Triazole-based P,N ligands: discovery of an enantioselective copper-catalyzed propargylic amination reaction
Detz, R.J.

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**CHAPTER 6**

**Synthesis and Application of Chiral ClickPhine-Type P,N Ligands**

![Chemical structure](image)

**Abstract:** A concise synthesis of chiral, enantiopure, ClickPhine P,N ligands is reported. Enantiopure, acetylene containing, building blocks were transformed via the Cu(I)-catalyzed azide-alkyne “click” cycloaddition and subsequent phosphine coupling into new ligands for transition metal catalysis. Preliminary experiments show the efficacy of these ligands in the Ir-catalyzed asymmetric hydrogenation of challenging olefins.

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6.1 INTRODUCTION

The exploration of new, sustainable, and more effective routes for organic synthesis remains a challenging task for synthetic chemists. In principle, an asymmetric catalyst provides the most efficient and environmentally friendly way to synthesize enantiomerically pure molecules. As a result, the field of asymmetric transition metal catalysis undergoes a continuing growth in both development and applications. Despite the fact that most transition metals are toxic, their special reactivity makes them very attractive as catalysts. The properties of such catalysts, e.g. activity, selectivity, and stability, may be influenced dramatically by coordinating ligands.\(^1\) It is therefore not surprising that many chiral ligands have been reported with different modes of action.

6.1.1 CLICKPHINE

As we have illustrated in Chapter 2, the synthesis of ClickPhine P,N ligands is easy and highly modular. This enables facile tuning of their steric and electronic properties for catalyst optimization purposes. Chiral ClickPhine ligands are even more attractive as they can be used for asymmetric transformations. In Chapter 3 we have shown that chirality may be introduced at three locations in ClickPhine-type ligands: chirality in the triazole N-substituent, a chiral phosphorus atom, or chirality in the backbone (see Chapter 3, Fig. 3.1). We focused on the latter for which enantiopure propargylic amines are required (Scheme 6.1).

![Scheme 6.1 Retrosynthetic scheme for the synthesis of chiral ClickPhine](image)

As is described in the three previous chapters, we have developed a new methodology providing enantioenriched propargylic amines in good yields. In the next paragraph the synthesis of enantiopure ClickPhine ligands starting from these propargylic amines is discussed.

6.2 SYNTHESIS OF CHIRAL CLICKPHINE

The first step in the synthesis of chiral ClickPhine ligands was the preparation of propargylic amines by the enantioselective copper-catalyzed propargylic amination of propargylic acetates 1. Subsequent triazole formation by the Cu(I)-catalyzed azide-alkyne cycloaddition afforded the desired triazolyl amines 2.\(^2\) Interestingly, most reagents required for this “click” reaction were already present in the preceding propargylic amination: copper(I), base, and the acetylene. As methanol was not expected to disturb the reaction, the azide may be added to
give a one pot procedure. Indeed, after full consumption of the propargylic acetate, azide addition provided triazole 2 in high yield without loss of enantioselectivity. The products obtained after the reaction were highly crystalline allowing further enantioenrichment by recrystallization. The first attempt was very promising as one recrystallization step gave the single enantiomer in good yield (Table 6.1, entry 1).

Table 6.1 Preparation of optically pure triazolyl amines 2.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>R'&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R'&lt;sup&gt;2&lt;/sup&gt;</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;1&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;2&lt;/sup&gt;</th>
<th>yield (%) recryst.</th>
<th>ee (%) recryst.</th>
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</thead>
<tbody>
<tr>
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<td>H</td>
<td>2-OMe</td>
<td>Ph</td>
<td>2a</td>
<td>94 (84)</td>
<td>&gt;99</td>
<td>63</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>OMe</td>
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<td>Ph</td>
<td>2b</td>
<td>75 (83)</td>
<td>&gt;99</td>
<td>23</td>
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<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>Bn</td>
<td>2c</td>
<td>75 (85)</td>
<td>99</td>
<td>17</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;-Ph</td>
<td>2d</td>
<td>90 (84)</td>
<td>94</td>
<td>68</td>
<td>94</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 5 (1.0 equiv), ArNH<sub>2</sub> (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 (determined by TLC) the azide (1.0 equiv) was added.

With other compounds we were not that fortunate and several recrystallization cycles were required for sufficient enantioenrichment, sacrificing the chemical yields (entries 2 and 3). Also the 4-trifluoromethylphenyl substituted triazole 2d was obtained, illustrating the ease of ligand variation via this method (entry 4).

### 6.2.1 AMINE DEPROTECTION

To create an extra site for ligand modification, removal of the o-anisidyl moiety from the triazolyl amine 2a was explored. Although this reaction is well documented,<sup>3</sup> deprotection of triazolyl amine 2a proved to be challenging. Snapper et al. reported the use of an excess of PhI(OAc)<sub>2</sub> to remove the o-anisidyl moiety from 3, which gave after acetylation the product in good yield without loss of the enantioselectivity.<sup>3b</sup> In our hands, 4a was obtained in good yield after treatment of 3 with PhI(OAc)<sub>2</sub> and subsequent N-Boc protection (Table 6.2, entry 1), but application of this method to substrate 2a only gave small amounts of the product (entries 2 and 3). The protocol required slow addition of the substrate to the PhI(OAc)<sub>2</sub> solution with a syringe pump. To prevent crystallization of 2a in the syringe, dichloromethane was used as cosolvent without affecting the outcome of the reaction. The addition of acid to
### Table 6.2 Various methods for amine deprotection.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>conditions</th>
<th>product</th>
<th>yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>PhI(OAc)$_2$ (4.0 equiv), MeOH/CH$_3$CN (3:1)</td>
<td>4a</td>
<td>62$^b$</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>PhI(OAc)$_2$ (4.0 equiv), MeOH/CH$_3$CN/CH$_2$Cl$_2$ (8:1:1), 0 °C</td>
<td>4b</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>PhI(OAc)$_2$ (4.0 equiv), MeOH/CH$_3$CN/CH$_2$Cl$_2$ (14:5:1), rt</td>
<td>4b</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>PhI(OAc)$_2$ (4.0 equiv), TFA (4.0 equiv), MeOH/CH$_3$CN/CH$_2$Cl$_2$ (10:2:3), rt</td>
<td>4b</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>PhI(OAc)$_2$ (4.0 equiv), H$_2$SO$_4$ (4.0 equiv), MeOH/CH$_3$CN (3:1), rt</td>
<td>4b</td>
<td>33</td>
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<tr>
<td>6</td>
<td>2a</td>
<td>Ce(NH$_4$)$_2$(NO$_3$)$_6$ (2.2 equiv), H$_2$SO$_4$ (2.4 equiv), CH$_3$CN, 10 °C</td>
<td>4b</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>2a</td>
<td>DDQ (4.0 equiv), CH$_2$Cl$_2$/MeOH (4:1), rt</td>
<td>4b</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>2a</td>
<td>H$_2$IO$_6$ (1.0 equiv), H$_2$SO$_4$ (2.0 equiv), CH$_3$CN/H$_2$O (3:1), rt</td>
<td>4b</td>
<td>-25$^c$</td>
</tr>
<tr>
<td>9</td>
<td>2a</td>
<td>TCCA (0.5 equiv), H$_2$SO$_4$ (2.5 equiv), CH$_3$CN/H$_2$O (7:1), rt</td>
<td>4b</td>
<td>-36$^c$</td>
</tr>
</tbody>
</table>

*Isolated yield after column chromatography. $^b$ Isolated yield after column chromatography of the Boc-protected amine. $^c$ Yield of the crude product after extraction.
the Phl(OAc)$_2$ solution gave slightly better results and afforded product 4b in 32-33% yield (entries 4 and 5). This beneficial “acid” effect was also observed by Rutjes et al. during removal of the $p$-methoxyphenyl (PMP) group by several oxidizing agents. They suggested that the initially formed benzoquinone-derived iminium ion (5 in Scheme 6.3) was hydrolyzed under the acidic reaction conditions to the desired free amine 4. In addition to this, protonation of the triazole ring in our system would probably also hamper the side reaction to ketone 7 (Scheme 6.3, path B) as will be explained below. Not satisfied with the results obtained so far, 2a was subjected to other oxidative reagents. Ceric ammonium nitrate, which has also been used for removal of the $o$-methoxyphenyl (OMP) function, only gave 21% of 4b (entry 6). Using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) no formation of product 4b was observed at all (entry 7).

A screening of several oxidizing reagents revealed a new methodology for mild and efficient deprotection of the amine protecting PMP group, as was reported by Rutjes et al. They found that periodic acid and trichloroisocyanuric acid (TCCA) in the presence of sulfuric acid were particularly effective for $N$-PMP removal. Both protocols were applied to substrate 2a (entries 8 and 9), however, no improvement was observed. Although some of the desired product was formed, LC-MS analysis revealed that chlorination of one of the aromatic rings had occurred.

The major problem for all applied conditions may be the oxidatively labile benzylic position next to the nitrogen. Starting from 3, the electron-rich anisidyl moiety is oxidized affording amine 4 after aqueous workup (Scheme 6.3, path A). If the benzylic position is more prone to oxidation, as might be the case for 2a, the iminium intermediate 6 is formed eventually giving ketone 7 (path B). Indeed, we found that ketone 7 was one of the major side products (LC-MS and NMR analysis) starting from 2a.

![Scheme 6.3 Supposed mechanism of oxidative $o$-anisidyl cleavage](image)

In addition to the chemical methods, Rutjes et al. also reported a laccase-mediated deprotection of PMP protected amines. Thus, a last attempt to achieve proper $o$-anisidyl removal was performed with two different commercially available enzymes, laccase T from...
**Trametes versicolor** and laccase AB from *Agaricus bisporus*. In a mixture of phosphate buffer (100 mM)/DMSO (1:1) substrate 2a and 3 were subjected to the enzymes, both with and without the mediator 2,2’-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS). With substrate 3, besides several unidentified sideproducts, traces of product 4a were detected by HPLC, although in such low extent that isolation was not worthwhile. Due to the high crystallinity, substrate 2a did not dissolve in the reaction mixture and so no products were detected. A higher percentage of DMSO (>50%) to dissolve 2a would probably inactivate the enzymes and was not tested.

In the end, the most reliable way to deprotect amine 2a was with PhI(OAc)₂, which gave also the best results for the propargylic amines (*e.g.* 3).

### 6.2.2 Phosphine Coupling

After the difficulties with amine deprotection we decided to continue the ligand synthesis with the protected secondary amines. Treating secondary amine 2a with triethylamine and chlorodiphenylphosphine gave no phosphinated product. The secondary amine was not nucleophilic enough to react with the phosphine chloride and a stronger base was required to form the amide anion. After several attempts we managed to synthesize ligand 5a in high yield after deprotonation of the amine with *n*-butyllithium and subsequent addition of chlorodiphenylphosphine (Scheme 6.4).

![Scheme 6.4 Phosphine coupling affording ClickPhine ligands 5](image)

The ligand was prone to hydrolysis, which led to the formation of substantial amounts of starting amine 2a during workup. To reduce the amount of hydrolyzed product, the reaction mixture was purified by flash chromatography under basic conditions (using Et₃N). However, we could not avoid that some free amine (unreacted or formed by hydrolysis) ended up in the final product. The crude ligand was used as such for metal complexation (see section 6.4.1). The more hindered chlorodi(o-tolyl)phosphine ([o-Tol]₂PCl) was also coupled to amine 2 using the same conditions. The product was obtained in 57% purity only due to the presence of unreacted amine and hydrolyzed chlorophosphine (presumably due to water trapped in the crystals of the starting amine). Purification attempts such as flash chromatography under basic conditions resulted in complete hydrolysis of the ligand. Therefore, the crude mixture was used without further purification in the metal complexation step (see section 6.4.1). The yields of the ligands as depicted in the scheme (Scheme 6.4) are corrected for their impurities, based on ¹H NMR. The difference in geometry around the phosphorus atom of both ligands, caused
by the sterically demanding o-tolyl substituents in 5b, was clearly observed in $^{31}$P NMR: ligand 5a gave a signal at 55.5 ppm, while 5b was detected at 45.6 ppm.

With the successful synthesis of the enantiopure ClickPhine P,N ligands 5 in hand, we succeeded in applying the propargylic amines as versatile building blocks for ligand synthesis underscoring the applicability of the enantioselective copper-catalyzed propargylic amination.

### 6.3 Proline Derived Ligands

Due to its special reactivity and selectivity in catalysis, proline is considered as a privileged structural motif in catalyst design.\(^7\) Along these lines, several metal complexes of proline-based P,N ligands have been published that show high reactivities and selectivities in various catalytic reactions.\(^8\) In 2002, Xu and Gilbertson synthesized and tested proline-based phosphine-oxazoline ligands, such as 6, which have a similar structure as our target ligands. The palladium complexes of these ligands were successfully applied in allylic substitution reactions. When 1,3-diphenylprop-2-enyl acetate was used both dimethyl malonate and benzylamine were found to be effective nucleophiles, affording the products in 94% ee and 93% ee, respectively (Scheme 6.5).

![Scheme 6.5 Proline-based P,N ligand 6 in the Pd-catalyzed allylic substitution](image)

We envisaged a route to an analogous chiral ClickPhine type P,N ligand starting from alkyne-containing proline analogue 11, which was prepared from Boc-protected (S)-proline 7.\(^9\) After the copper-catalyzed azide-alkyne “click” reaction and deprotection of the amine, the resulting triazolyl amine 14 could be functionalized with a phosphorus moiety furnishing the anticipated P,N ligand 16 (Scheme 6.6).

![Scheme 6.6 Retrosynthesis of the proline-derived P,N ligand](image)

We started our synthesis with the preparation of the well described alkyne-containing proline derivative 11, starting from N-Boc protected S-proline 7 (Scheme 6.7).\(^10\) After reduction of the carboxylic acid with borane dimethyl sulfide in THF, alcohol 8 was obtained.
in high yield after extraction. Subsequent Swern oxidation gave aldehyde 9 in high yield, which was converted into alkyne 11 after treatment with K$_2$CO$_3$ and the Bestmann-Ohira reagent (9). Via this route 11 was available in multiple grams and appeared to be a useful chiral building block for a series of enantiopure ClickPhine P,N ligands.

Scheme 6.7 Synthesis of alkyne-containing proline building block

The copper-catalyzed azide-alkyne cycloaddition gave triazole-containing N-Boc protected proline 12 and 13 in high yields after chromatography. Although we only performed the reaction with benzyl and phenyl azide, the azide may be varied according to the ClickPhine strategy, as is illustrated in Chapter 2.

Removal of the Boc-group was accomplished in quantitative yield by treatment of 12 or 13 with concentrated aqueous hydrogen chloride in ethyl acetate. The direct use of the HCl salt in the coupling reaction with chlorodiphenylphosphine did not work. During the course of this research, Reddy et al. reported the preparation of 14 in very high yield (92%) by treatment of 12 with 5 M aqueous HCl in ethanol, followed by basic workup and chromatography. They used the pyrrolidine-triazole conjugate 14 as an organocatalyst in the asymmetric Michael addition of cyclohexanone to β-nitrostyrenes and obtained products in high yield and up to 94% ee. Fortunately, also in our hands the Reddy conditions provided free amines 14 and 15 in high yield (Scheme 6.8). Finally, reaction of 14 with chlorodiphenylphosphine gave proline derived ligand 16 in good yield, as was also demonstrated by the $^{31}$P NMR signal (45.8 ppm).

Scheme 6.8 Formation of the proline derived ligand 16

Introduction of the phosphorus moiety in the last step of the sequence gave us the opportunity to make other type of P,N ligands. Coupling of the HCl salt of 14 with (S-binol)phosphorous chloride at 50 °C furnished the phosphoramidite ligand 17 (Scheme 6.9).
This observation is in sharp contrast with the route described above, where the coupling did not work starting from the HCl salt. Probably, the phosphination requires elevated temperatures for effective conversions. NMR analysis of phosphoramidite ligand 17 and its diastereoisomer (prepared with (R-binol)phosphorous chloride) revealed the formation of two diastereoisomers in a ratio of approximately 4:1, as was indicated by both $^1$H and $^{31}$P NMR ($^{31}$P signals: 149.5 and 150.7 ppm) indicating that partial racemization of 14-HCl had occurred. Because it is known that especially aldehyde 9 (Scheme 6.7) is sensitive towards racemization, we compared the optical rotation of 11 with the literature value and, surprisingly, found them to be similar ([α]$_D^{24}$ = −68, c 1.1 in CHCl$_3$; lit.$^{14}$ [α]$_D^{21}$ = −67.3, c 0.67 in CHCl$_3$). Although this suggested no racemization until this step, the optical rotation of 12 was lower than reported by Reddy ([α]$_D^{24}$ = −34, c 0.8 in CHCl$_3$; lit.$^{12}$ [α]$_D^{25}$ = −42.7, c 0.8 in CHCl$_3$). Because racemization during the Cu-catalyzed azide-alkyne cycloaddition is very unlikely to occur, the optical rotation of 11 was compared with another literature report now measured in methanol. A clear difference in the values was observed ([α]$_D^{20}$ = −74, c 0.5 in MeOH; lit.$^{10a}$ [α]$_D^{20}$ = −99, c 0.015 in MeOH), revealing an inaccuracy in the literature, but more importantly, the partial racemization of alkyne 11. This indeed suggests that during the preparation or handling of aldehyde 9 some racemization had occurred. Later we found that by careful treatment of the aldehyde racemization could be prevented, providing 11 in enantiopure form via our described route (Scheme 6.7). Now the optical rotation of 11 in methanol corresponded with the literature value and in addition, the value measured in chloroform was higher: [α]$_D^{20}$ = −98 (c 0.5 in CHCl$_3$).

![Scheme 6.9 Formation of the phosphoramidite ligand 17](image)

Although not optically pure, phosphoramidite ligand 17 was obtained in good yield according to $^{31}$P NMR, demonstrating that the P-group is easily varied starting from the proline-derived building block. Due to the partial racemization, the proline-derived ligands were not tested in catalysis. Nevertheless, we will discuss the synthesis of the Ir complex of 16 in the next paragraph.

### 6.4 IR-CATALYZED HYDROGENATION

In the last decade, iridium complexes with chiral P,N ligands have emerged as a powerful class of catalysts for the asymmetric hydrogenation of highly challenging olefins (also known
as largely unfunctionalized olefins. Crabtree was the first to demonstrate the remarkable activity of cationic Ir complexes with a monophosphine and pyridine as ligands in the hydrogenation of variously substituted olefins. In 1998, Pfaltz and co-workers recognized that their Ir complexes with bidentate phosphino-oxazoline (PHOX) ligands (19) greatly resemble the coordination sphere of the iridium center in the Crabtree catalyst 18. Indeed, the catalysts were active in the asymmetric hydrogenation of olefins like 20. However, problems with deactivation of the catalyst made it necessary to use strictly anhydrous conditions and a high catalyst loading (4 mol%). Further optimization of the system revealed that replacement of the PF$_6^-$ anion with BARF (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) had a dramatic effect on the conversion and allowed lower catalyst loading (<1 mol%). This eventually led to a very efficient, air stable, and easy to handle catalyst (21) that provided 22 in excellent yield and enantioselectivity (Scheme 6.10).

![Scheme 6.10 Asymmetric hydrogenation of 20 by Ir PHOX catalyst 21](image_url)

In addition to the Ir PHOX catalysts, a number of other P,N iridium catalysts have been reported as active catalysts in the asymmetric hydrogenation of highly challenging olefins (Scheme 6.11). In these analogs the six-membered ring structure, formed from the ligand and the iridium center, is usually retained. To date, the mechanistic aspects of the Ir-catalyzed asymmetric hydrogenation are still unclear. Based on NMR measurements and DFT (density functional theory) calculations on an Ir complex such as 21 after H$_2$ addition, it was suggested that steric interactions play a more important role than electronic factors.
Scheme 6.11 A selection of P,N ligands used for the Ir-catalyzed asymmetric hydrogenation of 20 (yield and ee of 22, as obtained after the catalysis with the ligands, is shown underneath the ligands)

6.4.1 CLICKPHINE IRIDIUM COMPLEXES

The similarities of the ClickPhine P,N ligands, described in this chapter, with many of these ligands triggered us to investigate their behavior in the Ir-catalyzed hydrogenation of highly challenging alkenes. Therefore, three new Ir-BARF complexes with ClickPhine ligands were prepared. Crude ligands 5a and 5b, still containing the amine and for 5b also some hydrolyzed chlorophosphine (see section 6.2.1), were used in the metal complexation step. Fortunately, the impurities did not disturb the complexation and the desired cationic Ir-BARF complexes 27a and 27b were formed (Scheme 6.12).

Scheme 6.12 Formation of Ir-BARF complexes 27a and 27b, and 28

The apolar origin of the BARF anion even allowed the purification of the Ir-BARF complexes by silica gel chromatography. In principle, the unreacted amine can be recovered in this chromatographic step. The yield of the isolated Ir complex, as depicted in the scheme,
is therefore calculated from the amount of iridium added. Also complexation of the proline derived ligand 16 with the Ir precursor resulted, after exchange of the chloride for the BARF anion, in clean formation of the desired cationic complex 28.

The structures of the iridium complexes were characterized by NMR analysis. The $^1$H NMR signal of the triazole proton shifted, after reaction of 5a with the Ir(cod)Cl dimer, 2.5 ppm to lower field (from 7.7 to 10.2 ppm). After anion-exchange, a shift back to 8.1 ppm was observed for the Ir-BARF complex. In all three complexes, the carbon atoms of the 1,5-cyclooctadiene ring that coordinated trans to phosphorus were detected at lower field, compared to those coordinating trans to nitrogen: $^{13}$C signals trans to P at ca. 95 ppm; trans to N at ca. 65 ppm. This was expected, because the strong Ir-P interaction weakens the Ir-cod bond giving the olefin more sp$^2$-character. An expected difference in geometry around the phosphorus atoms of complexes 27a and 27b was observed, indicated by their $^{31}$P signals (55.9 and 67.9 ppm, respectively). The $^{31}$P signal for ligand 28 was detected at 50.1 ppm, which is in agreement with the observed $^{31}$P signal for similar structures.\textsuperscript{18}

6.4.2 CATALYSIS

In some preliminary experiments, Ir complexes 27a and 27b were employed as catalysts in the hydrogenation of challenging alkenes (Table 6.3).

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>substrate</th>
<th>conversion\textsuperscript{\textordfphotoscript{c}} (%)</th>
<th>$ee$\textsuperscript{\textordfphotoscript{d}} (%)</th>
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<td>1</td>
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<td>23</td>
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<tr>
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<td>15</td>
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<tr>
<td>3\textsuperscript{b}</td>
<td>27a</td>
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<td>67</td>
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<td>4\textsuperscript{b}</td>
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<td><img src="4" alt="image" /></td>
<td>94</td>
<td>23</td>
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<tr>
<td>5\textsuperscript{b}</td>
<td>27a</td>
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<td>-</td>
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<td>27b</td>
<td><img src="6" alt="image" /></td>
<td>94</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: in the autoclave the substrate was stirred in CH$_2$Cl$_2$ with 1 mol% Ir complex at 25 °C and 50 bar H$_2$. \textsuperscript{b} Reaction performed at 35 °C. \textsuperscript{c} Conversion was determined after 16 h by GC. \textsuperscript{d} Enantioselectivity was determined by chiral HPLC or GC.
In a first attempt, the hydrogenation of benchmark substrate *trans*-α-methylstilbene was studied using complex 27a. A good *ee* value was obtained of 77%, albeit with low conversion (entry 1). Complex 27b was far more active and afforded the product in quantitative yield (according to GC analysis), however, now showing a low enantioselectivity (15% *ee*, entry 2). These results demonstrate the peculiar dependence of both the reactivity and the selectivity on the substituents attached to the phosphorus. The same trend was observed for the tetrasubstituted alkene, 1-methoxy-4-(3-methylbut-2-en-2-yl)benzene (entries 3 and 4). With the last tested substrate, 4-methyl-1,2-dihyronaphthalene, almost no reaction was observed with complex 27a. The use of complex 27b gave the hydrogenated product again in high yield, though without selectivity. Apparently, the substituents on the phosphorus atom have a large influence on the performance of the catalyst and fine-tuning may result in an improved performance. Although the first results look promising, more experiments are required to obtain a more distinct picture about the catalytic scope and selectivity of the ClickPhine-derived Ir complexes.

6.5 Conclusions

Enantiopure propargylic amines obtained via the enantioselective copper-catalyzed propargylic amination, were applied in the synthesis of a new series of chiral ClickPhine P,N ligands. The copper-catalyzed azide-alkyne cycloaddition, followed by phosphination, gave access to the anticipated ligands in good yields. In addition, a proline-derived P,N ligand was prepared, which unfortunately was partly racemized, making it less relevant to test it in catalysis. Three Ir-BARF complexes of the novel ligands have been prepared. Two of these have been employed as catalysts in the hydrogenation of highly challenging alkenes. Preliminary experiments revealed that the hydrogenated products could be obtained with promising selectivities (up to 77% *ee*).

6.6 Acknowledgements

M. M. E. Delville is acknowledged for her contribution to this chapter. J. A. J. Geenevasen is appreciated for his help with the structural determination of several compounds by NMR spectrometry. J. M. M. Verkade (Radboud University Nijmegen) is thanked for his help with the amine deprotection. J. Wassenaar and dr. A. J. Sandee are kindly acknowledged for the nice collaboration on the Ir catalysis project. A. M. van der Burg provided the binol-derived phosphorous chlorides, which is really appreciated.
6.7 EXPERIMENTAL SECTION

General Remarks – The general information is described in Chapter 2 and 3.

General procedure for the propargylic amination with in situ cycloaddition. Copper iodide (0.05 equiv) and 2,6-bis((4R,5S)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (diPh-pybox, 0.055 equiv) were suspended in methanol. The mixture was stirred for 20 minutes 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 total conversion of the propargylic acetate. When finished, a solution of azide (1 equiv) in methanol was added to the mixture. After full consumption of the 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(1-phenyl-1H-1,2,3-triazol-4-yl)methyl)aniline (2a). The general procedure was followed with the enantiomer of the ligand. Compound 1a (35 mg, 0.20 mmol), 1-phenylprop-2-ynyl acetate, was added to the catalyst suspension and cooled to 0 °C before adding the mixture of o-anisidine (45 µL, 0.4 mmol) and DIPEA. After stirring for 5 hours phenylazide (24 µL, 0.22 mmol) was added at room temperature. The mixture was stirred for an additional 22 hours. 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): [α]₂⁰ D +2 (c 0.5, CHCl₃). HPLC conditions: Chiralcel AD (4.6 x 250 mm), 85:15 heptane:HO-i-Pr, 1.0 mL/min, λ = 254 nm. ¹H NMR (400 MHz); δ (ppm) = 7.73 (d, J = 0.3 Hz, 1H, triazole CH), 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, CH), 5.27 (d, J = 3.6 Hz, 1H, NH), 3.88 (s, 1H, OMe); ¹³C NMR (101 MHz); δ (ppm) = 151.4, 147.1, 141.7, 137.1, 137.0, 129.7, 129.0, 128.8, 128.9, 127.9, 127.9, 127.2, 127.1, 121.1, 120.5, 120.0, 117.5, 111.4, 109.4, 55.6, 55.5; FTIR (film, cm⁻¹); 3428 (m), 3143 (w), 3064 (m), 2835 (w), 1600 (s), 1509 (s), 1458 (s), 1424 (m), 1343 (m), 1224 (m), 1128 (m), 1039 (m), 910 (m); Anal. calcd. for C₂₂H₂₀N₄O: C, 74.14; H, 5.66; N, 15.72. Found: C, 74.07; H, 5.71; N, 15.64; HRMS (FAB+) m/z: calcd. (MH⁺) 357.1715, found 357.1716.

(R)-2-Methoxy-N-((4-methoxyphenyl)(1-phenyl-1H-1,2,3-triazol-4-yl)methyl)aniline (2b). The general procedure was followed as illustrated above. The starting material was 1-(4-methoxyphenyl)prop-2-ynyl acetate (612 mg, 3.0 mmol) and the total amount of MeOH was 25 mL. As nucleophile o-anisidine (680 µL, 6.0 mmol) was used. After 7 hours, slowly warming from −18 to 0 °C, phenylazide (357 mg, 3.0 mmol) was added and the mixture was stirred for 17 h before the filtration was performed. Silica gel column chromatography (gradient: 0.5 to 2.0% of MeOH in CH₂Cl₂) gave 2b 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): [α]₂⁰ D −26 (c 0.5, CHCl₃); mp (single enantiomer) 160-162 °C. HPLC conditions: Chiralcel AD (4.6 x 250 mm), 80:20 heptane:HO-i-Pr, 1.0 mL/min, λ = 254 nm, 20 min (major isomer), 48 min (minor isomer). ¹H NMR (400 MHz); δ (ppm) = 7.72-7.67 (m, 3H), 7.50-7.46 (m, 4H), 7.20-7.10 (m, 8H), 6.83-6.70 (m, 3H), 6.53 (d, J = 7.7 Hz, 1H, CH), 5.82 (d, J = 3.7 Hz, 1H, CH), 5.27 (d, J = 3.6 Hz, 1H, NH), 3.88 (s, 1H, OMe); ¹³C NMR (101 MHz); δ (ppm) = 151.4, 147.1, 141.7, 137.1, 137.0, 129.7, 129.0, 128.8, 128.9, 127.5, 126.2, 121.1, 120.5, 120.0, 117.5, 111.4, 109.4, 55.6, 55.5; FTIR (film, cm⁻¹); 3428 (m), 3143 (w), 3064 (m), 2835 (w), 1600 (s), 1509 (s), 1458 (m), 1424 (m), 1343 (m), 1224 (m), 1128 (m), 1039 (m), 910 (m); Anal. calcd. for C₂₂H₂₀N₄O: C, 74.14; H, 5.66; N, 15.72. Found: C, 74.07; H, 5.71; N, 15.64; HRMS (FAB+) m/z: calcd. (MH⁺) 357.1715, found 357.1716.
(S)-N-((1-Benzyl-1H-1,2,3-triazol-4-yl)(phenyl)methyl)aniline (2c).

The general procedure was followed as illustrated above with the enantiomer 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 nucleophile aniline (365 µL, 4.0 mmol) was used. After 6 hours, slowly warming from −18 to 10 °C, benzylazide (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: 0.8% MeOH in CH₂Cl₂) gave 2c in good yield (512 mg, 75% yield, 85% ee). Recrystallization from EtOAc (2 portions, 406 mg, 89% ee), and stirring in CH₂Cl₂/c-hexane (3:1) and, after filtration, again in CH₂Cl₂/c-hexane (1:1) gave the almost enantiopure product (115 mg, 17% yield, 99% ee): [α]₂⁰⁺D −1 (c 0.25, CHCl₃); mp (single enantiomer) 175-178 °C. HPLC conditions: Chiralcel AD (4.6 x 250 mm), 80:20 heptane:HO⁻i-Pr, 0.8 mL/min, λ = 254 nm, 28 min (minor isomer), 31 min (major isomer).

(S)-N-(Phenyl(1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)aniline (2d). The general procedure was followed as illustrated above 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 nucleophile aniline (182 µL, 2.0 mmol) was used. After 6 hours 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 2d in good yield (353 mg, 90% yield, 84% ee). Recrystallization from EtOAc/c-hexane for one night gave the enantioenriched product (266 mg, 68% yield, 94% ee). HPLC conditions: Chiralcel AD (4.6 x 250 mm), 80:20 heptane:HO⁻i-Pr, 1.0 mL/min, λ = 254 nm, 29.4 min (minor isomer), 34.6 min (major isomer). ¹H NMR (400 MHz); 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 (t, J = 7.3 Hz, 1H), 6.65 (d, J = 7.9 Hz, 2H), 5.80 (d, J = 2.8 Hz, 1H), 4.77 (br s, 1H, NH); ¹³C NMR (101 MHz); δ (ppm) = 151.7, 146.9, 141.3, 139.4, 130.8 (q, JCF = 33.2 Hz, CCF₃), 129.3, 129.2, 128.2, 127.2 (q, JCF = 3.7 Hz, C-CCF₃), 123.6 (q, JCF = 272.3 Hz, CF₃), 120.5, 119.9, 118.5, 113.9, 55.7, 55.8.

(S)-N-(2-Methoxyphenyl)-1,1-diphenyl-N-(phenyl(1-phenyl-1H-1,2,3-triazol-4-yl)methyl)phosphinamine (5a). A solution of amine 2a (50 mg, 0.14 mmol, >99% ee) in dry THF was cooled to −78 °C before n-BuLi (97 µL, 0.15 mmol, 1.6 M solution in hexanes) was added slowly. After 15 minutes Ph₂PCl (28 µL, 0.15 mmol) was added dropwise to the yellow
solution until the yellow colour disappeared. After 2 hours some drops of Et$_3$N were added and the solution was evaporated to dryness. Silica gel chromatography (CH$_2$Cl$_2$/PE 2:1 + 1% Et$_3$N) afforded product 12 as a white foam (66 mg, 87% yield), containing 4% of amine 11 (see $^1$H-NMR): [α]$^20_D$ −30 (c 1.0, CHCl$_3$).

1H NMR (400 MHz); δ (ppm) = 7.74 (s, 1H, triazole CH), 7.60 (d, $J$ = 8.0 Hz, 2H), 7.49-7.45 (m, 6H), 7.29-7.21 (m, 9H), 7.02-6.95 (m, 2H), 6.61-6.55 (m, 2H), 6.20 (d, $J$ = 8.0 Hz, 1H, CH), 3.37 (s, 1H, OMe);

$^{13}$C NMR (101 MHz); δ (ppm) = 156.7, 151.0 (d, $J$ = 3.6 Hz), 141.7 (d, $J$ = 3.9 Hz), 140.0 (d, $J$ = 14.7 Hz), 139.5 (d, $J$ = 15.2 Hz), 137.3, 135.7, 133.6 (d, $J$ = 22.1 Hz), 133.2 (d, $J$ = 20.7 Hz), 131.9, 129.7, 129.6, 128.6, 128.4, 128.0, 127.8, 127.7, 127.6, 127.4, 127.0, 121.0 (d, $J$ = 3.2 Hz), 120.4, 119.9, 111.1, 64.0 (d, $J$ = 23.4 Hz), 54.9; $^{31}$P NMR (162 MHz); δ (ppm) = 55.5 (s); HRMS (FAB+) m/z: calcd. (MH$^+$) 541.2157, found 541.2155.

(S)-N-(2-Methoxyphenyl)-N-(phenyl(1-phenyl-1H-1,2,3-triazol-4-yl)methyl)-1,1-di(o-tolyl)phosphinamine (5b). To a solution of amine 2a (59 mg, 0.17 mmol) in dry THF (4 mL) was added n-BuLi (1.04 mL, 0.17 mmol, 0.16 M in hexanes) at −78 °C. The resulting yellow solution was stirred for 20 min at −78 °C. To this solution, a solution of chlorodi(o-tolyl)phosphine (41 mg, 0.17 mmol) was added at −78 °C. The reaction mixture was stirred for 0.5 h and then allowed to warm to room temperature. The resulting colorless solution was filtered through a plug of silica gel, and the solvent was removed in vacuo affording a white foam. The crude product 5b could not be purified for reasons of instability and was used in 57% purity for the next step. Yield (based on purity): 48 mg (0.085 mmol, 51%).

$^1$H NMR (300 MHz); δ (ppm) = 8.01 (m, 1H), 7.70 (s, 1H, triazole CH), 7.68 (d, $J$ = 10.2 Hz, 2H), 7.53-6.94 (m, 15H), 6.78-6.64 (m, 2H), 6.51 (m, 1H), 6.25 (d, $J$ = 4.8 Hz, 1H, CH), 3.36 (s, 3H, OMe), 2.31 (s, 3H), 2.12 (s, 3H); $^{31}$P NMR (121.5 MHz); δ (ppm) = 45.6 (s).

(S)-tert-Butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (8). Boc-L-proline 7 (4.30 g, 20.0 mmol) was dissolved in dry THF (120 mL) followed by slow addition of BH$_3$·DMS (2M in THF, 12.5 ml, 25.0 mmol) in 45 minutes. The mixture was stirred at reflux for 2.5 h and allowed the cool to room temperature, followed by evaporation of the solvent under reduced pressure. After addition of CH$_2$Cl$_2$ (60 mL) the organic layer was washed with H$_2$O (25 mL), saturated NaHCO$_3$-solution (100 mL) and saturated NaCl-solution (100 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporation of solvent gave product 8 (4.0 g, 99% yield). NMR spectra were corresponding with literature.

(S)-tert-Butyl 2-formylpyrrolidine-1-carboxylate (9). Dry DMSO (5.8 mL, 81.6 mmol), dissolved in CH$_2$Cl$_2$ (30 mL), was slowly added in 40 minutes to a solution of oxalyl chloride (2M in CH$_2$Cl$_2$, 25.5 mL, 51.0 mmol) in CH$_2$Cl$_2$ (100 mL) at −78 °C. Afterwards, a solution of 8 (8.21 g, 40.8 mmol) in CH$_2$Cl$_2$ (50 mL) was added to the mixture. After stirring for 75 minutes, DIPEA (28.4 mL, 163 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was washed 3 times with 0.5 M HCl (aq, 70 mL), 3 times with water (70 mL) and once with saturated NaCl-solution (70 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporation of solvent gave product 9 (7.2 g, 88% yield) in good yield. NMR spectra were corresponding with literature.
(S)-tert-Butyl 2-ethynylpyrrolidine-1-carboxylate (11). A solution of 9 (7.1 g, 35.7 mmol) in MeOH (70 mL) and a solution of dimethyl 1-diazo-2-oxopropylphosphonate \(10\) (7.6 g, 39.6 mmol) in MeOH (100 mL) were added to a suspension of \(\text{K}_2\text{CO}_3\) (9.9 g, 71.4 mmol) in MeOH (70 mL). After 24 hours, more \(10\) (0.69 g, 3.6 mmol) was added and the reaction mixture was stirred for an additional 2 hours. At that time \(\text{H}_2\text{O}\) (100 mL) was added and the mixture was extracted with \(\text{Et}_2\text{O}\) (200 mL). After separation, the organic layer was washed once with saturated aqueous \(\text{NaHCO}_3\)-solution (100 mL) and was dried over anhydrous \(\text{Na}_2\text{SO}_4\). Evaporation and silica gel chromatography (PE/EtOAc 2:1) provided product \(11\) (4.6 g, 67% yield): \([\alpha]^{24}_D -68\) (c 1.1, \(\text{CHCl}_3\)), lit.\(^{14a}\) \([\alpha]^{21}_D -67.3\) (c 0.67, \(\text{CHCl}_3\)). NMR spectra were corresponding with literature.\(^{14a}\)

(S)-tert-Butyl 2-(1-benzyl-1\(H\)-1,2,3-triazol-4-yl)pyrrolidine-1-carboxylate (12). \(\text{CuSO}_4\cdot5\text{H}_2\text{O}\) (192 mg, 0.77 mmol) and sodium ascorbate (608 mg, 3.1 mmol) were dissolved in water (6.5 mL) and added to a solution of \(11\) (2.5 g, 12.8 mmol) and benzylazide (1.6 mL, 12.8 mmol) in THF (6.5 mL). After stirring for 18 h, a saturated aqueous solution of \(\text{NH}_4\text{Cl}\) (50 mL) and \(\text{Et}_2\text{O}\) (50 mL) were added and the layers were separated. The water layer was extracted with \(\text{Et}_2\text{O}\) (50 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous \(\text{NaCl}\)-solution (20 mL). The organic layer was dried over anhydrous \(\text{Na}_2\text{SO}_4\) and evaporated to dryness, affording \(12\) as a white solid (3.8 g, 91% yield). Either recrystallization from EtOAc gave the pure product (68%) or silica gel chromatography (EtOAc/PE 2:3) gave the pure product in good yield (0.72 g, 89% yield): \([\alpha]^{20}_D -43\) (c 0.8, \(\text{CHCl}_3\)); mp 84-86 °C. \(^{1}H\) NMR (400 MHz); \(\delta\) ppm = (mixture of rotamers 5:4) 7.42-7.17 (m, 6H), 5.56-5.41 (m, 2H), 4.98-4.94 (m, 1H), 3.50-3.37 (m, 2H), 2.42-1.80 (m, 4H), 1.42 and 1.19 (s, 9H); \(^{13}C\) NMR (101 MHz); \(\delta\) ppm = (mixture of rotamers) 154.5 and 154.2, 151.4 and 149.8, 134.8, 129.1 and 129.0, 128.7 and 128.5, 128.0, 122.2 and 120.6, 79.4, 54.1, 53.7 and 52.8, 46.7 and 46.3, 33.0 and 31.0, 28.5 and 28.4, 24.4 and 23.3; FTIR (film, cm\(^{-1}\)); 2975 (m), 2874 (m), 1689 (s), 1453 (w), 1396 (s); HRMS (FAB+) \(m/z\): calcd. (MH\(^{+}\)) 329.1978, found 329.1979. Data corresponds with literature, although no comments on rotamers were made.\(^{12}\)

(S)-tert-Butyl 2-(1-phenyl-1\(H\)-1,2,3-triazol-4-yl)pyrrolidine-1-carboxylate (13). \(\text{CuSO}_4\cdot5\text{H}_2\text{O}\) (32 mg, 0.13 mmol) and sodium ascorbate (101 mg, 0.51 mmol) were dissolved in water (0.5 mL) and added to a solution of \(11\) (0.50 g, 2.6 mmol) and benzylationzide (0.31 g, 2.6 mmol) in THF (2 mL). After stirring for 18 h, the mixture was concentrated under reduced pressure before addition of a saturated aqueous solution of \(\text{NH}_4\text{Cl}\) (10 mL) and \(\text{Et}_2\text{O}\) (10 mL). After separation of the layers, the water layer was extracted with \(\text{Et}_2\text{O}\) (2 \(\times\) 10 mL). The combined organic layers were washed with saturated aqueous \(\text{NaCl}\)-solution (10 mL) and dried over anhydrous \(\text{MgSO}_4\). Evaporation of the solvent gave \(13\) as a yellowish solid (0.77 g, 96% yield). Silica gel chromatography (EtOAc/PE 2:3) gave the pure product in good yield (0.72 g, 89% yield): \([\alpha]^{20}_D -43\) (c 1.0, \(\text{CHCl}_3\)). \(^{1}H\) NMR (400 MHz); \(\delta\) ppm = (mixture of rotamers 5:4) 7.92 and 7.75 (br s, 1H), 7.70 (dd, \(J = 8.2\) Hz, \(J = 0.6\) Hz, 2H), 7.52-7.35 (m, 3H), 5.09 (m, 1H), 3.60-3.40 (m, 2H), 2.49 (m, 0.55H), 2.35-2.12 (m, 2H), 1.96 (m, 1.45H), 1.45 and 1.36 (s, 9H).

(S)-1-Benzyl-4-(pyrrolidin-2-yl)-1\(H\)-1,2,3-triazole HCl salt (14·HCl). To a solution of Boc-protected amine \(12\) (3.5 g, 10.7 mmol) in EtOAc (18 mL) was slowly added a concentrated aqueous solution of HCl (37 w%, 9

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mL). The reaction mixture was stirred for 3 hours before the solvent was removed under reduced pressure. Coevaporation with EtOH (4 × 5 mL) and drying under vacuum overnight (50 °C) provided product 14·HCl (2.9 g, 99% yield) in quantitative yield: [α]D20 −4 (c 1.0, EtOH). 1H NMR (CD3OD, 400 MHz); δ (ppm) = 8.15 (s, 1H), 7.41-7.35 (m, 5H), 5.65 (s, 2H), 4.85 (t, J = 7.7 Hz, 1H), 3.45-3.42 (m, 2H), 2.53-2.46 (m, 1H), 2.34-2.15 (m, 3H); 13C NMR (CD3OD, 101 MHz); δ (ppm) = 142.7, 135.1, 128.7, 128.4, 127.9, 123.8, 54.7, 53.8, 45.1, 29.7, 23.3; FTIR (film, cm−1); 3388 (br, s), 2983 (s), 2882 (s), 2746 (s), 2549 (m); HRMS (FAB+) m/z: calcd. (MH+ +) 229.1453, found 229.1443.

(S)-1-Benzyl-4-((pyrrolidin-2-yl)-1H-1,2,3-triazole (14). Boc-amine 12 (100 mg, 0.30 mmol) was dissolved in EtOH (3 mL) and to this solution aqueous HCl (0.5 mL, 5 M) was added at 0 °C. The mixture was stirred for 3 h at room temperature and afterwards concentrated by evaporation under reduced pressure. The residue was dissolved in CH2Cl2 (10 mL) and quenched with saturated NaHCO3 (aq, 10 mL). After separation of the layers, the water layer was extracted with CH2Cl2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na2SO4 and evaporated to dryness. Silica gel chromatography (CH2Cl2 + 2% Et3N + 2% to 4% MeOH) afforded amine 14 (64 mg, 94% yield): [α]D20 −8 (c 1.3, CHCl3) (lit. [α]D25 −15 (c 1.0, CHCl3)). 1H NMR (400 MHz); δ (ppm) = 7.41-7.35 (m, 4H), 7.30-7.26 (m, 2H), 5.50 (s, 2H, CH2), 4.29 (t, J = 6.7 Hz, 1H), 3.14-3.08 (m, 1H), 3.00-2.94 (m, 1H), 2.23-2.17 (m, 1H, HCH + NH), 1.93-1.83 (m, 3H); 13C NMR (101 MHz); δ (ppm) = 151.8, 134.8, 129.1, 128.7, 128.2, 120.5, 54.8, 54.2, 46.7, 46.7, 32.6, 25.4. NMR spectra do not correspond with literature, the use of a different solvent is suspected.

(S)-1-Phenyl-4-(pyrrolidin-2-yl)-1H-1,2,3-triazole (15). Boc-amine 13 (100 mg, 0.32 mmol) was dissolved in EtOH (3 mL) and to this solution aqueous HCl (0.5 mL, 5 M) was added at 0 °C. The mixture was stirred for 3 h at room temperature and afterwards concentrated by evaporation under reduced pressure. The residue was dissolved in CH2Cl2 (10 mL) and quenched with saturated NaHCO3 (aq, 10 mL). After separation of the layers, the water layer was extracted with CH2Cl2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na2SO4 and evaporated to dryness. Silica gel chromatography (CH2Cl2 + 2% Et3N + 2% to 4% MeOH) afforded free amine 15 (64 mg, 94% yield): 1H NMR (400 MHz); δ (ppm) = 7.92 (s, 1H), 7.73-7.70 (m, 2H), 7.53-7.49 (m, 2H), 7.44-7.40 (m, 1H), 4.42 (t, J = 6.9 Hz, 1H), 3.18-3.15 (m, 1H), 3.07-3.02 (m, 1H), 2.28-2.24 (m, 1H), 2.10 (br s, 1H), 1.99-1.85 (m, 3H); 13C NMR (101 MHz); δ (ppm) = 152.2 (c q), 137.3 (d, J = 8.8 Hz, c q), 138.6 (d, J = 15.0 Hz, c q), 135.0 (c q), 132.5 (d, J = 19.9 Hz), 132.0 (d, J = 19.6 Hz), 129.1, 128.6 (d, J = 2.1 Hz), 140
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128.3, 128.26, 128.24, 128.20, 128.18, 128.08, 59.7 (d, J = 31.3 Hz), 54.1, 47.2 (d, J = 6.7 Hz), 34.0 (d, J = 6.0 Hz), 25.7; $^{31}$P NMR (162 MHz); δ (ppm) = 45.8.

**1-Benzyl-4-((2S)-1-((11bS)-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)pyrrolidin-2-yl)-1H-1,2,3-triazole (17).**

$^{14}$HCl (0.10 g, 0.38 mmol) was dissolved in toluene (2 mL) and triethylamine (1 mL) and subsequently evaporated to dryness to remove traces of water (repeated two times with only toluene). Afterwards $^{14}$HCl was dissolved in toluene (10 mL) and triethylamine (0.5 mL) and heated to 50 °C. After slow addition of (S-binol)phosphorous chloride (1.2 mL, 0.34 mmol), the mixture was stirred for 3.5 h at 50 °C. The mixture was cooled to room temperature and filtrated over celite. Evaporation provided ligand 17 together with its diastereomer (67% and 18% according to $^{31}$P NMR).

**Ir complex with diphenylphosphine ligand (27a).** To a solution of ligand 5a (47 mg, purity 85%, ~0.075 mmol) in dry CH$_2$Cl$_2$ (3 mL) chlorobis(cycloocta-1,5-diene)diirdium ([Ir(cod)Cl]$_2$, 25 mg, 0.037 mmol) was added. After 2 hours of stirring at room temperature the solvent was evaporated. NMR analysis demonstrated the formation of the complex (signal of triazole-H shifts from 7.74 ppm (free ligand) to 10.2 ppm (complex); $^{31}$P from 55.4 ppm (free ligand) to 55.2 ppm (complex). The complex was dissolved in CH$_2$Cl$_2$ (3 mL) and the chloride was exchanged for a BARF anion by addition of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (66 mg, 0.074 mmol). Silica gel chromatography (Et$_2$O to Et$_2$O/CH$_2$Cl$_2$ 3:1) afforded complex 27a as a orange/red solid (112 mg, 89% yield, which contained 5% of an unidentified isomeric complex observed by NMR, $^{31}$P-NMR minor isomer at 39.7 ppm): [α]$_{20}^{D}−$51 (c 0.5, CHCl$_3$).

**1H NMR (400 MHz);** δ (ppm) = 8.07 (s, 1H, triazole CH), 7.88 (br s, 2H), 7.78-7.70 (br m, 10H, 2x ArH + 8x o-H-BARF), 7.57-7.50 (br m, 10H, 6x ArH + 4x p-H-BARF), 7.46-7.38 (m, 2H), 7.38-7.30 (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, cod-CH), 5.78 (br d, J = 22.3 Hz, 1H, CH), 5.18 (br s, 1H, cod-CH), 2.75 (s, 3H, OMe), 2.60-2.47 (m, 1H, cod-CH), 2.47-2.36 (m, 2H, cod), 2.36-2.23 (m, 2H, cod), 1.93-1.76 (m, 1H, cod); $^{13}$C NMR (101 MHz); δ (ppm) = 162.0 (q, J$_{CB}$ = 49.9 Hz, 4C, c$_q$ BARF), 156.3 (c$_q$ COMe), 148.6 (d, J$_{CP}$ = 5.4 Hz, c$_q$ triazole), 135.6 (c$_q$), 135.3, 135.1 (br, 8C, BARF), 134.1 (c$_q$), 132.4, 132.3, 132.0, 131.8 (c$_q$), 131.5, 131.4, 131.2 (c$_q$), 131.0 (c$_q$), 130.8, 130.4 (c$_q$), 129.8 (d, J$_{CP}$ = 2.6 Hz), 129.5, 129.2 (qq, J$_{CF}$ = 31.5 Hz, J$_{CB}$ = 2.7 Hz, c$_q$ BARF C-CF$_3$), 128.4, 128.3 (d, J$_{CP}$ = 11.0 Hz), 128.0 (d, J$_{CP}$ = 11.3 Hz), 124.8 (q, J$_{CF}$ = 273 Hz, c$_q$ BARF CF$_3$), 121.8 (CH triazole), 121.2, 120.8, 117.6 (q, J$_{CB}$ = 3.5 Hz, 4C, BARF), 112.3, 97.3 (d, J$_{CP}$ = 10.5 Hz, cod-CH), 92.7 (br, cod-CH), 69.1 (br, cod-CH), 65.5 (br, cod-CH), 65.5 (d, J$_{CP}$ = 13.6 Hz, CH), 54.5 (OMe), 33.2 (cod-C$_2$H$_5$), 31.9 (cod-C$_2$H$_5$), 30.0 (cod-C$_2$H$_5$), 29.2 (cod-C$_2$H$_5$); $^{31}$P NMR (162 MHz); δ (ppm) = 55.9 (s); HRMS (FAB+) m/z: calcd. (M$^+$) 841.2647, found 841.2651.
Ir complex with di(o-tolyl)phosphine ligand (27b). Ligand 5b (14.0 mg, 24.6 μmol) and [Ir(cod)Cl]₂ (8.3 mg, 12.3 μmol) were dissolved in CH₂Cl₂ (2 mL) and stirred at room temperature for 1.5 h. To the resulting bright orange solution, NaBARF (32.8 mg, 37.0 μmol) and H₂O (2 mL) were added and the heterogeneous mixture was stirred vigorously for 10 min. The aqueous phase was removed and extracted twice with CH₂Cl₂ (2 × 4 mL). The combined organic phases were washed with H₂O (5 mL), dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (CH₂Cl₂) to give 27b (24 mg, 14 μmol, 56%) as an orange solid. ¹H NMR (300 MHz); δ (ppm) = 7.74-7.64 (m, 12H), 7.56 (m, 8H), 7.36-7.23 (m, 6H), 7.12-7.04 (m, 3H), 6.95 (d, 1H, 1H, 1H, cod), 6.47 (m, 2H), 6.17 (d, J = 8.1 Hz, 1H), 6.10 (t, J = 8.6 Hz, 1H), 5.84 (d, J = 8.0 Hz, 1H), 5.54 (m, 1H, cod CH), 5.49 (m, 1H, cod CH), 4.49 (m, 1H, cod CH), 4.12 (m, 1H, cod CH), 3.25 (d, J = 14.5 Hz, 4C, cₐ BARF C-Cₐ CF₃), 2.71 (s, 3H, OMe), 2.55-2.44 (m, 2H, cod), 2.37 (m, 1H, cod), 2.20 (m, 2H, cod), 1.96-1.85 (m, 4H), 1.75-1.71 (m, 1H, cod); ³¹P NMR (121 MHz); δ (ppm) = 67.9 (s).

Ir complex with proline-derived ligand (28). Ligand 16 (80 mg, 0.19 mmol) and [Ir(cod)Cl]₂ (67 mg, 0.11 mmol) were dissolved in CH₂Cl₂ (8 mL) and stirred at room temperature for 1.5 h. To the resulting bright orange solution, NaBARF (168 mg, 0.22 mmol) and H₂O (8 mL) were added and the heterogeneous mixture was stirred vigorously for 10 min. The aqueous phase was removed and extracted twice with CH₂Cl₂ (2 × 10 mL). The combined organic phases were washed with H₂O (10 mL), dried over MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (CH₂Cl₂) to give 28 (220 mg, 0.14 mmol, 72%) as an orange solid; [α]²⁰ D +11 (c 1.0, CHCl₃). ¹H NMR (500 MHz); δ (ppm) = 7.78-7.72 (m, 2H), 7.72 (br s, 8H), 7.51-7.48 (m, 8H), 7.46-7.32 (m, 8H), 7.24-7.22 (m, 2H), 5.96-5.90 (m, 1H, cod), 5.51 (A of AB, d, 1H, J = 14.5 Hz), 5.45 (B of AB, d, 1H, J = 14.5 Hz), 4.95-4.87 (m, 2H, cod + NCH), 3.52-3.48 (m, 1H, cod), 2.77-2.71 (m, 1H, NCH₂), 2.43-2.18 (m, 1H, cod), 1.96-1.85 (m, 4H), 1.75-1.71 (m, 1H, cod); ¹³C NMR (126 MHz); δ (ppm) = 161.9 (q, J_CB = 49.8 Hz, 4C, cₐ BARF), 151.6 (cₐ triazole), 135.0 (br, 8C, BARF), 134.4 (d, J = 14.0 Hz), 132.5 (cₐ), 132.3, 131.9, 131.8 (cₐ), 131.5 (d, J = 10.6 Hz), 130.3, 129.9, 129.3, 129.2, 129.1 (q, J_CF = 31.7 Hz, cₐ BARF C-Cₐ CF₃), 128.6, 128.3 (cₐ), 124.8 (q, J_CF = 273 Hz, cₐ BAr₅ CF₃), 121.3, 117.7 (4C, BARF), 97.8 (d, J_CF = 11.8 Hz, cod-CH), 95.7 (d, J_CF = 12.6 Hz, cod-CH), 68.7 (cod-CH), 64.6 (cod-CH), 57.9 (d, J_CF = 13.1 Hz, NCH), 56.5 (CH₃Ph), 47.6 (d, J_CF = 4.7 Hz, NCH₂), 34.1 (d, J_CF = 3.8 Hz), 31.3, 31.2 (d, J_CF = 8.1 Hz), 30.5, 28.3, 26.1 (d, J_CF = 4.7 Hz); ³¹P NMR (203 MHz); δ (ppm) = 50.1 (s).

General procedure for the asymmetric hydrogenation. The hydrogenation experiments were carried out in a stainless steel autoclave (150 mL) charged with an insert suitable for 5 reaction vessels (including Teflon mini stirring bars) for conducting parallel reactions. In a typical experiment, the reaction vessels were charged with 2.5 μmol of Ir-catalyst and 0.25 mmol of alkene substrate in 2.5 mL of CH₂Cl₂. Before starting the catalytic reactions, the charged autoclave was purged three times with 15 bar of dihydrogen and then pressurized at 50 bar H₂. The reaction mixtures were stirred at 25 °C for 16 h. After catalysis the pressure was reduced to 1.0 bar and the conversion and enantiomeric purity were determined by chiral GC or HPLC. Prior to analysis, the solvent was evaporated, hexane
was added and the sample was filtered through SiO$_2$. Analysis for the reaction with substrate 1-methoxy-4-(3-methylbut-2-en-2-yl)benzene: Interscience Focus GC with Supelco BETA DEX 225 column (start at 50 °C, with 1 °C/min to 130 °C); 68.1 min (major enantiomer), 68.8 min (minor enantiomer), 74.3 min (substrate). Analysis for the reaction with substrate trans-α-methylstilbene: Shimadzu HPLC with Chiralcel OJH column (0.5% iPrOH in hexane, 0.7 mL/min, $\lambda = 215$ nm); 16.9 min (minor enantiomer), 26.6 min (major enantiomer), 31.1 min (substrate).

1-Methoxy-4-(3-methylbut-2-en-2-yl)benzene was prepared following a literature procedure, using Pd(PPh$_3$)$_4$ as the catalyst.$^{21}$

4-Methyl-1,2-dihydronaphthalene was prepared following a literature procedure.$^{22}$

6.8 REFERENCES AND NOTES


2. The preparation of triazolyl amines 2 is not the first reported. In 2007, similar compounds were synthesized in the group of Botta as potential antimicrobial agents. The copper-catalyzed azide-alkyne cycladdition was performed with enantiopure propargylic amines obtained by kinetic enzymatic resolution of racemic propargylic amines. Castagnolo, D.; Dessì, F.; Radi, M.; Botta, M. Tetrahedron: Asymmetry 2007, 18, 1345-1350.


