Asymmetric Catalysis

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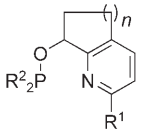
Enantio- and Diastereoselective Hydrogenation of Farnesol and O-Protected Derivatives: Stereocontrol by Changing the C=C Bond Configuration**

*Aie Wang, Bettina Wüstenberg, and Andreas Pfaltz**

We recently reported a class of chiral iridium catalysts derived from pyridylphosphine ligands **1**, which for the first time have allowed highly selective asymmetric hydrogenation of



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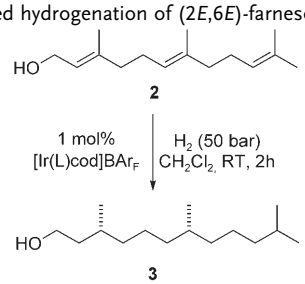
1a: n = 2, R^1 = H, R^2 = *o*Tol
1b: n = 2, R^1 = Me, R^2 = *o*Tol
1c: n = 2, R^1 = Ph, R^2 = *o*Tol
1d: n = 2, R^1 = Ph, R^2 = Cy
1e: n = 2, R^1 = Ph, R^2 = *t*Bu
1f: n = 1, R^1 = Ph, R^2 = *o*Tol
1g: n = 1, R^1 = Ph, R^2 = Cy
1h: n = 1, R^1 = Ph, R^2 = *t*Bu

unfunctionalized trialkyl-substituted C=C bonds.[1,2] Unlike rhodium or ruthenium diphosphine complexes, these catalysts do not require any special coordinating group next to the C=C bond. Enantiofacial selection by the catalysts in this case results from discrimination between the H atom and a sterically more demanding alkyl group at the monosubstituted olefinic C atom. Consequently, *cis* and *trans* olefins are converted into products of opposite configuration.[1] Thus, the sense of asymmetric induction can be controlled by proper choice of the double bond geometry. In this way, two or more stereogenic centers can be introduced with the desired relative and absolute configuration by hydrogenation of a di- or polyene.[3]

Herein we report the asymmetric hydrogenation of farnesol and O-protected derivatives to demonstrate the potential of this strategy. This class of substrates was chosen because efficient routes to all four *cis*/*trans* isomers were available,[5] and we were interested in comparing the reactivity of the two trialkyl-substituted C=C bonds with the allylic alcohol unit in its free and protected form. Furthermore, hexahydrofarnesol, which can be readily prepared by this route in any of the four possible stereoisomeric forms,[6] is an important building block for the syntheses of vitamins E and K[7] or related antioxidants,[8] and insect pheromones.[9] It also has an important function as a constituent of ether lipids in archea[10] and was identified as a precursor of many terpenoid compounds in plants[11] and geological sediments.[12]

Initial screening of a series of chiral N,P ligands was performed with (2*E*,6*E*)-farnesol by using 1 mol% of catalyst in dichloromethane at room temperature in the presence of hydrogen (50 bar)(Table 1). Because the two prochiral C=C units are *E*-configured, the sense of chiral induction at the two reaction sites was expected to be the same, leading either to the 3*R*,7*R* or 3*S*,7*S* isomer depending on the absolute configuration of the ligand. The best enantio- and diastereoselectivities were obtained with iridium complexes derived from ligands which carried a methyl or phenyl substituent at the position next to the pyridine N atom. Among the six-membered ring derivatives **1a**–**e**, ligand **1c**, which has a

Table 1: Ir-catalyzed hydrogenation of (2*E*,6*E*)-farnesol.[a]



L	3*S*,7*R* [%][b]	3*R*,7*R* [%][b]	3*R*,7*S* [%][b]	3*S*,7*S* [%][b]	*ee* [%] of (*R*,*R*)-**3**
1a *S*	37.8	31.0	14.9	16.2	31
1b *R*	5.5	2.1	25.7	66.5	−94
1c *S*	6.4	92.2	1.3	0.3	99.3
1d *R*	18.6	12.9	34.9	33.3	−44
1e *S*	33.2	26.8	19.4	20.6	13
1f *R*	5.7	0.3	7.0	86.9	−99.3
1g *R*	8.2	2.2	19.1	70.4	−94
1h *S*	16.0	80.3	3.1	0.8	98
4	23	1	4	72	−97
5	13.5	0.5	7	79	−99

[a] For detailed reaction conditions see the Supporting Information; cod = cycloocta-1,5-diene, BAr$_F$ = tetrakis[bis-3,5-(trifluoromethyl)phenyl]borate. [b] Determined by GC methods. See the Supporting Information.

[*] Dr. A. Wang, Dr. B. Wüstenberg,[+] Prof. Dr. A. Pfaltz
Department of Chemistry
University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)
Fax: (+41) 61-267-1103
E-mail: andreas.pfaltz@unibas.ch
[+] Current address: Research Center Chemical Process Technology
DSM Nutritional Products
P.O. Box 3255, 4002 Basel (Switzerland)

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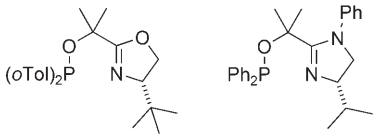
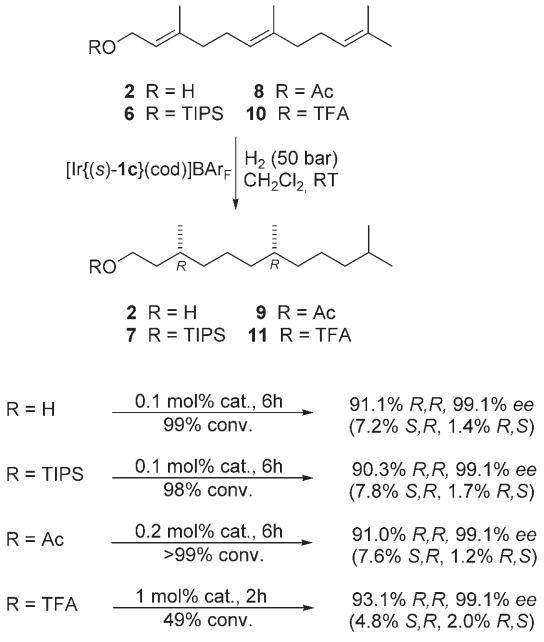
phenyl substituent on the pyridine ring and two *ortho*-tolyl groups on the P atom, proved to be most effective. The 3*R*,7*R* product was formed in 92% yield and 99% *ee*, implying that the C=C bond next to the hydroxy group was hydrogenated with a facial selectivity of 93:7 and the central C=C bond reacted with an even higher selectivity of 98:2. The corresponding five-membered ring derivative (**1f**) gave a similarly high stereoselectivity. Interestingly, in the five-membered ring series of ligands, **1g** and **1h**, which have cyclohexyl and *tert*-butyl groups, respectively, on the P atom, also induced high stereoselectivities, whereas the analogous six-membered ring derivatives **1d** and **1e** gave very poor results. Most of the oxazoline- and imidazoline-based N,P ligands examined gave only low selectivities, the exception being the selectivity of ligands **4** and **5**.[13]



4 **5**

Hydrogenation of (2*E*,6*E*)-farnesol under optimized conditions with 0.1 mol% [Ir{(*S*)-**1c**}(cod)]BAr_F yielded hexahydrofarnesol with 99% conversion to a product mixture containing 91% of the 3*R*,7*R* isomer in 99% *ee* (Scheme 1). Virtually the same result was obtained in a preparative-scale reaction (10 mmol; see the Experimental Section). The corresponding triisopropylsilyl protected farnesol (**6**) showed very similar reactivity and was converted into the saturated silyl ether **7** with essentially the same enantio- and diastereoselectivity.



Scheme 1. Ir-catalyzed hydrogenation of (2*E*,6*E*)-farnesol derivatives. TIPS = triisopropylsilyl; TFA = trifluoroacetoxy.

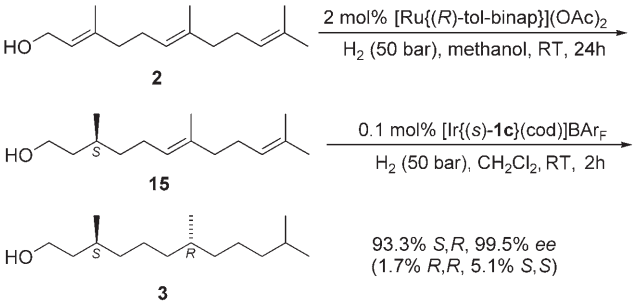
Electron-withdrawing protecting groups such as acetoxy or trifluoroacetoxy groups reduced the reactivity of the C=C bond next to the oxygen atom. Acetate **8** required 0.2 mol% of the catalyst for full conversion to the product, but the stereoselectivity was essentially the same as for the free and silyl-protected farnesol. Hydrogention of trifluoroacetate **10** was significantly slower and gave only 49% conversion after 2 hours with 1 mol% of catalyst. However, the stereoselectivity was somewhat higher than in the reactions of the corresponding alcohol, silyl ether, and acetate substrates. The electron-poor C=C bond next to the trifluoroacetoxy group was less reactive (only 50% reduction after full consumption of the substrate) than the two trialkyl-substituted C=C bonds (100% reduction). The difference in reactivity between these two types of C=C bonds was even larger in toluene: 66% of 6,7,10,11-tetrahydrofarnesyl trifluoroacetate was obtained, in addition to 2% of 10,11-dihydrofarnesyl trifluoroacetate and 32% of the fully hydrogenated product. Although this difference in reactivity is not sufficiently large for a completely selective hydrogenation of the two trialkyl-substituted C=C bonds (without affecting the allylic trifluoroacetate unit), the option to lower the reactivity of allylic alcohols by protection with electron-withdrawing groups may prove useful in other cases.

Next we studied the hydrogenation of all four stereoisomers of farnesol (Scheme 2). The required isomerically pure substrates were prepared according to the procedures reported by Wiemer and co-workers.[5c] By using catalyst [Ir{(*S*)-**1c**}(cod)]BAr_F under standard conditions, the four isomers were converted into the fully saturated products in essentially quantitative yield. As expected, *E*-configured C=C bonds gave rise to the *R* configuration in the product with the catalyst derived from (*S*)-**1c**, whereas stereogenic centers with the *S* configuration were formed from *Z*-configured C=C bonds. Consequently, hydrogenation of each of the four geometrical isomers of farnesol with the same catalyst led to a different stereoisomer. In all cases, the major diastereoisomer

Scheme 2. Ir-catalyzed hydrogenation of farnesol stereoisomers.

was formed with greater than 90% selectivity in very high enantiomeric purity (greater than 99% *ee*). The *Z*-configured C=C bond of the allylic alcohol unit reacted with a somewhat higher facial selectivity (96–97%) than the corresponding *E*-configured C=C bond (93–95%), whereas the facial selectivity of the central trisubstituted C=C bond was virtually independent of the *E* or *Z* geometry (98%).

The stereoselective syntheses of the four hexahydrofarnesol stereoisomers is also possible by stepwise hydrogenation using Ru and Ir catalysts (Scheme 3). As shown by the



Scheme 3. Consecutive Ru- and Ir-catalyzed hydrogenation of (2*E*,6*E*)-farnesol.

groups of Noyori and others[14], allylic alcohols are hydrogenated by Ru–diphosphine catalysts with high enantioselectivity, whereas trialkyl-substituted C=C bonds lacking an adjacent coordinating hydroxy group do not react. In this way, (3*S*)-dihydrofarnesol **15** was prepared in 96% *ee* by using [Ru{(*R*)-tol-binap}](OAc)$_2$. Subsequent hydrogenation of the remaining two C=C bonds with the Ir catalyst derived from ligand (*S*)-**1c** produced (3*S*,7*R*)-hexahydrofarnesol with greater than 99% *ee* in 93% diastereomeric purity. Since the Ru and Ir catalysts are available in both enantiomeric forms, all four stereoisomers of hexahydrofarnesol are accessible from the same farnesol isomer by proper choice of the configuration of the two catalysts.

In summary, we have shown two efficient and flexible strategies for the introduction of multiple stereogenic centers by asymmetric hydrogenation of a polyene. By using the same catalyst with different geometrical isomers of the substrate, all possible stereoisomeric products can be prepared in high enantiomeric purity. Alternatively, if the substrate contains different types of C=C bonds, one with and the other without an adjacent coordinating group, consecutive hydrogenation may be performed by using first a chiral Rh or Ru catalyst, which does not react with unfunctionalized olefins, and subsequent use of a chiral Ir catalyst. Both strategies open up new possibilities for the synthesis of complex molecules.

Experimental Section

Iridium-catalyzed hydrogenation of farnesol: Under a nitrogen atmosphere, (2*E*,6*E*)-farnesol (**2**) (2.22 g, 10 mmol) and [Ir{(*S*)-**1c**}(cod)]BAr$_F$ (16 mg, 0.01 mmol) were dissolved in dichloromethane (25 mL) in an autoclave (120 mL) equipped with an overhead stirrer. The autoclave was pressurized with H_2 (50 bar) and the solution was stirred at 700 rpm for 12 h at room temperature (H_2 was supplied every 2 h to maintain the pressure). Hydrogen was carefully released and the reaction mixture was concentrated under reduced pressure. The residue was loaded onto a short plug of silica gel (3.5 × 7 cm) and washed with of diethyl ether (250 mL; freshly distilled, peroxide-free). Concentration of the ether solution provided hexahydrofarnesol **3** as a colorless oil (2.22 g, 97%). Analytical data and determination of stereoselectivity: see the Supporting Information.

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