Synthesis and applications of chiral ligands based on the bicarbazole skeleton

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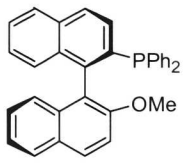
CHAPTER 5

AN INTRAMOLECULAR STAUDINGER APPROACH TOWARDS *P,N*-LIGANDS*

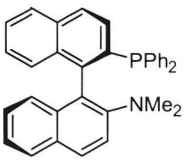
5.1 Introduction

5.1.1 MAP-type ligands

Ligands based on non-symmetrically substituted 1,1'-binaphthyls find widespread use in homogeneous catalysis.[1] Within this class two well-known examples are the C_1-symmetrical methoxyphosphine MOP and amino phosphine MAP ligands (Chart 1).[2] The hetero-bidentate MAP-type *P,N*-ligands stand out by their high reactivities and selectivities in several transition metal-catalyzed reactions such as Hartwig-Buchwald aminations, (enantioselective) Suzuki-Miyaura couplings and the formation of aryl ethers.



MOP



MAP

For the synthesis of enantiopure MAP-type ligands BINOL seems the most logical starting material as both optical antipodes are commercially available at a decent price. Surprisingly, only one synthetic route towards MAP-type ligands starting from BINOL has been reported, namely by Noyori and co-workers (Scheme 5.1).[3]

This sequence started with the mono-phoshinylation of BINOL ditriflate **2**, followed by a nickel mediated cyanation of the obtained phosphine oxide **3**. Partial hydrolysis of nitrile **4** yielded amide **5** in an excellent yield. The key reaction in this sequence was the Hofmann rearrangement of **5** with bromine in a basic methanol solution to give carbamate **6**. Hydrolysis with aqueous KOH in methanol afforded the primairy amine and subsequent reduction of the phosphine oxide by treatment with Cl_3SiH afforded the desired des-methyl-MAP **7** in seven steps from BINOL in an excellent overall yield of 70%. Amine **7** is an important intermediate for the synthesis of several MAP-type ligands.[2,3]

To date two other general routes towards enantiopure MAP ligands have been disclosed starting from 2,2'-dibromo-1,1'-bisnaphthalene **8**[4] and NOBIN (Scheme 5.2).[5,6] A common feature in both routes is that the phosphine or phosphine oxide parts are the last groups to be incorporated. The conversion of dibromide **8** to amine **9** involves several steps including a resolution. A lithiation-halogen exchange protocol was used to obtain MAP-type ligands **1** from **9**.

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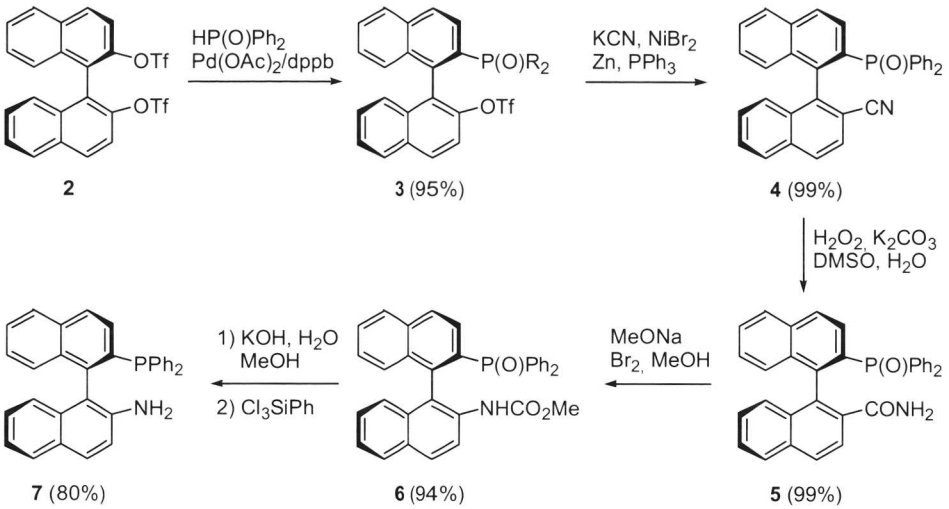
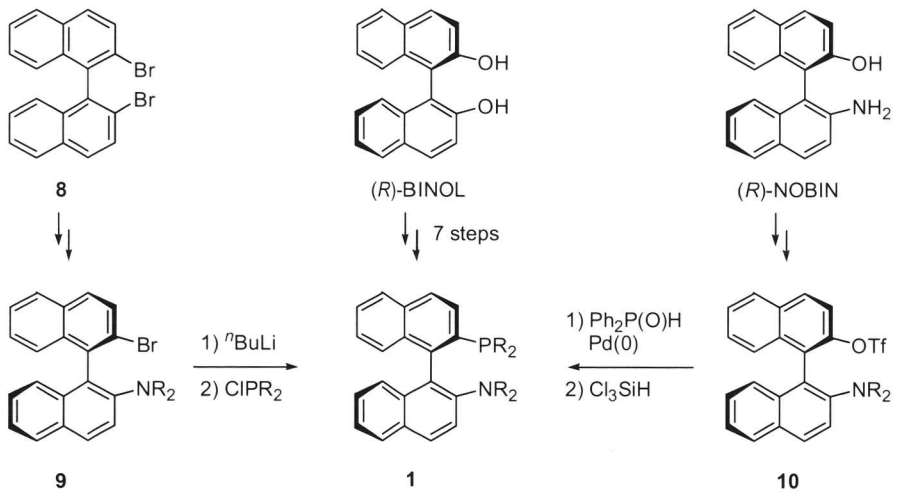
* Part of this Chapter was published in: P.N.M. Botman, O. David, A. Amore, J. Dinkelaar, M. T. Vlaar, K. Goubitz, J. Fraanje, H. Schenk, H. Hiemstra, J. H. van Maarseveen, *Angew. Chem., Int. Ed.* **2004**, *43*, 3471.



Scheme 5.1 Synthesis of MAP-type ligands from BINOL by Noyori and co-workers.

The transformation of NOBIN to **1** is less laborious and consists of amine functionalization followed by a Pd-catalyzed cross-coupling of the aryltriflate with diphenylphosphine oxide and subsequent reduction of the phospine.

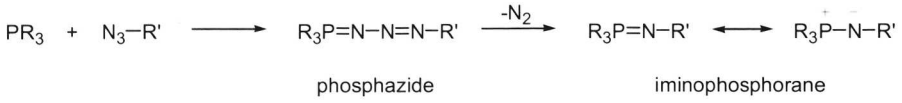


Scheme 5.2 Synthetic strategies towards MAP-type ligands.

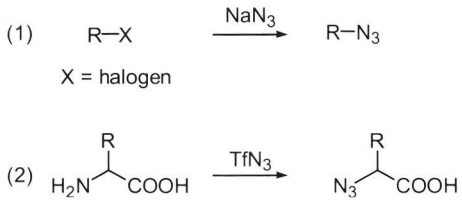
Summerizing, a number of synthetic routes towards MAP-type *P,N*-ligands have been reported, starting from different bisnaphthyl precursors. Strategies beginning with BINOL are advantageous because of the commercial availability of both enantiomers. In this chapter a new synthetic route towards MAP-ligands is presented starting from BINOL, based on the Staudinger reaction.

5.1.2 The Staudinger reaction

Since the discovery of the reaction between tertiary phosphines with organic azides to form iminophosphoranes by Staudinger and Meyer in 1919[7] this imination reaction has been investigated extensively and has found many synthetic applications.[8] The classical Staudinger reaction is a two-step process involving an electrophilic addition of an azide to a phosphorus (III) centre followed by elimination of molecular nitrogen from the intermediate phosphazide giving an iminophosphorane. The generated products often cannot be prepared by any other method.



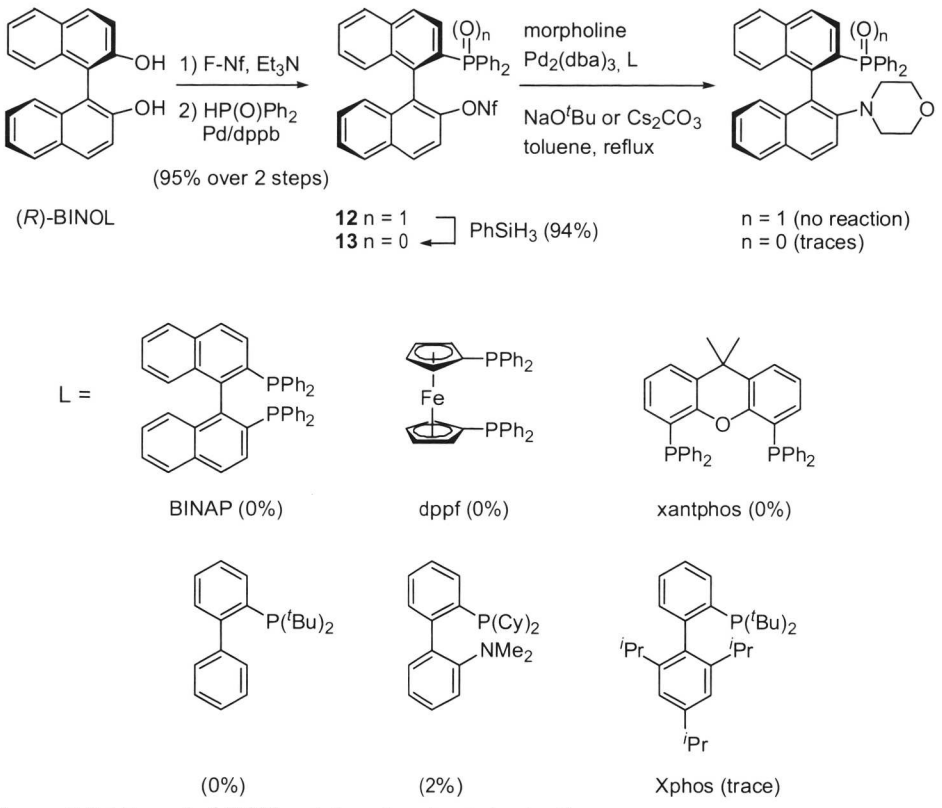
A wide variety of tertiary phosphines, including trialkyl and triaryl phosphines, are employed in the reaction mostly yielding the product quantitatively. However, the accessible triphenylphosphine is commonly used as phosphine source. Among the large number of azides reported to undergo the Staudinger successfully are alkyl, aryl and metal containing organic azides. Two practical ways to synthesise azides are the substitution reaction between organic halogen compounds and the azide anion (1) or an azido-transfer reaction between triflic azide and e.g. an amino acids (2).



The iminophosphoranes can function as precursors for several reactions. The P=N moiety can, for example, be hydrolysed or reduced, but for the application described here advantage is taken of the high nucleophilicity of the iminophosphorane nitrogen. This reactivity was recently demonstated in our group with the work on intramolecular Staudinger ligations towards cyclopeptides.[9]

5.2 Initial Pd-catalyzed amination attemps towards biaryl *P,N*-ligands

For the synthesis of a series of MAP-ligands varying in the amine substituents we set out to start from BINOL. However, we chose to reverse the order of reactions applied as compared to previous routes. Thus, we wished to first introduce the phosphorus moiety starting from BINOL-dinonaflate (**11**), followed by the amine group applying a Buchwald-Hartwig amination (Scheme 5.3).



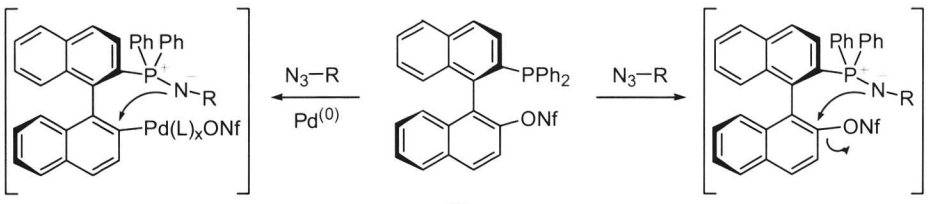
Scheme 5.3 Attempted Pd(0)-catalyzed amine introductions.

The required phosphine nonaflate **13** was prepared in three steps from (*R*)-BINOL based on literature procedures of the triflate analogue in an overall yield of 89%.[10] The feasibility of this approach is suggested by several reports describing the successful introduction of phosphines, phosphine oxides in the triflate analogue of **13** *via* transition metal catalysis.[11] When phosphine nonaflate **13** or phosphine oxide nonaflate **12** were reacted under commonly applied amination conditions using ligands like BINAP, dppf, xantphos and three biphenyl ligands in combination with $Pd_2(dba)_3$, NaO^tBu or Cs_2CO_3 as base and morpholine as the nucleophile, mostly starting material was recovered (Scheme 5.3). Only when Xphos[12] or the *P,N*-ligand (2-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethylamine[5,13] was used in the amination of **13** traces of product could be detected by ^1H NMR.[14]

5.3 The Staudinger approach for the synthesis of *P,N*-ligands

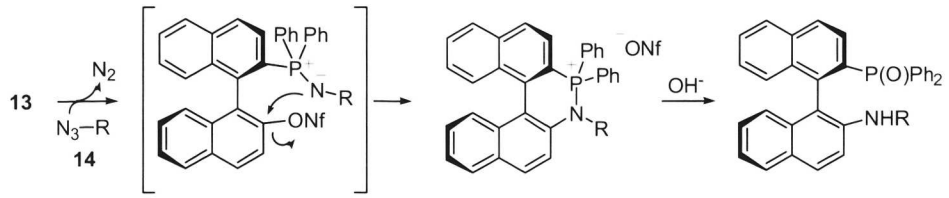
We then envisioned the possibility of amine introduction into phosphine **13** by a Staudinger reaction with alkyl or aryl azides (Scheme 5.4). In this approach advantage is

taken from the nucleophilicity of the iminophosphorane nitrogen atom generated *in situ*. The amination could be Pd-catalyzed in principle. An intramolecular amination of the intermediate aryl-Pd complex, obtained after oxidative addition of a Pd(0) species into the aryl-nonaflate bond, would lead to the desired *P,N*-ligands. The highly nucleophilic iminophosphorane nitrogen could also directly substitute the nonaflate moiety in an intramolecular aromatic substitution reaction. Initial attempts showed that reaction of phosphine **13** with octyl azide in toluene for 20 hours at 115 °C with a catalytic amount of $Pd(OAc)_2$ and (2-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethylamine (Scheme 5.3) yielded a variety of products. However, when the $Pd(OAc)_2$ and the ligand were omitted from the mixture, only one product could be detected on ^{31}P NMR.



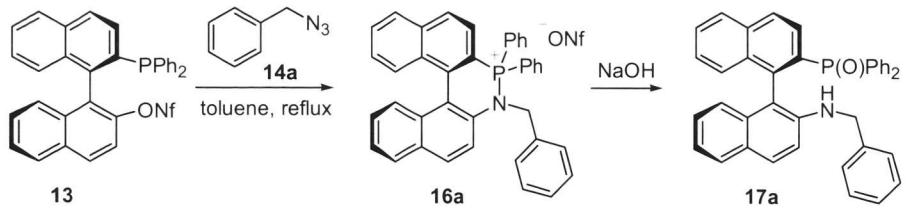
Scheme 5.4 Intramolecular aminations towars *P,N*-ligands.

Indeed, further investigations proved that treatment of phosphine **13** with an alkyl azide generates iminophosphorane **15.** Substitution of the nonaflate by the nitrogen atom yields aminophosphonium salt **16** which provides MAP(O)-type compound **17** after basic hydrolysis (Scheme 5.5).



Scheme 5.5 The Staudinger approach towards MAP(O)-type ligands.

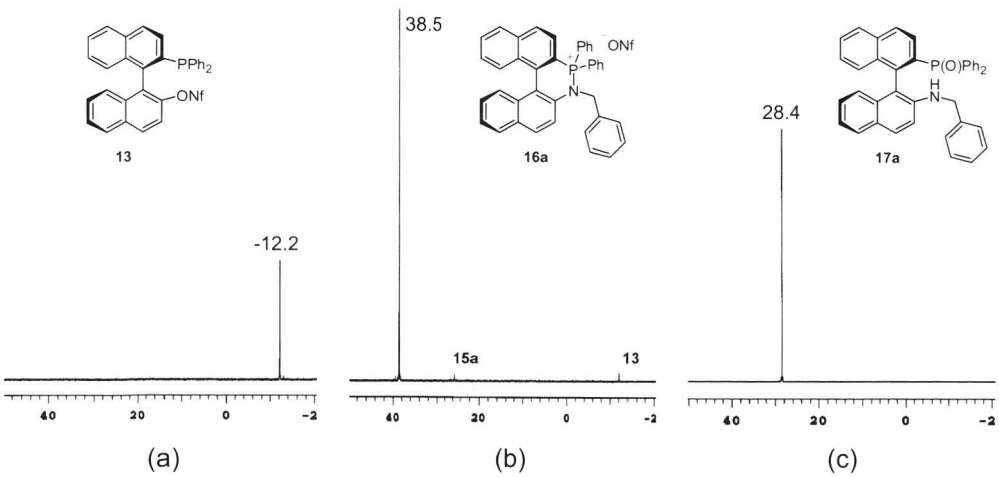
The application of iminophosphorane nitrogen atoms as nucleophiles in such an unprecedented intramolecular S_NAr reaction gives efficient access to MAP-ligands. This strategy is especially attractive because after the reaction the phosphorus atom is an essential element in the product instead of waste as in usual Staudinger approaches. In addition, as compared to the current synthetic routes to MAP-type *P,N*-ligands, the required number of synthetic steps are reduced significantly. Finally, this new method gives access to analogues which to date can only be prepared with great difficulty or not at all.



Scheme 5.6 Reaction between monophosphine **13** and benzyl azide.

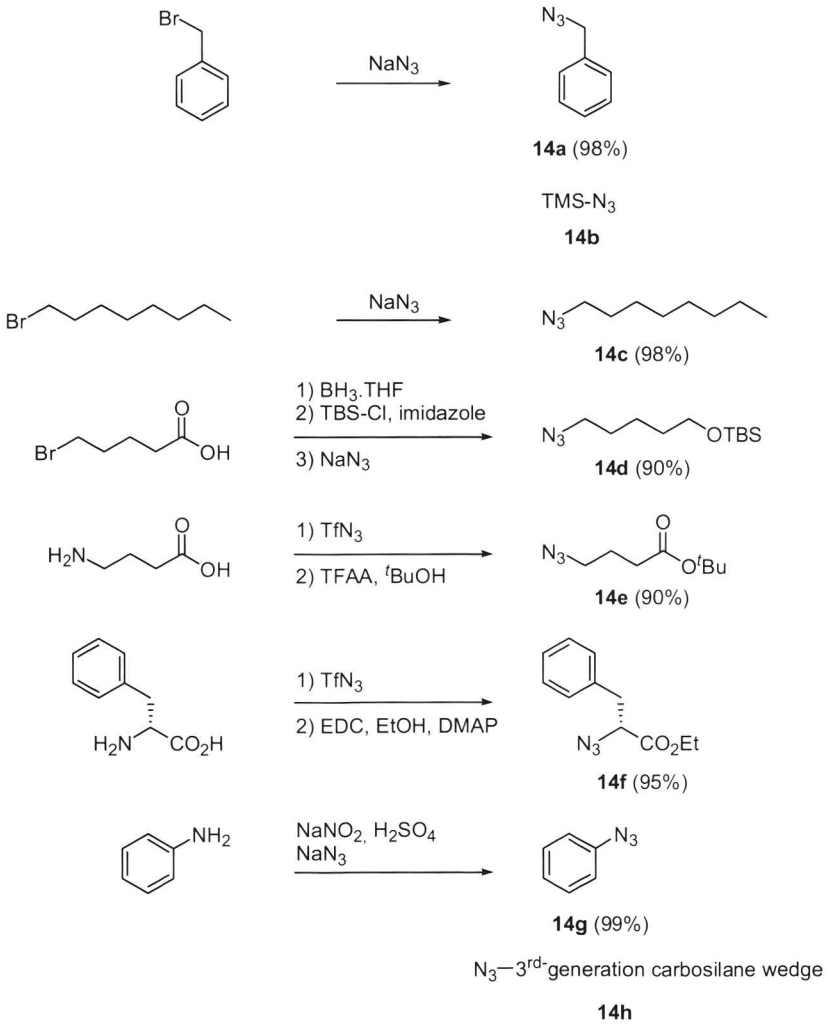
In order to optimize the Staudinger approach to *P,N*-ligands, equimolar amounts of phosphino nonaflate **13** and benzyl azide **14a** were heated at reflux in toluene (Scheme 5.6). The progess of the reaction was monitored by ^{31}P NMR (Figure 5.1).[15] After 20 hours the starting material **13** (Figure 5.1a) was nearly quantitatively converted into the anticipated aminophosphonium salt **16a** and a small amount of iminophosphorane **15a** (Figure 5.1b). After optimization the crude reaction mixture contained solely the desired product. Evaporation of the solvent yielded **16a** as an air-stable colorless oil. Hydrolysis of the *P,N*-bond was accomplished by refluxing the salt in a mixture of EtOH, THF and aqueous 0.1M NaOH (1/1/1, v/v/v) and after work-up **17a** was isolated in 99% yield (Figure 5.1c).

Figure 5.1 ^{31}P NMR spectra of (a) starting phosphine **13**, (b) crude reaction mixture containing mainly phosphonium salt **16a**, (c) MAP(O)-type product **17a**.



To show the broad synthetic scope of this new reaction to 2-diphenylphosphinoxo-2-amino 1,1'-binaphthyls **17** we reacted phosphino nonaflate **13** with a diverse set of azides **14a-h** (Scheme 5.7). Azides **14a** and **14c** were synthesized *via* nucleophilic substitution reactions of NaN_3 with benzyl bromide and octyl bromide,[16] respectively. Trimethylsilyl azide **14b** was commercially available. TBS-protected 5-azido-pentanol **14d** was obtained from 5-bromovaleric acid in three step sequence involving a borane mediated acid reduction,

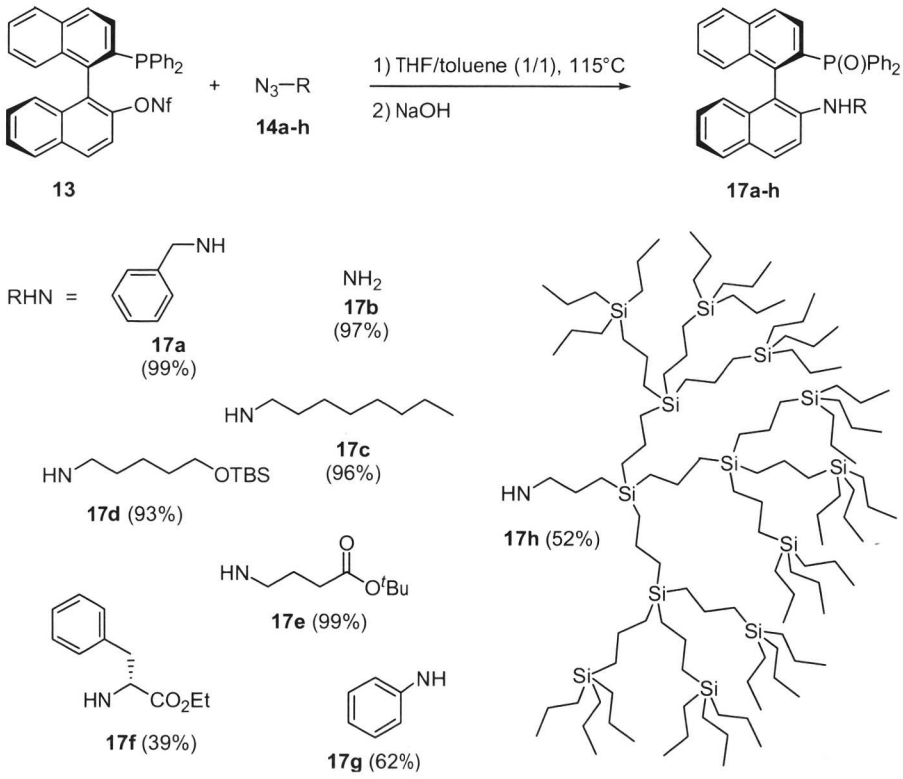
TBSCl protection of the hydroxyl and bromine substitution with NaN_3.[17] 4-Bromobutyric acid and (*R*)-phenylalanine were reacted in a diazo-transfer reaction with *in situ* generated TfN_3[18] providing, after protection of the carboxylic acids the corresponding azido carboxylic esters **14e**[19] and **14f**. Phenyl azide **14g** was synthesized from aniline applying a diazotation reaction with $NaNO_2$, H_2SO_4 and NaN_3. Azido functionalized dendritic carbosilane wedge **14h**, finally, was obtained *via* a substitution reaction of the iodide functionalized wedge by using NaN_3 (see Chapter 4, Scheme 4.5).[20]



Scheme 5.7 Synthesis of azides **14a-h**.

Introduction of a primary amine was accomplished by starting from trimethylsilyl azide **14b** (Scheme 5.8). Stirring **13** with 20 equivalents of TMS-azide for 48 hours in refluxing

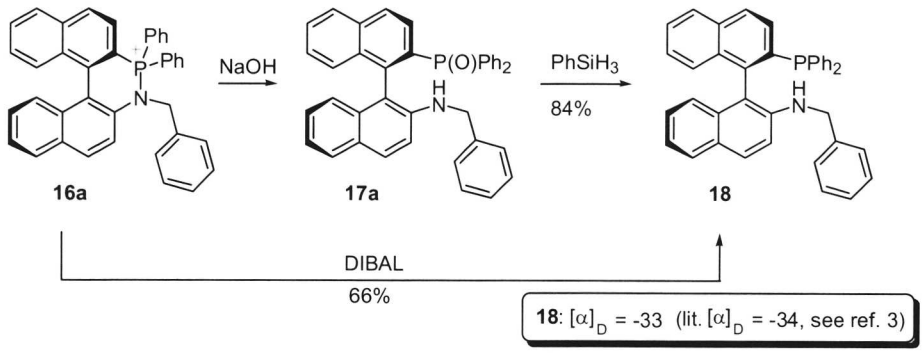
toluene in a sealed tube provided **17b** in an isolated yield of 35% after hydrolysis. The yield could be improved to nearly quantitative by performing the reaction in a mixture of THF/toluene (1/1, v/v), due to an acceleration of the iminophosphorane formation. The choice for THF as co-solvent was based on the results reported by Hemming *et al.* and Peterson Jr. *et al.*[21] concerning the reaction between PPh_3 and TMS-N_3. The Staudinger reaction proceeded at room temperature in THF, while the reaction needed elevated temperatures when performed in toluene or mesitylene. Hence, by applying this new methodology (adding 12 equivalents of TMS-azide in three portions) des-methyl MAP(O) **17b** can be synthesized in 4 steps from BINOL in an overall yield of 87%, which is comparable to the known synthetic route (86% over 6 steps, see Scheme 5.1). Comparison of the optical rotation of **17b** with literature data revealed that no racemization had taken place during the reaction sequence ($[\alpha]_D^{21}$ = -205 (c = 0.12, $CHCl_3$), lit: $[\alpha]_D^{24}$ = -199 (c = 1.0, $CHCl_3$).[3] Also, we could not observe any change in the optical rotation after heating of **17c**, bearing the small NH_2 group and thus most prone to racemization, for 10 minutes at 300 °C. Prolonged heating led to decomposition of the product. These experiments showed that racemization under the normal reaction conditions is very unlikely to occur.



Scheme 5.8 Synthesis of a variety of *P,N*-ligands.

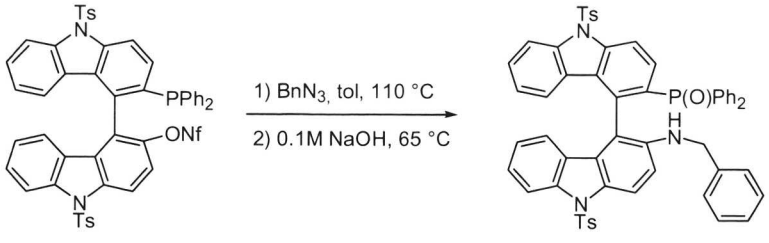
Other alkyl azides employing alkyl, ether or ester functionalities all reacted readily providing **17c**, **17d**, and **17e** in yields of 96%, 93%, and 99%, respectively (Scheme 5.8). Treatment of **13** with α-azido ester **14f** gave **17f** in a 39% yield. During the reaction partial racemization occurred providing 9% of the epimer.

Despite the lower nucleophilicity of the intermediate *N,N*-diaryl iminophosphorane nitrogen atom, phenyl azide **14g** reacted smoothly to give **17g** in a yield of 62%, underscoring the versatility of this new approach. The very bulky third-generation carbosilane dendritic wedge featuring an azide in the focal point could be introduced from **14h** to give **17h** in a yield of 52%.



Scheme 5.9 Direct reduction of aminophosphonium salts.

For future applications of **17a-h** in catalysis, reduction to the corresponding phosphine is required. As an example **17a** was treated with phenylsilane at 114 °C for 17 hours providing **18** in a yield of 84% (Scheme 5.9). A more convenient method would be direct hydride promoted cleavage of the *P,N*-bond of the intermediate phosphonium salts **16**. Indeed, after treatment of **16a** with DIBAL-H clean reduction occurred to **18** in 66% yield.

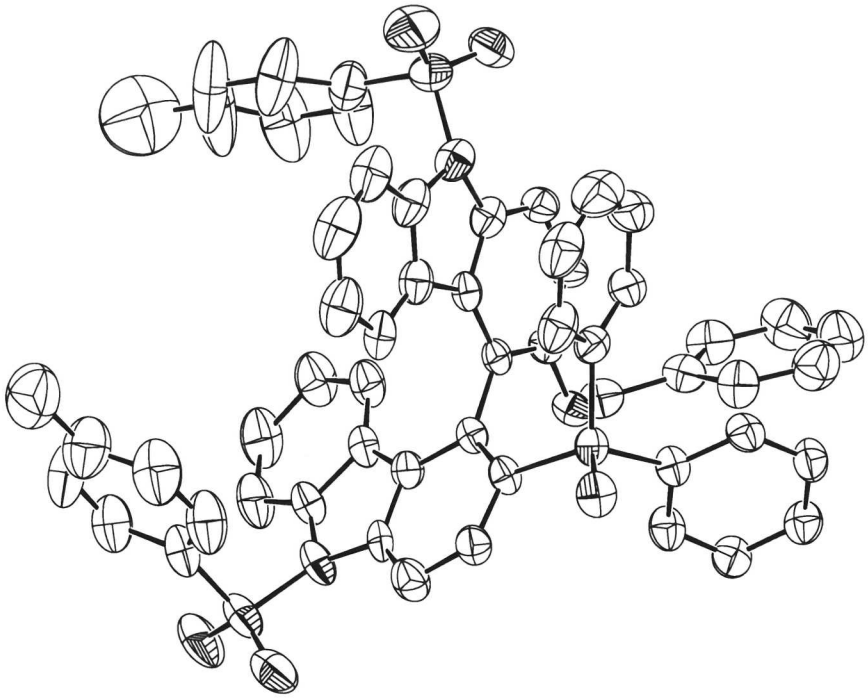


19 **20** (94%)

Scheme 5.10 BICOL derived *P,N*-ligands.

Finally, reaction of racemic BICOL derived phosphino-nonaflate **19** (see Chapter 3, Scheme 3.2) with benzyl azide **14a** followed by hydroxide treatment gave phosphine oxide **20** in an excellent yield of 94% (Scheme 5.10). The structure of racemic **20** was secured by X-ray analysis (Figure 5.2).

Figure 5.2. ORTEP drawing of the crystal structure of *P,N*-ligand **20**.



5.4 Conclusions

In conclusion, we have shown that the synthetic potential of the 85-year old Staudinger reaction between phosphines and azides is still far from exhausted. The Staudinger reaction between phosphine-nonaflate biaryls and azides provides, *via* an unprecendented S_NAr reaction, a wide range of MAP(O)-type ligands in high yields in only four steps from BINOL in enantiopure form.

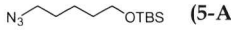
5.5 Acknowledgements

Dr. O. David is gratefully indebted for the skilful completion of the research described in this chapter. A. Amore is acknowledged for the generous gift of dendritic azide **14h**. J. Dinkelaar and M. Vlaar are kindly acknowledged for their contributions to this chapter. J. Fraanje and K. Goubitz are thanked for the crystal structure determination.

5.6 Experimental section

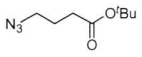
General remarks

For experimental details see section 2.6 and 3.8. All NMR spectra were determined in $CDCl_3$ (unless states otherwise). ^{19}F NMR spectra were recorded on a Varian Inova-500 (470.4 MHz). Chemical shifts are given in ppm downfield from $CFCl_3$.



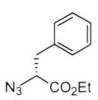
(5-Azido-pentyloxy)-*tert*-butyl-dimethyl-silane (14d)

To a solution of NaN_3 (83 mg, 1.28 mmol) in DMSO (2 mL) was added 5-bromo-pentyloxy-TBS (0.30 g, 1.07 mmol). The solution was stirred for 65 h at room temperature. The mixture was diluted by adding Et_2O (40 mL) and washed with H_2O (4 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (pentane:Et_2O = 10:0→10:1) afforded **14d** as a colourless oil (0.25 g, 1.03 mmol, 96%). ^1H NMR (400 MHz): δ = 3.61 (t, *J* = 6.4, 2H, OCH_2), 3.27 (t, *J* = 6.9, 2H, N_3CH_2), 1.51-1.66 (m, 4H), 1.40-1.46 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz): δ = 62.9, 51.4, 32.3, 28.7, 25.9, 23.1, 18.3, -5.3. IR: υ 2930, 2858, 2095. HRMS (EI): calcd for $C_7H_{16}N_3Osi$ (*M*-^{t}Bu): 186.1063, found: 186.1060.



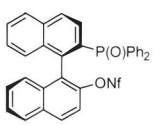
4-Azido-butyric acid *tert*-butyl ester (14e)

To a solution of 4-azido-butyric acid (0.30 g, 2.33 mmol) in 3.5 mL THF at -40 °C was added drop wise TFAA (0.70 mL, 5.0 mmol). After 30 min. a solution of *tert*-butanol (3.0 mL, 32 mmol) in THF (0.6 mL) was added and the reaction mixture was stirred for 17 h at room temperature. The reaction was quenched by pouring the solution into an aqueous saturated $NaHCO_3$ solution (50 mL). The mixture was extracted with Et_2O (2 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (pentane:Et_2O = 20:1→10:1) afforded **14e** as a colourless oil (0.42 g, 2.28 mmol, 98%). ^1H NMR (400 MHz): δ = 3.33 (t, *J* = 6.7, 2H, N_3CH_2), 2.31 (t, *J* = 7.2, 2H, $C(O)CH_2$), 1,86 (m, 2H, $N_3CH_2CH_2$), 1,45 (s, 9H, $OC(CH_3)_3$). ^{13}C NMR (125 MHz): δ = 171.9, 80.5, 50.6, 32.3, 28.0, 24.3. IR: υ 2981, 2101, 1731.



2-Azido-3-phenyl-propionic acid ethyl ester (14f)

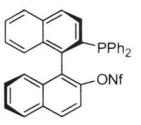
To a solution of (*R*)-2-azido-3-phenyl-propionic acid (710 mg, 3.71 mmol) in CH_2Cl_2 (90 mL) was added DMAP (48 mg, 0.39 mmol) and ethanol (1mL). After stirring for 5 minutes at room temperature EDC (1.42 g, 7.42 mmol) was added and the orange suspension was stirred for another 19 h. The mixture was diluted by adding CH_2Cl_2 (100 mL) and washed with H_2O (2 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford **14f** as a yellow oil (0.781 g, 3.56 mmol, 96%), which was spectroscopically identical as described in the literature.



(*R*)-1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 2`-(diphenylphosphinoyl)-[1,1`]binaphthalenyl-2-yl ester (12)

To a solution of (*R*)-BINOL (4.61 g, 16.1 mmol) in acetonitrile (160 mL) was added Et_3N (9.0 mL, 64.4 mmol) and F-$SO_2C_4F_9$ (7.2 mL, 40.3 mmol). After stirring the mixture for 1 h, EtOAc (200 mL) was added and the organic phase was washed twice with H_2O (100 mL) and an aqueous saturated Na_2HSO_3 solution (100 mL). The organic layer was dried over Na_2SO_4

and concentrated *in vacuo*. The crude dinonaflate (**11**) was dissolved in DMSO (47 mL) and $Pd(OAc)_2$ (0.36 g, 1.61 mmol), dppb (0.69 g, 1.61 mmol), diphenylphosphine oxide (4.88 g, 24.2 mmol) and DIPEA (11.2 mL, 64.4 mmol) were added and the solution was stirred for 4 h at 115 °C. After cooling the mixture to room temperature EtOAc (400 mL) was added and the organic phase was washed four times with a mixture of H_2O (100 mL), aqueous saturated $NaHCO_3$ solution (150 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (PE:EtOAc = 1:1→1:2) afforded **12** as an off-white foam (11.5 g, 15.3 mmol, 95%). ^1H NMR (400 MHz): δ = 8.00 (dd, *J* = 8.6, 2.1, 1H), 7.93 (d, *J* = 8.2, 1H), 7.90 (d, *J* = 9.1, 1H), 7.83 (d, *J* = 8.2, 1H), 7.65 (d, *J* = 8.6, 1H), 7.62 (d, *J* = 8.6, 1H), 7.57 (t, *J* = 7.1, 1H), 7.35-7.50 (m, 9H), 7.35 (dt, *J* = 8.4, 1.0, 1H), 7.23-7.27 (m, 4H), 7.17 (d, *J* = 8.6, 1H), 7.13 (dt, *J* = 8.3, 1.0, 1H), 6.97 (d, *J* = 8.4, 1H). ^{31}P NMR (121.5 MHz): δ = 29.1. IR: υ 3059, 1420, 1239, 1204. HRMS (FAB+): calcd for $C_{36}H_{23}F_9O_4PS$ (M+H$^+$): 753.0911, found: 753.0903. $[\alpha]_D$ = +34 (c = 1.05, $CHCl_3$).

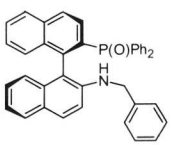


(*R*)-1,1,2,2,3,3,4,4,4-Nonafluoro-butane-1-sulfonic acid 2`-diphenylphosphanyl-[1,1`]binaphthalenyl-2-yl ester (13)

A solution of **12** (4.00 g, 5.32 mmol) in phenylsilane (32 mL) was stirred at 114 °C for 17 h. After addition of EtOAc (40 mL) the mixture was concentrated *in vacuo*. Purification by column chromatography (PE:EtOAc = 25:1→10:1) afforded **13** as an off-white foam (3.68 g, 5.00 mmol, 94%). ^1H NMR (400 MHz): δ = 8.09 (d, *J* = 9.0, 1H), 7.91-7.96 (m, 3H), 7.58 (d, *J* = 9.0, 1H), 7.52 (t, *J* = 7.0, 1H), 7.44-7.48 (m, 2H), 7.25-7.32 (m, 6H), 7.18-7.21 (m, 2H), 7.07-7.13 (m, 3H), 7.00-7.03 (m, 2H), 6.92 (d, *J* = 8.5, 1H). δ = ^{31}P NMR (121.5 MHz): δ = -12.2. ^{19}F NMR: δ = -80.9, -110.5, -121.3, -126.2. IR: υ 3054, 1421, 1239, 1204. HRMS (FAB+): calcd for $C_{36}H_{23}F_9O_3PS$ (M+H$^+$): 737.0962, found: 737.0954. $[\alpha]_D$ = -5.6 (c = 1.00, $CHCl_3$).

General procedure for the Staudinger reaction:

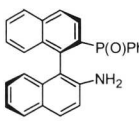
Phosphine **13** was added to a solution of an azide (1.2 equiv.) in toluene (2 mL). The reaction was stirred at 115 °C until all the phosphine was consumed (the reaction was monitored by ^{31}P NMR of an aliquot in C_6D_6). The mixture was cooled to room temperature and concentrated *in vacuo*. The remaining phosphonium salt was stirred for 2 h at 65 °C in a mixture of THF (2 mL), EtOH (2 mL) and aqueous 0.1N NaOH (2 mL). After cooling the mixture, Et_2O (20 mL) was added and the organic phase was washed with H_2O (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification was performed by column chromatography.



(*R*)-Benzyl-[2`-(diphenyl-phosphinoyl)-[1,1`]binaphthalenyl-2-yl-amine (17a)

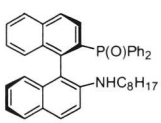
Phosphine **13** (150 mg, 0.20 mmol) was reacted with azidomethyl-benzene **14a** (33 mg, 0.24 mmol) according to the general procedure. After 17 h the reaction mixture was concentrated *in vacuo* yielding phosphonium salt **16a** as a yellow oil: ^1H NMR (500 MHz): δ = 8.25 (m, 1H), 8.15 (d, *J* = 8.5, 1H), 7.89-7.96 (m, 5H), 7.77-7.80 (m, 2H), 7.66-7.70 (m, 2H), 7.51-7.62 (m, 7H), 7.45 (t, *J* = 7.5, 1H), 7.39 (t, *J* = 7.5, 1H), 7.26 (m, 1H), 7.19 (t, *J* = 7.0, 1H), 7.07-7.12 (m, 5H), 5.79 (dd, *J* = 17.5, 5.0, 1H), 4.74 (dd, *J* = 17.5, 11.0, 1H). ^{31}P NMR (202.4 MHz): δ = 38.5. ^{19}F NMR: δ = -80.9, -114.5, -121.4, -125.8. HRMS (FAB+): calcd for $C_{39}H_{29}NP$ (M-ONf): 542.2038, found: 542.2050. $[\alpha]_D$ = -205 (c = 1.07, $CHCl_3$). After hydrolysis of the intermediate and

purification by column chromatography (Et_2O:pentane = 4:1→15:1) afforded **17a** (0.11 g, 0.20 mmol, 99%) as a yellow foam. ^1H NMR (500 MHz): δ = 8.02 (d, *J* = 8.5, 1H), 7.96 (d, *J* = 8.0, 1H), 7.90 (dd, *J* = 11.5, 9.0, 1H), 7.73 (d, *J* = 11.0, 1H), 7.72 (d, *J* = 11.5, 1H), 7.58 (t, *J* = 6.5, 1H), 7.42-7.50 (m, 3H), 7.25-7.36 (m, 10H), 7.22 (m, 1H), 7.03-7.08 (m, 2H), 6.97 (t, *J* = 6.5, 1H), 6.78-6.88 (m, 2H), 6.86 (d, *J* = 9.0, 1H), 6.60 (d, *J* = 8.5, 1H), 4.42 (s, 2H), 4.19 (br s, 1H). ^{13}C NMR (125 MHz, non-aromatic only): δ = 48.2. ^{31}P NMR (202.4 MHz): δ = 28.4. HRMS (FAB+): calcd for $C_{39}H_{31}NOP$ (*M*+H$^+$): 560.2143, found: 560.2139. $[\alpha]_D$ = -172 (c = 0.47, $CHCl_3$).



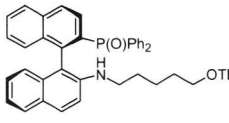
(*R*)-2`-(Diphenyl-phosphinoyl)-[1,1`]binaphthalenyl-2-ylamine (17b)

Phosphine **13** (120 mg, 0.16 mmol) was reacted with TMS-azide **14b** (75 mg, 0.65 mmol) according to the general procedure. After 12 h the reaction mixture was recharged with 75 mg of TMS-azide, and this operation was repeated once more after an additional 12 h. The reaction mixture was concentrated *in vacuo* yielding phosphonium salt **16b** as a yellow oil: ^{31}P NMR (202.4 MHz): δ = 37.3. Hydrolysis of the intermediate and purification by column chromatography (EtOAc:PE = 2:1→3:1) afforded **17b** (74 mg, 0.158 mmol, 97%) as a yellow foam. ^1H NMR (400 MHz): δ = 8.00 (dd, *J* = 8.5, 1.5, 1H), 7.94 (d, *J* = 8.5, 1H), 7.86 (dd, *J* = 11.5, 8.5, 1H), 7.66 (d, *J* = 11.5, 1H), 7.65 (d, *J* = 11.5, 1H), 7.56 (t, *J* = 7.0, 1H), 7.51 (d, *J* = 9.0, 1H), 7.46 (d, *J* = 8.0, 1H), 7.40 (t, *J* = 7.0, 1H), 7.21-7.33 (m, 6H), 7.00-7.05 (m, 2H), 6.86-6.96 (m, 4H), 6.54 (d, *J* = 8.5, 1H), 3.90 (br s, 2H). ^{31}P NMR (202.4 MHz): δ = 27.6. IR: υ 1625, 1175, 1118. HRMS (FAB+): calcd for $C_{32}H_{25}NOP$ (*M*+H$^+$): 470.1674, found: 470.1651. $[\alpha]_D$ = -205 (c = 0.12, $CHCl_3$).



(*R*)-[2`(Diphenyl-phosphinoyl)-[1,1`]binaphthalenyl-2-yl]-octyl-amine (17c)

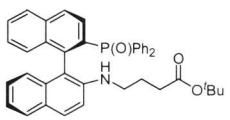
Phosphine **13** (150 mg, 0.20 mmol) was reacted with 1-azido-octane **14c** (38 mg, 0.24 mmol) according to the general procedure. After 17 h the reaction mixture was concentrated *in vacuo* yielding phosphonium salt **16c** as a yellow oil: ^{31}P NMR (202.4 MHz): δ = 37.3. Hydrolysis of the intermediate and purification by column chromatography (Et_2O:pentane = 1:1→4:1) afforded **17c** (0.11 g, 0.19 mmol, 96%) as an off-white foam. ^1H NMR (500 MHz): δ = 8.02 (dd, *J* = 8.5, 2.0, 1H), 7.90-7.94 (m, 2H), 7.61-7.64 (m, 2H), 7.56 (t, *J* = 7.3, 1H), 7.40-7.52 (m, 2H), 7.39 (t, *J* = 7.0, 1H), 7.24-7.31 (m, 6H), 7.08 (t, *J* = 7.0, 1H), 7.02 (t, *J* = 7.5, 1H), 6.96 (t, *J* = 7.0, 1H), 6.89-6.93 (m, 2H), 6.85 (d, *J* = 8.5, 1H), 6.58 (d, *J* = 8.5, 1H), 3.55 (br s, 1H), 3.04-3.14 (m, 2H), 1.42-1.49 (m, 2H), 1.20-1.33 (m, 10H), 0.90 (t, *J* = 7.0, 3H). ^{13}C NMR (125 MHz, non-aromatic only): δ = 44.2, 31.7, 29.7, 29.2, 29.1, 26.9, 22.6, 14.0. ^{31}P NMR (202.4 MHz): δ = 28.8. IR: υ 3400, 3054, 2924, 2853, 1619, 1598. HRMS (FAB+): calcd for $C_{40}H_{41}NOP$ (*M*+H$^+$): 582.2926, found: 582.2915. $[\alpha]_D$ = -139 (c = 0.36, $CHCl_3$).



(*R*)-[5-(*tert*-Butyl-dimethyl-silanyloxy)-pentyl]-[2`-(diphenyl-phosphinoyl)-[1,1`]binaphthalenyl-2-yl]-amine (17d)

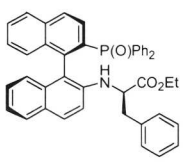
Phosphine **13** (150 mg, 0.20 mmol) was reacted with (5-azido-pentyloxy)-*tert*-butyl-dimethyl-silane **14d** (60 mg, 0.24 mmol) according to the general procedure. After 17 h the reaction mixture was concentrated *in vacuo* yielding phosphonium salt **16d** as a yellow oil: ^{31}P NMR (202.4 MHz): δ = 37.4. Hydrolysis of the intermediate and purification by column chromatography (Et_2O:pentane = 2:1→8:1) afforded **17d** (0.13 g, 0.19 mmol, 93%) as an off-

white foam. ^{1}H NMR (500 MHz): δ = 8.02 (dd, *J* = 8.5, 2.0, 1H), 7.89-7.97 (m, 2H), 7.62-7.66 (m, 2H), 7.58 (t, *J* = 7.5, 1H), 7.47-7.52 (m, 2H), 7.41 (t, *J* = 7.5, 1H), 7.22-7.33 (m, 6H), 7.01-7.08 (m, 2H), 6.96 (t, *J* = 7.0, 1H), 6.85-6.91 (m, 3H), 6.56 (d, *J* = 8.5, 1H), 3.57 (br s, 1H), 3.54 (t, *J* = 6.5, 2H), 3.12 (m, 2H), 1.43-1.50 (m, 4H), 1.23-1.30 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (125 MHz, non-aromatic only): δ = 63.0, 44.2, 32.5, 29.6, 26.9, 23.2, 18.2 -5.3. ^{31}P NMR (202.4 MHz): δ = 28.5. IR: υ 3325, 2946, 1631, 1489. HRMS (FAB+): calcd for $C_{43}H_{49}NO_2PSi$ (*M*+H$^+$): 670.3270, found: 670.3267. $[\alpha]_D$ = -130 (c = 0.53, $CHCl_3$).



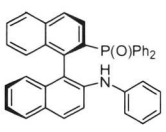
(*R*)-4-[2`-(Diphenyl-phosphinoyl)-[1,1`]binaphthalenyl-2-ylamino]-butyric acid *tert*-butyl ester (17e)

Phosphine **13** (100 mg, 0.14 mmol) was reacted with 4-azido-butyric acid *tert*-butyl ester **14e** (33 mg, 0.18 mmol) according to the general procedure. After 17 h the reaction mixture was concentrated *in vacuo* yielding phosphonium salt **16e** as a yellow oil: ^{31}P-NMR (202.4 MHz): δ = 37.8. Hydrolysis of the intermediate (using aqueous 0.1N $NaHCO_3$ instead of aqueous 0.1N NaOH) and purification by column chromatography (EtOAc:PE = 2:1→3:1) afforded **17e** (82 mg, 0.13 mmol, 99%) as a yellow foam. ^{1}H NMR (500 MHz): δ = 8.00 (dd, *J* = 8.5, 1.5, 1H), 7.94 (d, *J* = 8.5, 1H), 7.86 (dd, *J* = 11.5, 8.5, 1H), 7.66 (d, *J* = 11.5, 1H), 7.65 (d, *J* = 11.5, 1H), 7.56 (t, *J* = 7.0, 1H), 7.51 (d, *J* = 9.0, 1H), 7.46 (d, *J* = 8.0, 1H), 7.40 (t, *J* = 7.0, 1H), 7.21-7.33 (m, 6H), 7.00-7.05 (m, 2H), 6.86-6.96 (m, 4H), 6.54 (d, *J* = 8.5, 1H), 3.70 (br s, 1H), 3.17 (m, 2H), 2.19 (t, *J* = 7.0, 2H), 1.77 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, non-aromatic only): δ = 172.6, 80.1, 43.5, 32.8, 28.0, 25.2. ^{31}P NMR (202.4 MHz): δ = 28.5. IR: υ 3400, 3055, 2925, 2854, 1724, 1619, 1598. HRMS (FAB+): calcd for $C_{40}H_{39}NO_3P$ (*M*+H$^+$): 612.2668, found: 612.2671. $[\alpha]_D$ = -112 (c = 0.52, $CHCl_3$).



(*R*)-2-[2`-(Diphenyl-phosphinoyl)-[1,1`]binaphthalenyl-2-ylamino]-3-phenyl-propionic acid ethyl ester (17f)

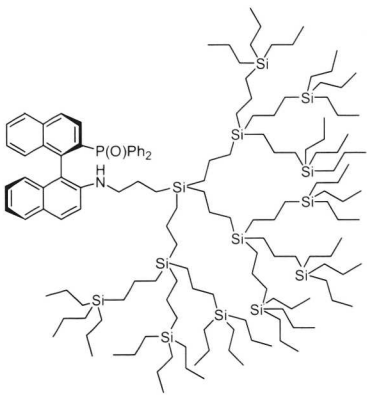
Phosphine **13** (188 mg, 0.25 mmol) was reacted with (*R*)-2-azido-3-phenyl-propionic acid ethyl ester **14f** (84 mg, 0.38 mmol) according to the general procedure. After 17 h the reaction mixture was concentrated *in vacuo* yielding phosphonium salt **16f** as an yellow oil: ^{31}P NMR (202.4 MHz): δ = 38.4. Hydrolysis of the intermediate (using water instead of aqueous 0.1N NaOH) and purification by column chromatography (EtOAc:PE = 3:2) afforded **17f** (64 mg, 0.09 mmol, 39%) as an off white foam. ^{1}H NMR (400 MHz): δ = 8.00 (dd, *J* = 8.6, 1.7, 1H), 7.93-7.98 (m, 2H), 7.54-7.56 (m, 1H), 7.59 (d, *J* = 7.9, 1H), 7.41 (d, *J* = 8.9, 1H), 7.27-7.34 (m, 5H), 7.19-7.21 (m, 3H), 7.09-7.13 (m, 5H), 6.99-7.08 (m, 4H), 6.90-6.92 (m, 2H), 6.68 (d, *J* = 8.3, 1H), 6.47 (d, *J* = 8.9, 1H), 5.4 (br s, 1H), 4.12-4.15 (m, 1H), 3.80-3.93 (m, 2H), 2.89-2.99 (m, 2H), 0.94 (t, *J* = 7.1, 3H). ^{13}C NMR (125 MHz, non-aromatic only): δ = 173.1, 60.7, 58.1, 39.2, 13.9. ^{31}P NMR (202.4 MHz): δ = 27.7. IR: υ 3410, 3140, 2930, 1729, 1620, 1598, 1496, 1437. HRMS (EI): calcd for $C_{43}H_{36}NO_3P$ (*M*$^+$): 645.2433, found: 645.2437. $[\alpha]_D$ = -30.5 (c = 1.07).



(*R*)-[2`-(Diphenyl-phosphinoyl)-[1,1`]binaphthalenyl-2-yl]-phenyl-amine (17g)

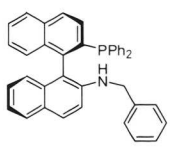
Phosphine **13** (105 mg, 0.14 mmol) was reacted with azido-benzene **14g** (54 mg, 0.19 mmol) according to the general procedure. After 72 h the reaction mixture was concentrated *in vacuo* yielding phosphonium salt **16g** as a yellow oil: ^{31}P NMR (202.4 MHz): δ = 35.6. Hydrolysis of the intermediate and purification by column chromatography

(EtOAc:PE = 3:7) afforded **17g** (48 mg, 0.09 mmol, 62%) as an off white foam. ^{1}H NMR (400 MHz): δ = 7.91-7.95 (m, 3H), 7.88 (d, *J* = 8.2, 1H), 7.65 (d, *J* = 8.6, 1H), 7.62 (d, *J* = 8.6, 1H), 7.46-7.56 (m, 7H), 7.23-7.30 (m, 3H), 7.10-7.15 (m, 3H), 6.94-6.97 (m, 3H), 6.80-6.92 (m, 1H), 6.71-6.76 (m, 3H), 6.53 (d, *J* = 8.4, 1H). ^{31}P NMR (202.4 MHz): δ = 29.3. IR: υ 3395, 3049, 2936, 2852. HRMS (FAB+): calcd for $C_{38}H_{29}NOP$ (*M*+H$^+$): 546.1987, found: 546.1984. $[\alpha]_D$ = -48 (c = 0.53, $CHCl_3$).



3rd-Generation carbosilane dendrimer attached to the (*R*)-bisnaphthyl skeleton (17h)

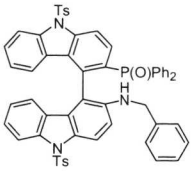
Phosphine **13** (27 mg, 36 µmol) was reacted with azido-3rd-generation carbosilane wedge **14h** (89 mg, 42 µmol) according to the general procedure. After 48 h the reaction mixture was concentrated *in vacuo* yielding phosphonium salt **16h** as a yellow oil: ^{31}P NMR (202.4 MHz): δ = 37.4. Hydrolysis of the intermediate (using 10 mL of THF instead of 2 mL) and purification by column chromatography (with hexane to elute the starting wedge **14h**, followed by CH_2Cl_2) afforded **17h** (56 mg, 22 µmol, 52%) as a yellow oil. ^{1}H NMR (400 MHz): δ = 8.00 (dd, *J* = 8.7, 1.9, 1H), 7.93-7.95 (m, 2H), 7.52-7.57 (m, 3H), 7.20-7.26 (m, 6H), 7.08-7.10 (m, 1H), 6.96-7.00 (m, 1H), 6.92-6.94 (m, 3H), 6.77 (d, *J* = 8.4, 1H), 6.55 (d, *J* = 8.3, 1H), 3.54 (br s, 1H), 3.05 (m, 1H), 2.99 (m, 1H), 1.65 (m, 2H), 1.29-1.34 (m, 78H), 0.92-0.96 (m, 81H), 0.07-0.56 (m, 104H). ^{13}C NMR (125 MHz, non-aromatic only): δ = 32.0, 18.8, 17.6, 15.5. ^{31}P NMR (202.4 MHz): δ = 28.0. MS (MALDI-TOF) calcd for $C_{152}H_{291}NOPSi_{13}$: 2541.944, 2542.948, 2543,947, found: 2541.949, 2542.949, 2543,949. $[\alpha]_D$ = -14.4 (c = 2.21, $CHCl_3$).



(*R*)-Benzyl-[2`-(diphenyl-phosphino)-[1,1`]binaphthalenyl-2-yl-amine (18)

Phosphine **13** (108 mg, 0.15 mmol) was reacted with azidomethyl-benzene **14a** (25 mg, 0.18 mmol) according to the general procedure. After 17 h the reaction mixture was concentrated *in vacuo* yielding phosphonium salt **16a** as a yellow oil: ^{31}P NMR (202.4 MHz): δ = 38.5. The salt was redissolved in THF and DIBAL-H (1.5M in toluene, 416 µL, 0.62 mmol) was added at 0.5 mL of degassed water. The volatiles were evaporated and the residue purified by column chromatography (CH_2Cl_2) to afford **18** (52 mg, 95 µmol, 66%) as a yellow foam. ^{1}H NMR (500 MHz): δ = 7.88-7.90 (m, 2H), 7.82 (d, *J* = 8.9, 1H), 7.71 (d, *J* = 8.9, 1H), 7.53-7.65 (m, 2H), 7.49-7.51 (m, 2H), 7.03-7.47 (m, 17H), 6.97-7.00 (m, 1H), 6.62 (d, *J* = 8.4, 1H), 4.18 (dd, *J* = 15.7, 6.1, 1H), 4.01 (dd, *J* = 15.3, 5.8, 1H), 3.70 (br s, 1H). ^{13}C NMR (125 MHz, non-aromatic only): δ = 47.7. ^{31}P NMR (202.4 MHz): δ = -13.9. IR: υ 1603, 1499, 1345. HRMS (EI): calcd for $C_{39}H_{30}NP$ (*M*$^+$): 543.2116, found: 543.2119. $[\alpha]_D$ = -33 (c = 0.79, $CHCl_3$).

Reduction of phosphine oxide **17a** (11 mg, 14 µmol) according to the procedure used to prepare **13** (see above) produced phosphine **18** (9 mg, 12 µmol, 84%), which was spectroscopically and optically identical with **18** obtained after DIBAL-H reduction of the phosphonium salt as described above.



Benzyl-[3`(diphenyl-phosphinoyl)-9,9`-bis-(toluene-4-sulfonyl)-9H,9`H-[4,4`]bicarbazolyl-3-yl]-amine (20)

Phosphine **19** (150 mg, 0.13 mmol) was reacted with azidomethyl-benzene **14a** (23 mg, 0.17 mmol) according to the general procedure. After 17 h the reaction mixture was concentrated *in vacuo* yielding the phosphonium salt as a yellow oil: ^{31}P NMR (202.4 MHz): δ = 38.8. Hydrolysis of the intermediate and purification by column chromatography (Et_2O:pentane = 2:1→6:1) afforded **20** (0.12 g, 0.125 mmol, 94%) as an off-white powder. ^{1}H NMR (500 MHz): δ = 8.53 (d, *J* = 7.5, 1H), 8.21 (d, *J* = 8.5, 1H), 8.04 (d, *J* = 8.5, 1H), 8.03 (d, *J* = 9.0, 1H), 7.86 (dd, *J* = 12.5, 8.5, 1H), 7.74-7.78 (m, 2H), 7.71 (d, *J* = 8.0, 2H), 7.62 (d, *J* = 8.0, 1H), 7.48 (t, *J* = 7.5, 1H), 7.36-7.39 (m, 2H), 7.24-7.28 (m, 1H), 7.12-7.18 (m, 12H), 6.79-6.82 (m, 2H), 6.53-6.60 (m, 4H), 5.89 (d, *J* = 8.0, 1H), 5.57 (d, *J* = 8.0, 1H), 4.48 (br s, 1H), 4.36 (m, 2H), 2.33 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, non-aromatic only): δ = 48.8, 21.5, 21.5. ^{31}P NMR (202.4 MHz): δ = 27.4. IR: υ 3400, 2922, 1599, 1517. HRMS (FAB+): calcd for $C_{57}H_{45}N_3O_5PS_2$ (*M*+H$^+$): 946.2538, found: 946.2556.

Crystal structure of (±)-20.

Abstract.

$C_{57}H_{44}N_3O_5PS_2$, M_r = 946.1, monoclinic, $P2_1/a$, a = 12.159(2), b = 20.352(5), c = 20.815(12)Å, β = 102.34(2)°, V = 5032(3)Å^3, Z = 4, D_x = 1.25 gcm^{-3}, λ(CuKα) = 1.5418Å, μ(CuKα) = 1.670 mm^{-1}, F(000) = 1976, room temperature, Final R = 0.082 for 5106 observed reflections.

Experimental (For references concerning the X-ray determination: Chapter 3, experimental section).

A crystal with dimensions 0.20 x 0.20 x 0.50 mm approximately was used for data collection. A total of 5472 unique reflections were measured within the range -15≤h≤13, 0≤k≤25, 0≤l≤26. Of these, 5106 were above the significance level of 4σ(F_{obs}) and were treated as observed. The range of (sin θ)/λ was 0.035-0.626Å (3.1≤θ≤74.8°). Two reference reflections ([0 2 0], [1 1 3]) were measured hourly and showed no decrease during the 137 h collecting time. Unit-cell parameters were refined by a least-squares fitting procedure using 23 reflections with 39.84≤2θ≤40.87. Corrections for Lorentz and polarisation effects were applied. Absorption correction was performed with the program PLATON, using Ψ-scans of five reflections, with coefficients in the range 0.851-0.981. The structure was solved by the PATTY option of the DIRDIF-99 program system.

After isotropic refinement a ΔF synthesis revealed some residual electron density, probably due to a solvent molecule, but they could not be interpreted as such. This electron density was corrected for with the SQUEEZE option of PLATON, based on the BYPASS-procedure.[22] The volume of the solvent area was 220 Å^3, positioned around 0.0;0.5;0.5 and the electron-count corrected for was 89. The hydrogen atoms were calculated. Full-matrix least-squares refinement on F, anisotropic for the non-hydrogen atoms and isotropic for the hydrogen atoms, restraining the latter in such a way that the distance to their carrier remained constant at approximately 1.0Å and keeping their atomic displacement parameters fixed at U = 0.1 Å^2, converged to R = 0.082, R_w = 0.081, (Δ/σ)max = 0.06, S = 1.08. A weighting scheme w = [8. + 0.01*(σ(Fobs))^2 + 0.01/(σ(Fobs))]$^{-1}$ was used. During refinement atom C20 turned out to behave extremely anisotropic, so it was decided to refine C20 isotropically and fix the three H-atoms connected to C20 at their calculated positions. A final difference Fourier map revealed a residual electron density between -0.92 and 0.91 eÅ^{-3}. Scattering factors were taken from

International Tables for X-ray Crystallography. The anomalous scattering of P and S was taken into account.[23] All calculations were performed with XTAL3.7, unless stated otherwise.
Crystallographic data (excluding structure factors) for the structure reported in this chapter have been deposited with the Cambridge Crystallographic Data Centre. No. CCDC 239743. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]

5.7 References and Notes

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