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

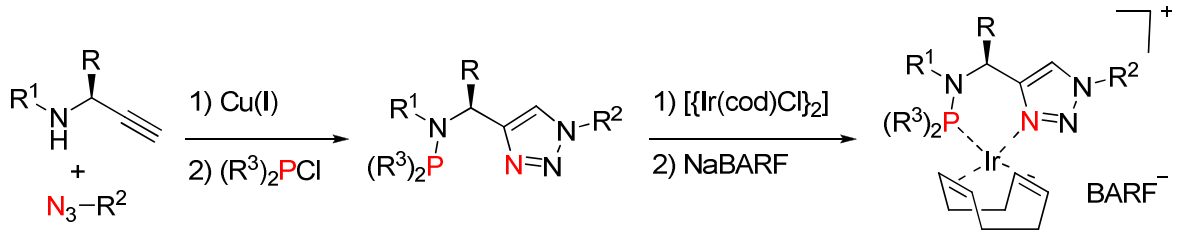
Detz, R.J.

Publication date
2009

Document Version
Final published version

CHAPTER 6

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



cod = 1,5-cyclooctadiene, BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

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.

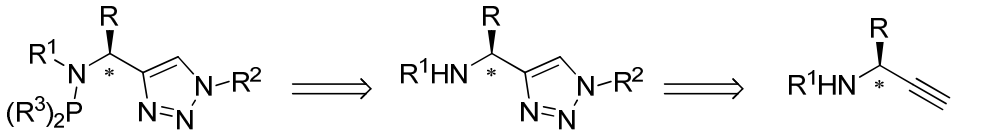
* Part of this chapter has been published: Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3777-3780.

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

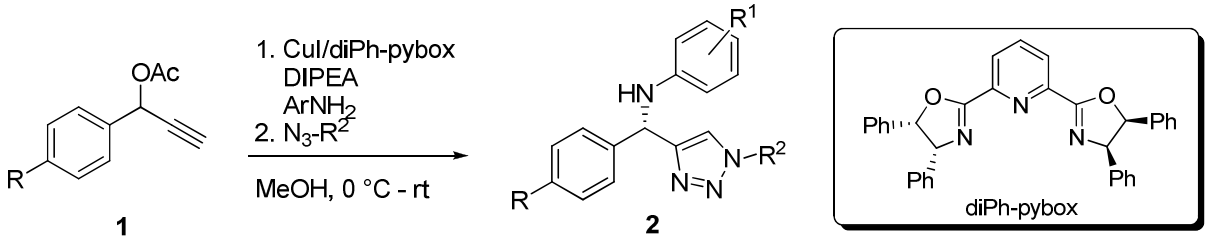
As is described in the three previous chapters, we have developed a new methodology providing enantioenriched propargylic amines in good yields. In the next paragraph the synthesis of enantiopure ClickPhine ligands starting from these propargylic amines is discussed.

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**.[a]



entry	R	R^1	R^2	product	yield (%) (*ee* (%))	yield (%) recryst.	*ee* (%) recryst.
1	H	2-OMe	Ph	**2a**	94 (84)	63	> 99
2	OMe	2-OMe	Ph	**2b**	75 (83)	23	> 99
3	H	H	Bn	**2c**	75 (85)	17	99
4	H	H	4-CF_3-Ph	**2d**	90 (84)	68	94

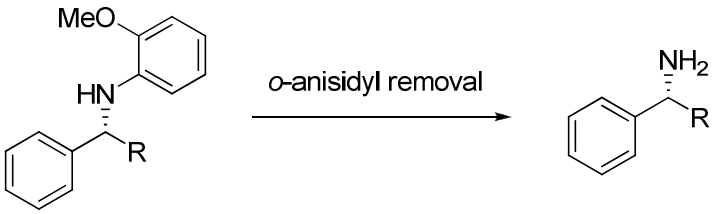
[a] Reaction conditions: **5** (1.0 equiv), $ArNH_2$ (2.0 equiv), DIPEA (4 equiv), CuI (0.05-0.10 equiv), and the ligand (0.06-0.12 equiv) were stirred in methanol at 0 °C. After full conversion (determined by TLC) the azide (1.0 equiv) was added.

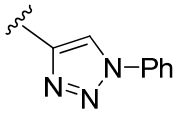
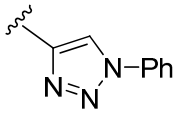
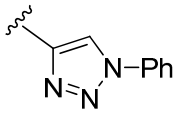
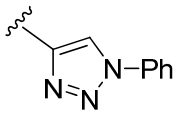
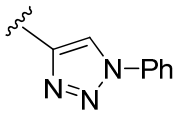
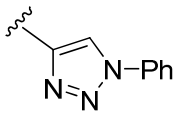
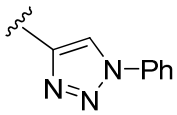
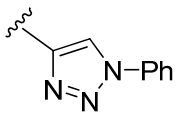
With other compounds we were not that fortunate and several recrystallization cycles were required for sufficient enantioenrichment, sacrificing the chemical yields (entries 2 and 3). Also the 4-trifluoromethylphenyl substituted triazole **2d** was obtained, illustrating the ease of ligand variation 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,[3] deprotection of triazolyl amine **2a** proved to be challenging. Snapper *et al.* reported the use of an excess of $PhI(OAc)_2$ to remove the *o*-anisidyl moiety from **3**, which gave after acetylation the product in good yield without loss of the enantioselectivity.[3b] In our hands, **4a** was obtained in good yield after treatment of **3** with $PhI(OAc)_2$ 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 $PhI(OAc)_2$ 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.



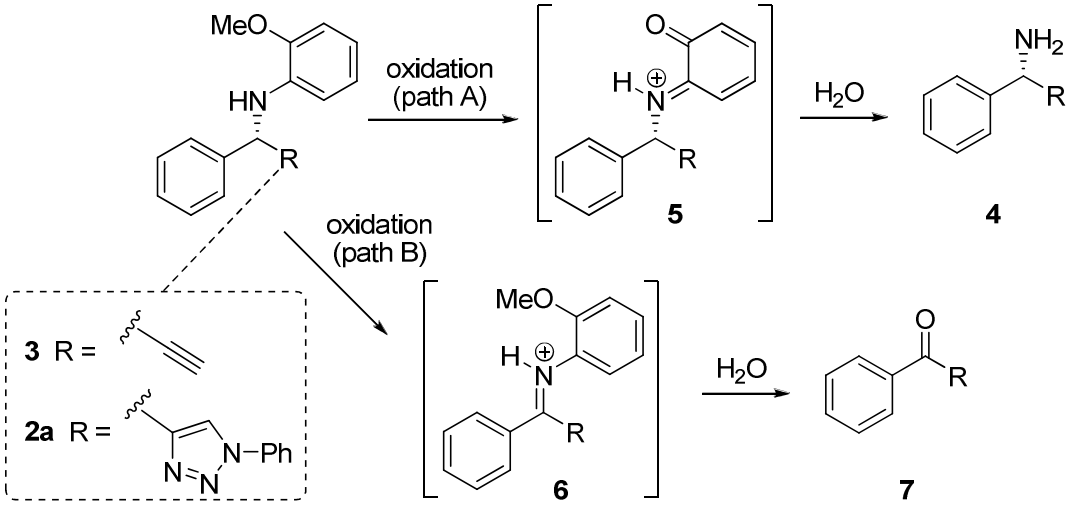
entry		R	conditions	product	yield[a] (%)
1	**3**		$PhI(OAc)_2$ (4.0 equiv), $MeOH/CH_3CN$ (3:1)	**4a**	62[b]
2	**2a**		$PhI(OAc)_2$ (4.0 equiv), $MeOH/CH_3CN/CH_2Cl_2$ (8:1:1), 0 °C	**4b**	14
3	**2a**		$PhI(OAc)_2$ (4.0 equiv), $MeOH/CH_3CN/CH_2Cl_2$ (14:5:1), rt	**4b**	22
4	**2a**		$PhI(OAc)_2$ (4.0 equiv), TFA (4.0 equiv), $MeOH/CH_3CN/CH_2Cl_2$ (10:2:3), rt	**4b**	32
5	**2a**		$PhI(OAc)_2$ (4.0 equiv), H_2SO_4 (4.0 equiv), $MeOH/CH_3CN$ (3:1), rt	**4b**	33
6	**2a**		$Ce(NH_4)_2(NO_3)_6$ (2.2 equiv), H_2SO_4 (2.4 equiv), CH_3CN, 10 °C	**4b**	21
7	**2a**		DDQ (4.0 equiv), CH_2Cl_2/MeOH (4:1), rt	**4b**	-
8	**2a**		H_5IO_6 (1.0 equiv), H_2SO_4 (2.0 equiv), CH_3CN/H_2O (3:1), rt	**4b**	~25[c]
9	**2a**		TCCA (0.5 equiv), H_2SO_4 (2.5 equiv), CH_3CN/H_2O (7:1), rt	**4b**	~36[c]

[a] 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 $PhI(OAc)_2$ 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.[5] 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,[4] only gave 21% of **4b** (entry 6). Using 2,3-dichloro-5,6-dicyano-l,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.*[5] 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

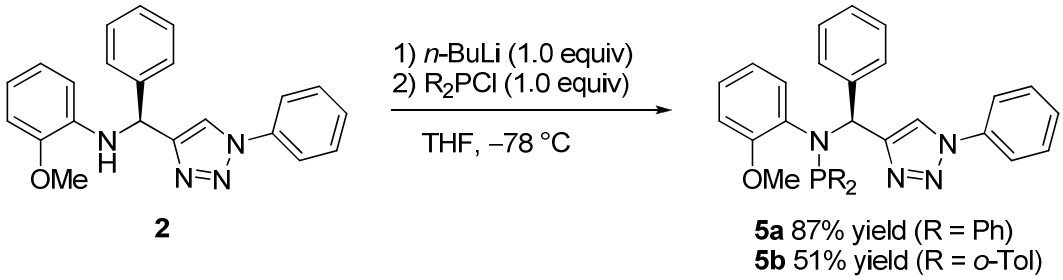
In addition to the chemical methods, Rutjes *et al*. also reported a laccase-mediated deprotection of PMP protected amines.[6] Thus, a last attempt to achieve proper *o*-anisidyl removal was performed with two different commercially available enzymes, laccase T from

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**

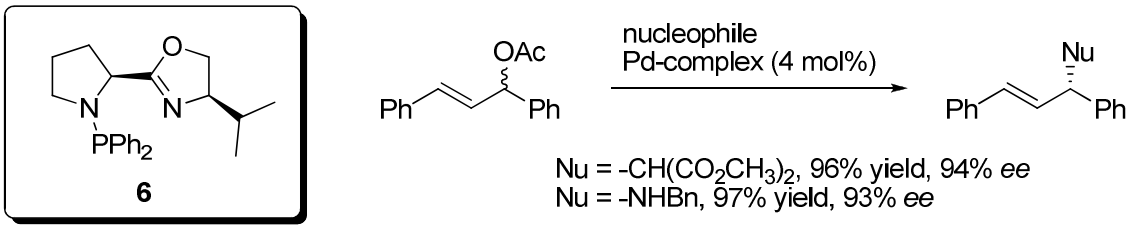
The ligand was prone to hydrolysis, which led to the formation of substantial amounts of starting amine **2a** during workup. To reduce the amount of hydrolyzed product, the reaction mixture was purified by flash chromatography under basic conditions (using Et_3N). However, we could not avoid that some 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)$_2$PCl) 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 ^{1}H 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.

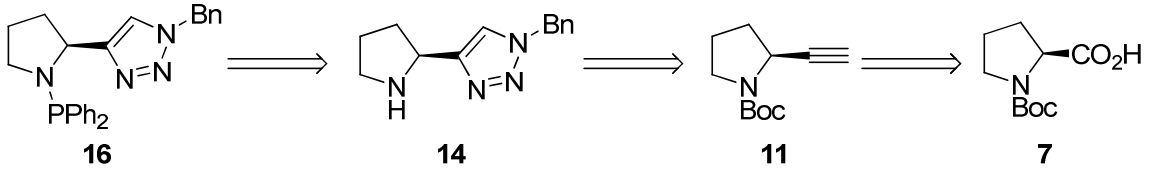
6.3 PROLINE DERIVED LIGANDS

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

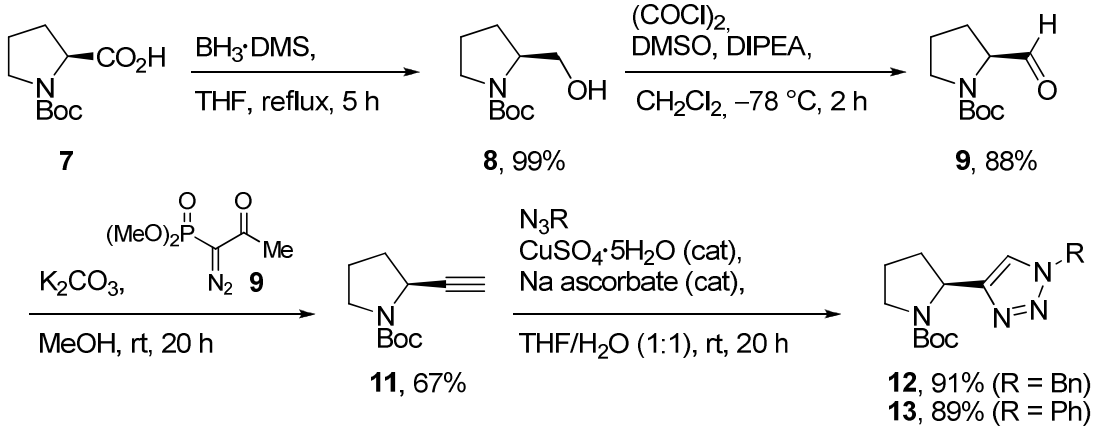
We envisaged a route to an analogous chiral ClickPhine type P,N ligand starting from alkyne-containing proline analogue **11**, which was prepared from Boc-protected (*S*)-proline **7**.[9] After the copper-catalyzed azide-alkyne "click" reaction and deprotection of the amine, the resulting triazolyl 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

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

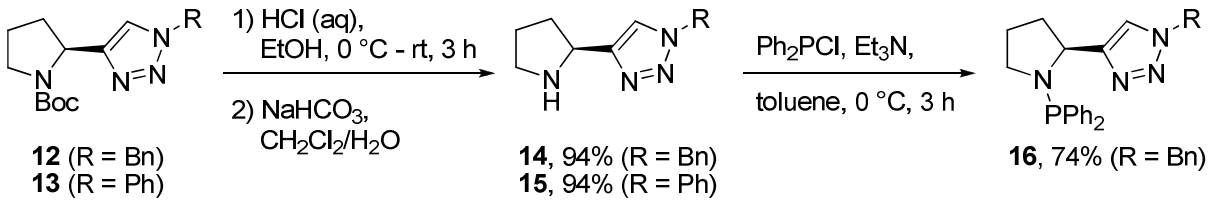
in high yield after extraction. Subsequent Swern oxidation gave aldehyde **9** in high yield, which was converted into alkyne **11** after treatment with K_2CO_3 and the Bestmann-Ohira reagent (**9**).[11] Via this route **11** was available in multiple grams and appeared to be a useful chiral building 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.

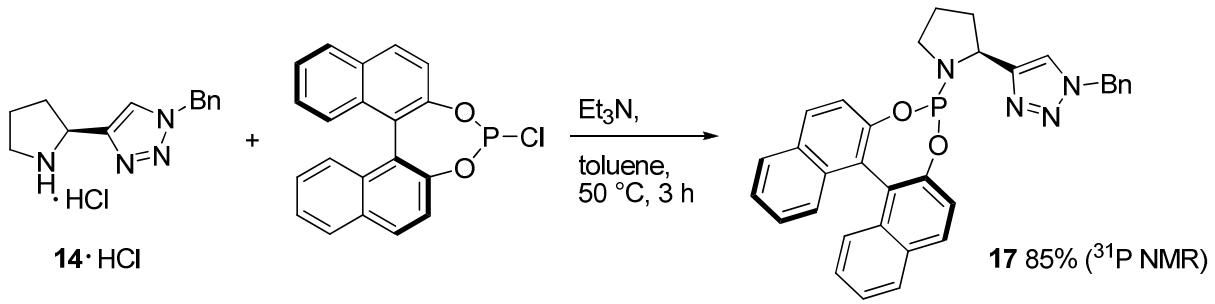
Removal of the Boc-group was accomplished in quantitative yield by treatment of **12** or **13** with concentrated aqueous hydrogen chloride in ethyl acetate. The direct use of the HCl salt in the coupling reaction with chlorodiphenylphosphine did not work. During the course of this research, Reddy *et 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.[12] 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,[13] we compared the optical rotation of **11** with the literature value and, surprisingly, found them to be similar ($[\alpha]_D^{24}$ = −68 , c 1.1 in $CHCl_3$; lit.[14] $[\alpha]_D^{21}$ = −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 ($[\alpha]_D^{24}$ = −34 , c 0.8 in $CHCl_3$; lit.[12] $[\alpha]_D^{25}$ = −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 (($[\alpha]_D^{20}$ = −74 , c 0.5 in MeOH; lit.[10a] $[\alpha]_D^{20}$ = −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: $[\alpha]_D^{20}$ = −98 (c 0.5 in $CHCl_3$).



14· HCl

17 85% (^{31}P NMR)

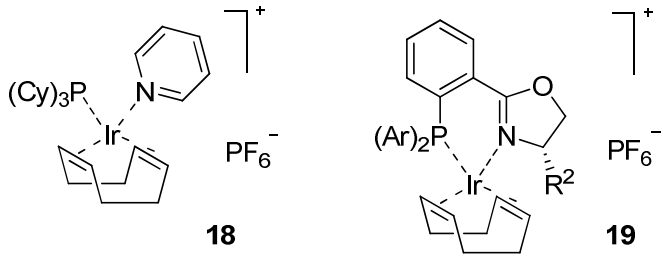
Scheme 6.9 Formation of the phosphoramidite ligand **17**

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.

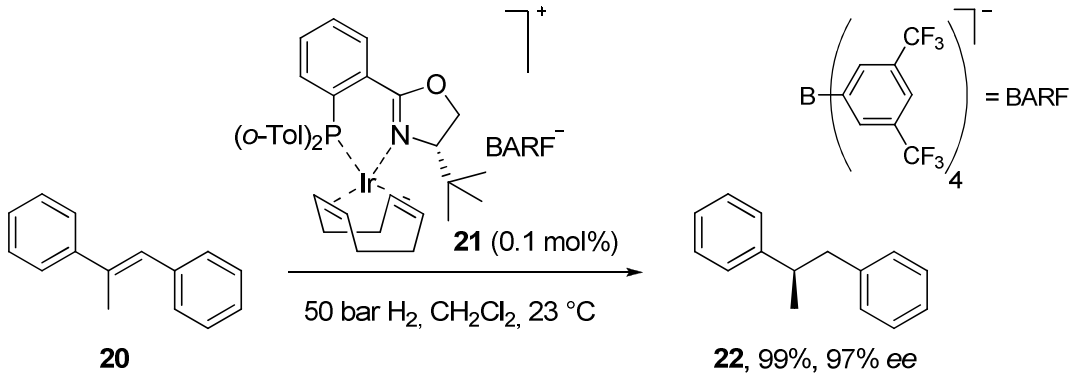
6.4 Ir-Catalyzed Hydrogenation

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).[15] 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.[16] In 1998, Pfaltz and co-workers recognized that their Ir complexes with bidentate phosphinooxazoline (PHOX) ligands (**19**) greatly resemble the coordination sphere of the iridium center in the Crabtree catalyst **18**.[17]

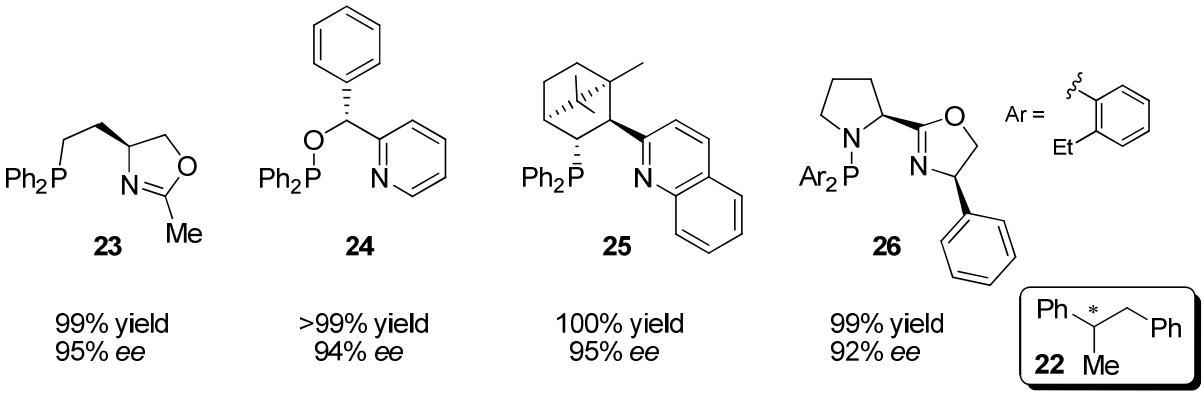


Indeed, the catalysts were active in the asymmetric hydrogenation of olefins like **20**. However, problems with deactivation of the catalyst made it necessary to use strictly anhydrous conditions and a high catalyst loading (4 mol%). Further optimization of the system revealed that replacement of the 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**

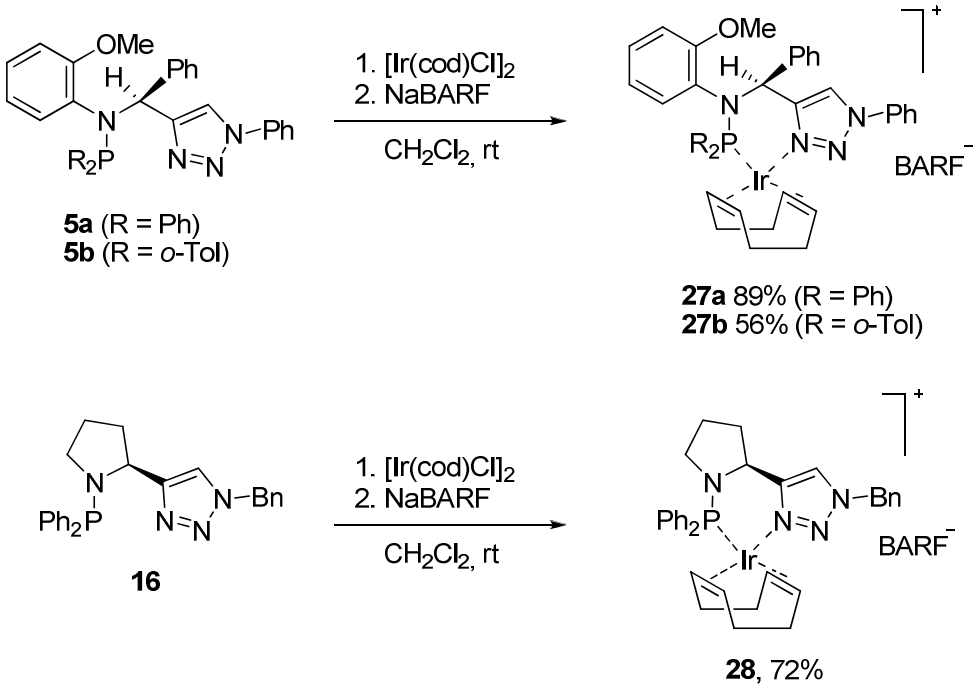
In addition to the Ir PHOX catalysts, a number of other P,N iridium catalysts have been reported as active catalysts in the asymmetric hydrogenation of highly challenging olefins (Scheme 6.11).[8,15] In these analogs the six-membered ring structure, formed from the ligand and the iridium center, is usually 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.[15b]



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,

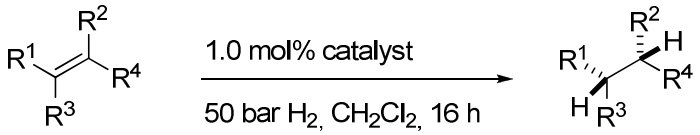
is therefore calculated from the amount of iridium added. Also complexation of the proline derived ligand **16** with the Ir precursor resulted, after exchange of the chloride for the BARF anion, in clean formation of the desired cationic complex **28**.

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.[18]

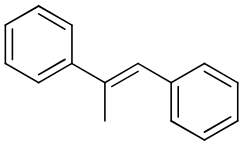
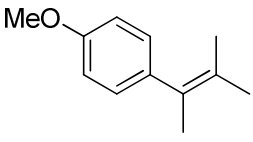
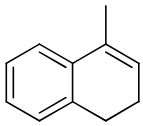
6.4.2 CATALYSIS

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

Table 6.3 Ir-catalyzed hydrogenation of three different alkenes.[a]



substrate product

entry	catalyst	substrate	conversion[c] (%)	*ee*[d] (%)
1	**27a**		23	77
2	**27b**		100	15
3[b]	**27a**		7	67
4[b]	**27b**		94	23
5[b]	**27a**		3	-
6[b]	**27b**		94	0

[a] Reaction conditions: in the autoclave the substrate was stirred in CH_2Cl_2 with 1 mol% Ir complex at 25 °C and 50 bar H_2. [b] Reaction performed at 35 °C. [c] Conversion was determined after 16 h by GC. [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-dihydronaphthalene, 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*).

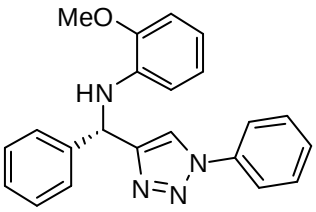
6.6 Acknowledgements

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.

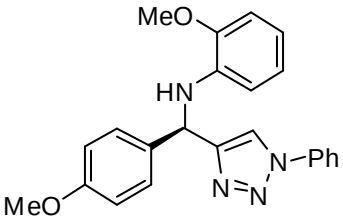
6.7 EXPERIMENTAL SECTION

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 CH_2Cl_2) gave the pure product.

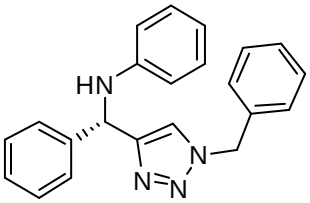


(*S*)-2-Methoxy-*N*-(phenyl(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-aniline (2a). The general procedure was followed with the enantiomer of the ligand. Compound **1a** (35 mg, 0.20 mmol), 1-phenylprop-2-ynyl acetate, was added to the catalyst suspension and cooled to 0 °C before adding the mixture of *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*): $[\alpha]^{20}_D$ +2 (c 0.5, $CHCl_3$). HPLC conditions: Chiralcel AD (4.6 x 250 mm), 85:15 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm. ^{1}H 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); ^{13}C NMR (101 MHz); δ (ppm) = 151.4, 147.1, 141.7, 137.1, 137.0, 129.7, 129.0, 128.8, 127.9, 127.2, 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 (s), 1424 (m), 1343 (m), 1224 (s), 1128 (m), 1039 (m), 910 (m); Anal. cacld. for $C_{22}H_{20}N_4O$: 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.

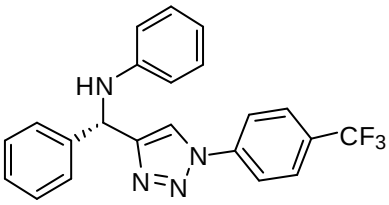


(*R*)-2-Methoxy-*N*-((4-methoxyphenyl)(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)aniline (2b). The general procedure was followed as illustrated above. The starting material was 1-(4-methoxyphenyl)prop-2-ynyl acetate (612 mg, 3.0 mmol) and the total amount of MeOH was 25 mL. As nucleophile *o*-anisidine (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 CH_2Cl_2) 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*): $[\alpha]^{20}_D$ –26 (c 0.5, $CHCl_3$); 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). ^{1}H NMR (400 MHz); δ (ppm) = 7.72-7.67 (m, 3H), 7.50-7.46

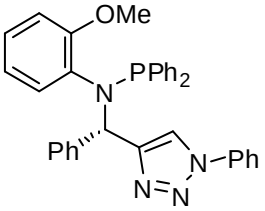
(m, 2H), 7.43-7.40 (m, 3H), 6.92-6.89 (m, 2H), 6.81-6.69 (m, 3H), 6.53-6.50 (m, 1H), 5.73 (s, 1H, CH), 5.2 (br s, 1H, NH), 3.87 (s, 3H, OMe), 3.80 (s, 3H, OMe); ^{13}C NMR (101 MHz); δ (ppm) = 159.2 (c_q), 151.7 (c_q), 147.1 (c_q), 137.1 (c_q), 137.0 (c_q), 133.7 (c_q), 129.7, 128.7, 128.4, 121.1, 120.5, 120.0, 117.4, 114.4, 111.4, 109.4, 55.5, 55.3, 55.0.



(*S*)-*N*-((1-Benzyl-1*H*-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 CH_2Cl_2) gave **2c** in good yield (512 mg, 75% yield, 85% *ee*). Recrystallization from EtOAc (2 portions, 406 mg, 89% *ee*), and stirring in CH_2Cl_2/*c*-hexane (3:1) and, after filtration, again in CH_2Cl_2/*c*-hexane (1:1) gave the almost enantiopure product (115 mg, 17% yield, 99% *ee*): $[\alpha]^{20}_D$ −1 (c 0.25, $CHCl_3$); 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). ^{1}H NMR (400 MHz); δ (ppm) = 7.44 (d, *J* = 8.5 Hz, 2H), 7.37-7.19 (m, 8H), 7.16 (s, 1H, triazole-H), 7.13-7.09 (m, 2H), 6.70 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 7.7 Hz, 2H), 5.69 (d, *J* = 4.0 Hz, 1H), 5.49 (A of AB, d, *J* = 15.0 Hz, 1H), 5.42 (B of AB, d, *J* = 15.0 Hz, 1H), 4.80 (d, *J* = 3.6 Hz, 1H, NH); ^{13}C NMR (101 MHz); δ (ppm) = 150.8 (c_q), 147.1 (c_q), 141.8 (c_q), 134.7 (c_q), 129.2 (4C), 129.0, 128.8, 128.0, 127.8, 127.1, 121.7, 118.1, 113.9, 55.7, 54.3.

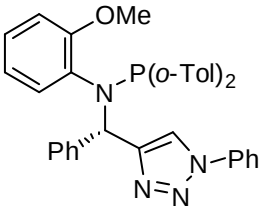


(*S*)-*N*-(Phenyl(1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)aniline (2d). The general procedure was followed as illustrated above with the enantiomer of the ligand. The starting material was 1-phenylprop-2-ynyl acetate (174 mg, 1.0 mmol) and the total amount of MeOH was 10 mL. As nucleophile 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% CH_2Cl_2 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). ^{1}H 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); ^{13}C NMR (101 MHz); δ (ppm) = 151.7, 146.9, 141.3, 139.4, 130.8 (q, J_{CF} = 33.2 Hz, CCF_3), 129.3, 129.2, 128.2, 127.3, 127.2 (q, J_{CF} = 3.7 Hz, C-CCF_3), 123.6 (q, J_{CF} = 272.3 Hz, CF_3), 120.5, 119.9, 118.5, 113.9, 55.8.

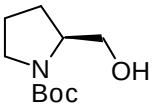


(*S*)-*N*-(2-Methoxyphenyl)-1,1-diphenyl-*N*-(phenyl(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)phosphinamine (5a). A solution of amine **2a** (50 mg, 0.14 mmol, >99% *ee*) in dry THF was cooled to −78 °C before *n*-BuLi (97 μL, 0.15 mmol, 1.6 M solution in hexanes) was added slowly. After 15 minutes Ph_2PCl (28 μL, 0.15 mmol) was added dropwise to the yellow

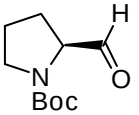
solution until the yellow colour disappeared. After 2 hours some drops of Et_3N were added and the solution was evaporated to dryness. Silica gel chromatography (CH_2Cl_2/PE 2:1 + 1% Et_3N) afforded product **12** as a white foam (66 mg, 87% yield), containing 4% of amine **11** (see ^{1}H-NMR): $[\alpha]^{20}_D$ −30 (c 1.0, $CHCl_3$). ^{1}H 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), 7.40-7.36 (m, 3H), 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.



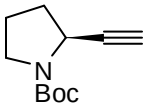
(*S*)-*N*-(2-Methoxyphenyl)-*N*-(phenyl(1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,1-di(*o*-tolyl)phosphinamine (5b). To a solution of amine **2a** (59 mg, 0.17 mmol) in dry THF (4 mL) was added *n*-BuLi (1.04 mL, 0.17 mmol, 0.16 M in hexanes) at −78 °C. The resulting yellow solution was stirred for 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).



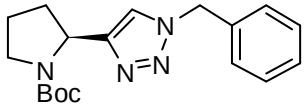
(*S*)-*tert*-Butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (8). Boc-L-proline **7** (4.30 g, 20.0 mmol) was dissolved in dry THF (120 mL) followed by slow addition of BH_3·DMS (2M in THF, 12.5 ml, 25.0 mmol) in 45 minutes. The mixture was stirred at reflux for 2.5 h and allowed the cool to room temperature, followed by evaporation of the solvent under reduced pressure. After addition of CH_2Cl_2 (60 mL) the organic layer was washed with H_2O (25 mL), saturated $NaHCO_3$-solution (100 mL) and saturated NaCl-solution (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness providing product **8** (4.0 g, 99% yield). NMR spectra were corresponding with literature.[19]



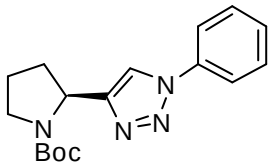
(*S*)-*tert*-Butyl 2-formylpyrrolidine-1-carboxylate (9). Dry DMSO (5.8 mL, 81.6 mmol), dissolved in CH_2Cl_2 (30 mL), was slowly added in 40 minutes to a solution of oxalyl chloride (2M in CH_2Cl_2, 25.5 mL, 51.0 mmol) in CH_2Cl_2 (100 mL) at −78 °C. Afterwards, a solution of **8** (8.21 g, 40.8 mmol) in CH_2Cl_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_2SO_4 and evaporation of solvent gave product **9** (7.2 g, 88% yield) in good yield. NMR spectra were corresponding with literature.[19]



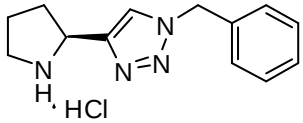
(*S*)-*tert*-Butyl 2-ethynylpyrrolidine-1-carboxylate (11). A solution of **9** (7.1 g, 35.7 mmol) in MeOH (70 mL) and a solution of dimethyl 1-diazo-2-oxopropylphosphonate **10**[20] (7.6 g, 39.6 mmol) in MeOH (100 mL) were added to a suspension of K_2CO_3 (9.9 g, 71.4 mmol) in MeOH (70 mL). After 24 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 H_2O (100 mL) was added and the mixture was extracted with Et_2O (200 mL). After separation, the organic layer was washed once with saturated aqueous $NaHCO_3$-solution (100 mL) and was dried over anhydrous Na_2SO_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, $CHCl_3$), lit.[14a] $[\alpha]^{21}_D$ −67.3 (c 0.67, $CHCl_3$). 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). $CuSO_4 \cdot 5H_2O$ (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 NH_4Cl (50 mL) and Et_2O (50 mL) were added and the layers were separated. The water layer was extracted with Et_2O (50 mL). The combined organic layers were washed with water (20 mL) and saturated aqueous NaCl-solution (20 mL). The organic layer was dried over anhydrous Na_2SO_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 to pure EtOAc) (89% yield): $[\alpha]^{20}_D$ −34 (c 0.8, $CHCl_3$), lit.[12] $[\alpha]^{25}_D$ −42.7 (c 0.8, $CHCl_3$); mp 84-86 °C. ^{1}H NMR (400 MHz); δ (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); δ (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]

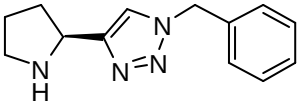


(*S*)-*tert*-Butyl 2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)pyrrolidine-1-carboxylate (13). $CuSO_4 \cdot 5H_2O$ (32 mg, 0.13 mmol) and sodium ascorbate (101 mg, 0.51 mmol) were dissolved in water (0.5 mL) and added to a solution of **11** (0.50 g, 2.6 mmol) and phenylazide (0.31 g, 2,6 mmol) in THF (2 mL). After stirring for 18 h, the mixture was concentrated under reduced pressure before addition of a saturated aqueous solution of NH_4Cl (10 mL) and Et_2O (10 mL). After separation of the layers, the water layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl-solution (10 mL) and dried over anhydrous $MgSO_4$. 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, $CHCl_3$). ^{1}H NMR (400 MHz); δ (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).

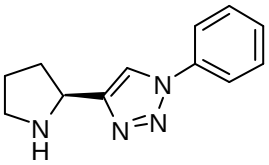


(*S*)-1-Benzyl-4-(pyrrolidin-2-yl)-1*H*-1,2,3-triazole HCl salt (14·HCl). To a solution of Boc-protected amine **12** (3.5 g, 10.7 mmol) in EtOAc (18 mL) was slowly added a concentrated aqueous solution of HCl (37 w%, 9

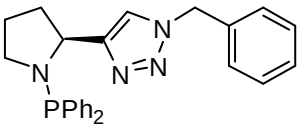
mL). The reaction mixture was stirred for 3 hours before the solvent was removed under reduced pressure. Coevaporation with EtOH (4 × 5 mL) and drying under vacuum overnight (50 °C) provided product **14**·HCl (2.9 g, 99% yield) in quantitative yield: $[\alpha]^{20}_D$ −4 (c 1.0, EtOH). ^{1}H NMR (CD_3OD, 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); ^{13}C NMR (CD_3OD, 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)-1*H*-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 CH_2Cl_2 (10 mL) and quenched with saturated $NaHCO_3$ (aq, 10 mL). After separation of the layers, the water layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. Silica gel chromatography (CH_2Cl_2 + 2% Et_3N + 2% to 4% MeOH) afforded amine **14** (64 mg, 94% yield): $[\alpha]^{20}_D$ −8 (c 1.3, $CHCl_3$) (lit.[12] $[\alpha]^{25}_D$ −15 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz); δ (ppm) = 7.41-7.35 (m, 4H), 7.30-7.26 (m, 2H), 5.50 (s, 2H, CH_2), 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, 2H, *H*CH + NH) 1.93-1.83 (m, 3H); ^{13}C NMR (101 MHz); δ (ppm) = 151.8, 134.8, 129.1, 128.7, 128.2, 120.5, 54.8, 54.2, 46.7, 32.6, 25.4. NMR spectra do not correspond with literature, the use of a different solvent is suspected.[12]

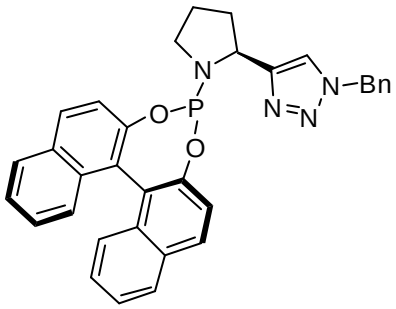


(*S*)-1-Phenyl-4-(pyrrolidin-2-yl)-1*H*-1,2,3-triazole (15). Boc-amine **13** (100 mg, 0.32 mmol) was dissolved in EtOH (3 mL) and to this solution aqueous HCl (0.5 mL, 5 M) was added at 0 °C. The mixture was stirred for 3 h at room temperature and afterwards concentrated by evaporation under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL) and quenched with saturated $NaHCO_3$ (aq, 10 mL). After separation of the layers, the water layer was extracted CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. Silica gel chromatography (CH_2Cl_2 + 2% Et_3N + 2% to 4% MeOH) afforded free amine **15** (64 mg, 94% yield). ^{1}H 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); ^{13}C NMR (101 MHz); δ (ppm) = 152.2 (c_q), 137.3 (c_q), 129.8, 128.7, 120.6, 119.0, 54.8, 46.8, 32.7, 25.5.

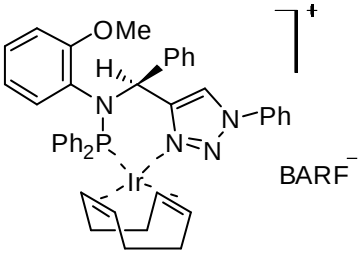


(*S*)-1-Benzyl-4-(1-(diphenylphosphino)pyrrolidin-2-yl)-1*H*-1,2,3-triazole (16). The reaction was performed under argon atmosphere. To a solution of pyrrolidine **14** (60 mg, 0.26 mmol) in dry toluene (5 mL), triethylamine (45 µl, 0.32 mmol) was added. The reaction mixture was cooled to 0 °C, followed by slow addition of Ph_2PCl (49 µL, 0.26 mmol). Filtration over a short pad of celite and evaporation of the solvents provided product **14** as a colorless oil (80 mg, 74% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.27-7.07 (m, 16H), 5.34 (A of AB, d, *J* = 14.9 Hz, 1H), 5.30 (B of AB, d, *J* = 14.9 Hz, 1H), 4.87-4.84 (m, 1H), 3.11-3.09 (m, 1H), 2.93-2.89 (m, 1H), 2.27-2.20 (m, 2H), 1.94-1.78 (m, 2H); ^{13}C NMR (101 MHz); δ (ppm) = 153.3 (c_q), 139.1 (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),

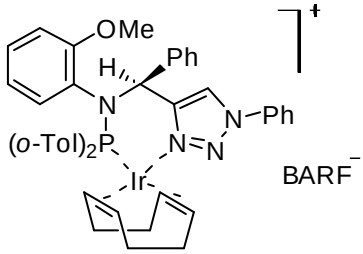
128.3, 128.26, 128.24, 128.20, 128.18, 128.08, 121.4 (d, J = 2.6 Hz), 59.7 (d, J = 31.3 Hz), 54.1, 47.2 (d, J = 6.7 Hz), 34.0 (d, J = 6.0 Hz), 25.7; ^{31}P NMR (162 MHz); δ (ppm) = 45.8.



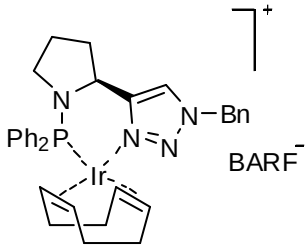
1-Benzyl-4-((2*S*)-1-((11b*S*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)pyrrolidin-2-yl)-1*H*-1,2,3-triazole (17). **14**·HCl (0.10 g, 0.38 mmol) was dissolved in toluene (2 mL) and triethylamine (1 mL) and subsequently evaporated to dryness to remove traces of water (repeated two times with only toluene). Afterwards **14**·HCl was dissolved in toluene (10 mL) and triethylamine (0.5 mL) and heated to 50 ºC. After slow addition of (*S*-binol)phosphorous chloride (1.2 mL, 0.34 mmol), the mixture was stirred for 3.5 h at 50 ºC. 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). ^{1}H NMR (400 MHz); δ (ppm) = (major isomer) 8.06 -7.80 (m, 4H), 7.59-7.00 (m, 14H), 5.58 (A of AB, d, 1H, J = 14.9 Hz), 5.42 (B of AB, d, 1H, J = 14.9 Hz), 5.19-5.11 (m, 1H), 3.20-3.10 (m, 1H), 2.85-2.77 (m, 1H), 2.55-2.45 (m, 1H), 2.31-2.24 (m, 2H), 1.80-1.70 (m, 1H); ^{31}P NMR (162 MHz); δ (ppm) = 149.5 (major) and 150.7 (minor).



Ir complex with diphenylphosphine ligand (27a). To a solution of ligand **5a** (47 mg, purity 85%, ~0.075 mmol) in dry CH_2Cl_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_2Cl_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_2O to Et_2O/CH_2Cl_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): $[\alpha]^{20}_{D}$ –51 (c 0.5, $CHCl_3$). ^{1}H 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), 7.57-7.49 (br m, 10H, 6x ArH + 4x *p*-H-BARF), 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, cod-CH), 5.78 (br d, J = 22.3 Hz, 1H, CH), 5.18 (br s, 1H, cod-CH), 3.27 (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), 2.22-1.98 (m , 3H, 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-CH_2), 31.9 (cod-CH_2), 30.0 (cod-CH_2), 29.2 (cod-CH_2); ^{31}P NMR (162 MHz); δ (ppm) = 55.9 (s); HRMS (FAB+) m/z: calcd. (M^+) 841.2647, found 841.2651.



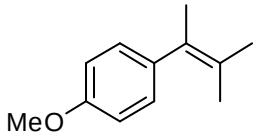
Ir complex with di(*o*-tolyl)phosphine ligand (27b). Ligand **5b** (14.0 mg, 24.6 μmol) and $[Ir(cod)Cl]_2$ (8.3 mg, 12.3 μmol) were dissolved in CH_2Cl_2 (2 mL) and stirred at room temperature for 1.5 h. To the resulting bright orange solution, NaBARF (32.8 mg, 37.0 μmol) and H_2O (2 mL) were added and the heterogeneous mixture was stirred vigorously for 10 min. The aqueous phase was removed and extracted twice with CH_2Cl_2 (2 × 4 mL). The combined organic phases were washed with H_2O (5 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2) to give **27b** (24 mg, 14 μmol, 56%) as an orange solid. ^{1}H 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 (t, *J* = 8.0 Hz, 1H), 6.56 (m, 1H), 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* = 15.3 Hz, 1H, cod), 2.91 (d, *J* = 15.6 Hz, 1H, cod), 2.71 (s, 3H, OMe), 2.55-2.44 (m, 2H, cod), 2.37 (m, 1H, cod), 2.20 (m, 2H, cod), 2.17 (s, 3H), 2.02 (s, 3H), 1.85 (m, 1H, cod); ^{31}P NMR (121 MHz); δ (ppm) = 67.9 (s).



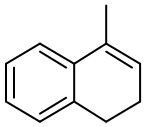
Ir complex with proline-derived ligand (28). Ligand **16** (80 mg, 0.19 mmol) and $[Ir(cod)Cl]_2$ (67 mg, 0.11 mmol) were dissolved in CH_2Cl_2 (8 mL) and stirred at room temperature for 1.5 h. To the resulting bright orange solution, NaBARF (168 mg, 0.22 mmol) and H_2O (8 mL) were added and the heterogeneous mixture was stirred vigorously for 10 min. The aqueous phase was removed and extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with H_2O (10 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (CH_2Cl_2) to give **28** (220 mg, 0.14 mmol, 72%) as an orange solid: $[\alpha]^{20}_D$ +11 (c 1.0, $CHCl_3$). ^{1}H 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), 3.16-3.12 (m, 1H, NCH_2), 2.82-2.79 (m, 1H, cod), 2.77-2.71 (m, 1H, NCH_2), 2.43-2.18 (m, 6H), 2.07-2.00 (m, 1H, cod), 1.96-1.85 (m, 4H), 1.75-1.71 (m, 1H, cod); ^{13}C NMR (126 MHz); δ (ppm) = 161.9 (q, J_{CB} = 49.8 Hz, 4C, c_q BARF), 151.6 (c_q, triazole), 135.0 (br, 8C, BARF), 134.4 (d, *J* = 14.0 Hz), 132.5 (c_q), 132.3, 131.9, 131.8 (c_q), 131.5 (d, *J* = 10.6 Hz), 130.3, 129.9, 129.3, 129.2, 129.1 (q, J_{CF} = 31.7 Hz, c_q BARF C-CF_3), 128.6, 128.3 (c_q), 124.8 (q, J_{CF} = 273 Hz, c_q BAr_F CF_3), 121.3, 117.7 (4C, BARF), 97.8 (d, J_{CP} = 11.8 Hz, cod-CH), 95.7 (d, J_{CP} = 12.6 Hz, cod-CH), 68.7 (cod-CH), 64.6 (cod-CH), 57.9 (d, J_{CP} = 13.1 Hz, NCH), 56.5 (CH_2Ph), 47.6 (d, J_{CP} = 4.7 Hz, NCH_2), 34.1 (d, J_{CP} = 3.8 Hz), 31.3, 31.2 (d, J_{CP} = 8.1 Hz), 30.5, 28.3, 26.1 (d, J_{CP} = 4.7 Hz); ^{31}P 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 CH_2Cl_2. Before starting the catalytic reactions, the charged autoclave was purged three times with 15 bar of dihydrogen and then pressurized at 50 bar H_2. 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% *i*PrOH in hexane, 0.7 mL/min, λ = 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

1 (a) Chaloner, P. A.; Esteruelas, M. A.; Joó, F.; Oro, L. A. *Homogeneous Hydrogenation*; Kluwer: Dordrecht, 1994. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1. (c) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*, Wiley: New York, 1992; (d) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.

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 cycloaddition 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.

3 (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409-10410. (b) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003,** *5*, 3273-3275. (c) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734-3735. (d) Joffe, A. L.; Thomas, T. M.; Adrian Jr., J. C. *Tetrahedron Lett.* **2004**, *45*, 5087-5090. (e) Cozzi, P. G.; Rivalta, E. *Angew. Chem. Int. Ed.* **2005**, *44*, 3600-3603.

4 (a) Adrian, J. M.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett.* **1999**, *40*, 2457-2460. (b) Ota, H.; Chyouma, T.; Iso, S.; Satoh, T. *Tetrahedron Lett.* **2004**, *45*, 3903-3907. (c) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756-6764.

5 Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2006**, *47*, 8109-8113.

6 Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Schoemaker, H. E.; Schürmann, M.; van Delft, F. L.; Rutjes, F. P. J. T. *Adv. Synth . Catal.* **2007**, *349*, 1332-1336.

7 For proline as organocatalyst, see: (a) List, B.; Lerner, r. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267. For selected reviews on proline catalysis, see: (c) List, B. *Acc. Chem. Res.* **2004**, *37*, 548-557. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569.

8 (a) Gilbertson, S. R.; Xie, D. *Angew. Chem. Int. Ed.* **1999**, *38*, 2750-2752. (b) Gilbertson, S. R.; Xie, D.; Fu, Z. *J. Org. Chem.* **2001**, *66*, 7240-7246. (c) Hiroi, K.; Suzuki, Y.; Abe, I. *Tetrahedron: Asymmetry* **1999**, *10*, 1173-1188. (d) Kuznetsov, V. F.; Yap, G. P. A.; Alper, H.

Organometallics **2001**, *20*, 1300-1309. (e) Jiang, B.; Huang, Z.; Cheng, K. *Tetrahedron: Asymmetry* **2006**, *17*, 942-951.
9 Bock, V. D.; Speijer, D. Hiemstra, H.; van Maarseveen, J. H. *Org. Biomol. Chem.* **2007**, *5*, 971-975.
10 (a) Dickson, H. D.; Smith, S. C.; Hinkle, K. W. *Tetrahedron Lett.* **2004**, *45*, 5597-5599. (b) Paul, A.; Bittermann, H.; Gmeiner, P. *Tetrahedron* **2006**, *62*, 8919-8927.
11 (a) Müller, S.; Liepold, B.; Roth, G.; Bestmann, H. J. *Synlett* **1996**, *6*, 521-522. (b) Roth, G.; Liepold, B.; Müller, S.; Bestmann, H. J. *Synthesis* **2004**, *1*, 59-62.
12 Chandrasekhar, S.; Tiwari, B.; Parida, B. B.; Reddy, Ch. R. *Tetrahedron: Asymmetry* **2008**, *19*, 495-499.
13 Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081-3087.
14 (a) Reginato, G.; Mordini, A.; Messina, F.; Degl'Innocenti, A.; Poli, G. *Tetrahedron* **1996**, *52*, 10985-10996. (b) Barrett, A. G. M.; Hopkins, B. T.; Love, A. C.; Tedeschi, L. *Org. Lett.* **2004**, *6*, 835-837.
15 Recent reviews: (a) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272-3296. (b) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402-1411. A selection of other papers: (c) Trifonova, A.; Diesen, J. S.; Andersson, P. G. *Chem. Eur. J.* **2006**, *12*, 2318-2328. (d) Schrems, M. G.; Neumann, E.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8274-8276. (e) Bell, S.; Wüstenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, *311*, 642-644.
16 Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331-338.
17 Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899.
18 Blanc, C.; Agbossou-Niedercorn, F.; Nowogrocki, G. *Tetrahedron: Asymmetry* **2004**, *15*, 2159-2163.
19 Reed, P.E.; Katzenellenbogen, J.A. *J. Org. Chem.* **1991**, *56*, 2624-2634.
20 (a) Callant, P.; D'Haenens, L.; Vanderwalle, M. *Synth. Commun.* **1984**, *14*, 155; (b) Roth, G. J.; Liepold, B.; Muller, S.; Bestmann, H. J. *Synthesis*, **2004**, *1*, 59-62.
21 Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2003**, 1091-1096.
22 Silva Jr., L. F.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguetto, A. C. *Org. Lett.* **2007**, *9*, 1433-1436.