Asymmetric Catalysis

DOI: 10.1002/ange.201107910

Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Allylic Alcohols by an Enantioselective Isomerization/Transfer Hydrogenation Mechanism**

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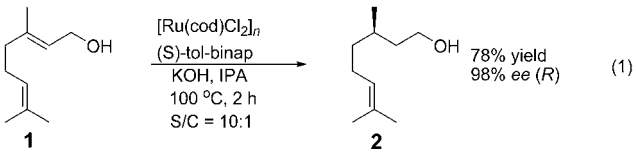
Asymmetric transfer hydrogenation (ATH) has emerged as a major pathway in asymmetric catalysis since it can be performed with a large variety of substrates, experimental simplicity, and a high level of enantiocontrol. In addition, it uses economical and environmentally friendly hydrogen sources (isopropyl alcohol, formate), and the operational safety is better than of traditional asymmetric hydrogenation using hydrogen gas.[1] ATH has been applied to enantioselective reduction of ketones/aldehydes,[2] imines,[3] activated olefins,[4] and aromatic heterocycles.[5] However, in spite of examples of gaseous asymmetric hydrogenation of allylic alcohols,[6] and non-asymmetric Ru-catalyzed reduction of allylic alcohols through an isomerization/transfer hydrogenation mechanism recently reported by Cadierno et al.,[7] there are no published cases of ATH of these important substrates. Allylic alcohols are abundant in natural sources such as essential oils, and widely used as starting materials and/or major components in food, fragrance and pharmaceutical industries.[8] Herein, we report the first ATH of allylic alcohols—a reaction that occurs through an enantioselective isomerization/transfer hydrogenation mechanism with high enantioselectivity and yield.

Initially, we developed the ATH of geraniol (**1**; 0.01 M) in isopropyl alcohol (IPA) with 2 equiv of KOH per Ru atom by using an in situ prepared mixture of $[Ru(cod)Cl_2]_n$ and (S)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl(Ru/(*S*)-tol-binap) catalyst [Eq. (1); cod = cyclooctadienyl]. After degassing, the reaction was run at 100 °C for 2 h to produce (*R*)-citronellol (**2**) in 78 % isolated yield and 98 % *ee*.



(1)

It is remarkable to note that the yield, *ee* and configuration is equivalent to those of gaseous asymmetric hydrogenation which must be performed at very high pressures of 70–100 atm.[9] However, the ATH conditions are much safer as they are performed at only a slightly elevated pressure due to the volatility of IPA at 100 °C. As will be discussed later, the reaction can be run effectively at the boiling point of IPA by using [{(*S*)-tol-binap}$RuCl_2$(*p*-cymene)].

According to Equation (1), a substrate/catalyst molar ratio of 10:1 is necessary to obtain full conversion. As with ATH reactions of ketones, the reaction is catalytic in KOH.[10] The optimum amount of KOH is 2 equiv with respect to Ru. For example, 1.4 equiv of KOH leads to less than 30 % conversion in 22 h. When KOH is increased to 2.9 equiv per Ru, by-products rise to 12 % and the *ee* decreases. One of the major by-products is γ-geraniol,[11] which is observed to undergo ATH to citronellol in low *ee* (see below).

Other hydrogen donors tested were cyclohexanol and 2-pentanol. Both alcohols convert geraniol to citronellol within 2 to 4 h in moderate *ee* (Table 1). However, the high boiling point of cyclohexanol (160 °C) made isolation difficult and the *ee* only ranged from 66 to 72 %. An interesting effect occurs with a chiral hydrogen donor, such as *rac*-, (*S*)- and (*R*)-2-pentanol. The highest enantioselectivity occurs with either the racemic alcohol (77–79 % *ee*) or (*S*)-2-pentanol (72 % *ee*), whereas (*R*)-2-pentanol gives low selectivity (26 % *ee*). This indicates that the chirality of the hydrogen donor can play an important role in the enantioselectivity of this process.

Table 1: Asymmetric transfer hydrogenation of geraniol in different solvents/hydrogen donors.[a]

Entry	Solvent	*T* [°C]	Conv. [%][b]	*ee*[c] (*R*)
1	IPA	100	100	98
2	2-pentanol	100	84	79
3	2-pentanol	120	100	77
4	(*S*)-2-pentanol	120	100	72
5	(*R*)-2-pentanol	120	100	26
6	cyclohexanol[d]	100	74	72
7	cyclohexanol[d]	160	100	66

[a] Reaction time is 2 h. [b] Conversions measured by GC. [c] *ee* analysis measured with a GC Column RT-BetaDEXsa 30 m × 0.32 mm ID × 0.25 μm. [d] Reaction time is 4 h.

The ATH of geraniol in IPA was evaluated with other chiral diphosphine ligands. Table 2 shows that the bidentate ligands (*S*)-tol-binap, (*R*)-binap and (*S*,*S*)-*i*PrDuPhos produced the highest conversions and enantioselectivities. With

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[**] We thank Dr. Mahavir Prashad, Head of Chemical Development Unit, Novartis Pharmaceuticals Corporation (East Hanover, NJ), for the support of R.W.'s Ph.D program. We also thank Merck and Co., Inc., for supporting a doctoral fellowship for J.M.L. We thank Celgene Corp. for assistance with ^2H NMR spectroscopy.

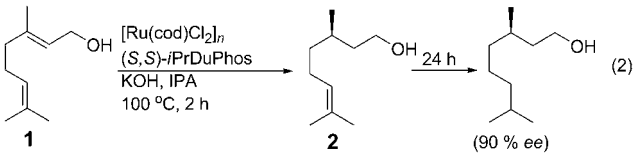
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107910.

Table 2: ATH of geraniol with different chiral ligands.

Entry	Ligand	*t* [h]	% Citronellol[a] (conv. [%][a])	*ee* [%],[b] config
1	(*S*,*S*)-diop	20	31 (38)	0
2	(*S*)-PhanePhos	29	20 (24)	9, *R*
3	(*S*,*S*)-MeDuPhos	2	80 (92)	75, *R*
4	(*S*,*S*)-Et-bpe	2	56 (80)	31, *R*
5	(*S*)-tol-binap	2	98 (100)	98, *R* (78%)[c]
6	(*R*)-binap	2	92 (100)	87, *S*
7	(*S*,*S*)-*i*PrDuPhos	2	50 (100)	84, *R*
8[c]	(*S*,*S*)-*i*PrDuPhos	24	98[d] (100)	90, *R*[d]

[a] Conversions and yields measured by GC. [b] *ee* analysis measured on the (*R*)-Mosher ester on a Chiralcel OJ-H column (Daicel, 250 mm × 4.6 mm). [c] 78% yield of isolated product by column chromatography. [d] Yield and *ee* of dihydrocitronellol; molar ratio of geraniol/$[Ru(cod)Cl_2]_n$/KOH/ligand = 2:1:2:2.

(*S*,*S*)-*i*PrDuPhos (entries 7 and 8, Table 2), the reduction of the prochiral double bond is complete at 2 h but after 24 h both the allylic and the unfunctionalized C6–C7 double bonds are reduced (note: S/C is 2:1) to give (*R*)-dihydrocitronellol in 90% *ee* [Eq. (2)]. This indicates that Ru/*i*PrDuPhos is a more reactive catalyst than Ru/tol-binap.



(2)

Catalysts with (*S*)-tol-binap and (*S*,*S*)-*i*PrDuPhos were selected for further evaluation for ATH of allylic alcohols nerol (**3**), 3-phenyl-2-buten-1-ol (**4**), *trans*-*trans*-farnesol (**5**), and homoallylic alcohol γ-geraniol (**6**).[11] Other prochiral olefin substrates include 3-phenylbut-2-enoic acid (**7**), 3-methylcyclohex-2-enone (**8**), and *trans*-methylstilbene (**9**).[12] Table 3 shows the isolated/GC yields and enantioselectivities for substrates **1** to **9**. Nerol (**3**) is reduced to (*S*)-citronellol in 70% isolated yield and 93% *ee* with (*S*)-tol-binap and the chirality of the product is the same as in the gaseous asymmetric reaction.[9] DuPhos ligands are known to give the same configuration with either *E* or *Z* olefins under gaseous hydrogenation;[13] similarly, ATH of geraniol (**1**) and nerol (**3**) with (*S*,*S*)-*i*PrDuPhos both give (*R*)-citronellol in 83–84% *ee*. The substrate 3-phenyl-2-buten-1-ol (**4**) gives 90% isolated yield but lower *ee* (72%) with (*S*)-tol-binap. Since **4** it is not susceptible to over-reduction, it is best reduced with (*S*,*S*)-*i*PrDuPhos giving (*R*)-3-phenylbutan-1-ol in 99% yield (GC), 93% *ee*.

Low enantioselectivity is observed for other prochiral substrates **6**–**9**. Better results have been reported for α,β-unsaturated acids[4g,14] and ketones.[1h,15] The ATH of γ-geraniol (**6**) occurs in 41% conversion in 2 h and 51% in 6 h. At higher base concentration (4 equiv KOH), the extent of conversion increases to 88% in 2 h, but the *ee* decreases to 8%. These results are in contrast with the gaseous hydrogenation of γ-geraniol which is very rapid and occurs in high *ee* (93% *ee*).[11] These results indicate that this reaction is most suited for ATH of allylic alcohols and suggest a specific mechanism (see below).

Since the in situ catalyst preparation method leads to an imprecisely defined catalyst precursor, we were interested in

Table 3: ATH of various substrates with (*S*)-tol-binap (A) and (*S*,*S*)-*i*PrDuPhos (B).

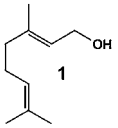
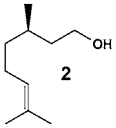
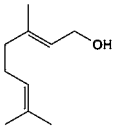
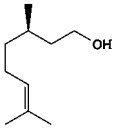
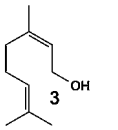
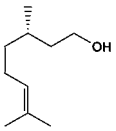
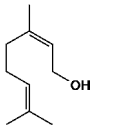
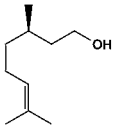
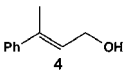
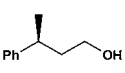
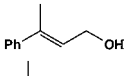
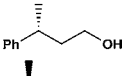
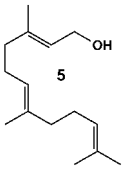
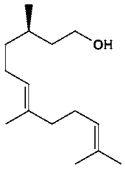
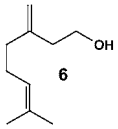
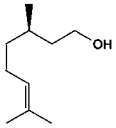
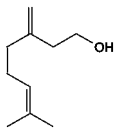
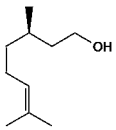
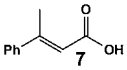
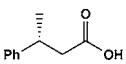
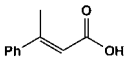
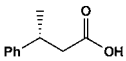
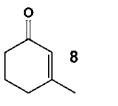
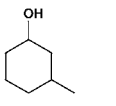
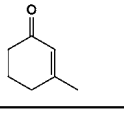
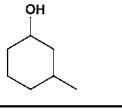
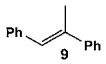
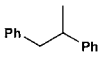
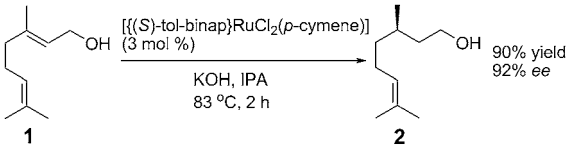
	Substrate	Product	Ligand	*t* [h]	% Product[a] (conv. [%][a])	*ee* [%], config[c]
1			A	2	98 [78][b] (100)	98, *R*
2			B	2	50 (100)	84, *R*
3			A	2	96 [70][b] (100)	93, *S*
4			B	24	62 (100)	83, *R*
5			A	12	99 [90][b] (100)	72, *S*
6			B	2	99 (100)	93, *R*
7			A[f]	16[g]	82 [65][b] (100)	81, *R*
8			A	2 6	19 (41) 36 (51)	34, *R* 33, *R*
9[e]			A	2 6	64 (88) 64 (87)	7, *R* 8, *R*
10[c]			A	96	93 (98)	12, *R*
11			B	2	96 (100)	9, *R*
12			A	48	23 6 (97)	17, *cis*, *S*,*R* 16, *trans*, *R*,*R*
13			B	1	34 9 (98)	8, *cis*, *S*,*R* 14, *trans*, *R*,*R*

Table 3: (Continued)

	Substrate	Product	Lig-and	*t* [h]	% Product[a] (conv. [%][a])	*ee* [%], config[c]
14			B	24	18 (18)	0

[a] Conversions and yield determined by GC. [b] Yield of isolated products. [c] *ee* of entries 1–4, 8, and 9 were measured by HPLC with the (*R*)-Mosher ester on an OJ-H column or GC column RT-BetaDEXsa 30 m × 0.32 mm ID × 0.25 μm; *ee* of entries 5 and 6 were measured with the acetate on an OJ-H column; *ee* of entries of 10, 11, and 14 were measured directly on an OJ-H column; for entries 12 and 13 the *cis/trans* isomers were measured by GC on a DB-23 column (J&W Scientific, 15 m × 0.32 mm) and the *ee* of the *trans* isomer was measured by proton-decoupled ^{13}C NMR spectroscopy. [d] 2.5 equiv of KOH per substrate was used. [e] 4 equiv of KOH per substrate was used. [f] [$RuCl_2${(*S*)-tol-binap}(*p*-cymeme)] as catalyst. [g] Reaction temperature 83 °C.

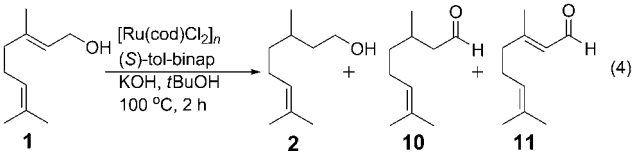
performing ATH with a pre-made catalyst. With [{(*S*)-binap}$RuCl_2$] geraniol was converted to (*R*)-citronellol in 93% *ee* and 85% isolated yield. This *ee* is higher than that obtained from the in situ prepared (*R*)-binap complex (Table 2 entry 6, 87% *ee*) with, of course, the opposite configuration. This catalyst also converts nerol (**3**) to (*S*)-citronellol in 91% *ee*. So far, [{(*S*)-tol-binap}$RuCl_2$(*p*-cymene)] has proven to be the easiest to handle catalyst as indicated by the ability to use higher concentrations of geraniol (0.1M), lower catalyst loading (3 mol%), and lower temperature (83 °C) [Eq. (3)].



(3)

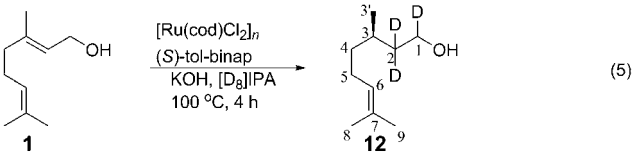
It is intriguing that the reaction gives the same stereochemical configuration as the gaseous reaction but that the scope is limited to allylic alcohols. Thus, we investigated the reaction mechanism. Enantioselective isomerization of allylic amines to enamines is a well-developed transformation and has been applied at industrial scale.[9c,16] The isomerization of allylic alcohols has been extensively studied in recent years,[7,17] and there are several reports of the asymmetric version of this process.[18] As previously discussed, Cadierno et al. reported a nonchiral ruthenium-catalyzed isomerization/transfer hydrogenation of allylic alcohols in which a ketone intermediate was clearly identified.[7] Experiments to determine the reaction mechanism are described below.

The first experiment involved using the ATH conditions in THF solvent [Eq. (4)] and resulted in 47% conversion to give 13% of citronellol (**2**), 21% of citronellal (**10**), and 13% of citral (**11**). This result indicates geraniol itself becomes the hydrogen donor giving the hydrogenated product citronellol (**2**) and the dehydrogenated product citral (**11**). Citronellal (**10**) forms as an intermediate in the isomerization of geraniol.[7]



(4)

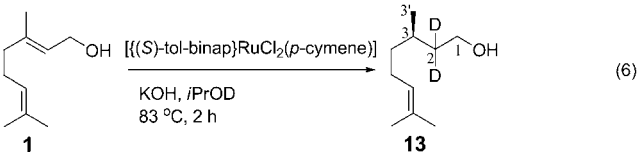
Several deuterium labeling experiments were then performed. The ATH of geraniol with [D_8]IPA [Eq. (5)] produced [D_3]citronellol (**12**) as the major product after aqueous workup. This structure was confirmed by GC/MS and NMR spectroscopy.



(5)

The GC/MS showed a molecular ion peak with a mass of 159, which indicated the formation of [D_3]citronellol (**12**). The ^{1}H NMR spectrum indicated only one hydrogen was present on C1. The presence of two deuteriums on C2 and the absence of deuterium on C3 was confirmed by ^{13}C NMR and HMQC spectroscopy. Because of **12**, we can rule out both gaseous hydrogenation and outer-sphere hydrogen transfer mechanisms.[6]

ATH of geraniol with *i*PrOD [Eq. (6)] produced after aqueous workup [D_2]citronellol (**13**) as confirmed by GC/MS and NMR spectrsocopy.

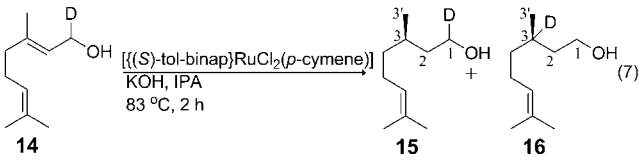


(6)

The GC/MS showed a molecular ion peak of 158 corresponding to [D_2]citronellol (**13**). The ^{1}H NMR, COSY and ^{13}C-DEPT135 results showed no detectable hydrogen on the C2 position; the ^{13}C NMR spectrum showed clear coupling between C2 and two deuterium atoms.

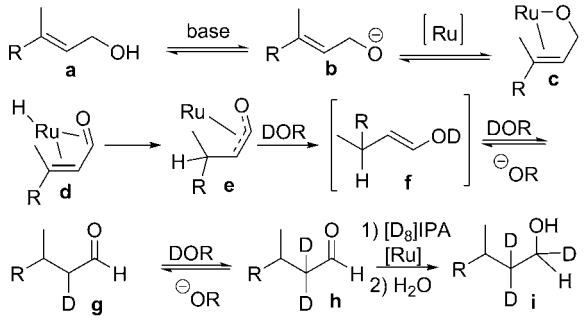
Finally, another key deuterium labeling experiment was the ATH of 2-deuteriogeraniol[19] (**14**) [Eq. (7)]. The only molecular ion found in GC/MS is at 157 corresponding to the mono-deuterated citronellol **15** and **16**. The ^{1}H NMR spectrum showed increased amount of hydrogen (from 1.0 to 1.3) on C1; the ^{13}C NMR and DEPT135 spectra clearly showed a mixture of **15** and **16** with a triplet for C1 (one H/one D) corresponding to **15** and a singlet for C1 (with 2 hydrogens) corresponding to **16**. The ^{2}H NMR spectrum confirmed the presence of deuterium at C3.

These observations lead us to conclude that the ATH of geraniol proceeds through a new combination of mechanisms.



First, there is an enantioselective 1,3-intramolecular hydrogen shift.[18] Second, there is transfer hydrogenation which provides the reduced product. The combined enantioselective isomerization/transfer hydrogenation results in an overall ATH process which, to our knowledge, has not been reported.

Scheme 1 shows a proposed stepwise mechanism consistent with the deuterium incorporations found in Equations (5)–(7). Initially, the allylic alcohol coordinates to the



Scheme 1. Proposed mechanism for the ATH of geraniol.

Ru after deprotonation with KOH base (**a**–**c**). The asymmetric induction step occurs during the Ru-assisted 1,3-hydrogen shift through enal intermediate **d** to enolate **e** and enol **f**.[20] Deuterium incorporation on C2 occurs in two equilibrium tautomerization steps with the enol giving aldehydes **g** and **h**. Finally, transfer hydrogenation of the aldehyde through a [Ru]–D intermediate gives **i**. This mechanism indicates allylic isomerization as the key asymmetric induction step and is the reason for excellent selectivity for allylic alcohols and low selectivity for other unsaturated substrates.

In conclusion, we report a new asymmetric transfer hydrogen reaction that enables reduction of allylic alcohols in high yield and excellent enantioselectivity. We have developed a screening process that prepares the catalyst in situ by supplying a metal source, a chiral bidentate phosphine ligand, base, and hydrogen donor solvent. Also, the reaction may be performed using a commercially available chiral catalyst complex, [{(*S*)-tol-binap}$RuCl_2$(*p*-cymene)]. The configuration of the product is the exact same as in the gaseous hydrogenation reaction which makes it very convenient to predict stereochemistry. Mechanistic studies reveal an enantioselective isomerization/transfer hydrogenation process which is a new combination of mechanisms. Compared with conditions of high-pressure hydrogenation that is often necessary for asymmetric reduction of allylic alcohols, this new reaction is very promising as it occurs in high yield, high *ee* and does not require hydrogen gas.

Experimental Section

Under an atmosphere of argon or nitrogen, a degased solution of geraniol (0.01M, 10 mL) in isopropyl alcohol (IPA), $[Ru(cod)Cl_2]_n$ (0.001M), KOH (0.002M), and chiral ligand (0.002M) (alternatively, 0.001M of [{(*S*)-tol-binap}$RuCl_2$(*p*-cymene)]) was added to a Schlenk flask equipped with a magnetic stirbar and covered with a fresh rubber septum. Three freeze(liquid N_2)–pump–thaw cycles were performed and the flask was transferred to an oil bath at 100 °C and stirred in a closed system for 2 h. (With [{(*S*)-tol-binap}$RuCl_2$(*p*-cymene)] degassing was performed by three pump–fill cycles and heating occurred at 83 °C.) The solvent was evaporated under vacuum and the product was purified by chromatography on silica gel with pentane/ethyl acetate as the eluent. Enantiomeric purity determinations are indicated in the footnotes of the Tables and in the Supporting Information.

Received: November 9, 2011
Revised: December 2, 2011
Published online: January 20, 2012

Keywords: allylic alcohols · asymmetric catalysis · asymmetric transfer hydrogenation · isomerization · phosphine ligands

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