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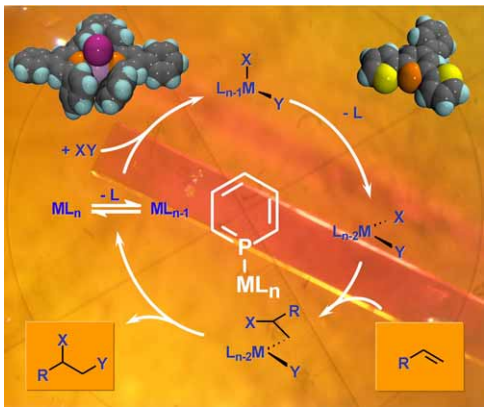

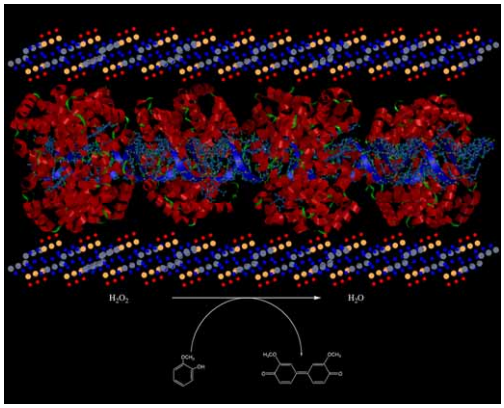

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Development of pinene-derived N,P ligands and their utility in catalytic asymmetric hydrogenation

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New diastereomeric N,P-ligands, derived from the natural product (+)-α-pinene, have been synthesized and evaluated in iridium-catalyzed asymmetric hydrogenation. The ligands are tetrahydroquinoline derivatives synthesized directly from commercially available α-pinene utilizing resolution or recrystallization to separate diastereomers. In reduction of a range of different trisubstituted alkenes the catalysts express very different activities ranging from no activity to high activity. One of the catalysts gives good ee values for some substrates.

Introduction

Asymmetric hydrogenation of olefins has become an important technique for the synthesis of chiral materials in both academic and industrial settings. Historically, this transformation is accomplished using various chiral P,P- and N,P-ligands complexed to rhodium or ruthenium.[1] Although widely used in industrial applications, these catalysts are often quite dependent on olefin functionalization. During the past decade, in addition to ruthenium and rhodium catalysts, iridium complexes have received intense interest as powerful enantioselective catalysts capable of reducing both unfunctionalized[2] and functionalized[3] alkenes with high enantioselectivity.

Crabtree reported the first homogenous achiral iridium hydrogenation catalysts in 1977,[4] and in 1997–1998 Pfaltz reported the first chiral iridium catalysts.[5] Since then, several highly successful chiral N,P-ligands have been developed and used for iridium-catalyzed asymmetric hydrogenation.[2] Some of these chiral ligands are synthesized from enantiomerically pure α-amino acids, however many efficient catalysts known to date are based on chiral ligands prepared by chromatographic resolution techniques.[2,6,7] The need to resolve enantiomers often hampers the usefulness of a catalyst in industrial applications because it requires expensive equipment, is time-consuming and requires vast amounts of solvent. Furthermore, these homogenous catalysts are non-recyclable due to trimerization of the active catalyst complex after the olefin has been consumed[8,9] so the synthesis costs need to be kept at a minimum.

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Starting from an enantiomerically pure chiral substrate and synthesizing pairs of diastereomeric ligands should lead to easier purification, avoid the need for preparative chiral HPLC and offer an opportunity to study how a minor structural change affects the catalyst activity. Furthermore, starting from a cheap substance derived from the chiral pool might allow the development of a short and inexpensive synthetic route.

Among the most efficient iridium complexes for asymmetric hydrogenation that have been developed to date are those based on the thiazole-phosphine ligands (**1**, Fig. 1) developed in our laboratory.[7,10] These complexes reduce a broad range of alkenes with excellent conversion and stereoselectivity. Pfaltz and co-workers recently explored the potential of a number of tetrahydroquinoline-based phosphinite–Ir complexes such as **2**, Fig. 1, in iridium-catalyzed asymmetric hydrogenations with very good results.[11] Based on the structures of **1** and **2** we envisioned that complexes **3–6** might prove to be effective catalysts. DFT calculations also showed that the transition state conformations of the complexes **1** and **3**, with a coordinated alkene, are similar.

The ligands used in complexes **3–6** can be synthesized from (+)-α-pinene, a readily available natural product and one of the classic terpenes.[12] α-Pinene has been subject to extensive research and is presently used in a number of industrial applications, mainly for production of polyterpene resins.[13] Malkov and Kocovsky, Chelucci and von Zelewsky have used α-pinene derivatives to incorporate chirality into ligands used for various transition-metal-catalyzed processes.[14] Asymmetric allylic substitution and oxidation, cyclopropanation of styrenes and enantioselective reduction of acetophenone are some examples. Malkov and Kocovsky have used iridium catalysts based on α-pinene in asymmetric Heck reactions[15] and Knochel and co-workers have used iridium

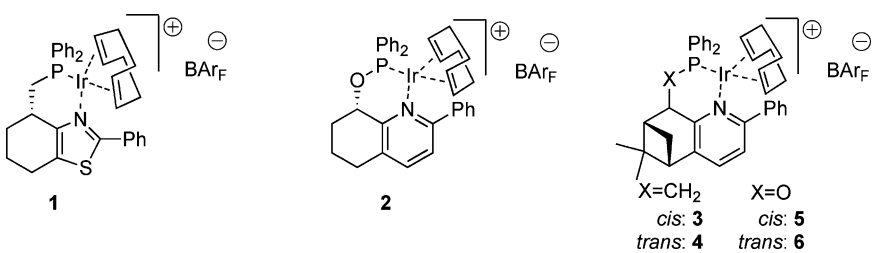
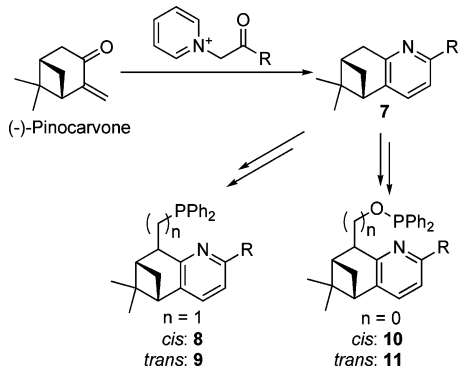


Fig. 1 The thiazole complex **1**,[10] tetrahydroquinoline complex **2**,[11] and the pinene-based diastereomeric ligands in complexes **3–6**.

catalysts based on (+)-norpinone for asymmetric hydrogenation of alkenes with good results.[16]

UV-catalyzed oxidation of (+)-α-pinene to (−)-pinocarvone[17] and subsequent Kröhnke annulation[18] using different Kröhnke salts allows for the synthesis of a range of interesting tetrahydroquinoline derivatives, **7** Scheme 1. The extensive work by Chelucci and von Zelewsky in functionalizing the benzylic 8-position of compound **7** opens up synthetic routes to the potential N,P-ligands **8–11**. Although slight modifications in the synthetic routes could also produce five- and seven-membered chelating ligands, Scheme 1, we prioritized ligands **8–11** due to the promising calculated results and to the many examples showing six-membered chelates to generally be the most effective in iridium-catalyzed asymmetric hydrogenation.



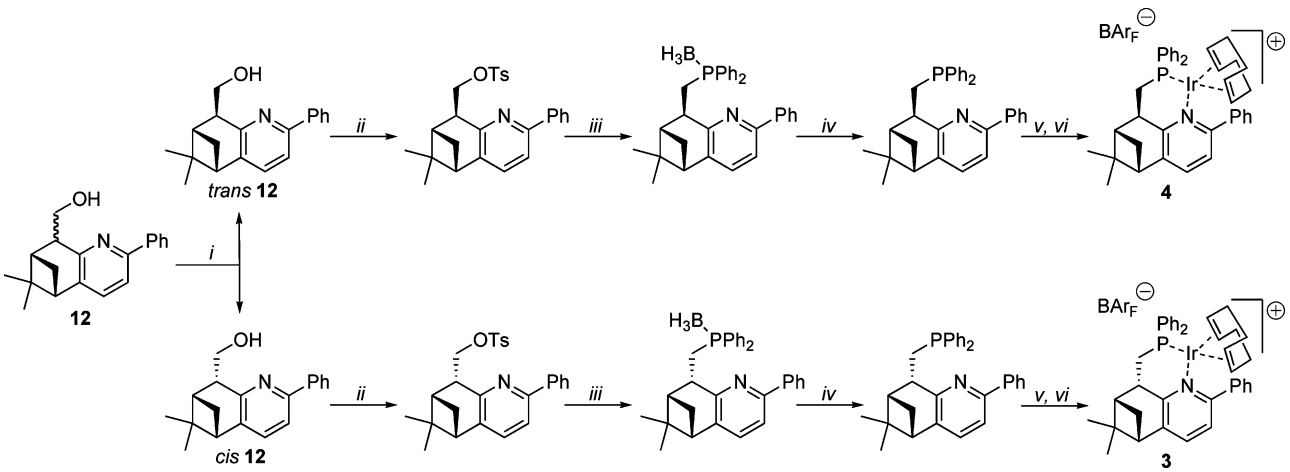
Scheme 1 Annulation of (−)-pinocarvone with different Kröhnke salts gives a set of central intermediates **7**, which subsequently can be transformed to a range of different ligands.

Results and discussion

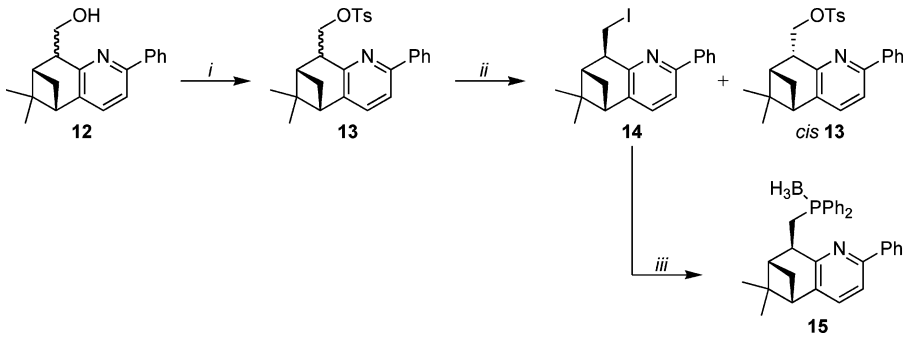
Synthesis of phosphine iridium complexes 3 and 4

Our initial synthetic strategy, outlined in Scheme 2, was to generate a diastereomeric mixture of the phenyl derivative **12** and separate its diastereomers by column chromatography, a procedure reported by Chelucci *et al.*[19] starting from the phenyl derivative of compound **7**. We planned to separately tosylate the pure *cis* and *trans* isomers of the alcohol **12** and then displace the TsO function with the powerful nucleophile $BH_3Ph_2P^-$ to generate the stable boron-protected ligand. After simple removal of the BH_3 protecting group, the resulting pyridine-phosphines should easily complex iridium, yielding compounds **3** and **4**. Andersson[6] successfully used this approach to generate compound **1** and various derivatives.

We found the reported synthesis of compound **12** from (+)-α-pinene to proceed readily, yielding a 6 : 5 *cis : trans* mixture which unfortunately could not be separated using our flash-chromatography equipment. Derivatization of **12** to common esters and chiral salts was performed and the derivatives were subjected to column chromatography and/or recrystallization but we could not separate the isomers. Tosylation of **12** gave a diastereomeric mixture **13** (Scheme 3) from which we failed to isolate the pure isomers. At this stage we decided to temporarily abandon the separation and attempt to move on by substituting the diastereomeric mixture with $BH_3Ph_2P^-$ as we had planned to do for the pure diastereomers, Scheme 2. Unfortunately this procedure yielded only a minor amount of the *trans* phosphine and trace amounts of its *cis* isomer after optimization of the reaction conditions. This indicates that the bicyclic pinene system contributes significant steric bulk to the area of the electrophilic carbon, preventing effective substitution by the sterically demanding boron-protected diphenylphosphine. This hypothesis is supported by the fact that the substitution of tosyl with $BH_3Ph_2P^-$ in the thiazole system (Fig. 1) proceeds smoothly. In order to grasp the effect of nucleophile size on the reaction and find clues towards a useful synthetic route to **3** and **4**, we tested unprotected $LiPPh_2$ as nucleophile under similar conditions. Indeed, this reaction gave higher yields but these were still modest, especially for the *cis* phosphine. Substitution with sodium azide gave good conversion of both tosylate isomers to the corresponding azides, although the *cis* substitution seems to compete to a greater extent with the elimination of tosylate to give the terminal alkene. Further, the *trans* tosylate was readily substituted by iodide under Finkelstein conditions, whereas the *cis* tosylate was untouched, Scheme 3. Interestingly, the *trans* iodide was easily phosphorylated by



Scheme 2 Proposed synthetic strategy for complexes **3** and **4** from the known intermediate **12**. (*i*) Column chromatography (DCM : Pentane : Et_2O 7 : 3 : 0.5); (*ii*) TsCl, Pyridine, DCM, r.t., o.n.; (*iii*) $HPPh_2$–BH_3, ^{n}BuLi, THF/DMF, −78 °C to 40 °C, o.n.; (*iv*) $HNEt_2$, r.t, o.n.; (*v*) $[Ir(COD)Cl]_2$, DCM, reflux, 45 min; (*vi*) $NaBAr_F$, H_2O, r.t, 1 h.



Scheme 3 Diastereoselective iodination of tosylate **13** and subsequent phosphorylation formed compond **15**. (*i*) TsCl, Pyridine, DCM 0 °C to r.t. o.n. 80%; (*ii*) NaI, acetone, reflux, 14 h, 40% **14**; (*iii*) $HPPh_2$–BH_3, BuLi, THF/DMF, −78 °C to 40 °C, 21 h, 48%.

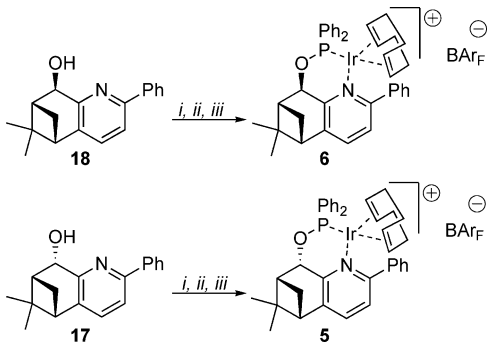
boron-protected diphenylphosphine under the same conditions applied to the tosylate, and yielded compound **15**. The loss of iodide might be favored over that of tosylate in substitution by $BH_3Ph_2P^-$ due to its "softer" leaving group character and/or lesser steric constraints: a smaller leaving group, apart from contributing smaller bulk to the reactive site, should also be subject to less rotational hindrance arising from interactions between the leaving group and one of the methyl groups on the pinene bridge. However, exchanging the tosyl group of **13** for a smaller mesyl did not improve the reactivity with $BH_3Ph_2P^-$.

Having observed the selective iodination of the *trans* tosylate and the reactivity of the iodide, we attempted the direct iodination of the diasteromeric alcohol mixture **12**. Reaction of **12** with iodine/triphenylphosphine in the presence of imidazole as a base at ambient temperature for 18 h gave resolution of the diastereomers resulting in *cis*-**12** diastereomerically pure in good yield, Scheme 4.

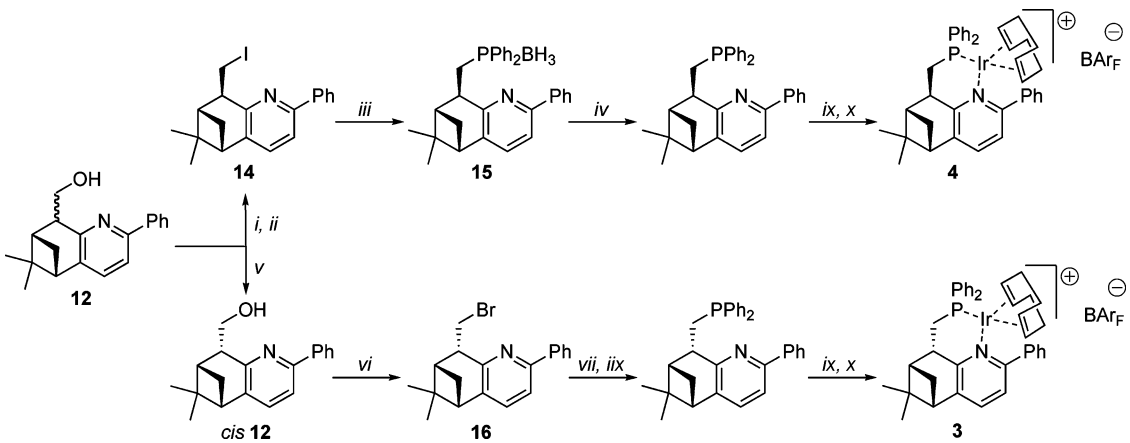
Due to the low reactivity of the *cis* isomer in S_N2 reactions we decided to attempt bromination of the alcohol *cis*-**12** by treating it with thionyl bromide. This yielded the bromine compound **16**, which, as expected, could not be substituted by $BH_3Ph_2P^-$. However, we succeeded in converting this alkyl bromide to the ligand by a conventional Grignard reaction using $ClPPh_2$ as the electrophile. The ligands were immediately converted to the iridium complexes **3** and **4**, Scheme 4.

Synthesis of phosphinite iridium complexes 5 and 6

Following a method developed by von Zelewsky and co-workers[20] the alcohols **17** and **18** (Scheme 5) were synthesized from the corresponding isobutyl ester using recrystallization and column chromatography to separate the diastereomers. Compounds **17** and **18** were each phosphorylated and complexed to iridium in a one-pot manner as described by Pfaltz *et al.* for simpler quinoline derivatives.



Scheme 5 Synthesis of complexes **5** and **6** from **17** and **18** (*i*) ^{n}BuLi, $ClPPh_2$, THF, 0 °C to r.t, o.n.; (*ii*) $[Ir(COD)Cl]_2$, DCM, reflux, 1.5 h; (*iii*) $NaBAr_F$, H_2O, r.t, 1.5 h, 11% for **5** and 41% for **6**.



Scheme 4 Resolution of compound **12** and synthesis of complexes **3** and **4**. (*i*) TsCl, Pyridine, DCM, 0 °C to r.t. o.n. 80%; (*ii*) NaI, acetone, reflux, 14 h, 40%; (*iii*) $HPPh_2$–BH_3, ^{n}BuLi, THF/DMF, −78 °C to 40 °C, 21 h, 48%; (*iv*) $HNEt_2$, r.t, o.n.; (*v*) I_2, PPh_3, Imidazole, DCM, r.t, 18 h, 40%; (*vi*) $SOBr_2$, 100 °C, 1.5 h, 65%; (*vii*) Mg, THF, reflux, 1 h; (*viii*) $ClPPh_2$, r.t, o.n.; (*ix*) $[Ir(COD)Cl]_2$, DCM, reflux, 45 min; (*x*) $NaBAr_F$, H_2O, r.t, 1 h, 20% **3** and 31% **4**.

Evaluation of complexes

Complexes **3–6** were evaluated as catalysts for asymmetric hydrogenation of several common trisubstituted alkenes under 30 bar hydrogen pressure. The reactions were performed at room temperature over 12 h with 0.5% catalyst loading. The reaction mixtures were analyzed using ^{1}H NMR spectroscopy to determine conversions and chiral HPLC-DAD or GC-MS to determine the enantiomeric excess.

As seen in Table 1 the four relatively similar complexes **3–6** have quite different properties. Complex **3** was the most active and selective among the complexes, and was therefore tested with additional substrates as well as at 100 bar hydrogen pressure. At 100 bar the conversions increased slightly whereas the ee values were retained, Table 2.

In general, compared to complexes **1** and **2**, these bulkier ligands are both less reactive and less selective. Repulsion between the pinene moiety and a phosphorus phenyl group may result in a conformational change that produces a more crowded active site as compared to that in the thiazole complex **1**. The smaller electron-rich alkenes were reduced better than bigger and electron-deficient ones.

In the phosphine case, the *cis*-ligand-containing complex hydrogenated olefins to a higher conversion than did the corresponding *trans*-ligand isomer. Interestingly, there was a significant difference in activity between the *cis*-ligated complexes **3** and **5**; the phosphine complex **3** generally gave higher conversions than the comparable phosphinite **5**. We suspect that complex **5** may decompose over the course of the reaction. The anomalously low yield in which complex **5** was prepared also suggests that it is less stable, possibly due to high steric strain about the metal.

Result from hydrogenations with catalysts derived from 98% (+)-α-pinene.

Ligands **3–6** have three chiral centres each: two in the pinene moiety, and one at the benzylic C-8 position. As the chiral centres of pinene are fixed, its inclusion in a ligand with another chiral centre produces two diastereomeric compounds. Assuming that both the pinene and C-8 chirality can induce stereoselection, the diastereomeric pair comprises one matched diastereomer, in which the directing effects of pinene and C-8 reinforce each other, and one mismatched diastereomer, in which these effects oppose one another. When comparing complexes **3–4** and **5–6** respectively, this effect is not seen to any significant degree. Instead, comparing the major enantiomers formed when reducing various alkenes using complexes **3–6** and complex **2**, Table 1, the chiral centre in the benzylic, C-8, position on the backbone of complexes **3–6** direct stereoselectivity. The pinene moiety does however have the effect of making the ring more rigid as compared to complexes **1** and **2**.

Conclusion

In conclusion, we have developed a synthetic route to a number of diastereomeric N,P-ligands based on the readily available natural product α-pinene. The synthesis does not require preparative HPLC but instead simple kinetic resolution or recrystallization yields diastereomerically pure ligands. One of the complexes, **3**, shows good efficiency and enantioselectivity in iridium-catalyzed asymmetric hydrogenation of small alkenes.

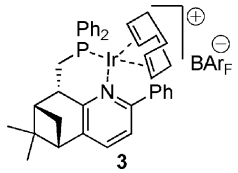
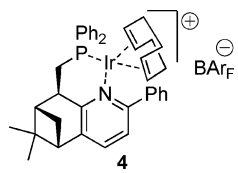
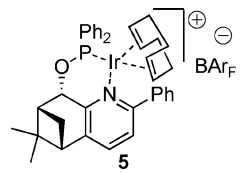
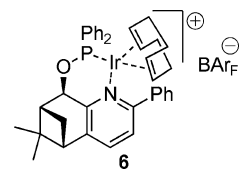
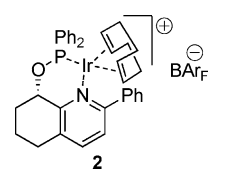
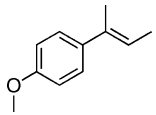
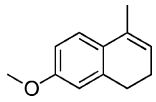
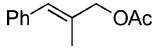
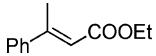
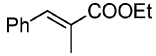
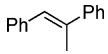
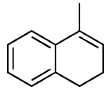
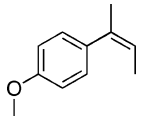
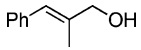
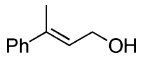
Experimental

All chemicals and solvents were used as supplied commercially unless noted. (+)-α-Pinene was purchased from Aldrich in 98% enantiomeric purity and used without further purification. THF was distilled under N_2 from a deep blue solution of sodium-benzophenone ketyl directly before use. DCM was freshly distilled from CaH_2 under N_2 prior to use. Flash chromatography was performed using silica gel 60 Å. For thin layer chromatography (TLC), 0.25 mm silica gel 60 F_{254} precoated plates were used. Spots on TLC plates were visualized using UV light or by soaking in a solution of phosphomolybdic acid (5%) in EtOH followed by heating. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian Unity 400 MHz spectrometer, ^{31}P NMR (121 MHz) spectra were recorded on a Varian Mercury plus 300 MHz spectrometer. All NMR spectra were acquired at ambient temperature. ^{1}H NMR shifts were referenced internally to $CHCl_3$ (δ 7.26) or d_5-DMSO (δ 2.50). ^{13}C NMR shifts were referenced internally to $CDCl_3$ (δ 77.16). Mass spectra were measured at 70 eV (EI) on a Bruker GC–MS using direct inlet. Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 FT/IR spectrometer. Optical rotation was measured on a Perkin-Elmer 241 polarimeter under standard conditions where temperature and concentration were accounted for. Enantiomeric excesses were determined using a Varian Saturn 2100T GC-MS equipped with (30 m × 0,25 mm) chiral columns supplied by Astec with electron impact ionization or using a HPLC system consisting of a Gilson 322 pump, Gilson 233XL autosampler and an Agilent 1100 diode-array detector equipped with chiral columns supplied by Daicel Chemical Industries.

(5*S*,7*S*,8*S*)- and (5*S*,7*S*,8*R*)-8-(hydroxymethyltosyl)-5,6,7,8-tetrahydro-6,6-dimethyl-2-phenyl-5,7-methanoquinoline (13)

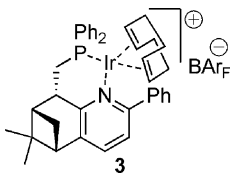
Compound **12** (300 mg, 1.1 mmol, 1.0 eq.) was dissolved in dry DCM (3 ml). Pyridine (3 ml) was added and the solution cooled to 0 °C followed by addition of TsCl (340 mg, 2.14 mmol, 2.0 eq). The solution was allowed to reach room temperature overnight. After evaporation of solvents the residue was dissolved in DCM (10 ml). The organic phase was washed with sat. aq. $NaHCO_3$ (5 ml), water (5 ml), brine and dried over $MgSO_4$. Evaporation of solvent gave 495 mg crude product that was purified using column chromatography (pentane : Et_2O : EtOAc 4 : 1 : 1) to give 380 mg pure tosylate **13** as white foam (80%). $R_f = 0.65$ (pentane : Et_2O : EtOAc 4 : 1 : 1); IR (neat) ν_{max} 2935, 1569, 1439, 1361, 1188, 1097, 964, 836, 762, 665; MS (EI) (*m*/*z*) (rel. int.) 434 (MH^+, 49%), 262 (92%), 261 (52%), 260 (83%), 249 (100%); ^{1}H NMR δ: 0.49 (s, 3H), 0.63 (s, 3H), 1.23 (d, 1H, $J = 9.5$), 1.34 (s, 3H), 1.36 (d, 1H, $J = 9.5$), 1.42 (s, 3H), 2.41 (s, 3H), 2.44 (s, 3H), 2.45–2.60 (m, 3H), 2.69–2.79 (m, 3H), 3.44 (td, 1H, $J = 9.7$ and 3.1), 3.56 (td, 1H, $J = 9.7$ and 3.1), 4.30 (m, 2H), 4.89 (dd, 1H, $J = 4.0$ and 9.8), 5.05 (dd, 1H, $J = 4.0$ and 9.8), 7.22–7.47 (m, 14H), 7.77 (m, 8H); ^{13}C NMR δ: 20.9, 21.7, 23.0, 26.3, 26.6, 28.7, 33.5, 39.6, 41.3, 41.4, 41.8, 44.0, 46.3, 46.5, 48.0, 71.7, 72.3, 117.7, 117.8, 126.49, 126.51, 127.1, 127.9, 128.1, 128.2, 128.6, 128.7, 129.8, 129.87, 129.88, 130.3, 133.1, 133.2, 134.0, 134.1, 139.2, 140.1, 141.2, 144.69, 144.74, 154.1, 154.3, 154.7;

Table 1 Asymmetric hydrogenation of alkenes applying complexes **3–6** under 30 bar H_2. Complex **2**[11] is included for comparison

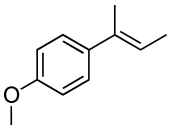
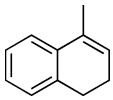
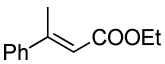
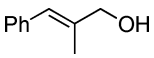
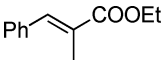
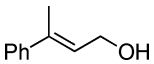
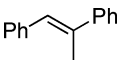
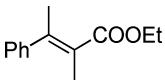
		 **3**		 **4**		 **5**		 **6**		 **2**	
Entry	Substrate	Conv. (%)	ee*(%)	Conv. (%)	ee*(%)	Conv. (%)	ee*(%)	Conv. (%)	ee*(%)	Conv. (%)	ee*(%)
1		80	97 (*S*)	20	49 (*R*)	59	34 (*S*)	75	33 (*R*)	>99	96 (*S*)
2		87	80 (*R*)	18	64 (*S*)	51	39 (*R*)	49	42 (*S*)	97	68 (*R*)
3		5	45 (*S*)	0	—	32	0	7	0	—	—
4		9	69 (*S*)	0	—	15	9 (*S*)	10	16 (*S*)	21	6 (*S*)
5		10	77 (*S*)	5	70 (*R*)	20	0	7	35 (*R*)	—	—
6		20	95 (*S*)	0	—	30	12 (*S*)	11	41 (*R*)	4	92 (*S*)
7		97	96 (*R*)	—	—	—	—	—	—	—	—
8		18	43 (*R*)	—	—	—	—	—	—	>99	87 (*R*)
9		5	45 (*S*)	—	—	—	—	—	—	64	90 (*S*)
10		20	90 (*S*)	—	—	—	—	—	—	—	—

*Results from hydrogenations with catalyst derived from 98% (+)-α-pinene.

Table 2 Asymmetric hydrogenation of alkenes applying complex **3** under 100 bar H_2



3

Entry	Substrate	Conv. (%)	ee* (%)			Conv. (%)	ee* (%)
1		100	94 (*S*)	5		100	97 (*R*)
2		27	70 (*S*)	6		5	42 (*S*)
3		10	55 (*S*)	7		100	86 (*S*)
4		35	94 (*S*)	8		0	—

*Results from hydrogenation with catalyst derived from 98% (+)-α-pinene.

(5*S*,7*S*,8*R*)-8-(iodomethyl)-5,6,7,8-tetrahydro-6,6-dimethyl-2-phenyl-5,7-methanoquinoline (14)

Compound **13** (110 mg, 0.25 mmol, 1.0 eq.) was dissolved in acetone (2 ml) and NaI (400 mg, 2.60 mmol, 10 eq.) was added. The mixture was refluxed for 14 h and then allowed to cool. After evaporation of the solvent, the residue was dissolved in H_2O (10 ml) and extracted with Et_2O (3 × 10 ml). The combined organic phases were dried over $MgSO_4$ and the solvent subsequently evaporated to give 98 mg crude product. Purification by column chromatography (Pentane : EtOAc 5 : 1) yielded 45 mg pure **14** (40%) as a colorless liquid. R_f = 0.70 (Pentane: EtOAc 5 : 1); $[\alpha]^{21.6}{}_D$ = + 13.5 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2928, 1590, 1423; 1234, 1170, 1028, 812, 764, 693; MS (EI) (m/z) (rel. int.) 390 (MH^+, 16%), 263 (21%), 262 (100%), 220 (23%), 218 (20%); ^{1}H NMR δ: 0.67 (s, 3H, 6-CH_3), 1.24 (d, 1H, *J* = 10.0, 9-CH_2), 1.49 (s, 3H, 6-CH_3), 2.63 (m, 2H, 7-CH and 9-CH_2), 2.84 (t, 1H, *J* = 5.6, 5-CH), 3.25 (dd, 1H, *J* = 11.7 and 9.6, CH_2I), 3.41 (td, 1H, *J* = 11.7 and 3.0, 8-CH), 4.37 (dd, 1H, *J* = 9.6 and 3.0, CH_2I), 7.30 (d, 1H, J = 7.9, PhH), 7.40 (d, 1H, *J* = 6.8, 4-CH), 7.47 (m, 3H, PhH and 3-CH), 8.01 (d, 2H, *J* = 7.9, PhH); ^{13}C NMR δ: 10.4, 21.0, 26.5, 28.8, 42.5, 44.6, 47.2, 47.5, 118.1, 126.7, 128.7, 128.9, 133.9, 139.5, 140.4, 154.8, 157.0;

(5*S*,7*S*,8*R*)-8-(diphenylphosphomethyl)-5,6,7,8-tetrahydro-6,6-dimethyl-2-phenyl-5,7-methanoquinoline borane adduct (15)

$HPPh_2$ borane adduct (90 mg, 0.45 mmol, 2.5 eq.) was dissolved in dry THF (2 ml) and the solution was cooled to −78 °C in inert atmosphere. n-BuLi (0.22 ml, 0.34 mmol, 1.9 eq.) was added dropwise and the solution stirred for 20 min at −78 °C and then at 0 °C for an hour. Iodide **14** (70 mg, 0.18 mmol, 1.0 eq.) dissolved in anhydrous DMF (2 ml) was added slowly. The mixture was slowly heated to 40 °C and kept stirring under argon for 20 h. The reaction mixture was then poured into 50% sat. aq. $NaHCO_3$ which was extracted with DCM (3 × 20 ml). The organic layer was washed with water (3 × 15 ml) and brine and dried over $MgSO_4$. Evaporation yielded 80 mg crude which was purified using column chromatography (toluene) to give 40 mg pure **15** (48%) as a white foam. R_f = 0.65 (pentane : EtOAc 4 : 1); $[\alpha]^{22.8}{}_D$ = + 36.9 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3010, 2900, 2390, 1546, 1430, 1110, 1060, 745, 690; MS (EI) (*m*/*z*) (rel. int.) 461 (M, 34%), 460 (70%), 370 (36%), 262 (100%); ^{1}H NMR δ: 0.60 (s, 3H, 6-CH_3), 1.35 (s, 3H, 6-CH_3) 0.72–1.41 (m, 4H, BH_3 and 9-CH_2), 2.26 (ddd, 1H, *J* = 6.2, 10.8, 15.0, 8-CH), 2.52 (m, 2H, CH and CH_2), 2.76 (t, 1H, *J* = 5.6, CH), 3.48 (t, 1H, *J* = 10.8, CH_2P), 3.58 (t, 1H, *J* = 15.0, CH_2P), 7.25 (d, 1H, *J* = 7.8, ArH), 7.38–7.53 (m, 9H, ArH), 7.67 (m, 1H, ArH), 7.76 (m, 2H, ArH), 8.07 (pd, 2H, ArH), 8.13 (m, 2H, ArH); ^{13}C NMR δ: 21.2, 26.6, 29.1 (d, J_P = 36, CH_2PPh_2), 29.5, 40.2, 41.5, 45.0, 46.6, 117.6, 126.8, 128.8 (d, J_P = 17), 128.9 (d, J_P = 10), 129.0, 131.1 (d, J_P = 2), 131.4 (d, J_P = 2), 132.1, 132.2, 133.1, 133.2, 133.8, 139.9, 140.9, 154.7, 158.8, 158.9; ^{31}P NMR δ: 16.5 (broad)

(5*S*,7*S*,8*S*)-8-(hydroxymethyl)-5,6,7,8-tetrahydro-6,6-dimethyl-2-phenyl-5,7-methanoquinoline (*cis* 12)

To a diastereomeric mixture of **12** (450 mg, 1.7 mmol, 1.0 eq.), I_2 (1.29 g, 5.1 mmol, 3.0 eq.), PPh_3 (1,33 g, 5.1 mmol, 3.0 eq.) and imidazole (350 mg, 5.1 mmol, 3.0 eq.) DCM (8 ml) was slowly added. The mixture was stirred under nitrogen for 18 h and then diluted with Et_2O (10 ml). The solvent was poured off and the residue washed with Et_2O (2 × 10 ml). The residue was extracted with DCM (3 × 10 ml) and the extracts stirred vigorously with

1 M HCl (5 ml) for 2 h followed by addition of sat. aq. $NaHCO_3$ until neutral. The phases were separated and the aqueous phase extracted with DCM (10 ml). The combined organic phases were washed with 5% aq. $Na_2S_2O_3$ and brine and dried over $MgSO_4$. Evaporation of solvent yielded 1.40 g crude that was purified by column chromatography (DCM : Pentane : Et_2O 7 : 3 : 0.5) to give 180 mg diastereomerically pure *cis* **12** (40%). Known compound, spectral data were in accordance with those previously reported.[19]

(5*S*,7*S*,8*S*)-8-(bromomethyl)-5,6,7,8-tetrahydro-6,6-dimethyl-2-phenyl-5,7-methanoquinoline (16)

Diastereomerically pure *cis*-alcohol **12** (260 mg, 0.98 mmol, 1.0 eq) was dissolved in $SOBr_2$ (2 ml) and the solution was heated to 110 °C under argon for 1.5 h. After cooling the reaction mixture was carefully quenched with H_2O and neutralized with sat. aq. $NaHCO_3$. The resulting suspension was extracted with DCM and the organic phase shaken with 5% aq. $Na_2S_2O_3$ and brine. Drying over $MgSO_4$ and evaporation of solvent gave 380 mg crude bromide. Column chromatography (pentane to pentane : EtOAc 5 : 1) yielded 220 mg **16** as a light yellow oil (65%). $R_f = 0.70$ (pentane : EtOAc 5 : 1); $[\alpha]^{22.8}{}_D = +79.1$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2934, 2868, 1735, 1568, 1454, 1436, 1203, 1026, 849, 764, 742, 699; MS (EI) (*m*/*z*) (rel. int.) 342 (M, 39%), 298 (22%), 262 (100%), 248 (37%), 218 (36%), 206 (19%); ^{1}H NMR δ: 0.73 (s, 3H, 6-CH_3), 1.42 (d, 1H, $J = 9.0$, 9-CH_2), 1.49 (s, 3H, 6-CH_3), 2.84 (m, 3H, 5-CH and 7-CH and 9-CH_2), 3.60 (dd, 1H, $J = 3.9$ and 11.5, 8-CH), 3.71 (t, 1H, $J = 11.2$, CH_2Br), 4.64 (dd, 1H, $J = 3.9$ and 11.2, CH_2Br), 7.32 (d, 1H, $J = 7.8$ ArH), 7.41 (m, 1H, ArH), 7.48 (m, 3H, ArH), 8.05 (m, 2H, ArH); ^{13}C NMR δ: 23.2, 26.9, 34.1, 36.6, 39.6, 42.6, 47.0, 51.3, 117.8, 126.6, 128.6, 128.8, 133.9, 139.4, 139.7, 154.5, 156.7;

Diphenylphosphine–Ir complex (3)

Mg-filings (33 mg, 1.3 mmol, 4.0 eq.) were heated under vacuum while stirring for 1 h, after cooling THF (2 ml) was added. Compound **16** (110 mg, 0.34 mmol, 1 eq.) dissolved in THF (1 ml) was added to the mixture and heated to 70 °C for 1 h. The solution was allowed to cool and $ClPPh_2$ (115 mg, 0.5 mmol, 1.5 eq.) was added dropwise. After stirring for 6 h at room temperature, the solvent was removed and the residue filtered through a short plug of silica eluting with toluene ($R_f = 0.55$). The product (90 mg, 0.2 mmol, 1 eq.) was dissolved in dry DCM (5 ml) and $[Ir(COD)Cl]_2$ (75 mg, 0.11 mmol, 0.55 eq.) was added. The solution was refluxed for 50 min and then allowed to cool. Water (5 ml) and $NaBAr_F$ (210 mg, 0.24 mmol, 1.2 eq.) was added and the mixture stirred vigorously at room temperature. The phases were then separated and the organic phase was dried over $MgSO_4$ and evaporated yielding 300 mg crude. Flash chromatography (Pentane : DCM 2 : 3) gave 110 mg pure complex **3** (20% overall yield). $R_f = 0.31$ (pentane : DCM 2 : 3); $[\alpha]^{21.2}{}_D = +5.6$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2947, 1610, 1438, 1354, 1280, 1160, 1124, 887, 839, 743, 682; ^{1}H NMR δ: 0.90 (s, 3H, 6-CH_3), 1.11 (m, 3H, COD–CH_2), 1.37 (d, 1H, $J = 11.1$, 9-CH_2), 1.53 (s, 3H 6-CH_3), 1.55–1.74 (m, 2H), 1.86 (m, 2H), 2.12 (m, 1H), 2.12 (m, 1H), 2.43 (dd, 1H, $J = 7.5$ and 12.4, 8-CH), 2.60 (m, 2H, CH_2PPh_2), 2.80 (m, 2H), 2.98 (m, 2H), 4.20 (t, 1H, $J = 7.2$, COD–CH), 4.36 (t, 1H, $J = 13.7$, CH_2PPh_2), 4.47 (t, 1H, $J = 7.2$, COD–CH), 7.16–7.25 (m, 2H, ArH), 7.35 (d, 1H, $J = 8.1$, ArH), 7.38–7.74 (m, 26H, ArH); ^{13}C NMR δ: 20.8, 23.7 (d, $J_P = 4$), 25.5, 26.2 (d, $J_P = 34$, CH2PPh$_2$), 28.1, 29.6, 35.3, 36.4 (d, $J_P = 5$), 42.6, 44.8 (d, $J_P = 6$), 46.6, 47.3 (d, $J_P = 13$), 67.4, 69.2, 77.4, 80.6 (d, $J_P = 18$), 89.6 (d, $J_P = 6$), 117.6 (septet, $J_F = 4$, BAr_F), 124.6, 124.7 (q, $J_F = 274$, BAr_F), 124.8, 129.0 (qq, $J_F = 32$ and $J_B = 3$, BAr_F), 129.4 (d, $J_P = 10$), 129.8 (d, $J_P = 10$), 130.0, 130.4 (d, $J_P = 9$), 131.3 (d, $J_P = 3$), 131.7, 132.2, 132.4, 133.4 (d, $J_P = 11$), 134.9 (BAr_F), 137.0, 139.3, 143.5, 159.5, 160.3 (d. $J_P = 2$), 161.8 (q, $J_B = 50$, BAr_F); ^{31}P NMR δ: 6.95

Diphenylphosphine–Ir complex (4)

Boron-protected ligand **15** (30 mg, 0.07 mmol, 1.0 eq.) was dissolved in freshly dried Et_2NH (1 ml) and the resulting solution stirred over night under argon. After evaporation of the Et_2NH the residue was filtered through a short plug of silica eluting with toluene ($R_f = 0.58$). The product was dissolved in dry DCM and $[Ir(COD)Cl]_2$ (28 mg, 0.04 mmol, 0.55 eq.) was added. After 50 min reflux, the solution was cooled and water (1 ml) was added followed by addition of $NaBAr_F$ (75 mg, 0.09 mmol, 1.2 eq.). The resulting solution was stirred vigorously for 1 h and the phases were then separated. The organic phase was dried over $MgSO_4$ and the solvent evaporated yielding 130 mg crude product. Flash chromatography (DCM : Pentane 3 : 2) gave 35 mg (31%) **4** as a bright orange foam. $R_f = 0.30$ (Pentane:DCM 2:3); $[\alpha]^{21.2}{}_D = +21.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ: 0.71 (s, 3H, 6-CH_3), 1.10 (m, 3H), 1.47 (s, 3H, 6-CH_3), 1.51 (d, 1H, $J = 9.5$, 9-CH_2), 1.62–1.87 (m, 3H), 2.14 (m, 1H), 2.57–2.77 (m, 4H), 2.97 (m, 3H), 3.75 (m, 1H), 4.00 (t, 1H, $J = 6.7$, COD–CH), 4.37–4.53 (m, 2H), 7.15–7.25 (m, 2H, ArH), 7.36 (d, 1H, $J = 7.7$, ArH), 7.39–7.75 (m, 26H, ArH); ^{13}C NMR δ: 23.6 (d, $J_P = 4$), 24.4, 25.5 (d, $J_P = 34$, CH_2PPh_2), 26.9, 28.1, 35.5, 35.7, 36.4 (d, $J_P = 5$), 41.2, 46.9, 47.7 (d, $J_P = 12$), 48.8 (d, $J_P = 5$), 68.9, 69.5, 79.0, 79.2, 89.3 (d, $J_P = 6$), 117.6 (septet, $J_F = 4$, BAr_F), 123.8, 124.5, 124.6 (q, $J_F = 272$, BAr_F), 129.0 (qq, $J_F = 31$ and $J_B = 3$,BAr_F), 129.3, 129.4, 129.9 (d, $J_P = 10$), 130.2, 130.3 (d, $J_P = 9$), 131.2 (d, $J_P = 2$), 131.9, 132.4 (d, $J_P = 2$), 133.6 (d, $J_P = 11$), 134.9 (BAr_F), 137.0, 139.3, 144.2, 159.7, 160.0, 161.8 (q, $J_B = 50$, BAr_F); ^{31}P NMR δ: 7.04

General procedure for preparation of complexes 5 and 6

Diphenylphosphinite–Ir complex (6). *trans*-Alcohol **18** (60 mg, 0.23 mmol, 1.0 eq.) was dissolved in THF (1 ml). After cooling to 0 °C BuLi (0.16 ml, 0.25 mmol, 1.1 eq.) was slowly added. After 20 min of stirring, $ClPPh_2$ (0.045 ml, 0.25 mmol, 1.1 eq.) was added dropwise and the solution was left to warm up to r.t. over night. The solvent was evaporated and the residue dissolved in DCM (5 ml). $[Ir(COD)Cl]_2$ (85 mg, 0.15 mmol, 0.65 eq.) was added and the solution refluxed under inert atmosphere for 1.5 h and then allowed to cool. Water (4 ml) and $NaBAr_F$ (250 mg, 0.28 mmol, 1.2 eq.) was added and the mixture stirred vigorously for an hour. The phases were separated and the organic phase dried over $MgSO_4$ and evaporated to give a crude brown solid. Flash chromatography (pentane : DCM 2 : 3) yielded 150 mg pure **6** as an orange foam (41%). $R_f = 0.40$ (pentane : DCM 2 : 3); $[\alpha]^{22.8}{}_D = -12.5$ (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2967, 1610, 1437, 1354, 1280, 1124, 981, 887, 839, 758, 713, 682; ^{1}H NMR δ: 0.85 (s, 3H, 6-CH_3), 1.13 (m, 1H, COD–CH_2), 1.26 (m, 2H, COD–CH_2), 1.61 (s, 3H,

6-CH_3), 1.77 (d, 1H, J = 10.2, 9-CH_2), 1.84 (m, 1H, COD–CH_2), 2.05 (m, 4H, COD–CH_2), 2.91 (m, 2H, 5-CH and COD–CH), 3.05 (m, 3H, 7-CH, 9-CH and COD–CH), 4.40 (m, 1H, COD–CH), 4.50 (m, 1H, COD–CH), 6.32 (dd, 1H, J = 3.5 and 7.0, 8-CH_2), 7.38 (m, 2H, ArH), 7.44–7.64 (m, 15H, ArH), 7.66–7.73 (m, 12H, ArH); ^{13}C NMR δ: 20.9, 24.1 (d, J_P = 2), 26.0, 28.5, 31.6, 34.7, 36.6 (d, J_P = 3), 45.6 (d, J_P = 10), 46.2, 47.1, 63.3, 70.8, 77.4, 81.7, 88.7 (d, J_p = 14), 97.1 (d, J_p = 9), 117.6 (septet, J_F = 4, BAr_F), 124.6 (q, J_F = 272, BAr_F), 125.5, 126.5, 128.9, 129.0 (qq, J_F = 31 and J_B = 3, BAr_F), 129.1, 129.3, 129.4 (d, J_P = 2), 129.5, 130.0, 130.1, 131.9 (d, J_P = 7), 132.3 (d, J_P = 2), 134.9 (BAr_F), 137.2, 139.1, 143.7, 154.9 (d, J_P = 2), 159.5, 161.8 (q, J_B = 50, BAr_F); ^{31}P NMR δ: 95.3

Diphenylphosphinite–Ir complex (5). 30 mg (11%) bright orange foam. R_f = 0.40 (Pentane : DCM 2 : 3); $[\alpha]^{22.8}_D$ = + 19.5 (c 1.0, $CHCl_3$); ^{1}H NMR δ: 0.76 (s, 3H, 6-CH_3), 1.11 (m, 1H, COD–CH_2), 1.27 (m, 2H, COD–CH_2), 1.53 (s, 3H, 6-CH_3), 1.61 (d, 1H, J = 9.8, 9-CH_2), 1.79 (m, 1H, COD–CH_2), 1.95 (m, 2H, COD–CH_2), 2.10 (m, 2H, COD–CH_2), 2.85 (m, 1H, COD–CH), 2.94 (m, 3H, 5-CH and 9-CH_2 and COD–CH), 3.11 (m, 1H, 7-CH), 2.40 (m, 2H, COD–CH), 6.37 (dd, 1H, J = 3.5 and 7.1, 8-CH_2), 7.28 (m, 2H, ArH), 7.43–7.61 (m, 15H, ArH), 7.64–7.80 (m, 12H, ArH); ^{13}C NMR δ: 23.9 (d, J_P = 3), 24.0, 26.4, 28.2, 28.4, 34.8, 36.2, 36.6 (d, J_P = 2), 42.6, 46.4, 64.6, 71.4, 83.3, 87.4 (d, J_P = 16), 97.0 (d, J_P = 8), 117.6 (septet, J_F = 4, BAr_F), 124.7 (q, J_F = 270, BAr_F), 125.4, 126.0, 128.8, 129.2 (qq, J_F = 31 and J_B = 3, BAr_F), 129.0, 129.2 (d, J_P = 6), 129.5, 130.2, 130.9 (d, J_P = 14), 131.9 (d, J_F = 2), 132.0, 132.6 (d, J_P = 3), 134.9 (BAr_F), 135.1, 137.2, 139.2, 144.3, 155.3, 159.9, 161.8 (q, J_B = 50, BAr_F); ^{31}P NMR δ: 100.1

General procedure for hydrogenation reactions and analysis

A vial was charged with substrate (0.25 mmol), catalyst (0.5 mol%) and anhydrous DCM (2.0 ml). The vial was placed in a high-pressure equipment which was purged three times before it was pressurized to 30 or 100 bar and held at this pressure for 12 h. The pressure was then released and the solvent evaporated off. The residue was dissolved in Et_2O (1.5 ml) and filtered through a short plug of Celite. The solvent was evaporated and the enantiomeric excess and conversion was determined.

Analyses were performed as previously described[21] except for (*E*)-3-phenyl-2-buten-1-ol which was separated by HPLC: AS–H; 96.5 : 3.5 heptane : isopropanol; 0.5 ml min^{-1}; t_{R1} = 19 min (*S*, major), t_{R2} = 22 min (minor) and the absolute configuration determined by optical rotation.[22]

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