CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201000595

Iridium-Catalyzed Asymmetric Hydrogenation of Unfunctionalized, Trialkyl-Substituted Olefins

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Dedicated to Professor Eiichi Nakamura on the occasion of his 60th birthday

Abstract: Chiral iridium complexes with bicyclic pyridine-based N,P ligands have emerged as efficient catalysts for the enantioselective hydrogenation of unfunctionalized trialkyl-substituted olefins. Optimization of the reaction conditions by variation of the solvent, pressure, and temperature led to enantiomeric excesses of up to 99%. Three pure alkenes, (*E*)-2-cyclohexyl-2-butene and (*E*)- and (*Z*)-3,4-dimethyl-2-pentene were converted into the corresponding chiral alkanes with 97%, 94%, and 93% *ee*, respectively. Hydrogenation of the three C=C bonds of both α- and γ-tocotrienyl acetate led to α- and γ-tocopheryl acetate with very high diastereoselectivity. The same catalysts were successfully applied in the hydrogenation of trisubstituted alkenes with a carboxylic ester or a keto group in the γ position. This reaction was used as a key step in a highly enantioselective synthesis of the pheromone of the caddisfly *Hesperophylax occidentalis*. The hydrogenation of a structurally analogous allylic alcohol also gave high enantioselectivities.

Keywords: asymmetric catalysis · hydrogenation · iridium · N,P ligands · olefins

Introduction

Asymmetric hydrogenation is one of the most reliable catalytic methods for the preparation of optically active compounds.[1] Since the early 1970s, when the well-known L-Dopa process was established at Monsanto,[2] hydrogenation has played a dominant role in industrial asymmetric catalysis.[3] An impressive number of chiral phosphine ligands have been developed, which induce very high enantioselectivity in rhodium- and ruthenium-catalyzed hydrogenation. However, the range of olefins that can be hydrogenated with high enantiomeric excess is limited, because both rhodium and ruthenium catalysts require the presence of a coordinating group next to the C=C bond such as an amide or hydroxy function. With unfunctionalized olefins these catalysts generally show low reactivity and unsatisfactory enantioselectivity.

Some years ago, we introduced a new class of hydrogenation catalysts, iridium complexes with chiral N,P ligands, which overcome these limitations.[4] Various unfunctionalized aryl-substituted olefins can be hydrogenated with high enantioselectivity and high catalytic efficiency using catalysts of this type.[5,6] Nonetheless, satisfactory results in the hydrogenation of purely alkyl-substituted olefins were elusive until recently, when we found a class of chiral iridium catalysts with bicyclic pyridine-phosphinites **1** as ligands[7] that gave high enantioselectivity in the hydrogenation of unfunctionalized, trialkyl-substituted olefins **2** and **3**.[8]

The application range of these catalysts is much broader compared to previously developed catalysts, as they do not require the presence of any particular substituent near the C=C bond. The sense of asymmetric induction can be controlled either by selecting the appropriate ligand enantiomer or by adjusting the double bond geometry in the substrate, because *E* and *Z* isomers are converted into products of opposite configuration. In this way, multiple stereocenters can be introduced in a single hydrogenation step, starting from substrates containing two or more C=C bonds of defined geometry. This strategy was recently demonstrated in the hydrogenation of γ-tocotrienyl acetate **4**[8] and the four *cis*–*trans* isomers of farnesol **5**.[9,10]

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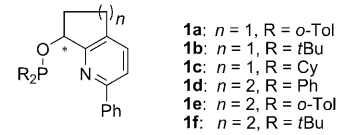
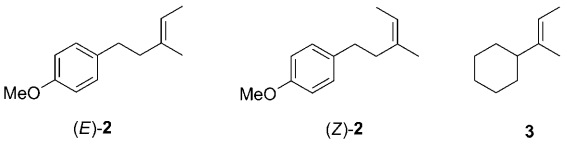
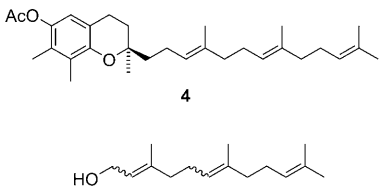






Herein we report the results of systematic optimization studies, which have led to improved efficiency and enantioselectivity, and describe additional applications that illustrate the scope of these catalysts.

Results and Discussion

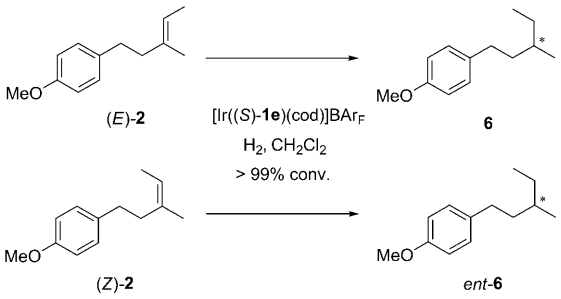
Optimization of the Reaction Conditions

In our previous work on the hydrogenation of trialkyl-substituted olefins,[8] we had evaluated pyridine-phosphinite ligands **1** under standard conditions (1 mol% of catalyst, 50 bar H_2 pressure, CH_2Cl_2, RT). In order to find the optimal conditions for hydrogenations of this type, we carried out a systematic study of the influence of the temperature, hydrogen pressure, solvent, and catalyst loading on the enantioselectivity and conversion. First, the hydrogenation of test substrates (*E*)- and (*Z*)-**2** was investigated, using the Ir complex derived from ligand (*S*)-**1e**, which we had previously identified as the best catalyst for these olefins (Table 1).

As shown in Table 1, high hydrogen pressures are not essential, as complete reactions and almost the same enantioselectivities were obtained with both *E* and *Z* isomers of olefin **2** when the pressure was lowered from 50 bar to 5 bar. The hydrogenation went smoothly even at 1 bar, although with somewhat reduced enantioselectivity. Under 5 bar of H_2 at room temperature, other solvents were tested. Besides dichloromethane, 1,2-dichloroethane and toluene proved to be effective solvents that gave similar results in the hydrogenation of olefin (*Z*)-**2** (1,2-dichloroethane, >99% conv., 98% *ee*; toluene, >99% conv., 96% *ee*).

The influence of temperature was examined at 5 bar of hydrogen pressure with 1 mol% of [Ir((*S*)-**1e**)(cod)]BAr_F (BAr_F = tetrakis[bis-3,5-(trifluoromethyl)phenyl]borate) as catalyst in dichloromethane (Table 2). For both *E* and *Z* isomers of olefin **2**, higher enantioselectivities were observed when the temperature was decreased from room temperature to −20 °C. Up to 96.1% *ee* and 99.3% *ee* were obtained for (*E*) and (*Z*)-**2** respectively. The reaction was still fast at −20 °C and went to completion within the standard time of 2 h. At −40 °C the rate became very slow and only 6% conversion was observed for (*Z*)-**2**.

Table 1. Influence of pressure on the hydrogenation of (*E*)- and (*Z*)-**2**.[a]



(*E*)-**2**	*P* [bar]	*ee* [%]	(*Z*)-**2**	*P* [bar]	*ee* [%]
	50	95 (+)		50	98 (−)
	25	95 (+)		25	98 (−)
	10	93 (+)		10	98 (−)
	5	94 (+)		5	98 (−)
	1	90 (+)		1	94 (−)

[a] Reaction conditions: 1 mol% of [Ir((*S*)-**1e**)(cod)]BAr_F, RT, 2 h, BAr_F = tetrakis[bis-3,5-(trifluoromethyl)phenyl]borate.

Table 2. Influence of temperature on the hydrogenation of (*E*)- and (*Z*)-**2**.[a]

(*E*)-**2**	*T* [°C]	*ee* [%]	(*Z*)-**2**	*T* [°C]	*ee* [%]
	23	94.1 (+)		23	98.0 (−)
	0	95.6 (+)		0	99.0 (−)
	−20	96.1 (+)		−20	99.3 (−)

[a] Reaction conditions: 1 mol% of [Ir((*S*)-**1e**)(cod)]BAr_F, 5 bar H_2, 2 h, CH_2Cl_2, >99% conversion.

Further studies (Table 3) showed that reducing the catalyst loading to 0.5 mol% had no effect on conversion and enantioselectivity. However, when only 0.1 mol% of catalyst was used, the reaction became very slow at low hydrogen pressure, so the pressure had to be increased to 50 bar in

Table 3. Optimized hydrogenation of (*E*)-**2** and (*Z*)-**2**.[a]

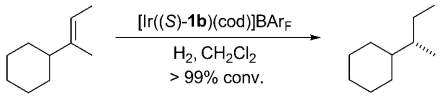
(*E*)-**2**	Cat. loading [mol%]	*P* [bar]	*T* [°C]	*t* [h]	*ee* [%]
	1	5	−20	2	96 (+)
	0.5	5	−20	3	96 (+)
	0.1	50	23	2	94 (+)
	0.1	50	−20	10	92 (+)
(*Z*)-**2**	Cat. loading [mol%]	*P* [bar]	*T* [°C]	*t* [h]	*ee* [%]
	1	5	−20	2	99.3 (−)
	0.5	5	−20	4	99.3 (−)
	0.1	50	23	2	98 (−)
	0.1	50	−20	10	98 (−)

[a] Reaction conditions: [Ir((*S*)-**1e**)(cod)]BAr_F, H_2, 2 h, CH_2Cl_2, >99% conversion.

order to obtain full conversion. At low catalyst loadings, the best results were obtained at high pressure and room temperature, whereas at −20 °C the enantioselectivities were somewhat lower and much longer reaction times were needed.

Cyclohexyl alkene **3** is a more demanding substrate than alkenes (*E*)- and (*Z*)-**2**, and only two ligands (*S*)-**1b** and (*S*)-**1f** have been identified so far that can induce enantioselectivities above 90% *ee* ((*S*)-**1b**, 97% *ee*; (*S*)-**1f**, 97% *ee*). Further studies showed that the five-membered ring derivative (*S*)-**1b** is superior to the corresponding six-membered ring analogue (*S*)-**1f**, as no decrease in enantisoselectivity was observed with (*S*)-**1b** when the pressure was lowered from 50 bar to 5 bar (Table 4). Even at 1 bar hydrogen pressure, the reduction went to completion within the standard reaction time of 2 h while the enantioselectivity decreased only slightly to 95% *ee*. With ligand (*S*)-**1f**, however, only 86% *ee* was obtained when the pressure was reduced to 10 bar.

Table 4. Optimized hydrogenation of (*E*)-2-cyclohexyl-2-butene (**3**).



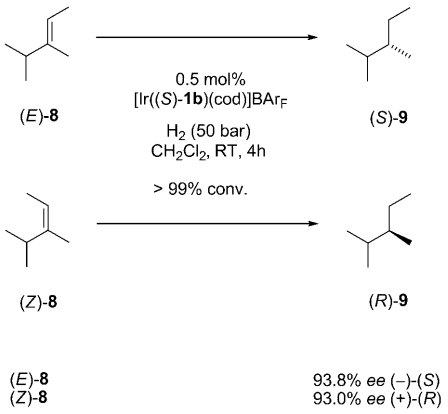
Cat. loading [mol%]	*P* [bar]	*T* [°C]	*t* [h]	*ee* [%]
1	50	23	2	97
1	5	23	2	97
1	1	23	2	95
1	5	−20	2	97
0.1	50	23	2	97
0.1	50	−20	10	95

With ligand (*S*)-**1b** at 5 bar hydrogen pressure, no apparent influence on the enantioselectivity was observed when the temperature was decreased to −20 °C. Reducing the catalyst loading from 1 mol% to 0.1 mol% had no significant effect on the enantioselectivity. As observed for substrates (*E*)- and (*Z*)-**2**, at low catalyst loadings and 50 bar hydrogen pressure the *ee* value decreased when the temperature was lowered to −20 °C. Thus, high pressure and ambient temperature seem to be optimal for hydrogenations with low catalyst loadings.

Hydrogenation of 3,4-Dimethyl-2-pentene (8)

Pure alkenes are difficult to study because standard methods for measuring the *ee* value often fail. We were fortunate that Prof. Schurig and co-workers at the University of Tübingen offered help with the analysis of chiral alkanes (see the Experimental Section). They were able to find a suitable chiral phase for determining the *ee* value of alkane **9** by GC, using two or three linked capillary columns with a mixed phase of chirasil-β-dex[11] and 6-*tert*-butyldimethylsilyl-2,3-*O*-methyl-β-cyclodextrin. This allowed us to study the hydrogenation of alkenes (*E*)- and (*Z*)-**8**, which are commercially available in high purity (Scheme 1).

Complex [Ir((*S*)-**1b**)(cod)]BAr_F, which proved to be the most effective catalyst in the hydrogenation of cyclohexylbutene **3** was again the catalyst of choice. Under 50 bar of hydrogen pressure, the hydrogenation of both isomers went smoothly with 0.5 mol% of catalyst, yielding 2,3-dimethylpentane (**9**) with 99% conversion. Enantioselectivies of 94% *ee* and 93% *ee* were obtained with (*E*)- and (*Z*)-**8**, respectively. Consistent with previous studies, the *E* and the *Z* isomer gave products of opposite configuration.

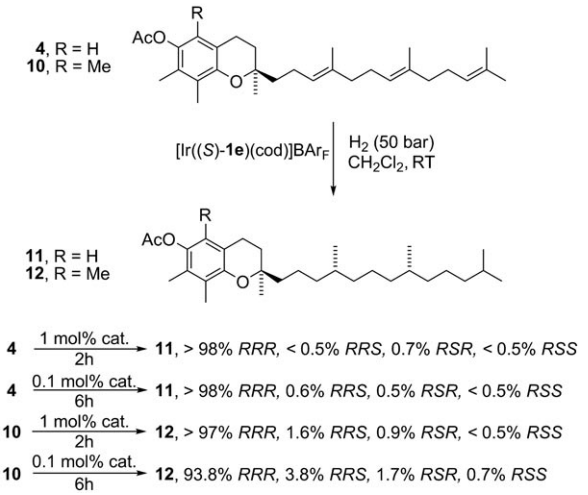


Scheme 1. Hydrogenation of 3,4-dimethyl-2-pentene (**8**).

Hydrogenation of Tocotrienyl Acetate

We have previously reported the highly diastereoslective hydrogenation of γ-tocotrienyl acetate **4**.[8] The pyridine-phosphinite (*S*)-**1e** had emerged as an optimal ligand in this case, inducing very high face selectivities in the hydrogenation of the two prochiral C=C bond units. Using 1 mol% of catalyst at 50 bar hydrogen pressure, the natural *RRR* isomer of γ-tocopheryl acetate was formed almost exclusively (Scheme 2).

We have studied this reaction in more detail and have found that the catalyst loading can be reduced to 0.1 mol% without affecting the stereoselectivity. Because the biologically most active component of vitamin E is α-tocopherol with three methyl groups at the benzene ring, it was of interest to examine the hydrogenation of the corresponding precursor, α-tocotrienyl acetate **10**. As expected the two derivatives **4** and **10** gave very similar results. Again the catalyst derived from ligand (*S*)-**1e** gave the best results and led to the *RRR* isomer of α-tocopheryl acetate with a stereoselectivity of greater than 97%. The lower stereoselectivity (94%) in the reaction with 0.1 mol% catalyst, compared to the analogous reaction of γ-tocotrienyl acetate **4**, is probably due to traces of impurities in the substrate, which had a stronger effect at low catalyst loadings. The highly stereoselective hydrogenation of tocotrienol derivatives, which makes it possible to introduce two stereogenic centers in

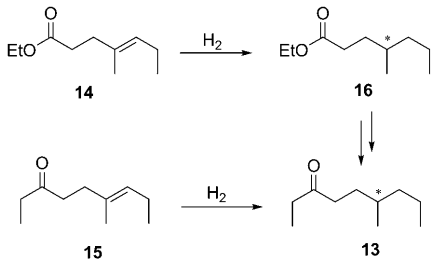


Scheme 2. Hydrogenation of γ- and α-tocotrienyl acetate.

one step with high efficiency, demonstrates the potential of this class of catalysts for the synthesis of complex chiral molecules.

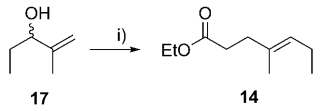
Synthesis of the Insect Pheromone 13

Alkyl chains with tertiary methyl-substituted asymmetric carbon atoms are found in many insect pheromones. The pheromone of the caddisfly *Hesperophylax occidentalis* **13** is a typical example.[12,13] We thought that Ir-catalyzed hydrogenation of an alkene precursor such as **14** or the analogous ethyl ketone **15** would be ideally suited for the introduction of the remote stereogenic center with high enantioselectivity (Scheme 3). From previous work we knew that ester as well as keto groups are not hydrogenated under standard conditions and do not interfere with the catalysis.



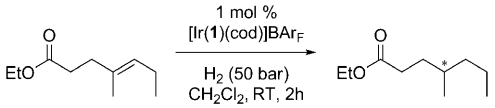
Scheme 3. Proposed synthetic pathway for the pheromone of the caddisfly **13**.

The γ,δ-unsaturated ester **14** was readily prepared from the commercially available allylic alcohol **17** in one step by a Johnson–Claisen rearrangement as reported by Evans et al. (Scheme 4).[14] Initial experiments with Ir complexes derived from ligands **1a–d** gave encouraging results with enantiomeric excesses of 90–95% (Table 5). For this substrate pyridine-phosphinite **1a** and **1e** were identified as the ligands of choice. Further experiments (Table 6) showed



Scheme 4. i) 1,1,1-triethoxypropane, propionic acid, 138 °C, 3 h (75%).

Table 5. Hydrogenation of (*E*)-ethyl-4-methylhept-4-enoate (**14**).



Ligand	Conversion [%][a]	*ee* [%][b]
(*R*)-**1a**	>99	95 (*R*)
(*R*)-**1b**	>99	91 (*R*)
(*R*)-**1c**	>99	90 (*R*)
(*S*)-**1c**	>99	91 (*S*)
(*S*)-**1d**	>99	90 (*S*)
(*R*)-**1e**	>99	95 (*R*)
(*S*)-**1e**[c]	>99	93 (*S*)

[a] Determined by GC on a chiral stationary phase. [b] Determined by GC; configuration determined by hydrolysis of ester **16** to the corresponding acid and comparison of the optical rotation with the reported value.[15] [c] 0.2 mol% catalyst was used.

Table 6. Hydrogenation of (*E*)-ethyl-4-methylhept-4-enoate (**14**) with [Ir((*R*)-**1a**)(cod)]BAr_F—effect of catalyst loading.[a]

Entry	Cat. loading [mol%]	Conversion [%][b]	*ee* [%][c]
1	1	>99	95 (*R*)
2	0.2	>99	95 (*R*)
3	0.1	>99	94 (*R*)
4	0.05	57	96 (*R*)
5[d]	0.05	57	96 (*R*)

[a] Reaction conditions: [Ir((*R*)-**1a**)(cod)]BAr_F, 50 bar H_2, CH_2Cl_2, RT, 2h. [b] Determined by GC. [c] Determined by chiral GC. [d] Reaction time was 3 h.

that the catalyst loading could be reduced to 0.1 mol% without notable effect on the *ee* value and conversion. With 0.05 mol% catalyst, the *ee* value remained high but the reaction stopped at 57% conversion.

The actual pheromone **13** can be synthesized by converting the saturated ester **16** to the corresponding ethyl ketone or, alternatively, by enantioselective hydrogenation of the unsaturated ketone **15** (Scheme 3). Ethyl ketone **15** was prepared from the unsaturated ester **14** by hydrolysis and conversion into the acid chloride, followed by reaction with ethylmagnesium bromide and catalytic amounts of Fe^{III} acetylacetonate (Scheme 5).[16] The hydrogenation of this substrate gave very similar results to those obtained with the corresponding ester **14** (Table 7) and led to the pheromone **13** with full conversion. As expected, the keto group was not reduced under these conditions.

This enantioselective hydrogenation of the trialkyl-substituted C=C bond of ketone **15** opens up a short, efficient route to the caddisfly pheromone **13** in high enantiomeric purity, which favorably compares with the previously reported asymmetric synthesis of this natural product.[13]

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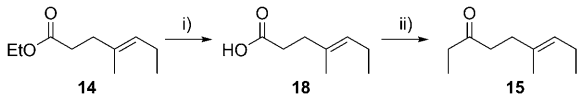


Scheme 5. i) NaOH, MeOH, H_2O (>95%); ii) $(COCl)_2$, DMF followed by $[Fe(acac)_3]$, EtMgBr, THF (64%).

Table 7. Hydrogenation of (*E*)-6-methylnon-6-en-3-one (**15**).

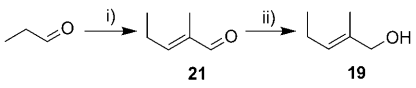
Ligand	Conversion [%][a]	*ee* [%][b]
(*R*)-**1a**	>99	95 (*R*)
(*R*)-**1b**	>99	92 (*R*)
(*R*)-**1c**	>99	90 (*R*)
(*S*)-**1d**	>99	92 (*S*)
(*R*)-**1e**	>99	96 (*R*)

[a] Determined by GC. In preparative reactions the yield of analytically pure product was >95%. [b] Determined by chiral GC on a chiral stationary phase; configuration determined by comparison with reported value for the optical rotation.[27]

Synthesis and Hydrogenation of Allylic Alcohol 19

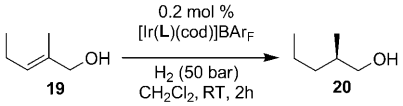
For comparison with the hydrogenations of substrates **14** and **15**, we also studied the hydrogenation of the allylic alcohol **19** with an analogous substitution pattern at the C=C bond, in order to see how a coordinating hydroxy group influenced the performance of the catalyst. The resulting saturated alcohol **20** is of industrial importance and BASF has developed a technical synthesis for the production of this compound in high enantiomeric purity.[17] The first step is a ruthenium-catalyzed hydrogenation of **19** at 200 bar hydrogen pressure, which affords the saturated alcohol in 75% *ee*. The *ee* value is then improved in a second step by kinetic resolution with a lipase.

Substrate **19** was synthesized from propanal by aldol condensation and subsequent reduction with sodium borohydride (Scheme 6).[18] Hydrogenation studies were carried out under standard conditions using 0.2 mol% catalyst at 50 bar hydrogen pressure (Table 8). All catalysts used in this screening gave full conversion within the standard reaction time of 2 h. Among the pyridine-phophinite ligands that were tested, **1a**, which had already proven to be one of the two optimal ligands for substrate **14**, gave the best results (91% *ee*). In addition, several other ligands, including the phox derivatives **22a**,**b** and **23a**,**b** were evaluated. The highest enantioselectivity in this series was obtained with ligand



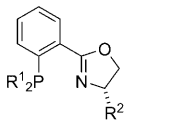
Scheme 6. i) NaOH, H_2O, 50°C (quant.); ii) $NaBH_4$, MeOH, room temperature (65%).

Table 8. Hydrogenation of (*E*)-2-methylpent-2-en-1-ol (**19**).

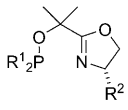


Ligands	Conversion [%][a]	*ee* [%][b]
(*R*)-**1a**	>99	91 (*R*)
(*R*)-**1c**	>99	74 (*R*)
22a	>99	8 (*R*)
22b	>99	64 (*R*)
23a	>99	76 (*R*)
23b	>99	91 (*R*)

[a] Determined by GC. [b] Determined by chiral GC; configuration determined by comparison with reported value for optical rotation.[19]



22a R^1 = Ph, R^2 = *i*Pr
22b R^1 = *o*-Tol, R^2 = *t*Bu



23a R^1 = Ph, R^2 = *i*Pr
23b R^1 = *o*-Tol, R^2 = *t*Bu

23b, which gave the same *ee* value as the pyridine-phosphinite **1a**. The good performance of this ligand contrasts the results of the hydrogenation of unfunctionalized trialkyl-substituted olefins, where oxazoline-derived ligands induce only modest enantioselectivity.

The results obtained with this substrate show that the presence of a coordinating hydroxy group next to the C=C bond does not have a beneficial effect, as observed for Rh and Ru catalysts. In fact, lower enantioselectivities (91% vs. 95% *ee*) were obtained than in the hydrogenation of the ester **14**. These findings are in line with the selectivities observed in the hydrogenation of tocopherol derivatives and farnesol, where the trialkyl-substituted C=C bonds were reduced with higher face selectivity than the allylic alcohol units. The good performance of Ir catalysts derived from ligands **1a** and **23b** demonstrates that Ir complexes of this type are useful catalysts for the hydrogenation of allylic alcohols which can outperform Ru or Rh catalysts.

Conclusions

Chiral iridium complexes with bicyclic pyridine-phosphinites **1** as ligands are highly efficient catalysts that give high enantioselectivity in the hydrogenation of unfunctionalized, trialkyl-substituted olefins. By variation of the hydrogen pressure, solvent, temperature, and catalyst loading, optimized conditions were found that gave 96–99% *ee* in the hydrogenation of alkenes (*E*)- and (*Z*)-**2** and **3** with 0.1 mol% catalyst.

Both α- and γ-tocotrienyl acetate can be hydrogenated with excellent diastereoselectivity under catalyst control with 0.1 mol% Ir complex derived from ligand **1e**, giving

the natural *RRR* form of the corresponding vitamin E derivative. This transformation stands out as the most straightforward and simplest method for the introduction of the two stereogenic centers in the tocopherol side chain. The potential of our catalysts in natural product syntheses is illustrated by the enantioselective synthesis of an insect pheromone **13**. Although a coordinating hydroxy group next to the C=C bond has no beneficial effect as observed for Rh and Ru catalysts, the results obtained with allylic alcohol **19** show that Ir P,N complexes can outperform Rh and Ru catalysts in the asymmetric hydrogenation of this substrate class.

Experimental Section

General: Reactions and manipulations of air- and moisture-sensitive compounds were performed in a nitrogen-filled glovebox or using standard Schlenk techniques, unless otherwise indicated. All chemicals were purchased from Acros Organics, Aldrich, Fluka, Merck, and TCI Chemicals, except for γ- and α-tocotrienyl acetate, which were gifts from Dr. Thomas Netscher, DSM Nutritional Products.

General procedure for iridium-catalyzed hydrogenation: Under nitrogen, substrate (0.05 or 0.1 mmol), the appropriate catalyst ($0.1–1\times10^{-3}$ mmol, 0.1–1 mol%), and dichloromethane (0.5 mL), or substrate (0.05 mmol) and 0.5 mL of a dichloromethane solution of catalyst (5×10^{-5} mmol, 0.1 mol%) were added to a glass vial (2 mL) charged with a magnetic stirrer. The vial was placed in an autoclave and sealed. The autoclave was pressurized with H_2 and the solution was stirred at 700 rpm for a certain time. Then hydrogen was carefully released and the reaction mixture concentrated under reduced pressure. Hexane (1 mL) was added and the mixture filtered through a 0.2 μm syringe filter or a plug of silica gel. Concentration of the hexane solution gave an oil, which was analyzed by GC or HPLC.

Hydrogenation of olefins 2, 3, and 4: Substrate syntheses and analytical procedures are described in reference [8].

Determination of the absolute configuration of 2-cyclohexylbutane (7): (*E*)-2-Phenyl-2-butene[20] (132 mg, 1.0 mmol) was hydrogenated under 50 bar of hydrogen at room temperature using [Ir((*S*)-**1b**)(cod)]BAr_F (16 mg, 0.01 mmol) as catalyst, giving (*S*)-(+)-2-phenylbutane (133 mg, 99%) in 98% *ee* (GC, G-TA, 70 KPa H_2, 50°C (40 min), $t_R=20.28$ min (major), $t_R=21.57$ min (minor)), $[\alpha]_D^{20}=+25.0$ ($CHCl_3$, $c=1.0$). Lit.[21] $[\alpha]_D^{20}=+10.4$ ($CHCl_3$, $c=0.5$). (*S*)-(+)-2-Phenylbutane (133 mg, 1.0 mmol) was then hydrogenated over Rh/C in water (1 mL) under 5 bar of hydrogen at 40°C for 24 h. The catalyst was filtered and rinsed with diethyl ether. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2×5 mL). The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated, giving (*S*)-(−)-2-cyclohexylbutane, $[\alpha]_D^{20}=-1.4$ ($CHCl_3$, $c=2.0$). Lit.:[22] $[\alpha]_D^{25}=+1.95$ (benzene) for the *R* enantiomer. Product **7** from the asymmetric hydrogenation of **3** had the same optical rotation ($[\alpha]_D^{20}=-1.4$ ($CHCl_3$, $c=2.0$) as the above authentic (*S*)-2-cyclohexylbutane.

Hydrogenation of (*E*)- and (*Z*)-3,4-dimethyl-2-pentene (8): Under nitrogen, 3,4-dimethyl-2-pentene (**8**) (196 mg, 2 mmol) and [Ir((*S*)-**1b**)(cod)]BAr_F (15 mg, 0.01 mmol) were dissolved in dichloromethane (10 mL) in an autoclave (120 mL) equipped with an overhead stirrer. The autoclave was pressurized to 50 bar with H_2 and the solution was stirred at 700 rpm for 4 h at room temperature. Then hydrogen was carefully released and the solvent was removed by Kugelrohr distillation. Pentane (2 mL) was added to the residue and the mixture filtered through a 0.2 μm syringe filter. The solution was then submitted to GC analysis.

2,3-Dimethyl-pentane (9): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.58–1.52$ (m, 1H), 1.40–1.33 (m, 1H), 1.20–1.1 (m, 2H), 0.88–0.85 (m, 6H), 0.80 (d, $J=6.6$ Hz, 3H), 0.79 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=40.8$, 32.1, 27.1, 20.7, 18.4, 15.3, 12.4 ppm, consistent with reported values[23]; for (*S*)-**9**: GC (50 m+25 m chirasil-β-Dex TM8,[11] 45°C, 1.8 bar H_2), $t_R=13.5$ min (minor), $t_R=13.9$ min (major); for (*R*)-**9**: GC (50 m+25 m+40 m chirasil-β-Dex TM8, 40°C, 2.1 bar H_2), $t_R=27.4$ min (major), $t_R=28.4$ min (minor). GC analysis was carried out by Dr. Harri Czesla and Prof. Volker Schurig (University of Tübingen). The absolute configuration of **9** was determined by comparison of the optical rotation with that reported in the literature.[24]

Hydrogenation of α-(*R*)-tocotrienyl acetate 10: Following the procedures reported, α-tocopheryl acetate was converted into the corresponding methyl ether for determining the diastereoselectivity.[25]

α-Tocopheryl acetate (12): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.59$ (t, $J=6.8$ Hz, 2H), 2.34 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.79 (m, 2H), 1.57–1.01 (m, 21H), 1.23 (s, 3H), 0.86 (d, $J=6.6$ Hz, 6H), 0.85 (d, $J=6.3$ Hz, 3H), 0.84 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=170.2$, 149.8, 140.9, 127.0, 125.3, 123.4, 117.8, 75.5, 39.8(2C), 37.9, 37.9, 37.8, 37.7, 33.2, 33.1, 31.4, 28.4, 25.2, 24.9, 23.1, 23.0, 21.4, 21.0, 21.0, 20.2, 20.1, 13.4, 12.5, 12.2 ppm.

α-Tocopherol: A mixture of tocopheryl acetate (0.05 mmol) and LiAlH4 (13 mg, 0.35 mmol) in THF (1 mL) was stirred at room temperature for 1.5 h and then cooled with ice before water (2.5 mL) was added cautiously. The mixture was stirred for 10 min and extracted with ether (3×5 mL). The organic portions were combined, dried (Na_2SO_4), and concentrated, giving an oil, which was subjected directly to etherfication without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.17$ (s, 1H), 2.60 (t, $J=6.8$ Hz, 2H), 2.16 (s, 3H), 2.11 (s, 6H), 1.78 (m, 2H), 1.60–1.00 (m, 21H), 1.23 (s, 3H), 0.87 (d, $J=6.8$ Hz, 6H), 0.85 (d, $J=6.6$ Hz, 3H), 0.84 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=145.9$, 144.9, 123.0, 121.4, 118.8, 117.8, 74.9, 40.2, 39.8, 37.9, 37.9, 37.8, 37.7, 33.2, 33.1, 32.0, 28.4, 25.2, 24.9, 24.2, 23.1, 23.0, 21.4, 21.2, 20.2, 20.1, 12.6, 12.2, 11.7 ppm.

α-Tocopheryl methyl ether: An aqueous solution of KOH (50% w/w, 40 uL, 0.5 mmol) was added to a solution of tocopherol (0.05 mmol) in DME (0.2 mL) and the mixture was stirred at room temperature for 10 min. Then dimethyl sulfate (24 uL, 0.25 mmol) was added and the reaction was stirred for 1.5 h. The reaction mixture was concentrated under reduced pressure and stirred in a mixture of water/hexane (2:1, 10 mL) for 5 min. The organic phase was separated and the aqueous phase was extracted with hexane (2×5 mL). The combined organic phases were dried (Na_2SO_4), concentrated, yielding an oil which was analyzed by GC. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=3.63$ (s, 3H), 2.58 (t, $J=6,8$ Hz, 2H), 2.18(s, 3H), 2.14(s, 3H), 2.08(s, 3H), 1.78 (m, 2H), 1.59–1.00 (m, 21H), 1.23 (s, 3H), 0.86 (d, $J=6.6$ Hz, 6H), 0.85 (d, $J=5.3$ Hz, 3H), 0.84 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=149.8$, 148.2, 128.1, 126.1, 123.3, 117.9, 75.2, 60.8, 40.5, 39.8, 37.9, 37.9, 37.8, 37.7, 33.2, 33.1, 31.7, 28.4, 25.2, 24.8, 24.3, 23.1, 23.0, 21.4, 21.0, 20.2, 20.1, 13.0, 12.2, 12.1 ppm; MS (EI, *m/z*): 444 (M^+, 100%), 179 (96%); elemental analysis (%) calcd for $C_{30}H_{52}O_2$ (444.74): C 81.02, H 11.78; found: C 81.06, H 11.80; GC: CP-Sil-88, 90 kpa H_2, 280°C (injection), 250°C (detector), 170°C (170 min), $t_R=142.75$ min (*RRS*), 144.99 min (*RRR*), 147.06 min (*RSR*), 148.95 min (*RSS*).

Synthesis of 14:[14] A mixture of 6.00 g (59.9 mmol) of 2-methyl-1-penten-3-ol, 38.9 g (240 mmol) of ethyl orthoacetate, and 0.53 mL (7.03 mmol) of propionic acid was heated to 138°C. The ethanol formed was removed by distillation. After 8 mL of ethanol had been collected (3 h), the solution was allowed to cool to ambient temperature and 5.6 mL of 3.5% aqueous acetic acid was added. After stirring for 1 h the solution was concentrated in vacuo (35°C/70 mbar). The colorless residue was dissolved in pentane (5 mL) and dried with $MgSO_4$. The suspension was loaded on top of a plug of silica gel ($d=5$ cm, h=3 cm, suspended in pentane) and eluted with pentane (200 mL). After removal of the solvent in vacuo (35°C/150 mbar) 9.06 g of a mixture of product **14** and a side product was obtained as a colorless liquid and used for the next step without further purification.

In another experiment the product was purified by distillation at 83°C and 11 mbar to yield 7.6 g (75%) of analytically pure product **14** (>97% *E*), whose ^{1}H NMR data were consistent with the reported values.[14]

Ethyl 4-methylheptanoate (16): Analytical data were consistent with reported values[26]; GC (Brechbühler β-cyclodextrin De*t*ButSil SE54 25 m×

0.25 mm, 60 KPa H_2, 40 °C (0 min), 0.4 °C min^{-1}, 75 °C (2 min), 10 °C min^{-1}, 180 °C (5 min)), t_R = 76.5 min (*S*), 77.4 min (*R*), 86.0 min (**14**).

Synthesis of 18: The mixture of product **14** and side product (9.06 g) was dissolved in MeOH (40 mL) and H_2O (20 mL). NaOH (8.52 g) was added and the suspension was stirred vigorously whereupon it heated up to boiling temperature. After stirring at 50 °C for 2 h the solvent and EtOH formed in the reaction were removed in vacuo (40 °C/100 mbar). The aqueous solution was washed with CH_2Cl_2 (3 × 50 mL), cooled to 0 °C, and acidified with a solution of 20 % HCl (35 mL). The pH was adjusted to 2 with a solution of 2 % HCl. The resulting cloudy solution was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo (40 °C/13 mbar) to yield 6.80 g (91 %, calculated over two steps) of (*E*)-4-methylhept-4-enoic acid (**18**) as a colorless liquid, whose ^{1}H NMR data were consistent with the reported values.[14]

Synthesis of 15: Compound **18** (1.00 g, 8.05 mmol) was dissolved in dry CH_2Cl_2 (7 mL) and the solution cooled to 0 °C. Then 0.82 mL (9.66 mmol) of $(COCl)_2$ and one drop of DMF were added. The solution was stirred for 15 min at 0 °C and 1.5 h at room temperature until gas evolution stopped. The solvent was removed in vacuo and the residue distilled (37 °C, 0.08 mbar) to yield 0.96 g (5.98 mmol) of acid chloride as a colorless oil. The acid chloride was immediately dissolved in dry THF (20 mL) and 63 mg (0.18 mmol, 3 %) of $[Fe(acac)_3]$ was added. The solution was cooled to 0 °C and 6.0 mL of EtMgBr (6.0 mmol, 1 M in THF) was added slowly over 1 h causing a color change from red to yellow to black. After stirring for an additional 15 min at 0 °C the reaction was quenched by addition of 1 M HCl (10 mL). The organic layer was separated and the aqueous phase washed with Et_2O (3 × 20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (30 mL), dried ($MgSO_4$), and concentrated in vacuo (40 °C/13 mbar). Purification by flash column chromatography (silica gel, pentane/Et_2O = 20:1) gave 0.80 g (5.16 mmol, 64 %) of product **15** as a colorless liquid.

(*E*)-6-Methylnon-6-en-3-one (15): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.3 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H), 1.59 (s, 3H), 1.97 (dq, $J_1 \approx J_2 \approx$ 7.3 Hz, 2H), 2.23 (t, J = 7.8 Hz, 2H), 2.42 (q, J = 7.3 Hz, 2H), 2.49 (t, J = 7.8 Hz, 2H), 5.12 ppm (broadened t, $J \approx$ 7.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): 7.8, 14.3, 15.9, 21.1, 33.6, 35.9, 41.1, 126.9, 133.0, 211.6 ppm; elemental analysis (%) calcd for $C_{10}H_{18}O$ (154.25): C 77.87, H 11.76; found: C 77.86, H 11.66.

Asymmetric hydrogenation of 15: Preparative reactions were carried out according to the general procedure and Table 7, using 1–5 mmol of substrate (3 mL CH_2Cl_2 per mmol **15**). After releasing hydrogen, the reaction solution was concentrated in vacuo at 30 °C. The resulting brown oil was Kugelrohr distilled (0.1 bar, 75 °C) to give product **13** in 95–97 % yield as a colorless oil.

6-Methylnonan-3-one (13): Analytical data consistent with reported values;[13,27] GC (Macherey–Nagel Hydrodex β-3P 25 m × 0.25 mm, 100 KPa H_2, 40 °C (5 min), 0.5 °C min^{-1}, 70 °C (0 min), 10 °C min^{-1}, 180 °C (10 min)), t_R = 58.5 min (*R*), 60.5 min (*S*), 65.5 min (**15**).

Synthesis of 21: Propanal (29.3 mL, 23.4 g, 0.4 mol) was added over a period of 1 h to a 1 M aqueous solution of sodium hydroxide at 50 °C. The mixture was further stirred for 1 h at 50 °C and, after cooling to room temperature, was extracted with diethyl ether (3 × 50 mL). The combined organic phases were dried over magnesium sulfate and concentrated in vacuo to yield 19.9 g (quant.) of analytically pure (*E*)-2-methylpent-2-enal (**21**), which was used in the next step without further purification. The ^{1}H NMR data were consistent with the reported values.[18a]

Synthesis of 19: To a solution of aldehyde **21** (18.6 g, 0.19 mol) in 300 mL of methanol, sodium borohydride (9.33 g, 0.25 mol) was slowly added during 30 min. The solution was kept at ambient temperature by the use of a water bath. After the addition was complete, the reaction was stirred for an additional 2 h. Then water (200 mL) was added, and the mixture extracted (3 × 100 mL) with diethyl ether. The combined organic phases were dried over $MgSO_4$, and the solvent was removed in vacuo to yield analytically pure (*E*)-2-methylpent-2-en-1-ol (**19**) (12.4 g, 65 %), whose ^{1}H and ^{13}C NMR data were consistent with the reported values.[18b]

2-Methylpentan-1-ol (20): Analytical data were consistent with the values reported[28]; GC (Brechbühler β-cyclodextrin De*t*ButSil SE54 25 m × 0.25 mm, 60 KPa H_2, 40 °C (0 min), 0.3 °C min^{-1}, 61 °C (2 min), 10 °C min^{-1}, 160 °C (5 min)), t_R = 59.9 min (*R*), 64.8 min (*S*), 73.6 min (**19**).

Acknowledgements

Financial support from the Swiss National Science Foundation, the Federal Commission for Technology and Innovation (KTI), and Novartis Pharma (Fellowship Award to A.W.) is gratefully acknowledged. R.P.A.F. is grateful to Fundação para a Ciência e Tecnologia (FCT) for a postdoctoral scholarship. We thank Dr. Thomas Netscher (DSM Nutritional Products) for helpful discussions and a gift of α- and γ-(*R*)-tocotrienyl acetate. Dr. Harri Czesla and Prof. Volker Schurig are specially acknowledged for their help in the determination of the enantiomeric excess of alkane **9**.

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Received: August 20, 2010
Published online: October 21, 2010

