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Asymmetric Hydrogenation

Iridium-Catalyzed Asymmetric Hydrogenation of 3,3-Disubstituted Allylic Alcohols in Ethereal Solvents

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Abstract: Ir-phosphinomethyl-oxazoline complexes have been identified as efficient, highly enantioselective catalysts for the asymmetric hydrogenation of 3,3-disubstituted allylic alcohols and related homoallylic alcohols. In contrast to other N,P ligand complexes, which require weakly coordinating solvents, such as dichloromethane, these catalysts perform well in more ecofriendly THF or 2-MeTHF. Their synthetic potential was demonstrated with the formal total synthesis of four bisabolane sesquiterpenes.

The asymmetric hydrogenation of prochiral allylic alcohols is an attractive method for the synthesis of enantioenriched alcohols with a stereogenic center in the 2- or 3-position. The products available by this route are versatile building blocks for the synthesis of natural products and pharmaceuticals and also play an important role in perfumery.[1] However, despite the wide range of substrates that nowadays can be hydrogenated efficiently with high enantioselectivity by using chiral metal complexes, state-of-the-art methods for the enantioselective reduction of allylic alcohols lack generality. Since Noyori's group seminal publication on the asymmetric hydrogenation of geraniol and nerol with Ru–2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) catalysts,[2] many further studies on asymmetric reductions of allylic alcohols have been reported,[3–5] and in particular, 2-methyl cinnamyl alcohol has become a standard substrate for the evaluation of new catalysts.[4] Nevertheless, examples of highly enantioselective reductions of 3,3-disubstituted allylic alcohols are still scarce.[2,5]

Thus, currently used methods for the preparation of enantioenriched alcohols with a stereogenic center in the 3-position are generally based on multistep sequences involving an initial enantioselective transformation carried out on a functionalized substrate, followed by adjustment of the oxidation state of the resulting product. As summarized in Figure 1, asymmetric S_N2' allylic alkylation,[6] 1,4-addition to α,β-unsaturated carbonyl compounds,[7] asymmetric isomerization of allylic alcohols to aldehydes,[8] asymmetric hydrogenation of α,β-unsaturated carboxylic acids,[9] esters[9] and aldehydes,[10] all give products that require further redox transformations to yield the target molecules. However, provided that a suitable catalyst can be found, the more direct approach by asymmetric hydrogenation is more attractive, as it affords the product in one step in the desired oxidation state.

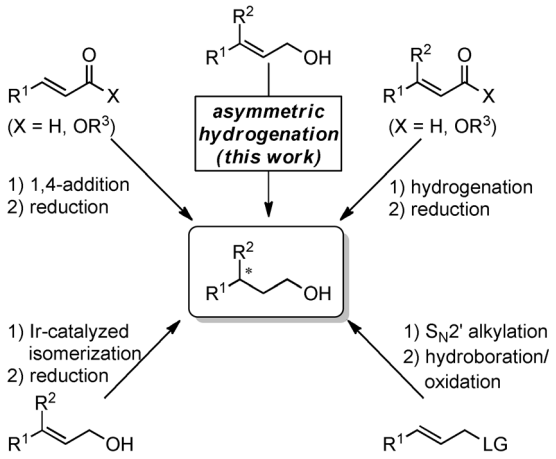

Figure 1. Synthetic routes to enantioenriched 3,3-disubstituted primary alcohols.

Herein, we report an efficient class of catalysts for this transformation, giving high enantioselectivities (*ee*) for a wide range of 3,3-disubstituted allylic alcohols and related homoallylic alcohols. Importantly, reactions could be performed in ecologically advantageous solvents, such as THF or 2-methyl-THF, rather than dichloromethane, which is commonly used as a standard solvent for iridium-catalyzed asymmetric hydrogenation.

In an initial screening of various iridium complexes derived from chiral N,P ligands with alcohol **1a** as substrate, the complex derived from phosphinomethyloxazoline **L4** performed best, giving 98% *ee* and full conversion (Table 1). Other ligands, which in the past had been successfully used in the hydrogenation of various functionalized and unfunctionalized trisubstituted olefins,[11] gave inferior results. Ligands, such as **L4**, have proven to be particularly effective for the hydrogenation of tetrasubstituted C=C bonds,[12] but have not found use for the hydrogenation of other substrate classes to date. Catalysts derived from **L4** or related phosphinomethyloxazolines are attractive, because the chiral ligands are readily accessible through several short synthetic routes.[12–13]

With a promising catalyst in hand, we examined the hydrogenation of **1a** with [Ir(cod)**L4**]BAr_F in different solvents

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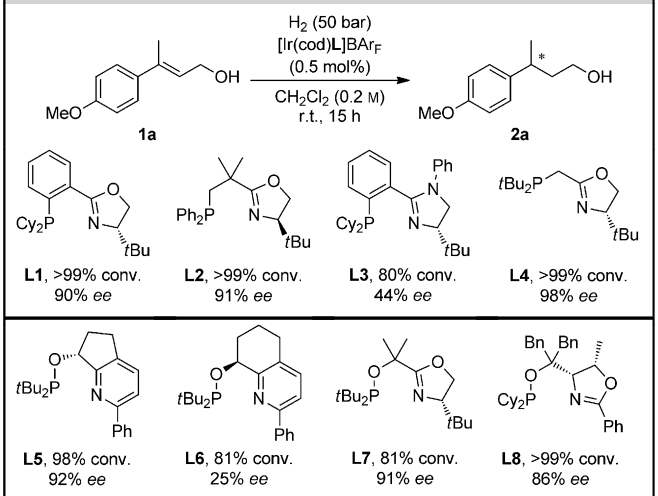
Table 1. Catalyst screening for the asymmetric hydrogenation of alcohol **1a**.[a]



[a] Conversion values were determined by GC analysis of the crude reaction mixtures, whereas enantioselectivity values were determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for further details). BAr_F = (tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate; cod = 1,5-cyclooctadiene.

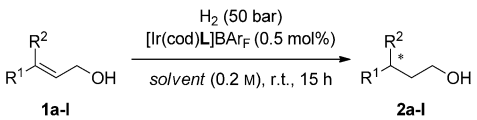
Table 2. Solvent screening for the asymmetric hydrogenation of alcohol **1a** with [Ir(cod)**L4**]BAr_F.[a]

Entry	Solvent	Conv. [%][b]	*ee* [%][c]
1	CH_2Cl_2	>99	97
2	PhCl	>99	95
3	*n*-hexane	82	99
4	EtOAc	93	99
5	acetone	92	95
6	*i*PrOH	<2	n.d.
7	THF	>99	98
8	2-MeTHF	>99	97

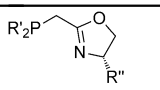
[a] Reaction conditions are similar to those given in Table 1, except for the choice of solvent. [b] Conversions were determined by GC analysis of the crude reaction mixtures. [c] Enantioselectivity values were determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for further details); n.d. = not determined.

(Table 2). Reactions in 1,2-dichloroethane and chlorobenzene proceeded with full conversion but slightly lower enantioselectivity than in dichloromethane (entries 1 and 2). In *n*-hexane and ethyl acetate, enantioselectivities reached 99% *ee*; however, at the expense of incomplete conversion under standard conditions (entries 3 and 4). A somewhat lower *ee* of 95 and 92% conversion were observed in acetone, whereas in isopropanol the catalyst was not active (Table 2, entries 5 and 6). Surprisingly, reactions in THF (Table 2, entry 7) and 2-methyltetrahydrofuran (entry 8) gave essentially the same results as reactions in the standard solvent dichloromethane. The excellent performance of the catalyst in these ethereal solvents contrasts the general experience that coordinating solvents cause significant inhibition of iridium catalysts.[11a,14,15] The use of THF and 2-MeTHF offers advantages from an ecological point of view as

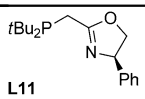
Table 3. Asymmetric hydrogenation of allylic alcohols **1**.[a]



Entry	R^1, R^2	THF	2-MeTHF
		L, Conv. [%], *ee* [%][a]	**L**, Conv. [%], *ee* [%][a]
1	4-$MeOC_6H_4$, Me (**a**)	**L4**, >99, 98, (−)-(*R*)	**L4**, >99, 97
2	Ph, Me (**b**)	**L9**, >99, 95, (−)-(*R*)	**L9**, >99, 90
3	4-MeC_6H_4, Me (**c**)	**L9**, >99, 95, (−)-(*R*)	**L9**, >99, 95
4	2-MeC_6H_4, Me (**d**)	**L9**, >99, 97, (−)	**L9**, 41, 93 **L9**, >99, 95[b]
5	2-Naphthyl, Me (**e**)	**L11**, 97, 95, (−)	**L11**, 98, 93
6	4-ClC_6H_4, Me (**f**)	**L11**, >99, 92, (+)	**L11**, >99, 90
7	Me, 4-ClC_6H_4 (**g**)	**L11**, 14, 50, (−)	**L11**, 8, 36
8	Ph, Cy (**h**)	**L11**, 94, 92, (+)	**L11**, >99, 90
9	*t*Bu, Ph,(**i**)	**L10**, 43, 96, (+)-(*R*)	**L10**, 10, n.d. **L11**, 68, 90[c]
10	*t*Bu, Me (**j**)	**L11**, >99, >99,[b] (−)-(*S*)	**L11**, >99, 95[b]
11	Cy, Me (**k**)	**L12**, >99, 88,[b] (+)-(*R*)	**L13**, >99, 60[b]
12	*i*Bu, Me (**l**)	**L11**, >99, 80,[b] (+)	**L9**, >99, >99,[b] (−)



L4 (R' = R'' = *t*Bu)
L9 (R' = *t*Bu, R'' = *i*Pr)
L10 (R' = *t*Bu, R'' = CH_2*t*Bu)
L12 (R' = Ph, R'' = *i*Pr)
L13 (R' = Ph, R'' = *t*Bu)



L11

[a] Conversion was determined by GC analysis of the crude reaction mixtures, whereas enantioselectivity values were determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for further details). [b] Catalyst (1 mol%) was used. [c] Reaction was carried out for 20 h with catalyst (2 mol%).

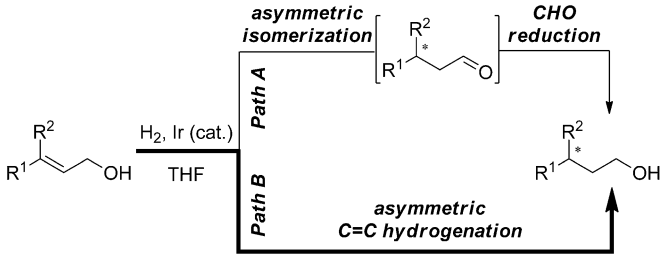
they are less toxic and less volatile than dichloromethane and do not produce chlorinated waste.[16] In particular, 2-MeTHF is considered an ecofriendly solvent, as it can be obtained from renewable resources[17] and has several advantages, such as low miscibility with water and high stability under acidic and basic conditions that render it attractive for industrial applications.[18]

Therefore, we extended our hydrogenation studies in THF and 2-MeTHF to a series of different 3,3-disubstituted allylic alcohols to evaluate the scope of the reaction. Table 3 summarizes the results obtained with [Ir(cod)**L4**]BAr_F and related catalysts derived from ligands **L9**–**13**. In general, slightly better results were observed in THF, although in most cases comparable levels of conversion and enantioselectivity were achieved in the two solvents (Table 3, entries 1, 3–7). Yet in one case (entry 12), the reaction in 2-MeTHF gave significantly higher enantioselectivity than in THF.

(*E*)-3-Methylcinnamyl alcohol (**1b**) and related aryl/methyl-substituted derivatives reacted with excellent enantioselectivities of 95–98% (Table 3, entries 1-5), except for the 4-chlorophenyl derivative **1f**, which gave slightly lower *ee* (entry 6). The corresponding *Z*-configured alcohol **1g** was considerably less reactive than **1f**, affording the enantiomeric product in 14% conversion and 50% *ee* in THF (entry 7). The sterically more hindered *ortho*-tolyl derivative **1d** required a somewhat

higher catalyst loading of 1 mol% instead of 0.5 mol% to achieve full conversion in 2-MeTHF. Although high conversion and good enantioselectivity could be achieved for the phenyl/cyclohexyl-substituted substrate **1h** (entry 8), a substantial decrease of conversion, but excellent *ee* value (99% in THF) was observed for the bulky phenyl/*tert*-butyl derivative **1i** (entry 9). On the other hand, the *tert*-butyl/methyl analogue **1j** gave full conversion at 1 mol% catalyst loading (entry 10). The dialkyl-substituted substrates **1k** and **1l** proved to be less reactive than the corresponding aryl/alkyl-substituted compounds, but at 1 mol% catalyst loading, full conversion was achieved. Although the enantioselectivity was only moderate for the cyclohexyl/methyl derivative **1k**, up to 99% *ee* was recorded for **1j** and **1l** by using the appropriate catalyst and solvent (entries 10 and 12). Overall, the results show that proper choice of the phosphinomethyloxazoline ligand and the solvent (THF or 2-MeTHF) is crucial for obtaining optimal results for a particular substrate.

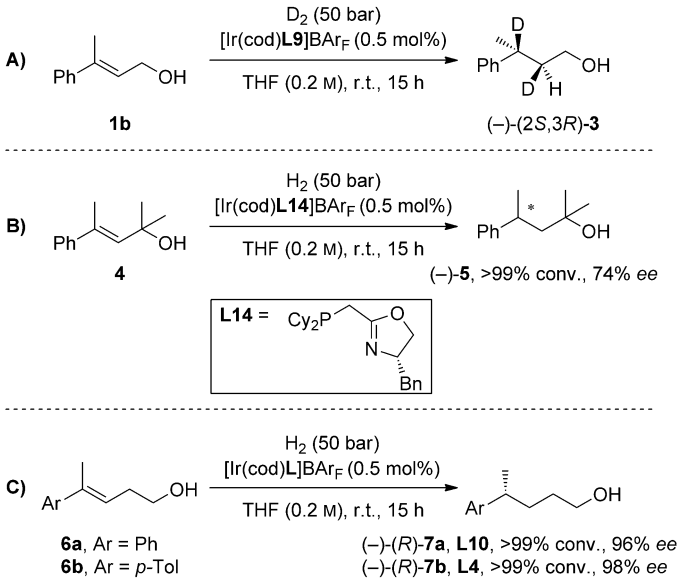
Two mechanistic pathways seem to be possible for these hydrogenations. Taking into account the work of Mazet and coworkers on the iridium-catalyzed asymmetric isomerization of allylic alcohols to the corresponding aldehydes,[8] a two-step process involving a formal 1,3-H shift to the saturated aldehyde followed by reduction of the C=O function may be proposed (Scheme 1, path A). Alternatively, the allylic alcohol



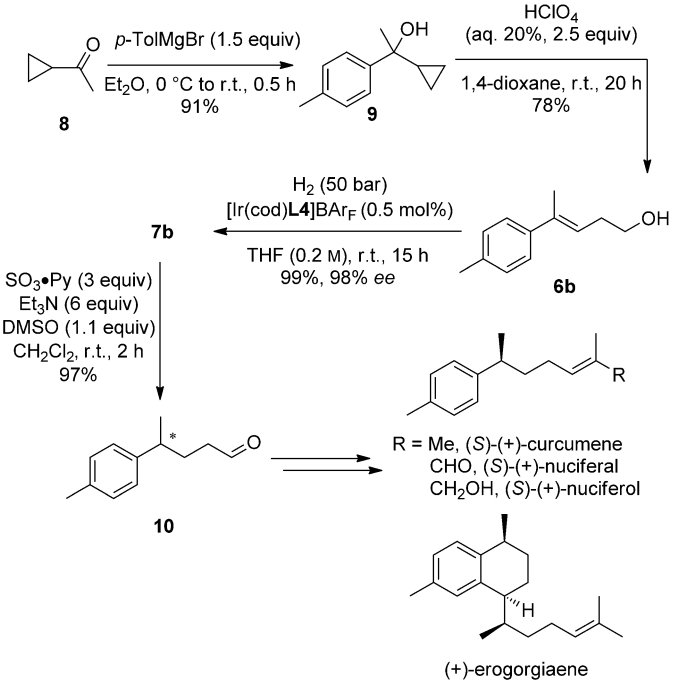
Scheme 1. Possible reaction pathways for the asymmetric reduction of allylic alcohols catalyzed by iridium complexes.

could undergo direct hydrogenation of the C=C bond (path B). To distinguish between the two pathways, we ran the hydrogenation of substrate **1b** with catalyst [Ir(cod)**L9**]BAr_F under a 50 bar of D_2 (Scheme 2, A). ^1H and ^2H NMR analysis of product **3** revealed complete deuterium incorporation (>90%) at C2 and C3, whereas no deuterium was detected at C1. This result is consistent with pathway B (see the Supporting Information for further details). Further support of pathway B came from the hydrogenation of the tertiary allylic alcohol **4** under the conditions previously used for primary allylic alcohols (Scheme 2B). Judicious choice of the iridium complex was necessary in this case to achieve full conversion and avoid the formation of unidentified by-products. By using [Ir(cod)**L14**]BAr_F as catalyst, alcohol **5** was formed with full conversion and 74% *ee*. The successful hydrogenation of homoallylic alcohols **6a** and **b** as well rules out pathway A, because isomerization to the corresponding aldehyde is not possible in this case (Scheme 2C). Both **6a** and **b** cleanly reacted to give the saturated alcohols **7a** and **b** with full conversion and excellent enantioselectivity.

The asymmetric hydrogenation of homoallylic alcohols of this type has considerable potential for application in organic synthesis. In fact, the reduction of **6b** to **7b** is a key step in the synthesis of four natural products, curcumene, nuciferal, nuciferol, and erogorgiaene. All these bisabolane sesquiterpenes can be accessed from **7b** via the corresponding aldehyde **10**.[19] Thus, the sequence leading to highly enantioenriched aldehyde **10** shown in Scheme 3 represents a formal



Scheme 2. Hydrogenation experiments in support of pathway B.



Scheme 3. Formal total synthesis of natural products through alcohol **6b**.

synthesis of these natural products.[20] We found that the homoallylic alcohol **6b** is readily accessible from commercially available cyclopropyl methyl ketone **8** by a two-step transformation involving Grignard addition followed by acid-catalyzed rearrangement of the tertiary alcohol **9**.[21] After iridium-catalyzed asymmetric hydrogenation of **6b**, the resulting chiral alcohol **7b** was converted to the aldehyde **10** by Parikh–Doering oxidation in 97% yield.[22] Compared to the most efficient published route to **10**, which is based on the enantioselective cyclopropanation of *para*-methylstyrene, the sequence shown in Scheme 3 is shorter, and the overall yield of **10** is higher (68% vs. 30–36%).[23]

In summary, we have identified an efficient ligand class for the iridium-catalyzed asymmetric hydrogenation of 3,3-disubstituted allylic alcohols, a type of substrate for which generally applicable catalysts were not available to date. The required ligands are structurally simple and readily accessible from enantiopure aminoalcohols by several short syntheses. Importantly, reactions can be carried out in THF or 2-MeTHF, which are ecologically advantageous and better suited for industrial applications than dichloromethane that is commonly used for iridium-catalyzed hydrogenation. In addition to 3,3-disubstituted allylic alcohols, analogous homoallylic alcohols were also hydrogenated with high enantioselectivities. The potential of this method was illustrated by a short and efficient synthesis of a highly enantioenriched precursor that has been used for the synthesis of several bisabolane sesquiterpenes.

Experimental Section

Procedure for the iridium-catalyzed asymmetric hydrogenation of 1a

In a glove box, the allylic alcohol **1a** (320 mg, 1.8 mmol) and [Ir(cod)**L4**]BAr_F (13 mg, 9 μmol, 0.5 mol%) were dissolved in THF (3.6 mL, 0.5 M) in a glass vial equipped with a magnetic stir bar. The reaction vial was placed into a high-pressure steel autoclave that was then sealed and brought outside the glove box. The autoclave was pressurized with H_2, purged with H_2 three times, and sealed under 50 bar H_2. The reaction was stirred for 15 h at RT. After release of H_2, the solution was concentrated in vacuo, and the catalyst was removed by filtration of the crude mixture through a plug of silica gel (2×0.5 cm) with *n*-hexane/MTBE 4:1 (15 mL). After washing with approximately 10 mL of the same solvent mixture, the solution was concentrated in vacuo to give **2a** (321 mg, 99% yield, 96% *ee*) as a colorless liquid.

Acknowledgements

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Keywords: allylic alcohols · green solvents · hydrogenation · iridium · natural products

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[15] The potentially coordinating hydroxy group does not seem to be responsible for the high reactivity of this catalyst observed in THF. Hydrogenation of (*E*)-1-(but-2-en-2-yl)-4-methoxybenzene, the analogue of substrate **1a**, possessing a methyl group instead of a hydroxymethyl group, gave 98% conversion and 93% *ee* in this solvent (1.0 mol% [Ir(cod)**L4**]BAr_F, THF (0.2 M), 50 bar H_2; see the Supporting Information for further details).
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[20] The catalyst based on **L4** produced the (*R*)-enantiomer of **7b**, which would give the unnatural enantiomers of the bisabolanes shown in Scheme 3. However, the opposite enantiomer of **L4** can be prepared from commercially available D-*tert*-leucine.

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