact on the reaction rate. Thus, the reaction with **4c**[11,12] bearing dmapen (R = CH_3) under typical conditions gave **2a** in only 7% yield (Table 1, entry 10). No isomerization products were formed when complex **5**,[13,15] having no N substituents, was employed (Table 1, entry 11). Ru complex **6**[16] bearing DMF as the second ligand (oligomeric form; n = approximately 2) showed moderate reactivity and chemoselectivity, but the *ee* value for **2a** was >99% (Table 1, entry 12). The cationic and dimeric tol-binap/RuCl type complexes **7**[17] and **8**[18] showed relatively lower catalytic activity (Table 1, entries 13 and 14). The catalyst system **9** consisting of $[RuCl_2(cod)]_n$ and tol-binap, which was utilized in the isomerization/transfer hydrogenation tandem reaction by Sowa and co-workers, did not work at all under the reaction conditions employed (Table 1, entry 15).[7] The use of $Ru(OCOCH_3)_2$ complex **10**, which is an efficient catalyst for hydrogenation of allylic alcohols, resulted in a sluggish isomerization (Table 1, entry 16).[19]

A series of allylic alcohols **1** with aromatic and aliphatic substituents was selectively converted into the chiral aldehydes **2** in excellent enantiomeric excess (Table 2). The isomerization of the *E* substrate **1b** with a tolyl group instead of a phenyl group proceeded with comparable reactivity and

Table 2: Enantioselective isomerizatioin of allylic alcohols **1** into aldehydes **2**.[a]



1 **2** **3**

a: R = C_6H_5, R' = iC_3H_7
b: R = 4-$CH_3C_6H_4$, R' = iC_3H_7
c: R = 4-$CH_3OC_6H_4$, R' = iC_3H_7
d: R = 4-ClC_6H_4, R' = iC_3H_7
e: R = C_6H_5, R' = *cyclo*-C_6H_{11}
f: R = C_6H_5, R' = C_2H_5
g: R = C_6H_5, R' = CH_3
h: R = iC_3H_7, R' = C_6H_5
i: R = CF_3, R' = C_6H_5
j: R = *cyclo*-C_6H_{11}, R' = CH_3
k: R = $(CH_3)_2C{=}CH(CH_2)_2$, R' = CH_3
l: R = CH_3, R' = $(CH_3)_2C{=}CH(CH_2)_2$
m: R = nC_4H_9, R' = CH_3

Entry	1	S/C[b]	*t* [h]	Conv. [%][c]	Yield [%][c]		*ee* [%][d]	
					2[e]	**3**	**2**	**3**
1[f]	**1a**	1000	1	99	90(80)	7	>99	>99
2	**1b**	900	1	98	87(80)	6	>99	>99
3	**1c**	1100	1	77	74(69)	2	>99	nd
4	**1d**	900	1	>99	92(78)	7	99	96
5	**1e**	1000	0.5	>99	92(81)	7	>99	>99
6	**1f**	200	1	79	70(67)	7	>99	84
7	**1g**	100	1	62	50(41)	10	99	78
8	**1h**	300	1	63	50(36)	10	>99	>99
9	**1i**	400	1	60	53(52)	5	>99[g]	nd
10	**1j**	600	1	62	58(58)	2	>99	nd
11	**1k**	200	1	61	58(58)	2	>99	nd
12	**1l**	200	1	92	83(68)	7	>99	nd
13	**1m**	100	1	89	75(59)	11	>99	nd

[a] Reactions were carried out using 0.4–1 mmol of allylic alcohol **1** in ethanol containing the Ru catalyst **4a** and KOH (Ru/KOH = 1:5) at 25 °C. The yield of the isolated product is given in parentheses. [b] Substrate/catalyst molar ratio. [c] Determined by GC or ^{1}H NMR analysis. [d] Determined by GC or HPLC analysis on a chiral stationary phase. [e] Less than 2% of the ethyl ester was contained in some cases. [f] 3 mmol scale reaction. [g] The absolute configuration was not determined.

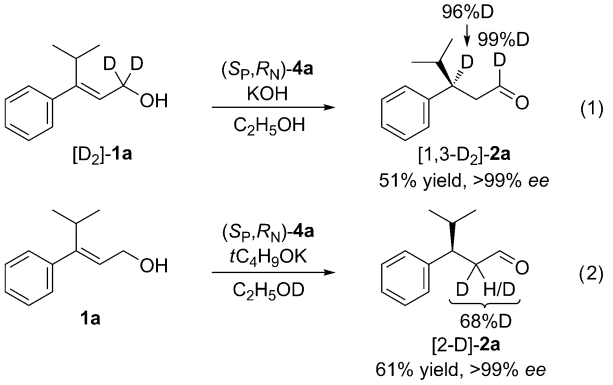
chemo- and enantioselectivity to those observed for the reaction of **1a** (Table 2, entries 1 and 2). The use of the substrate **1c**, having the electron-donating 4′-CH_3O substituent on the phenyl ring, slightly decreased the reaction rate but the high enantioselectivity was maintained (Table 2, entry 3). The use of **1d** with the electron-withdrawing Cl at the 4′-position on the phenyl ring accelerated the reaction (Table 2, entry 4). The isomerization of the (*E*)-3-cyclohexyl-3-phenyl-2-propen-1-ol (**1e**) was complete within 30 min to yield almost enantiomerically pure **2g** in 92% yield (Table 2, entry 5). The Ru catalyst had a shorter lifespan in the reactions of the phenyl ethyl (**1f**) and phenyl methyl (**1g**) allylic alcohols (Table 2, entries 6 and 7).[20] Therefore, complete conversion of the substrates was not achieved even with a larger catalyst loading (S/C = 100–200). However, the enantioselectivity of the products **2f** and **2g** was excellent.[21]

The isomerization of (*Z*)-4-methyl-3-phenyl-2-penten-1-ol (**1h**) afforded the *S* aldehyde **2h** in >99% *ee* (Table 2, entry 8), although the reactivity and chemoselectivity were lower than those in the reaction of the corresponding *E* substrate **1a** yielding the *R* aldehyde in >99% *ee* (see Table 2, entry 1).[22] The presence of the strongly electron-withdrawing group CF_3 at the γ position did not affect the enantioselectivity (Table 2, entry 9). Thus, the CF_3-substituted product **2i** was obtained in almost enantiomerically pure form.

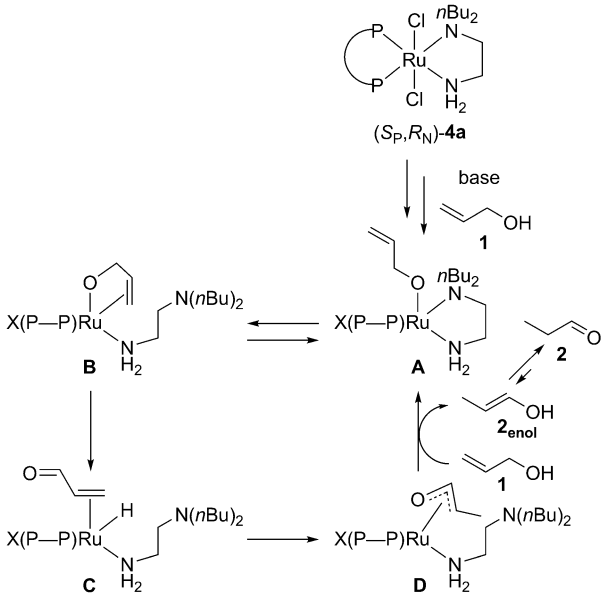
The reaction of the aliphatic substrate (*E*)-3-cyclohexyl-2-buten-1-ol (**1j**) with an S/C of 600 selectively afforded the chiral aldehyde **2j** in >99% *ee* (Table 2, entry 10). Geraniol (**1k**; *E* isomer) and nerol (**1l**; *Z* isomer) were transformed to (*R*)-citronellal (**2k**) and the *S* enantiomer **2l**, respectively, in >99% *ee* in both cases (Table 2, entries 11 and 12). **2k** is a key intermediate for the industrial synthesis of (−)-menthol.[23] It is worth noting that almost perfect enantioselectivity was achieved in the isomerization of the (*E*)-3-methyl-2-hepten-1-ol (**1m**; Table 2, entry 13). To our knowledge this is the first example of an isomerization showing high enantioselectivity for the allylic alcohols with a simple primary alkyl and methyl substituents.

The isomerization of the 1,1-dideuterated allylic alcohol [D_2]-**1a** under the standard conditions (S/C = 1000, 25 °C, 1 h) afforded the 1,3-dideuterated aldehyde [1,3-D_2]-**2a** in 51% yield and >99% *ee* [Scheme 2, Eq. (1)]. The high deuterium content of 96% at the C3-position indicates that a deuterium at the C1-position of [D_2]-**1a** predominantly migrated to the C3-position with perfect enantioselectivity. The reaction of **1a** in C_2H_5OD resulted in the deuterated aldehyde at the C2-position [2-D]-**2a** [Scheme 2, Eq. (2)]. Potassium *tert*-butoxide was used as a base instead of KOH to avoid formation of water. The deuterium content of 68% suggests that the aldehyde product was formed through the enol, which was protonated by the alcoholic media.

A plausible mechanism of the isomerization of allylic alcohols **1** with the (S_P,R_N)-**4a**/KOH catalyst system is shown in Scheme 3. The reaction requires a catalytic amount of alkaline base to achieve high reactivity, thus implying that **4a** is converted into the Ru allylic oxide complex **A**,[9b,24] in which X is an anionic ligand, such as Cl, OR, or H.[25] The Ru



Scheme 2. Deuterium labeled experiments.



Scheme 3. Plausible mechanism of isomerization of allylic alcohols **1** with (S_P,R_N)-**4a** in the presence of a base in ethanol. P—P = (*S*)-tol-binap; N(nBu)$_2$—NH_2 = (*R*)-dbapen; X = Cl, OR, H, etc.

complex **A** equilibrates with the olefin-coordinated species **B** through liberation of the N(nBu)$_2$ group of dbapen. The bulkiness of the N(nBu)$_2$ moiety in the Ru complex causes this ligand to be hemilabile.[26] β-Hydride elimination in species **B** forms a Ru hydride complex containing an α,β-unsaturated aldehyde (**C**). Hydride migration from the Ru center to the β-position of the enal affords the η^3-oxaallyl complex **D**. Replacement of the enol $\mathbf{2}_{enol}$ with the allylic alcohol **1** regenerates the Ru complex **A**. Reforming the chelate structure with dbapen could promote the release of $\mathbf{2}_{enol}$. Enol $\mathbf{2}_{enol}$ is readily converted into the aldehyde **2** in the presence of ethanol.

The enantioselectivity of this isomerization is only controlled by the tol-binap ligand, because the catalyst system of the Ru complex **6** without the diamine also showed excellent enantioselectivity (see Table 1, entry 12). Dbapen appears to be hemilabile enough to efficiently promote the reaction at the **D**→**A** step in the catalytic cycle. Use of the catalyst

systems involving **4c** and **5** bearing strong bidentate diamine ligands dramatically decreases the reactivity (see Table 1, entries 10 and 11), because the formation of the species **B** is prevented.

In summary, we have reported here the efficient enantioselective isomerization of primary allylic alcohols into the chiral aldehydes catalyzed by the [$RuCl_2$(tol-binap)-(dbapen)]/KOH system in ethanol. The reaction was carried out with an S/C in the range of 100–2000 at 25 °C for 0.5–1 h. A TON of about 1550 was achieved in the best case. A series of *E*- and *Z*-configured γ-substituted aromatic and aliphatic allylic alcohols, including a simple primary alkyl-substituted compound (*E*)-3-methyl-2-hepten-1-ol, were converted into the β-substituted aldehydes in at least 99 % *ee*. A plausible mechanism for this reaction, which is promoted by the hemilability of the dbapen/Ru chelate structure, was also discussed.

Experimental Section

Reaction procedure for the isomerization of **1a**: Ru complex (S_bR_N)-**4a** (3.2 mg, 2.9 μmol) was placed in a glass Schlenk flask with a magnetic stir bar. The flask was evacuated and refilled with argon. Allylic alcohol **1a** (513.6 mg, 2.91 mmol), ethanol (13.6 mL), and 15 mM KOH in ethanol (0.98 mL, 15 μmol) were added to the Schlenk flask through a syringe. The reaction mixture was stirred at 25 °C for 1 h, and a small aliquot was analyzed by GC (90 % yield, > 99 % *ee*). The solution was filtered through a short pad of silica gel by eluting with ether or methanol. After concentration, the residue was purified by silica gel column chromatography (eluted with *n*-hexane/ether = 7:1), to give (*R*)-4-methyl-3-phenylpentanal (**2a**) (colorless oil, 411.4 mg, 2.33 mmol, 80 %). $[\alpha]_D^{22} = -14.2$ ($c = 1.57$, CH_2Cl_2) [lit.,[2b] $[\alpha]_D^{20} = -17.3$ ($c = 1.38$, CH_2Cl_2, for *R* enantiomer with 92 % *ee*)]. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.77$ (d, $J = 6.7$ Hz, 3H), 0.95 (d, $J = 6.7$ Hz, 3H), 1.81–1.93 (m, 1H), 2.71–2.84 (m, 2H), 2.93–2.98 (m, 1H), 7.13–7.23 (m, 3H), 7.27–7.31 (m, 2H), 9.60 ppm (t, $J = 2.2$ Hz, 1H). GC analysis: column: CHIRASIL-DEX CB (0.32 mm × 25 m, depth of film = 0.25 μm); carrier gas: helium (60 kPa); column temp: 50 °C, 12 min hold, heating to 145 °C at a rate of 1 °C min^{-1}; detection: FID; retention time of (*R*)-**2a**: 73.7 min (> 99 %).

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[21] The isomerization/transfer hydrogenation tandem reaction of **1g** with the $[RuCl_2(cod)]_n$–tol-binap catalyst system (S/C = 10, 100 °C, 12 h) gave **3g** in 72 % *ee* (see Ref. [7]).

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