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Enantioselective Synthesis of Tunable Chiral Clickphine P,N-Ligands and Their Application in Ir-Catalyzed Asymmetric Hydrogenation

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Supporting Information

ABSTRACT: A small library of highly tunable chiral Clickphine P,N-ligands has been prepared in an enantioselective fashion by CuI-catalyzed asymmetric propargylic amination using a single chiral complex and a subsequent in situ cycloaddition click reaction. The scope of the propargylic amination to yield optically active triazolyl amines is described. The amines are transformed in a one-pot procedure to the corresponding Ir−Clickphine complexes, which serve as catalysts for the asymmetric hydrogenation of di-, tri-, and tetrasubstituted unfunctionalized alkenes. Enantioselectivities of up to 90% ee were obtained in these hydrogenations, which are among the best reported in the case of the tetrasubstituted substrate 2-(4′-methoxyphenyl)-3-methylbut-2-ene (9) (87% ee). This is a demonstration of the effective use of the chiral pool, as from one chiral catalyst a library of chiral Ir complexes has been synthesized that can hydrogenate various alkenes with high selectivity.

INTRODUCTION

Asymmetric catalysis is increasingly important for the preparation of chiral compounds for the pharmaceutical, agrochemical, and fine chemical industries.1 Typically, a metal complex based on a chiral ligand is used for asymmetric transformations, and often several chiral ligands need to be explored before a sufficiently selective complex can be identified. The preparation of chiral ligands is mostly based on the use of the available pool of chiral building blocks (i.e., sugars, amino acids), which are built in the ligand or used to prepare the chiral ligand.2 Remarkably, the use of asymmetric catalysis to prepare chiral ligands for direct use in a certain asymmetric conversion has hardly been explored. Several contributions deal with the asymmetric synthesis of chiral ligands, mainly chiral phosphines, but typically no further catalysis is performed with the synthesized ligands.3 We wondered whether it would be possible to use one chiral complex to prepare a library of bidentate ligands with a chiral backbone that in turn could be used in the exploration of a certain desired asymmetric transformation. This would result in the catalytic expansion of the chiral pool. In order to validate this concept, we studied the chiral synthesis of P,N-ligands for the iridium-catalyzed asymmetric hydrogenation of alkenes. Asymmetric hydrogenation of alkenes provides a means to rapidly access a vast range of chiral compounds relevant to pharmaceutical and agrochemical use.1,2 Whereas rhodium-based catalysts are used extensively for functionalized alkenes, iridium provides the catalysts of choice for unfunctionalized substrates.4 Recently, however, Ir catalysts have also been found to be applicable for increasingly functionalized substrates4b such as phosphorus-containing alkenes,5−7 furans,8 pyridine derivatives,9 imines,10−18 vinyl boronates,19 and α,β-unsaturated esters.20−22 With this increasing number of potential substrates, there is a demand for highly tunable chiral iridium catalysts that are able to convert these substrates with high enantioselectivity. Since the discovery of the high activity and selectivity of Ir−PHOX catalysts in the hydrogenation of imines and unfunctionalized alkenes by Pfaltz and co-workers,10b,23,24 P,N-ligands have been used frequently in Ir-catalyzed hydro-
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Scheme 1. Retrosynthesis of Chiral Clickphine P,N-Ligands Using Asymmetric Catalysis

Table 1. Preparation of Optically Pure Triazolyl Amines 2

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar1</th>
<th>Ar2</th>
<th>R'</th>
<th>product</th>
<th>yield (%) (ee (%))</th>
<th>yield (%) recryst.</th>
<th>ee (%) recryst.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>2-OMe-Ph</td>
<td>Ph</td>
<td>(S)-2a</td>
<td>91 (84)</td>
<td>63</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>4-OMe-Ph</td>
<td>2-OMe-Ph</td>
<td>Ph</td>
<td>(R)-2b</td>
<td>75 (82)</td>
<td>23</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>Bn</td>
<td>(S)-2c</td>
<td>75 (85)</td>
<td>17</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>2-OMe-Ph</td>
<td>Bn</td>
<td>(R)-2d</td>
<td>−</td>
<td>49</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>4-CF3-Ph</td>
<td>(S)-2e</td>
<td>90 (84)</td>
<td>68</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>2-naphthyl</td>
<td>2-OMe-Ph</td>
<td>Ph</td>
<td>(R)-2f</td>
<td>−</td>
<td>48</td>
<td>98</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 (1.0 equiv), ArNH2 (2.0 equiv), DIPEA (4 equiv), CuI (0.05–0.10 equiv), and the ligand (0.06–0.12 equiv) were stirred in methanol at 0 °C. After full conversion (as determined by TLC), the azide (1.0 equiv) was added. For entries 1, 3, and 5, bis(4S,5S)-diPh-pybox was used, and for entries 2, 4, and 6, bis(4R,5S)-diPh-pybox was used.

The majority of these ligands rely on chiral oxazolines and pyridines as the nitrogen atom donors. On the other hand, chiral triazole-containing P,N-ligands have not been used to date in Ir-catalyzed hydrogenations or successfully applied in any other asymmetric transformation. The use of achiral CuI complex potentially gives propargylic amines in high yield with retention of the stereochemistry. The absolute configuration of the products can be controlled by using either enantiomer of the diPh-pybox ligand (2,6-bis((4R,5S)-4,5-dihydrooxazol-2-yl)pyridine). The products obtained after the reaction were highly crystalline, allowing further enantioenrichment by recrystallization. The first attempt was directly promising: a single recrystallization step gave the single enantiomer in good yield (Table 1, entry 1).

RESULTS AND DISCUSSION

Propargylic Amination with in Situ Cycloaddition. The first step in the synthesis was the preparation of the propargylic amine by application of the enantioselective copper-catalyzed propargylic amination conditions to racemic propargylic acetate 1. Subsequent triazole formation by the CuI-catalyzed azide–alkyne cycloaddition would afford the desired triazolyl amines 2. Interestingly, most of the reagents required for this “click” reaction were already present in the propargylic amination: copper(I), base, and the acetylene. Since methanol would not disturb the reaction, the addition of the azide should be sufficient for a one-pot procedure. After full consumption of the propargylic acetate, azide addition indeed provided triazole 2 in high yield with retention of the stereochemistry. The absolute configuration of the products can be controlled by using either enantiomer of the diPh-pybox ligand (2,6-bis(4S,5S)-4,5-dihydrooxazol-2-yl)pyridine). The products obtained after the reaction were highly crystalline, allowing further enantioenrichment by recrystallization. The first attempt was directly promising: a single recrystallization step gave the single enantiomer in good yield (Table 1, entry 1).

With other compounds we were also able to isolate enantiopure triazolyl amines, although several recrystallization cycles were required for sufficient enantioenrichment, which lowered the yields (entries 2 and 3). Although no single enantiomer was obtained, the 4-trifluoromethylphenyl-substituted triazole 2e illustrates the ease of ligand variation via this method. In the case of 2d and 2f, the products crystallized in high ee from the reaction mixture, and in only one recrystallization step, optically pure product was obtained in moderate yield (entries 4 and 6).
enantiomers of the ligand enables the preparation of both (R)- and (S)-triazolyl amines.

The three-dimensional structure of triazolyl amines 2 was unambiguously confirmed by X-ray crystal structure determination of (R)-2d (Figure 1). Unfortunately, the configuration of the chiral center at C1 could not be reliably determined because of twinning of the crystal and the absence of a strong anomalous scatterer. The structure features two intramolecular S(5) hydrogen bonds with the NH group as donor and with the triazole-N1 and the OMe group as acceptors. These interactions are likely to increase the NH proton’s $sp^k$ value, as deprotonation proved difficult. A strong base such as n-butyllithium is necessary to remove this proton (vide infra).

The preparation of this type of triazolyl amines 2 is not the first reported. In 2007, similar compounds were synthesized by the group of Botta as potential antimicrobial agents. The copper-catalyzed azide−alkyne cycloaddition was performed with enantiopure propargylic amines obtained by kinetic enzymatic resolution of racemic propargylamines.

### One-Pot Synthesis of Ir−Clickphine Complexes

P−N bond formation is typically achieved by condensation of the amine with a phosphorus chloride in the presence of a weak base such as triethylamine. Application of these conditions to triazolyl amines 2 did not result in any reactivity toward the desired product, which is rationalized by the stabilizing hydrogen-bonding interactions of the NH proton with the triazole and OMe moieties. However, prior deprotonation of the amine with n-butyllithium followed by condensation with a phosphorus chloride gave the desired P,N-ligands in almost quantitative conversion (Table 2).

Unfortunately, these compounds proved to be highly moisture-sensitive, as they are prone to hydrolysis resulting in P−N bond cleavage, complicating chromatographic isolation. We demonstrated previously that isolation is feasible but with significant loss of...
material due to decomposition. Therefore, we decided to skip isolation of the ligands 3 and immediately perform complexation with Ir and counteranion exchange to give Ir–BARF complexes 4. These complexes are insensitive toward air and moisture and can even be purified by flash chromatography with dichloromethane. This results in the rapid one-pot synthesis of Ir complexes 4 from triazolyl amines 2 in good overall yield (50–70%), allowing the construction of a small library of chiral Ir–Clickphine complexes 4a–h (Table 2).

**Asymmetric Hydrogenation.** The potential of Ir–Clickphine complexes as catalysts for asymmetric hydrogenation was evaluated in the asymmetric hydrogenation of di-, tri-, and tetrasubstituted largely unfunctionalized alkenes 5, 7, and 9. When standard conditions for the hydrogenation of unfunctionalized alkenes (50 bar H₂) were used in the hydrogenation of the terminal aryl,alkyl-disubstituted substrate 5, a moderate ee of 47% was obtained with complex 4a (Table 3, entry 1). It was observed previously that lowering the dihydrogen pressure for this class of substrates can be beneficial for the enantioselectivity. Indeed, when the hydrogenation was conducted at ambient pressure, a good ee of 75% was obtained with complex 4a (entry 2). Evaluation of the whole library revealed quantitative conversions and ee’s of 69–75% for Clickphine complexes 4a–d containing a diphenylphosphine donor group. However, the use of disopropophosphine-functionalized complexes 4e–h resulted in reduced enantioselectivity (39–44% ee; entries 6–9). The lack of aromatic phosphine substituents may preclude necessary π-stacking interactions required to induce good ee.

The enantioselectivity (up to 75% ee) provided by Ir–Clickphine complexes for terminal disubstituted alkenes is lower than that provided by iridium catalysts based on ThrePHOX (up to 94% ee), phosphinite–oxazole (up to 97% ee), and phosphite–oxazoline ligands (up to 99% ee), but shows the ability of these complexes to induce significant enantioface discrimination for unfunctionalized alkenes. It should be noted that despite the recent successful examples cited above, many other iridium-based catalysts are completely unselective or unreactive for this substrate.

Encouraged by the results obtained in the hydrogenation of substituted alkene 5, we applied our Ir–Clickphine catalysts in the hydrogenation of trisubstituted α-methylstilbene (7) (Table 4). Higher pressures (50 bar H₂) and longer reaction times were necessary for the reaction to go to completion compared with those for the disubstituted substrate. Quantitative conversion and an ee of 86% were obtained after 20 h with 1 mol % complex 4a (entry 1). A higher catalyst loading of 2 mol % improved the ee to 90% and was therefore used for all further hydrogenations of 7 (entry 2). Variation of the substitution pattern on the backbone of the ligand (Ar and R') led only to slight differences in the enantioselectivity (86–90% ee; entries 3–5) while maintaining quantitative conversion. Similarly as for disubstituted alkene 5, complexes 4e–h based on disopropyl-functionalized phosphines gave lower enantioselectivity (51–72% ee; entries 6–9). α-Methylstilbene (7) is frequently used as a benchmark substrate for hydrogenation of unfunctionalized alkenes. The enantioselectivity obtained with Ir–Clickphine complex 4a (90% ee) is good compared with many known examples but not excellent, as over 99% ee has been reported for this substrate.

Next, we turned to the more challenging tetrasubstituted alkene 9, which is known to be notoriously unreactive with iridium catalysts. Initial attempts in the hydrogenation of 9 using a 1 mol % loading of Ir–Clickphine complex 4a and 50 bar H₂ gave only 5% conversion after 20 h but a promising enantioselectivity of 57% ee (Table 5, entry 1). Increasing the catalyst loading to 2 mol % resulted in 51% conversion and 78% ee (entry 2). Under these conditions, all of the Ir–Clickphine complexes were evaluated in the hydrogenation of substrate 9. For the diphenylphosphine-based complexes, we found a positive influence of the size of the Ar substituent on the conversion and ee (entries 2–5). The p-methoxophenyl-substituted complex 4b gave 82% ee at 84% conversion, and the 2-naphthyl derivative afforded 87% ee at 98% conversion. A benzyl substituent on the triazole (R') resulted in a slightly lower selectivity of 72% ee at 68% conversion. In analogy to the results obtained with substrates 5 and 7, the disopropylphos-
Table 5. Hydrogenation of 2-(4'-Methoxyphenyl)-3-methylbut-2-ene (9) by Ir–Clickphine Complexes 4a–h

<table>
<thead>
<tr>
<th>entry</th>
<th>complex</th>
<th>conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>4a</td>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>4a</td>
<td>51</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>4c</td>
<td>68</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>4d</td>
<td>98</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>4e</td>
<td>98</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>4f</td>
<td>99</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>4g</td>
<td>98</td>
<td>43</td>
</tr>
</tbody>
</table>

Reaction conditions: 2.0 mol % 4, [4] = 1 mM, 50 bar H2, CH2Cl2, rt. Conversion determined by GC after 20 h.

**EXPERIMENTAL SECTION**

General Experimental Procedures. All of the reactions were carried out under an atmosphere of argon using standard Schlenk techniques. THF, pentane, hexane, and diethyl ether were distilled from sodium benzophenone ketyl; CH2Cl2, isopropanol, and methanol were distilled from CaH2 and toluene was distilled from sodium under nitrogen. Except for the compounds given below, all of the reagents were purchased from commercial suppliers and used without further purification. The following compounds were synthesized according to published procedures: DiPh-pybox40 and substrates 84 and 99. High-resolution mass spectra were recorded on a four-sector mass spectrometer; for FAB-MS, 3-nitrobenzyl alcohol was used as the matrix.

General Procedure A: Cu-Catalyzed Propargylic Amination with in Situ Cycloaddition. Copper iodide (0.05 equiv) and 2,6-bis[4-halo-substituted diphenyl-4-halodihydroxazol-2-yl]pyridine (DiPhpybox) (0.055 equiv) were suspended in methanol. The mixture was stirred for 20 min before addition of a solution of the propargylic acetate (1 equiv) in methanol. At the indicated temperature (between −20 and 0 °C), a solution of nucleophile (2 equiv) and DIPEA (4 equiv) in methanol was added. The suspension was stirred until TLC analysis indicated complete conversion of the propargylic acetate. When the reaction was finished, a solution of azide (1 equiv) in methanol was added to the mixture. After full consumption of the azide, the mixture was stirred for an additional 2 h. The residue obtained after filtration contained the product and some acetylene. Filtration or evaporation gave the crude product. 

Silica gel chromatography (typically a small percentage of MeOH in CH2Cl2) gave the pure product.

(S)-2-Methoxy-N-(phenyl-1H-1,2,3-triazol-4-yl)methyl-aniline (2a). General Procedure A was followed with the enantiomer of the ligand. 1-Phenylprop-2-ynyl acetate (1a) (35 mg, 0.20 mmol) was added to the catalyst suspension, which was cooled to 0 °C before the addition of o-anisidine (45 μL, 0.4 mmol) and DIPEA (4 equiv) in methanol was added. After 5 h of stirring, phenyl azide (24 μL, 0.22 mmol) was added at room temperature. The mixture was stirred for an additional 22 h. The residue obtained after filtration contained the product and some ligand. Silica gel chromatography (EtOAc/PE 1:1) afforded product 2a as a white solid (65 mg, 91% yield, 84% ee). Recrystallization from EtOAc gave white crystals (45 mg, 63% yield, >99.5% ee). 

1H NMR (400 MHz, CDCl3): δ (ppm) = 7.33 (d, J = 0.3 Hz, 1H), 7.68 (d, J = 7.3 Hz, 2H), 7.56–7.31 (m, 8H), 6.83–6.70 (m, 3H), 6.53 (d, J = 7.7 Hz, 1H), 5.82 (d, J = 3.7 Hz, 1H), 5.27 (d, J = 7.3 Hz, 1H), 3.86 (s, 1H). 

C14H12N2O (238.23) requires: C, 80.75; H, 6.80; N, 12.45. Found: C, 80.70; H, 6.79; N, 12.43. 

General Procedure B: Cu-Catalyzed Propargylic Amination with in Situ Cycloaddition. Copper iodide (0.05 equiv) and 2,6-bis[4-halo-substituted diphenyl-4-halodihydroxazol-2-yl]pyridine (DiPhpybox) (0.055 equiv) were suspended in methanol. The mixture was stirred for 20 min before addition of a solution of the propargylic acetate (1 equiv) in methanol. At the indicated temperature (between −20 and 0 °C), a solution of nucleophile (2 equiv) and DIPEA (4 equiv) in methanol was added. The suspension was stirred until TLC analysis indicated complete conversion of the propargylic acetate. When the reaction was finished, a solution of azide (1 equiv) in methanol was added to the mixture. After full consumption of the azide, the mixture was stirred for an additional 2 h. The residue obtained after filtration contained the product and some acetylene. Silica gel chromatography (typically a small percentage of MeOH in CH2Cl2) gave the pure product.
15.64. HRMS (FAB+) m/z: [M + H]+ calcd for C23H23N4O3 407.1878; found 407.1874.

(S)-N-(1-Benzyl-1H-1,2,3-triazol-4-yl)(phenyl)methyl)aniline (2c).

General procedure A was followed with the anilinium of the ligand. The starting material was 1-phenylprop-2-ynyl acetate (348 mg, 2.0 mmol), and the total amount of MeOH was 25 mL. As the nucleophile, aniline (365 μL, 4.0 mmol) was used. After 6 h, slowly warming from −18 to 10 °C, benzyl azide (251 μL, 2.0 mmol) was added, and the mixture was stirred for 17 h before the solvent was evaporated. Silica gel column chromatography (gradient: 0.5 to 2.0% MeOH in CH2Cl2) gave 2c in good yield (863 mg, 75% yield, 82% ee). Two recrystallization steps from EtOAc gave the enantiopure product (270 mg, 23% yield, >99.5% ee). δ (ppm) = 7.32 (sext, 2H), 7.19–7.27 (m, 4H), 7.06 (m, 2H), 5.35 (br s, 1H), 3.87 (s, 3H), 3.80 (s, 3H). mp (single enantiomer) 160–162 °C. HPLC conditions: Chiralcel AD (4.6 mm × 250 mm), 80:20 heptane/HOAc, 0.1 mL/min, λ = 254 nm, 20 min (major isomer), 48 min (minor isomer).

1H NMR (400 MHz; CDCl3): δ (ppm) = 7.73–7.76 (m, 4H), 7.50–7.46 (m, 2H), 7.37–7.40 (m, 3H), 6.92–6.89 (m, 2H), 6.81–6.69 (m, 3H), 6.53–6.50 (m, 1H), 5.73 (s, 1H), 5.2 (br s, 1H), 3.87 (s, 3H), 3.80 (s, 3H).

13C{1H} NMR (101 MHz; CDCl3): δ (ppm) = 159.2 (Cq), 151.7 (Cq), 147.1 (Cq), 137.1 (Cq), 137.0 (Cq), 133.7 (Cq), 129.7, 128.7, 128.4, 121.1, 120.5, 120.0, 117.4, 114.4, 110.4, 109.5, 55.5, 55.5, 55.0. HRMS (FAB+) m/z: [M + H]+ calcd for C23H23N4O3 387.1821; found 387.1817.

(S)-N-(1-Benzyl-1H-1,2,3-triazol-4-yl)(phenyl)methyl)aniline (2d).

General procedure A was followed with the anilinium of the starting material was 1-phenylprop-2-ynyl acetate (348 mg, 2.0 mmol), and the total amount of MeOH was 25 mL. As the nucleophile, aniline (365 μL, 4.0 mmol) was used. After 6 h, slowly warming from −18 to 10 °C, benzyl azide (251 μL, 2.0 mmol) was added, and the mixture was stirred for 17 h before the solvent was evaporated. Silica gel column chromatography (gradient: 0.5% MeOH in CH2Cl2) gave 2c in good yield (863 mg, 75% yield, 82% ee). Two recrystallization steps from EtOAc gave the enantiopure product (270 mg, 23% yield, >99.5% ee). δ (ppm) = 7.32 (sext, 2H), 7.19–7.27 (m, 4H), 7.06 (m, 2H), 5.35 (br s, 1H), 3.87 (s, 3H), 3.80 (s, 3H). mp (single enantiomer) 160–162 °C. HPLC conditions: Chiralcel AD (4.6 mm × 250 mm), 80:20 heptane/HOAc, 0.1 mL/min, λ = 254 nm, 20 min (major isomer), 48 min (minor isomer).

1H NMR (400 MHz; CDCl3): δ (ppm) = 7.73–7.76 (m, 4H), 7.50–7.46 (m, 2H), 7.37–7.40 (m, 3H), 6.92–6.89 (m, 2H), 6.81–6.69 (m, 3H), 6.53–6.50 (m, 1H), 5.73 (s, 1H), 5.2 (br s, 1H), 3.87 (s, 3H), 3.80 (s, 3H).

13C{1H} NMR (101 MHz; CDCl3): δ (ppm) = 159.2 (Cq), 151.7 (Cq), 147.1 (Cq), 137.1 (Cq), 137.0 (Cq), 133.7 (Cq), 129.7, 128.7, 128.4, 121.1, 120.5, 120.0, 117.4, 114.4, 110.4, 109.5, 55.5, 55.5, 55.0. HRMS (FAB+) m/z: [M + H]+ calcd for C23H23N4O3 387.1821; found 387.1817.

(S)-N-(1-Benzyl-1H-1,2,3-triazol-4-yl)(phenyl)methyl)aniline (2e).

General procedure A was followed with the anilinium of the starting material was 1-phenylprop-2-ynyl acetate (174 mg, 1.0 mmol), and the total amount of MeOH was 10 mL. As the nucleophile, aniline (182 μL, 2.0 mmol) was used. After 6 h of stirring at 0 °C, 1-azido-4-(trifluoromethyl)benzene (187 mg, 1.0 mmol) was added, and the mixture was stirred for 22 h before the solvent was evaporated. Silica gel column chromatography (EtOAc/PE (1:4) with 10–20% CH2Cl2 to prevent crystallization) gave 2e in good yield (353 mg, 90% yield, 84% ee). Recrystallization from EtOAc/hexane for one night gave the enantiomer (562 mg, 68% yield, 94% ee). δ (ppm) = 7.84 (d, J = 8.7 Hz, 2H), 7.77–7.75 (m, 3H), 7.52 (d, J = 8.7 Hz, 2H), 7.41–7.30 (m, 3H), 7.17–7.13 (m, 2H), 6.74 (d, J = 7.9 Hz, 2H), 5.80 (d, δ = 2.8 Hz, 1H), 4.77 (br s, 1H). 13C{1H} NMR (101 MHz; CDCl3): δ (ppm) = 151.7, 146.9, 141.3, 139.4, 130.8 (q, J = 32.3 Hz, 2H), 129.3, 129.2, 128.2, 127.3, 127.2 (q, J = 37 Hz, 2H), 123.6 (q, J = 272.3 Hz, 2H), 120.5, 119.9, 118.5, 53.9, 55.8. HRMS (FAB+) m/z: [M + H]+ calcd for C25H25N2F6 595.1844; found 595.1848.
According to general procedure C, ligand (R)-3b (162 mg, 0.22 mmol), [IrCl(cod)]2 (74 mg, 0.11 mmol), NaBArF (244 mg, 0.28 mmol), and 10 mL of CH2Cl2 were used to give the complex as a brown solid (200 mg, 60% yield). \([\text{M}+\text{BArF}^+] \text{calcd for C46H43IrN4OP} 891.2933, \text{found 891.2893.}\]

**Complex 4f.** According to general procedure C, ligand (R)-3f (103 mg, 0.22 mmol), [IrCl(cod)]2 (73 mg, 0.11 mmol), NaBArF (248 mg, 0.28 mmol), and 10 mL of CH2Cl2 were used to give the complex as a brown solid (186 mg, 52% yield). \([\text{M}]+\text{BArF}^+] \text{calcd for C46H43IrN4OP} 891.2933, \text{found 891.2893.}\]
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3H), 0.34 (ddd, J = 21.4, 14.6, 6.9 Hz, 6H). 13C{1H} NMR (126 MHz; CDCl3); δ (ppm) = 161.9 (q, JCF = 49.8 Hz), 158.0 (Cq), 157.8, 134.9, 134.8, 133.3 (Cq), 132.2 (Cq), 131.1 (JCF = 9.7 Hz), 130.8, 130.5 (JCF = 5.1 Hz), 129.0 (JCF = 31.5 Hz, JC = 2.8 Hz, JCF = 28.8 Hz), 128.3 (JCF = 4.0 Hz), 128.2, 127.9 (Cq), 127.3, 126.8, 126.4, 125.8 (Cq), 125.7, 124.7, 124.1, 123.6 (Cq), 122.9, 121.5, 121.4 (Cq), 120.7, 120.66, 120.56, 117.6 (septuplet, JCF = 4.0 Hz), 112.8, 112.6 (JCF = 26.8 Hz), 94.3, 91.4, 87.7, 85.0 (JCF = 24.0 Hz), 54.7, 35.6, 35.3, 29.9, 27.4, 19.1, 16.6, 15.9. 31P{1H} NMR (202 MHz; CDCl3); δ (ppm) = 59.04 (s). HRMS (FAB+) m/z: [M − BaF]+ calcld for C30H45O5PNa 495.2712.3452, found 495.2742.

General Procedure for Hydrogenation Experiments at High Pressure. The hydrogenation experiments were carried out in a Chemspeed Technologies Accelerator SLT workstation under inert conditions. For a typical screening experiment, stock solutions of complexes (R)-4a−h and the substrates were prepared and subsequently mixed by the automated liquid handler. This procedure resulted in catalyst and substrate concentrations of 1.0 and 50 mmol, respectively, in the reactor. The hydrogenations were carried out at a dihydrogen pressure of 50 bar at room temperature for 20 h. Product samples were prepared directly after completion of the program and analyzed by chiral GC or HPLC.

Hydrogenation of Alkene 5. 2-Phenylbutane. The ee was determined by chiral GC analysis (Supelco β-DEX 225, isothermal at 55 °C): tR = 35.9 min (R), tR = 36.5 min (S).

Hydrogenation of Alkene 7. 1,2-Diphenylpropane. The ee was determined by chiral HPLC analysis (Chiralcel OJ-H, 0.8 mL min−1, n-hexane/IPrOH 99:0.5 v/v); tR = 8.9 min (R), tR = 11.9 min (S).

Hydrogenation of Alkene 9. 2-(+Methoxyphenyl)-3-methylbutane. The ee was determined by chiral GC analysis (Supelco β-DEX 225, 50 °C, 1 °C min−1, 130 °C); tR = 66.4 min (major), tR = 67.1 min (minor), tR = 72.6 min (substrate).

General Procedure for Hydrogenation Experiments at Ambient Pressure. A solution of 0.25 mmol of substrate and 1 mol % iridium complex (R)-4 (0.0025 mmol) in 2.5 mL of dry dichloromethane was prepared under argon in a 10 mL Schlenk flask. The reaction mixture was stirred for 120 min at rt with slow bubbling of hydrogen gas through the solution, introduced through a stainless-steel needle. After completion of the reaction, samples were taken and analyzed by chiral GC (see above).

X-ray Crystal Structure Determination of (R)-2d. C20H22N2O2. FW = 370.45, colorless needle, 0.54 mm × 0.12 mm × 0.06 mm, monoclinic, P21 (No. 4), a = 10.7827(4) Å, b = 5.5491(3) Å, c = 15.8189(8) Å, β = 92.6122(3)°, V = 945.33(8) Å3, Z = 2, Dcalc = 1.301 g/cm³, μ = 0.08 mm⁻¹. X-ray intensities were measured on a diffractometer with a rotating anode (graphite monochromator, λ = 0.71073 Å) at a temperature of 150(2) K. The crystal appeared to be twinned with a twofold rotation about hkl = (101) as the twin operation. This twin relationship was taken into account during the integration with Eval15 and absorption correction with the TWINABS software (0.62−0.75 correction range). 16104 Reflections were obtained up to a resolution of ((sinθ)/λ)max = 0.61 Å⁻¹. Because of the absence of strong anomalous scatterers, the absolute structure could not be determined reliably, and it was decided to merge the Friedel pairs, resulting in 944 unique reflections (Rint = 0.052), of which 1785 were observed [I > 2σ(I)]. The structure was solved with direct methods using SIR-92. Least-squares refinement was performed with SHELXL-97 on F² for all reflections using an HKLFS reflectivity file.27 The absolute configuration was assigned according to the enantiopure synthesis. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were introduced in calculated positions. The N−H hydrogen atom was refined freely with isotropic displacement parameters; all other hydrogen atoms were refined as rigid groups. 259 parameters were refined with 1 restraint. R1/wR2 [I > 2σ(I)]: 0.0354/0.0784. R1/wR2 [all refls]: 0.0429/0.0821. S = 1.048. Twin fraction = 0.124(s). Δρmax/Δρmin = −0.16/0.13 eÅ⁻³. Drawings, structure calculations, and checking for higher symmetry were performed with the PLATON software.38

ASSOCIATED CONTENT

Supporting Information
Copies of NMR spectral data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
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