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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. 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. 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. 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. Whereas rhodium-based catalysts are used extensively for functionalized alkenes, iridium provides the catalysts of choice for unfunctionalized substrates. Recently, however, Ir catalysts have also been found to be applicable for increasingly functionalized substrates such as phosphorus-containing alkenes, furans, pyridine derivatives, imines, vinyl boronates, and α,β-unsaturated esters. 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, P,N-ligands have been used frequently in Ir-catalyzed hydrogenation.

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Propargylic Amination with in Situ Cycloaddition. The first step in the synthesis was the preparation of the propargyl amine by application of the enantioselective copper-catalyzed propargylic amination conditions to racemic propargyl acetate 1. Subsequent triazole formation by the Cu1-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 propargyl amination: copper(II), 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 propargyl 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((4R,SS)-4,5-diphenyl-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). The availability of both genation and seem to be privileged for this transformation.25 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.26 The use of achiral triazole-containing P,N-ligands for highly regioselective allylic substitution reactions has been demonstrated by us.27,28 We anticipated the facile preparation of chiral P,N-ligands via CuI-catalyzed cycloaddition, allowing for easy derivatization and fine-tuning of the chiral pocket provided by the ligand. Importantly, asymmetric propargylic amination catalyzed by a Cu complex potentially gives propargylic amines in enantiomerically pure form,29,30 which is the basis of our chiral triazolyl P,N-ligands for highly regioselective allylic substitution. The corresponding Ir complexes are evaluated in the asymmetric hydrogenation of di-, tri-, and tetrasubstituted largely unfunctionalized alkenes.

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>
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<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>
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<td>Ph</td>
<td>(R)-2b</td>
<td>75 (82)</td>
<td>23</td>
<td>&gt;99</td>
</tr>
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<td>3</td>
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<td>2-OMe-Ph</td>
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<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>
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<tr>
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<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>
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</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,5R)-diPh-pybox was used, and for entries 2, 4, and 6, bis(4R,5S)-diPh-pybox was used.

Here we report a detailed study of the scope and limitations of the asymmetric Cu1-catalyzed propargylic amination with in situ cycloaddition to furnish chiral triazolyl amines 2, which are transformed into chiral P,N-ligands 3. The corresponding Ir complexes are evaluated in the asymmetric hydrogenation of di-, tri-, and tetrasubstituted largely unfunctionalized alkenes.

RESULTS AND DISCUSSION

■ RESULTS AND DISCUSSION

Scheme 1. Retrosynthesis of Chiral Clickphine P,N-Ligands Using Asymmetric Catalysis

Table 1. Preparation of Optically Pure Triazolyl Amines 2

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<td>Ph</td>
<td>(S)-2a</td>
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<td>&gt;99</td>
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<td>2</td>
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<td>75 (82)</td>
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<td>(R)-2d</td>
<td></td>
<td>49</td>
<td>&gt;99</td>
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<td>2-naphthyl</td>
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<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,5R)-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 triazole-containing P,N-ligands for highly regioselective allylic substitution reactions has been demonstrated by us.27,28 We anticipated the facile preparation of chiral P,N-ligands via CuI-catalyzed cycloaddition, allowing for easy derivatization and fine-tuning of the chiral pocket provided by the ligand. Importantly, asymmetric propargylic amination catalyzed by a Cu pybox complex potentially gives propargylic amines in enantiomerically pure form, which is the basis of our chiral triazolyl P,N-ligands for highly regioselective allylic substitution. The corresponding Ir complexes are evaluated in the asymmetric hydrogenation of di-, tri-, and tetrasubstituted largely unfunctionalized alkenes.

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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 $\text{sp}^3\text{K}_a$ 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.31,32 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 3 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

Table 2. One-Pot Synthesis of Ir−Clickphine Complexes 4

<table>
<thead>
<tr>
<th>entry</th>
<th>complex</th>
<th>R</th>
<th>$R'$</th>
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<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>Ph</td>
<td>Ph</td>
<td>$p$-MeO-C$_6$H$_4$</td>
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</tr>
<tr>
<td>3</td>
<td>4c</td>
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<td>Bn</td>
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</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>Ph</td>
<td>Ph</td>
<td>2-naphthyl</td>
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</tr>
<tr>
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<td>4e</td>
<td>iPr</td>
<td>Ph</td>
<td>Ph</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>iPr</td>
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<tr>
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<td>4g</td>
<td>iPr</td>
<td>Bn</td>
<td>Ph</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>iPr</td>
<td>Ph</td>
<td>2-naphthyl</td>
<td>60</td>
</tr>
</tbody>
</table>

$^a$Overall yields from triazolyl amine.
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 arylalkyl-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 diisopropylphosphine-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), and 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 disubstituted 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 diisopropyl-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 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-methoxyphosphanyl-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 diisopropylphos-
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>
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<tr>
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<td>4c</td>
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<td>4g</td>
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<td>43</td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>84</td>
<td>49</td>
</tr>
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</table>

*aReaction conditions: 2.0 mol ％ 4, [4] = 1 mM, 50 bar H2, CH2Cl2, rt.  
*bConversion determined by GC after 20 h.  
*Eanantioselectivity determined by chiral GC (Supelco β-DEX 225). In all cases the (−) enantiomer was obtained as the major product.  
*c1.0 mol ％ 4a.

phine-based complexes 4e−h give lower ee’s but good conversion (43−60％ ee, 84−99％ conversion; entries 6−9).

There are only few reports of efficient iridium catalysts for the hydrogenation of tetrasubstituted alkenes. Co and Kim37 reported 88％ ee at 22％ conversion after 24 h for the hydrogenation of 9 with an iminophosphoranylferrocene ligand. Pfaltz and co-workers have published several efficient catalysts for this substrate that give up to 92％ ee and full conversion at 50 bar.23,38,39 In the light of these precedents, the strategy is based on CuI-catalyzed enantioselective propargylic amination, in situ copper-catalyzed cycloaddition, and subsequent condensation with the phosphorus precursor to yield chiral Clickphine P,N-ligands. The scope of the reaction was investigated, and it was found that the protocol allows for substantial variation of the substituents, giving good yields (17−63％) and excellent ee’s after crystallization (94−99％ ee) for triazolyl amines 2a−f. Limitations arise only if the enantioselective step does not proceed with sufficient selectivity and the product cannot be further enantiomerically purified by recrystallization. The triazolyl amines were transformed into the corresponding P,N-ligands 3a−h after deprotonation with n-BuLi and reaction with the corresponding phosphorus chloride, and these ligands were reacted immediately to form Ir−Clickphine complexes.

CONCLUSION

We report here for the first time a catalytic strategy to generate libraries of chiral ligands using one chiral parent complex. The strategy is based on CuI-catalyzed enantioselective propargylic amination, in situ copper-catalyzed cycloaddition, and subsequent condensation with the phosphorus precursor to yield chiral Clickphine P,N-ligands. The scope of the reaction was investigated, and it was found that the protocol allows for substantial variation of the substituents, giving good yields (17−63％) and excellent ee’s after crystallization (94−99％ ee) for triazolyl amines 2a−f. Limitations arise only if the enantioselective step does not proceed with sufficient selectivity and the product cannot be further enantiomerically purified by recrystallization. The triazolyl amines were transformed into the corresponding P,N-ligands 3a−h after deprotonation with n-BuLi and reaction with the corresponding phosphorus chloride, and these ligands were reacted immediately to form Ir−Clickphine complexes. This resulted in a one-pot synthesis of a library of Ir−Clickphine ligands. The scope of the reaction was investigated, and it was found that the protocol allows for substantial variation of the substituents, giving good yields (17−63％) and excellent ee’s after crystallization (94−99％ ee) for triazolyl amines 2a−f. Limitations arise only if the enantioselective step does not proceed with sufficient selectivity and the product cannot be further enantiomerically purified by recrystallization. The triazolyl amines were transformed into the corresponding P,N-ligands 3a−h after deprotonation with n-BuLi and reaction with the corresponding phosphorus chloride, and these ligands were reacted immediately to form Ir−Clickphine complexes. This resulted in a one-pot synthesis of a library of Ir−Clickphine ligands. The scope of the reaction was investigated, and it was found that the protocol allows for substantial variation of the substituents, giving good yields (17−63％) and excellent ee’s after crystallization (94−99％ ee) for triazolyl amines 2a−f. Limitations arise only if the enantioselective step does not proceed with sufficient selectivity and the product cannot be further enantiomerically purified by recrystallization.

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 4f41 and 9.42 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 in Situ Cyclodaddition. Copper iodide (0.05 eq) and 2,6-bis((4R,5S)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (DiPh-pybox) (0.05 eq) 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 by TLC analysis, filtration or evaporation gave the crude product. Silica gel chromatography (typically a small percentage of MeOH in CH2Cl2) gave the pure product.

(5S)-2-Methoxy-N-(phenyl-1-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 2 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). For the compound containing derivatives suited for these substrates than the diisopropylphosphine-containing derivatives 4e−h (R = Pr). A likely explanation is the lack of π-stacking interactions with the substrate during the enantioface selection in the latter case. The effects of the other substituents (Ar1, Ar2, R’) on the enantioselectivity are more subtle and vary for the different substrates, which demonstrates the potential of fine-tuning of the catalyst by variation of these substituents. Most importantly, we report the modular synthesis of chiral Clickphine ligands by generating a small library using an enantioselective propargylic amination step based on one chiral Cu catalyst. The diversity in chirality generated is important because it shows that different efficient iridium catalysts can be made for various challenging unfunctionalized alkenes. We now aim to expand the substrate scope toward other substrates such as phosphinates, furans, and imines with a larger and more diverse library of Clickphine ligands.

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-pybox and substrates 4f and 9. 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 in Situ Cyclodaddition. Copper iodide (0.05 eq) and 2,6-bis((4R,5S)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (DiPh-pybox) (0.05 eq) 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 by TLC analysis, filtration or evaporation gave the crude product. Silica gel chromatography (typically a small percentage of MeOH in CH2Cl2) gave the pure product.
15.64. HRMS (FAB+) m/z: [M + H]+ calculated for C26H23N4O 407.1872, found 341.1766.

(R)-2-Methoxy-N-[1-(4-fluoromethyl)phenyl]-1H-1,2,3-triazol-4-yl)methyl)aniline (2e). General procedure A was followed with the enantiomer of the ligand. 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-azo-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 enantioenriched product (266 mg, 68% yield, 94% ee). [α]D 20° +10 (c 1.0, CHCl3); mp (single enantiomer) 162 °C. HPLC conditions: ChiralAD (4.6 mm × 250 mm), 80:20 heptane/HOAc (0.1 mL/min), λ = 210 nm (major isomer), 48 min (minor isomer). 34.6 min (major isomer). 3H NMR (400 MHz, CDCl3): δ (ppm) = 7.84 (d, J = 8.7 Hz, 2H), 7.77–7.75 (m, 1H), 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, 1H), 6.56 (d, J = 7.9 Hz, 2H), 5.80 (d, J = 2.8 Hz, 1H), 4.77 (br s, 1H). 13C{1H} NMR (100 MHz, CDCl3): δ (ppm) = 151.7, 146.9, 141.3, 139.4, 130.8 (J = 32.3 Hz, 1H), 129.3, 129.2, 128.2, 127.3, 127.2 (q, JCF = 3.7 Hz), 123.6 (q, JCF = 272.3 Hz), 120.5, 119.9, 118.5, 53.9, 55.8. HRMS (FAB+): m/z: [M + H]+ calculated for C26H23F3N4O7, 560.1065, found 547.0979.

(S)-2-Methoxy-N-[1-(4-fluoromethyl)phenyl]-1H-1,2,3-triazol-4-yl)methyl)aniline (2e). General procedure A was followed. The starting material was 1-phenylprop-2-ynyl acetate (300 mg, 1.3 mmol), and the total amount of MeOH was 20 mL. As the nucleophile, o- anisidine (302 μL, 2.7 mmol) was used. After 16 h, slowly warming from −18 to 0 °C, phenyl azide (160 mg, 1.3 mmol) was added, and the mixture was stirred for 17 h before the filtration was performed. The crude product was washed with cold MeOH and recrystallized from EtOAc to give enantiomerically pure white crystals (260 mg, 48% yield, 85% ee).

General Procedure B: Synthesis of Phosphinotriazole Ligands. 3. To a solution of triazolyl amine (R)-2 (1 equiv) in THF (50 mL) at −78 °C was added n-BuLi (2.5 M in hexanes, 105 equiv), and the resulting yellow solution was stirred for 15 min. The corresponding phosphorus chloride (1.05 equiv, Ph3PCl) for 3a–d and Pr3PCl for 3e–f was added, and the solution was stirred for 1 h while being allowed to warm to rt. Formation of the phosphinotriazole was checked by unlocked 31P NMR spectroscopy, which showed resonances at 56–60 and 135–138 ppm for 3a–d and 3e–f, respectively. Evaporation of the solvent in vacuo yielded a white foam, which was directly used without further purification for complexation with iridium.

General Procedure C: Synthesis of Iridium Complexes 4. The corresponding phosphinotriazole (1 equiv) and [IrCl(cod)]2 (0.5 equiv) were stirred in dichloromethane at rt for 1.5 h. NaBARF (1.25 equiv) and H2O (10 mL) were added, and the heterogeneous mixture was stirred vigorously for 10 min. The aqueous phase was removed and extracted with dichloromethane (2 × 10 mL). The combined organic phases were washed with H2O (10 mL), dried over MgSO4, and filtered, and the solvent was removed in vacuo by flash SiO2 chromatography (CH2Cl2) gave the product as a brown or red foam.

Complex 4a. According to general procedure C, ligand (R)-3a (144 mg, 0.26 mmol), [IrCl(cod)], (87 mg, 0.13 mmol), NaBARF (292 mg, 0.33 mmol), and 15 mL of CH2Cl2 were used to give the complex as an orange-red solid (233 mg, 53% yield). [α]D 20° +51 (c 0.5, CHCl3); 1H NMR (400 MHz, CDCl3): δ (ppm) = 8.07 (s, 1H), 7.88 (br s, 2H), 7.56–7.47 (m, 1H), 7.31–7.22 (m, 2H), 7.16–7.07 (m, 2H), 7.03–6.94 (m, 2H), 6.90–6.81 (m, 2H), 6.77–6.68 (m, 2H), 6.64–6.55 (m, 2H), 6.49–6.40 (m, 2H).

(S)-N-(Phenyl[1-(4-fluoromethyl)phenyl]-1H-1,2,3-triazol-4-yl)methyl)aniline (2e). General procedure A was followed with the enantiomer of the ligand. 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-azo-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 enantioenriched product (266 mg, 68% yield, 94% ee). [α]D 20° +10 (c 1.0, CHCl3); mp (single enantiomer) 162 °C. HPLC conditions: ChiralAD (4.6 mm × 250 mm), 80:20 heptane/HOAc (0.1 mL/min), λ = 210 nm (major isomer), 48 min (minor isomer). 34.6 min (major isomer). 3H NMR (400 MHz, CDCl3): δ (ppm) = 7.84 (d, J = 8.7 Hz, 2H), 7.77–7.75 (m, 1H), 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, 1H), 6.56 (d, J = 7.9 Hz, 2H), 5.80 (d, J = 2.8 Hz, 1H), 4.77 (br s, 1H). 13C{1H} NMR (100 MHz, CDCl3): δ (ppm) = 151.7, 146.9, 141.3, 139.4, 130.8 (J = 32.3 Hz, 1H), 129.3, 129.2, 128.2, 127.3, 127.2 (q, JCF = 3.7 Hz), 123.6 (q, JCF = 272.3 Hz), 120.5, 119.9, 118.5, 53.9, 55.8. HRMS (FAB+): m/z: [M + H]+ calculated for C26H23F3N4O7, 560.1065, found 547.0979. 
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7.78–7.70 (br m, 1H), 7.57–7.49 (br m), 7.46–7.38 (m, 2H), 7.38–7.30 (m, 2H), 7.29–7.22 (m, 2H), 7.22–7.15 (m, 2H), 7.14 (t, J = 7.6 Hz, 1H), 6.95–6.78 (m, 3H), 6.71 (br t, J = 7.3 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 6.24 (br s, 1H), 5.78 (br d, J = 22.3 Hz, 1H), 5.18 (br s, 1H), 3.27 (br s, 1H), 2.75 (s, 3H), 2.60–2.47 (m, 1H), 2.47–2.36 (m, 2H), 2.36–2.23 (m, 2H), 2.22–1.98 (m, 3H), 1.93–1.76 (m, 16H).

$^{1}
\text{H}NMR (100 MHz; CDCl}_3; \delta$ (ppm) = 12.0 ppm (s, CHCl$_3$); decomp.

4e Complex. According to general procedure C, ligand (R)-3e (162 mg, 0.29 mmol), [Ir(Cod)]$_2$ (74 mg, 0.11 mmol), NaBArF$_2$ (244 mg, 0.29 mmol), and 15 mL of CH$_2$Cl$_2$ were used to give the complex as a brown solid (286 mg, 60% yield).

7.38–7.20 (m, 1H), 7.06–6.86 (m, 2H), 6.86 (q, J = 7.7 Hz, 1H), 6.76 (d, J = 7.1 Hz, 1H), 5.93 (br s, 1H), 5.14 (d, J = 20.1 Hz, 1H), 5.03 (br s, 1H), 4.68 (br s, 1H), 4.57 (br s, 1H), 3.81 (s, 3H), 3.55–3.49 (m, 1H), 3.33–3.18 (m, 1H), 2.90–2.71 (m, 4H), 2.64–2.61 (m, 4H), 2.38–2.35 (m, 1H), 2.13–2.01 (m, 4H), 1.86–1.75 (m, 1H), 1.11 (d, J = 19.4, 6.7 Hz, 3H), 0.72–0.67 (d, J = 17.1, 6.6 Hz, 3H), 0.51–0.42 (m, 3H).

$^{31}$P{$^1$H} NMR (202 MHz; CDCl$_3$; $\delta$ (ppm) = 58.7 (s). HRMS (FAB+)+ m/z: [M + BArF]$^+$ calcd for C$_{6}$H$_{4}$Ir$_{2}$N$_{4}$O$_{2}$P 871.2839, found 871.2839.

4f Complex. According to general procedure C, ligand (R)-3f (143 mg, 0.29 mmol), [Ir(Cod)]$_2$ (97 mg, 0.15 mmol), NaBArF$_2$ (222 mg, 0.25 mmol), and 10 mL of CH$_2$Cl$_2$ were used to give the complex as a brown solid (268 mg, 60% yield).

7.38–7.20 (m, 1H), 7.06–6.86 (m, 2H), 6.86 (q, J = 7.7 Hz, 1H), 6.76 (d, J = 7.1 Hz, 1H), 5.93 (br s, 1H), 5.14 (d, J = 20.1 Hz, 1H), 5.03 (br s, 1H), 4.68 (br s, 1H), 4.57 (br s, 1H), 3.81 (s, 3H), 3.55–3.49 (m, 1H), 3.33–3.18 (m, 1H), 2.90–2.71 (m, 4H), 2.64–2.61 (m, 4H), 2.38–2.35 (m, 1H), 2.13–2.01 (m, 4H), 1.86–1.75 (m, 1H), 1.11 (d, J = 19.4, 6.7 Hz, 3H), 0.72–0.67 (d, J = 17.1, 6.6 Hz, 3H), 0.51–0.42 (m, 3H).

$^{31}$P{$^1$H} NMR (202 MHz; CDCl$_3$; $\delta$ (ppm) = 58.7 (s). HRMS (FAB+)+ m/z: [M + BArF]$^+$ calcd for C$_{6}$H$_{4}$Ir$_{2}$N$_{4}$O$_{2}$P 871.2839, found 871.2839.
Hydrogenation of Alkene 4. According to general procedure C, ligand (R)-3h (72 mg, 0.14 mmol), [Ir(COD)]2 (47 mg, 0.07 mmol), NaBArF4 (160 mg, 0.18 mmol), and 8 mL of CH2Cl2 were used to give the complex as a brown solid (140 mg, 60% yield). \[ \text{CF} = 4.0 \text{ Hz}, \text{J} \alpha = 10.78, \] \[ \text{J} \beta = 16.6, \text{J} \gamma = 15.9. \]<p>31P{1H} NMR (202 MHz; CDCl3): \( \delta = 15.8189(8) \) ppm (s).</p>Hydrogenation of Alkene 5. 2-Phenylbutane. The ee was determined by chiral GC analysis (Supelco \( \beta \)-DEX 225, isothermal at 55 °C): \( t_R = 35.9 \) min (R), \( t_R = 36.5 \) min (S).<p>Hydrogenation of Alkene 6. 1,2-Diphenylpropane. The ee was determined by chiral HPLC analysis (Chiralcel OJ-H, 0.8 mL min \(^{-1}\)) 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 50–100 mM, 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.</p>Propargyl Alcohol: An Alternative to Ethanol. 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).<p>X-ray Crystal Structure Determination of \( \text{R}-2 \text{-d.} \) \( \text{C}_9 \text{H}_8 \text{N}_2 \text{O}_2 \) \( \text{FW} = 370.45, \) colorless needle, 0.54 mm × 0.12 mm × 0.06 mm, monoclinic, \( \text{P}2_1 / n \) (No. 4), a = 10.7827(4) \text{ Å}, b = 5.5491(3) \text{ Å}, c = 15.8189(8) \text{ Å}, \alpha = 91.72(2), \beta = 92.612(2), \gamma = 94.53(3) \text{ Å}, \text{Z} = 2, \text{D}_{\text{calc}} = 1.301 g/cm\(^3\).</p>