Amino acid modified phosphine ligands for the development of artificial transition metalloenzymes

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Chapter 4

Phosphine Ligands modified with Amino Acids

Asymmetric Allylic Alkylation by means of Secondary Interactions between Chiral Ligand and Substrate

Abstract

Four bidentate phosphorus ligands with a nitrogen atom in the backbone were modified with amino acid fragments at an appropriate distance from the phosphino groups. The palladium catalysts, which were prepared in situ by mixing the amino acid-modified ligands and $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$, were examined for catalytic activity and enantioselectivity in the asymmetric allylic alkylation of 2-acetylcyclohexanone with cinnamyl acetate. The observed enantioselectivity was attributed to secondary interactions between the nucleophile and the amino acid fragments on the ligand.
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Introduction

A large number of chemical transformations make use of organometallic catalysts. The key to success of homogeneous catalysts using transition metals lies in the relative ease of catalyst modification by changing the ligand environment. Both the metal center and the large variety of ligands around it determine the properties of the catalyst.[1] Still, natural enzymes are more active and selective than any man-made organometallic catalytic system. One of the most interesting properties of enzymes is their ability to orient their substrate by using secondary interactions. In the past, various research groups have studied the implementation of this concept in homogeneous catalysis.[2] Van der Waals forces,[3] hydrogen bonding[4,5,6] and Lewis acid/base interactions[7,8,9] have been employed to combine non-covalent substrate binding with transition metal catalysis, thereby aiming at enzyme-like behavior.

Highly enantioselective formation of a quaternary chiral carbon center is an important goal in organic synthetic chemistry. A powerful and versatile method for achieving this is the palladium-catalyzed allylic alkylation reaction.[10] A large number of chiral ligands has been used and many substrates can be functionalized with high enantioselectivities. The ligands used in Pd-catalyzed asymmetric allylic alkylation reactions are based on three general concepts which are schematically depicted in Figure 1: a) creating a chiral environment around the metal center, b) introducing different electronic properties on the donor atoms, and c) attaching a (chiral) tether to coordinate the incoming nucleophile.

![Figure 1. Three general concepts for ligands used in asymmetric allylic alkylations.](image)

For the first class of ligands, Trost and coworkers introduced $C_2$-symmetrical diphosphines based on two 2-diphenylphosphinobenzoic acid units which are linked to a chiral backbone.[11] The chiral induction stems from the selective clockwise or anticlockwise rotation of the allyl moiety upon nucleophilic attack in the chiral pocket created by the conformation of the phenyl rings.[12] The potential of the second class of ligands was demonstrated by Pfaltz,[13] Helmchen[14] and Williams,[15] who employed phosphinooxazoline ligands possessing $C_1$-symmetry. A key concept of these P,N-ligands is the assumption of preferred attack of the nucleophile at the carbon atom of the allyl group $trans$ to the phosphorus atom because of the large $trans$ effect.[16] As example of the third class of ligands, the planar chiral ferrocenyl diphosphine ligands bearing aminohydroxy functionalized side chains developed by Hayashi et al. have
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given excellent results.\[17] The functional groups are thought to interact with the incoming nucleophile to bring about high stereoselectivity, thereby displaying enzyme-like behaviour.

A new stereogenic carbon center can be created either in the nucleophile or in the allylic substrate. Kagan and coworkers have reported the first example of the former type of alkylation in 1978, which involved the allylic alkylation of 2-acetylcyclohexanone.\[18] Conceptually, catalytic asymmetric alkylations of such substrates (β-ketoesters) are not straightforward. The enantioselective electrophilic attack of a palladium(allyl) intermediate to a stabilized prochiral nucleophile is not easily controlled by a chiral ligand on the palladium atom, which is at the opposite side of the allyl structure from the approaching nucleophile. Consequently, a chiral ligand on palladium is remote from the attacking nucleophile and has only a limited effect on the asymmetric alkylation reaction where the new asymmetric center is created on the nucleophile. In order for chiral ligands to affect stereochemical control in this reaction, they must transmit their stereochemical information through space.

To overcome this problem in the allylic alkylation of β-ketoesters several ligand systems have been developed which contain remote functional groups that are able to interact with the prochiral nucleophile.\[17b,19,20] Hayashi and coworkers designed diphosphine ligands containing a chiral amino acid residue remote from the achiral phosphino groups and demonstrated that these are fairly effective for the palladium-catalyzed asymmetric allylic alkylation of the sodium enolate of 2-acetylcyclohexanone with allyl acetate.\[18] The prochiral 1,3-diketone enolate is generally believed to be located far from the chiral ligand in the transition state of the nucleophilic attack on the chiral palladium(allyl) intermediate. The observed enantioselectivity of 52 % ee was attributed to the secondary interaction between the chiral amino acid of the ligand and the sodium enolate. Hayashi introduced the amino acids via a linker to a nitrogen atom in the backbone of the bidentate phosphorus ligand.

![Figure 2](image)

**Figure 2:** The phosphorus ligands 1 – 4.

As was shown by Hayashi and coworkers,\[19] the combination of strongly coordinating phoshine ligands with amino acids for secondary interactions allow the development of enantioselective bioinspired ligands for palladium-catalyzed asymmetric allylic alkylation reactions. In the present Chapter we introduce new ligand backbones. The four bidentate phosphorus ligands 1 – 4 (Figure 2) all contain a
nitrogen atom in the backbone that has been modified with amino acid-fragments at an appropriate distance from the phosphino groups. The corresponding palladium complexes will be examined for catalytic activity and enantioselectivity in the reaction of the sodium enolate of 2-acetylcyclohexanone with cinnamyl acetate.

Results and Discussion

– Synthesis of ligands 3 and 4.
The synthesis of diphosphine 3 is shown in Scheme 1. Monolithiation of 1,3-dibromobenzene at –90 °C with n-butyllithium and subsequent reaction with chlorodiphenylphosphine gave 3-(bromophenyl)diphenylphosphine (5).[21] Aniline 6 was synthesized by nucleophilic phosphination of 3-fluoroaniline,[22] and by the cross-coupling between 3-iodoaniline and diphenylphosphine.[23] The palladium-catalyzed cross-coupling reaction of arylbromine 5 and 3-(diphenylphosphorus)aniline (6) gave 3,3’-bis(diphenylphosphino)diphenylamine (3) as a white powder.

\[ \begin{align*}
\text{Br} & \quad \text{Ph}_2\text{P} & \\
\text{Br} & \quad \text{Br} & \\
\text{NH}_2 & \quad \text{Ph}_2\text{P} & \\
\text{F} & \quad \text{NH}_2 & \\
\text{F} & \quad \text{Br} & \\
\text{F} & \quad \text{NH}_2 & \\
\end{align*} \]

Scheme 1. Reagents and conditions: i. a) n-BuLi, THF, –90 °C, b) PPh\(_2\)Cl, THF, –90 °C, 85 %; ii. KPPh\(_2\), THF, reflux, 72 %; iii. Pd(OAc)\(_2\), DPEphos, NaO\(_t\)Bu, toluene, reflux, 47 %.

Attempts to introduce the phosphine moieties in a later stage of the synthetic route, as has been reported for the 2,2’-bis(diphenylphosphino)diphenylamine isomer, failed.[24]

\[ \begin{align*}
\text{F} & \quad \text{NH}_2 & \\
\text{F} & \quad \text{NH}_2 & \\
\text{Br} & \quad \text{Br} & \\
\text{F} & \quad \text{Br} & \\
\text{F} & \quad \text{I} & \\
\end{align*} \]

Scheme 2. Reagents and conditions: i. Pd(OAc)\(_2\), DPEphos, NaO\(_t\)Bu, toluene, reflux, 76 %; ii. Pd(OAc)\(_2\), DPEphos, NaO\(_t\)Bu, toluene, reflux, 82 %; iii. NaH, TBDMSCl, THF, reflux, 90 %.
The C-F bonds in di(3-fluorophenyl)amine (7) proved to be insufficiently activated for double nucleophilic phosphination (Scheme 2). Furthermore, the synthesis of diphosphine 3 starting from compound 8 or 9 using lithium or Grignard reagents was unsuccessful as in all cases mixtures of (unidentified) compounds were obtained.

Ligand 4 is based on the Bisphenol A backbone and has been reported by Van der Vlugt and coworkers in 2002.[25] Similar ligands with different backbone bridging-atoms have successfully been employed as catalyst components in the hydroformylation of 1-octene.[26] Palladium-catalyzed cross-coupling reaction of 4-bromoanisole with p-anisidine in the presence of sodium tert-butoxide in refluxing toluene produced diphenylamine 10 (Scheme 3).[27] Protection of the amine with the tert-butyldimethylsilyl-group allowed the use of lithium reagents for the introduction of the phosphine moieties. The methoxy-groups act as directing groups for the selective ortho-lithiation of both phenyl rings and the subsequent reaction with chlorodiphenylphosphine gave compound 12. Finally, desilylation with tetrabutylammoniumfluoride yielded diphosphine 4.

Scheme 3. Reagents and conditions: i. Pd(OAc)$_2$, dppf, NaOtBu, toluene, reflux, 64 %; ii. NaH, TBDMS, THF, reflux, 58 %; iii.a) n-BuLi, TMEDA, Et$_2$O, –15 °C, b) PPh$_2$Cl, hexanes, 0 °C, 50 %; iv. (n-Bu)$_4$NF∙3H$_2$O, THF, 62 %.

Functionalization of ligands 1 – 4.

Next, amino acids were introduced to compounds 1–4 to obtain chiral diphosphine ligands. The synthetic route towards Hayashi’s chiral ligand 15[19] is depicted in Scheme 4. Bis(2-diphenylphosphinoethyl)amine (1) was prepared and isolated as a crystalline, air-stable, hydrochloride salt according to Whitesides’ procedure.[28] The same procedure describes the preparation of carboxylic acid 14 by acylation of compound 1 with succinic anhydride. Alternatively, amine 1 was acylated with methyl 4-chloro-4-oxobutyrate to give methyl ester 13 which was subsequently hydrolyzed to obtain carboxylic acid 14 by treatment with lithium hydroxide. Condensation with L-valine methyl ester in the presence of a base and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloric acid (EDC) yielded the previously reported ligand 15.[19]
Scheme 4. Reagents and conditions: i. Et₃N, ClC(O)(CH₂)₂CO₂Me, CH₂Cl₂, 81 %; ii. LiOH·H₂O, THF, 88 %; iii. L-Val-OMe·HCl, Et₃N, EDC, CH₂Cl₂, 91 %.

In a similar fashion, chiral ligands 18 and 21 were obtained starting from respectively compound 3 and 4 (Scheme 5). Deprotonation of the nitrogen atom in compound 3 with sodium hydride, followed by the addition of methyl 4-chloro-4-oxobutyrate gave 16. This compound was converted into carboxylic acid 17 by treatment with LiOH, which was then reacted with L-valine methyl ester to yield amide 18.[29] It is noteworthy that the nitrogen atom in compounds 3 and 4 is not reactive enough to obtain carboxylic acid derivatives 17 and 20 respectively by acylation with succinic anhydride.

Scheme 5. Reagents and conditions: i. NaH, ClC(O)(CH₂)₂CO₂Me, THF, reflux, 16: 42 %, 19: 40 %; ii. LiOH·H₂O, THF, 17: 66 %, 20: 46 %; iii. L-Val-OMe·HCl, Et₃N, EDC, CH₂Cl₂, 18: 78 %, 21: 75 %.

The phenoxazine-based ligand Nixantphos (2) as developed by Van der Veen et al.[30] has been successfully anchored to silica support,[31] polystyrene support,[32] and dendrimers.[33] Using the method developed by Van der Veen and coworkers,[31] the relatively unreactive phenoxazine nitrogen in the now commercially available Nixantphos (2) was acylated with methyl 4-chloro-4-oxobutyrate to give ligand 22 (Scheme 6). The saponification of methylester 22 to obtain the corresponding carboxylic acid proved to be unsuccessful since the amide was hydrolyzed as well.[34] Recently, Ricken et al. reported the reaction between methyl acrylate and Nixantphos to give the corresponding product of a Michael addition (23).[33] With no amide bond present, methylester 23 was cleanly hydrolyzed to give carboxylic acid 24. Subsequently, Nixantphos derivative 24 was allowed to react with L-valine methyl ester in the presence of EDC and triethylamine to give 25 (Figure 3).
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Scheme 6. Reagents and conditions: i. Methyl acrylate, NBu₄Br, NaOMe, MeOH, reflux, 75%; ii. LiOH·H₂O, THF, 92%; iii. NaH, ClC(O)(CH₂)₂CO₂Me, THF, reflux, 66%.

The distance between the functional group (i.e. the amino acid) and the metal center in these catalysts is decisive for an effective interaction in terms of enantioselectivity. Varying the length of the linker chain has been shown to have a tremendous effect on the enantioselectivity in palladium-catalyzed allylic substitution reactions.[17,19] The choice of the linker chain not only determines the distance between the amino acid and the phosphorus atoms but also allows the amino acid fragments to be coupled at the C-terminus. Since the functional groups attached to the linker also affect the outcome of the catalytic reaction, this can result in a more selective catalyst. Bis(2-diphenylphosphinoethyl)amine 1 was acylated with phthalylglycyl chloride to give 26 (Scheme 7). The N-phthalimide is readily cleaved with hydrazine to give amine 27, which was then converted into amide 28 by condensation with optically active N-Fmoc-L-alanine.

Scheme 7. Reagents and conditions: i. Phthalylglycyl chloride, EtsN, CH₂Cl₂, 68%; ii. NH₂NH₂·H₂O, MeOH, 74%; iii. Fmoc-Ala-OH, EDC, CH₂Cl₂, 64%.

The bidentate phosphorus ligands 1 – 4 can also be directly acylated with amino acid fragments. For example, alanine derivatives 29 and 30 (Figure 3) were obtained by the reaction of Fmoc-Ala-Cl with respectively compound 4 and 1. In this manner the importance of the linker, and thus the distance of the chiral amino acid from the metal center, on the outcome of the catalytic reaction can be examined. Ligand 30 can be compared with its longer analogue 27.
The $^{31}$P {$^1$H} NMR spectra of the functionalized ligands based on 1, 3 and 4 are usually characterized by two singlets. The splitting appears after acylation and has been attributed to restricted rotation around the C-N amide bond. The inequivalence of the two phosphorus moieties is detected by $^1$H and $^{13}$C {$^1$H} NMR spectroscopy as well. Preliminary in situ complex formation studies of these ligands to palladium were not conclusive since broad signals in the $^{31}$P {$^1$H} NMR spectra were observed. The natural bite angle of ligand 4 was calculated to be between 130 and 140 degrees, which is probably too large for chelation. The calculations showed the presence of two different structures close in energy; one structure with $C_2$ and one with $C_s$ symmetry. Because of the rotational freedom of the aromatic rings in the backbone, the diphenylphosphino groups are not constrained to any particular mutual orientation. Van der Vlugt and coworkers showed that derivatives of ligand 4 containing different backbone bridging atoms form binuclear complexes. Also amido functionalized derivatives of 1 are known to form dimeric complexes in addition to chelating mononuclear complexes. These dimeric complexes displayed fluxional behaviour which was ascribed to restricted rotation around the amide bond leading to syn and anti conformations, resulting in broad signals in $^{31}$P {$^1$H} NMR spectroscopy.

- Catalysis
The chiral diphosphine ligands were examined for enantioselectivity in the palladium-catalyzed reaction of the sodium enolate of 2-acetylcyclohexanone (31) with cinnamyl acetate (32) in tetrahydrofuran. The reaction conditions and results are summarized in Table 1. Ligand 15, based on the flexible diethylamine backbone, provided product 33 with 42 % enantiomeric excess (Entry 1). In the related palladium-catalyzed alkylation of 2-acetylcyclohexanone and allyl acetate at $-50 \ degrees$C, ligand 15 has been reported to give the product in 52 % ee. The catalysts based on the new chiral ligands 18, 21 and 25 were less active and in addition displayed poor enantioselectivity. It should be noted that Hayashi et al. have proposed that a secondary interaction between the chiral ligand and the nucleophile accelerates the allylic alkylation by drawing the nucleophile up to the $\pi$-allyl and that in general the catalysts with higher stereoselectivity show higher catalytic activity.
Table 1. Asymmetric alkylation of 2-acetylcyclohexanone with cinnamyl acetate.[a]

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>T (°C)</th>
<th>conv. (%) [b]</th>
<th>ee (%) [c]</th>
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<tr>
<td>1</td>
<td>15</td>
<td>−30</td>
<td>79</td>
<td>42 (R)</td>
</tr>
<tr>
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<td>18</td>
<td>−30</td>
<td>15</td>
<td>3 (R)</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>−30</td>
<td>14</td>
<td>2 (R)</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>−30</td>
<td>17</td>
<td>2 (R)</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>−30</td>
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<td>8 (R)</td>
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<tr>
<td>7</td>
<td>30</td>
<td>−30</td>
<td>61</td>
<td>3 (R)</td>
</tr>
<tr>
<td>8</td>
<td>(R)-BINAP</td>
<td>−30</td>
<td>80</td>
<td>73 (S)</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>−40</td>
<td>76</td>
<td>45 (R)</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
<td>−40</td>
<td>66</td>
<td>15 (R)</td>
</tr>
<tr>
<td>11</td>
<td>29</td>
<td>−40</td>
<td>34</td>
<td>9 (R)</td>
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<tr>
<td>12</td>
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<td>25</td>
<td>85</td>
<td>29 (R)</td>
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<td>13</td>
<td>28</td>
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<td>8 (R)</td>
</tr>
<tr>
<td>14</td>
<td>(R)-BINAP</td>
<td>25</td>
<td>82</td>
<td>36 (S)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: [Pd(η3-C₃H₅)Cl]₂, [Pd] = 1.0 mM, 31/NaH/32/[Pd(η3-C₃H₅)Cl]₂/ligand = 100/125/150/0.5/1.1, t = 16 h, 2 mL THF. [b] Percentage conversion of 2-acetylcyclohexanone, determined by GC. [c] Enantiomeric excess of product, determined by chiral HPLC. Ligand abbreviation: BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

The diphosphine (R)-BINAP was used as control experiment, as Ito and coworkers showed that the chiral palladium complex generated in situ from [Pd(η3-C₃H₅)Cl]₂ and (R)-BINAP is a good catalyst for the catalytic asymmetric alkylation of 1,3-diketones.[38] Under the present reaction conditions, product 33 was obtained with 73% ee (Entry 8). It should be noted that the phenyl groups of BINAP are believed to induce the enantioselectivity by steric interactions with the approaching prochiral nucleophile.[39] Trost showed that the geometric requirements of a ligand with a chiral pocket transmitted its chirality to the β-ketoester nucleophile.[40] Consequently, the enantioselectivity displayed by the non-tethered ligand 29 (Entry 6) might find its origin in the enforced orientation of the diphenylamine backbone and not in non-covalent interactions between the amino acid residue and the nucleophile. The importance of linker chain length is shown by the lower selectivity of 30, which is a non-tethered analogue of ligand 28 (Entries 5 and 7).
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The enantioselectivities improved upon lowering the reaction temperature and vice versa. At –40 °C, the palladium complex based on ligand 28 provided product 33 with 15 % ee (Entry 10). Performing the reaction at room temperature resulted in lower enantioselectivities.

Conclusions

In conclusion, we synthesized diphosphine ligands containing a nitrogen atom in the backbone modified with amino acid-fragments at an appropriate distance from the phosphino groups which allows non-covalent secondary interactions between functionalized substrates and the ligand. We illustrated that the amino acid-modified chiral diphosphine ligands with the appropriate length of linker chain are effective in the palladium-catalyzed asymmetric alkylation 2-acetylcyclohexanone with cinnamyl acetate, albeit with low to moderate enantioselectivity. The catalysts may be regarded as artificial enzyme-like catalysts, in that the catalysts interact with the electrophile (allyl acetate) and the nucleophile (sodium enolate) simultaneously.

Experimental Section

General remarks. Unless stated otherwise, reactions were carried out under an atmosphere of argon using standard Schlenk techniques. THF, diethyl ether and hexanes were distilled from sodium/benzophenone. Tertiary amines, CH₂Cl₂ and methanol were distilled from CaH₂ and toluene was distilled from sodium. Deuterated solvents were distilled from the appropriate drying agents. Unless stated otherwise, all chemicals were obtained from commercial suppliers and used as received. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. NMR spectra were recorded on a Varian Mercury 300, a Varian Inova 500 or a Bruker Avance DRX-300 spectrometer. Chemical shifts are reported in ppm and are given relative to tetramethylsilane (1H, 13C), 85% H₃PO₄ (31P) and CCl₂F₂ (19F). Standard infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High Resolution Mass Spectra were recorded at the Department of Mass Spectrometry at the University of Amsterdam using Fast Atom Bombardment (FAB) ionization on a JOEL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP9021D/UPD system program. Samples were loaded in a matrix solution (3-nitrobenzyl alcohol) on to a stainless steel probe and bombarded with xenon atoms with an energy of 3KeV. Elemental analyses were carried out by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr (Germany).

(3-Bromophenyl)diphenylphosphine (5): This compound was prepared according to a literature procedure.[24] 1,3-Dibromobenzene (7.4 mL, 61.0 mmol) was dissolved in THF (200 mL) and cooled to –90 °C using an acetone/liquid nitrogen bath. n-BuLi (25.6 mL, 2.5 M in hexanes, 64.0 mmol) was
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added dropwise and the resulting cloudy solution was stirred at -90 °C. After 45 minutes chlorodiphenylphosphine (10.4 mL, 58.0 mmol) was added dropwise. The solution was allowed to warm to room temperature over the course of 2 hours, and was then filtered through a pad of Celite. The deep red resulting filtrate was concentrated under reduced pressure. The solids were then extracted with hexanes followed by filtration through a silica plug. Evaporation of the solvent gave 5 in 85 % yield (16.73 g) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.49-7.28 (m, 12H, H-arom), 7.22 (m, 2H, H-arom); ¹³C [¹H] NMR (75 MHz, CDCl₃): δ = 141.0 (d, J = 15.8 Hz, CP), 136.7 (d, J = 10.9 Hz, CH), 136.4 (d, J = 20.6 Hz, CP), 134.2 (d, J = 19.4 Hz, CH), 132.5 (d, J = 19.4 Hz, CH), 132.1 (CH), 130.5 (d, J = 6.1 Hz, CH), 129.5 (CH), 129.1 (d, J = 7.3 Hz, CH), 123.6 (d, J = 7.3 Hz, CBr); ³¹P [¹H] NMR (121 MHz, CDCl₃): δ = –3.42.

3-(Diphenylphosphorus)aniline (6): This compound was prepared according to a literature procedure.²² 3-Fluoroaniline (5.59 g, 50.3 mmol) and potassium diphenylphosphide (0.5 M in THF, 100 mL, 50.0 mmol) were combined and refluxed for 3 days. The THF was removed under reduced pressure, and the yellow solid was washed with degassed water (2 × 50 mL) and hexanes (50 mL). The residue was purified by silica gel flash column chromatography (eluent: CHCl₃) to give 6 (10.08 g, 72 %) as a white solid. ¹H NMR (300 MHz, CDCl₃): δ = 7.57-7.35 (m, 10H, H-arom), 7.15 (d, 1H, H-arom), 6.78 (m, 1H, H-arom), 6.67 (m, 1H, H-arom), 6.45 (m, 1H, H-arom), 3.60 (bs, 2H, NH₂); ¹³C [¹H] NMR (75 MHz, CDCl₃): δ = 146.5 (d, J = 7.3 Hz, CN), 138.0 (d, J = 10.4 Hz, PC), 137.3 (d, J = 11.0 Hz, PC), 133.8 (d, J = 19.5 Hz, CH), 129.5 (d, J = 7.3 Hz, CH), 128.7 (d, J = 11.5 Hz, CH), 128.5 (CH), 124.0 (d, J = 19.6 Hz, CH), 120.0 (d, J = 19.6 Hz, CH), 115.6 (CH); ³¹P [¹H] NMR (121 MHz, CDCl₃): δ = –3.54.

Bis(3-(diphenylphosphino)phenyl)amine (3): A Schlenk flask was charged with aniline 6 (5.55 g, 20.0 mmol), arylbromide 5 (6.82 g, 20.0 mmol), Pd(OAc)₂ (0.023 g, 0.10 mmol), DPEphos (0.081 g, 0.15 mmol), sodium tert-butoxide (2.89 g, 30 mmol) and toluene (30 mL). The reaction mixture was stirred for 24 h at reflux temperature. After cooling the reaction mixture to room temperature, the reaction mixture was quenched with water (30 mL). The organic layer was extracted with toluene (2 × 15 mL). The combined organic solution was dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5 → 10 % ethyl acetate in light petroleum) to afford compound 3 in 47 % yield (5.0 g) as a white solid. ¹H NMR (300 MHz, CD₂Cl₂): δ = 7.37-7.29 (m, 20H, H-arom), 7.18 (dt, J = 7.8 Hz, J = 1.8 Hz, 2H, H-arom), 6.98 (m, 2H, H-arom), 6.90 (dt, J = 7.8 Hz, J = 1.8 Hz, 2H, H-arom), 6.84 (dt, J = 7.8 Hz, J = 1.2 Hz, 2H, H-arom), 5.79 (bs, 1H, NH); ¹³C [¹H] NMR (75 MHz, CD₂Cl₂): δ = 143.4 (d, J = 7.3 Hz, CN), 139.2 (d, J = 11.0 Hz, CP), 137.8 (d, J = 11.0 Hz, CP), 134.2 (d, J = 19.5 Hz, CH), 129.8 (d, J = 7.3 Hz, CH), 129.3 (CH), 129.1 (d, J = 7.3 Hz, CH), 126.7 (d, J = 20.8 Hz, CH), 123.0 (d, J = 19.5 Hz, CH), 117.9 (CH); ³¹P [¹H] NMR (121 MHz, CD₂Cl₂): δ = –3.81; HRMS (FAB+): m/z calcd. for C₃₆H₃₀NP₂ (M+H⁺): 538.1854; found: 538.1857; anal. calcd. for C₃₆H₂₉NP₂: C 80.43, H 5.44, N 2.61; found: C 80.50, H 5.35, N 2.27.
Di(3-fluorophenyl)amine (7): A Schlenk flask was charged with 3-fluoroaniline (5.56 g, 50.0 mmol), 1-bromo-3-fluorobenzene (8.75 g, 50.0 mmol), Pd(OAc)$_2$ (0.056 g, 0.25 mmol), DPEphos (0.202 g, 0.375 mmol), sodium tert-butoxide (7.21 g, 75 mmol) and toluene (50 mL). The reaction mixture was stirred for 16 h at reflux temperature. After cooling the reaction mixture to room temperature, the reaction mixture was quenched with water (50 mL). The organic layer was extracted with toluene (2 x 15 mL). The combined organic solutions were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (5 % ethyl acetate in light petroleum) to afford 7 in 76 % yield (7.80 g) as a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.30-7.25 (m, 2H, H-arom), 6.88-6.84 (m, 4H, H-arom), 6.74-6.70 (m, 2H, H-arom), 5.86 (bs, 1H, NH); $^{13}$C {1H} NMR (125 MHz, CDCl$_3$): $\delta$ = 163.6 (d, $J$ = 245 Hz, CF), 144.1 (d, $J$ = 10.1 Hz, CN), 130.5 (d, $J$ = 10.2 Hz, CH), 113.5 (d, $J$ = 2.5 Hz, CH), 108.0 (d, $J$ = 21.5 Hz, CH), 104.7 (d, $J$ = 25.0 Hz, CH); $^{19}$F {1H} NMR (282 MHz, CDCl$_3$): $\delta$ = –111.88; HRMS (FAB+): m/z calcd. for C$_{12}$H$_{10}$F$_2$N ($M$+H$^+$): 206.0781; found: 206.0778; anal. calcd. for C$_{12}$H$_{9}$F$_2$N: C 70.24, H 4.42, N 6.83; found: C 70.18, H 4.48, N 6.77.

Di(3-bromophenyl)amine (8): Following the procedure as described for the synthesis of compound 7, di(3-bromophenyl)amine was obtained starting from 3-bromoaniline (6.88 g, 40.0 mmol) and 1-bromo-3-iodobenzene (11.32 g, 40.0 mmol). Purification by flash column chromatography on neutral Al$_2$O$_3$ (diethyl ether) afforded 8 in 82 % yield (10.70 g) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.20-7.19 (m, 2H, H-arom), 7.16-7.08 (m, 4H, H-arom), 6.99-6.97 (m, 2H, H-arom), 5.65 (bs, 1H, NH); $^{13}$C {1H} NMR (125 MHz, CDCl$_3$): $\delta$ = 143.7 (CN), 130.7 (CH), 124.5 (CH), 123.1 (CBr), 120.8 (CH), 116.6 (CH); HRMS (FAB+): m/z calcd. for C$_{12}$H$_9$Br$_2$N: 326.9082; found: 326.9086; anal. calcd. for C$_{12}$H$_9$Br$_2$N: C 44.07, H 2.77, N 4.28; found: C 44.16, H 2.95, N 4.33.

N-(tert-Butyldimethylsilyl)-bis(3-bromophenyl)amine (9): Sodium hydride (1.22 g, 60 % in mineral oil, 30.4 mmol) was added to a solution of 8 (8.28 g, 25.3 mmol) in THF (60 mL) and this solution was stirred for 1 h at reflux temperature. To the reaction mixture was added a solution of tert-butyldimethylsilyl chloride (5.39 g, 35.7 mmol) in THF (20 mL). The solution was stirred another 3 h at reflux temperature. After cooling to room temperature, the solution was diluted with ethyl acetate (100 mL) and washed with water (80 mL). The organic layer was dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: light petroleum) to afford 9 in 90 % yield (10.02 g) as a colourless oil which became solid upon standing. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.17-7.07 (m, 6H, H-arom), 6.90-6.87 (m, 2H, H-arom), 0.96 (s, 9H, tBu), 0.20 (s, 6H, Si(CH$_3$)$_3$); $^{13}$C {1H} NMR (125 MHz, CDCl$_3$): $\delta$ = 150.4 (CN), 130.1 (CH), 130.0 (CH), 126.0 (CH), 124.6 (CH), 122.5 (CBr), 27.8 (C(CH$_3$)$_3$), 20.4 (C(CH$_3$)$_3$), –1.7 (Si(CH$_3$)$_3$); HRMS (FAB+): m/z calcd. for C$_{18}$H$_{24}$Br$_2$NSi (M+H$^+$): 442.0025; found: 442.0028.

Di(4-methoxyphenyl)amine (10): This compound was prepared according to a slightly modified literature procedure.$^{[27]}$ A Schlenk flask was charged with 4-bromoanisole (9.35 g, 50.0 mmol), p-anisidine (6.16 g, 50.0 mmol), Pd(OAc)$_2$ (0.084 g, 0.38 mmol), dppf (0.28 g, 0.50 mmol), sodium tert-
butoxide (6.25 g, 65.0 mmol) and toluene (50 mL). The reaction mixture was stirred for 16 h at reflux temperature. After cooling the reaction mixture to room temperature, the reaction mixture was diluted with water (40 mL) and methylene chloride (80 mL). The aqueous layer was extracted with methylene chloride (2 × 50 mL). The combined organic solution was dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was washed with heptane and purified by silica gel flash column chromatography (eluent: 5 % ethyl acetate in light petroleum) to afford 10 in 64 % yield (7.28 g) as a white solid. \(^1\)H NMR (500 MHz, CDCl₃): δ = 6.97-6.95 (m, 4H, H-arom), 6.90-6.85 (m, 4H, H-arom), 3.81 (s, 6H, OCH₃); \(^{13}\)C \({\text{\{}}^1\text{H}\) NMR (125 MHz, CDCl₃): δ = 154.2 (CO), 137.9 (CN), 119.5 (CH), 114.7 (CH), 55.6 (OCH₃).

**N-(tert-Butyldimethylsilyl)-bis(4-methoxyphenyl)amine (11):** Sodium hydride (1.52 g, 60 % in mineral oil, 38.1 mmol) was added to a solution of 10 (7.28 g, 31.8 mmol) in THF (80 mL) and this solution was stirred for 2 h at reflux temperature. To the reaction mixture was added a solution of tert-butyldimethylsilyl chloride (6.70 g, 44.5 mmol) in THF (20 mL). The solution was stirred another 16 h at reflux temperature. After cooling to room temperature, the solution was diluted with ethyl acetate (100 mL) and washed with water (100 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5 % ethyl acetate in light petroleum) to afford 11 in 58 % yield (6.29 g) as a yellow oil. \(^1\)H NMR (500 MHz, CDCl₃): δ = 6.98 (dd, \(J = 9.8\) Hz, \(J = 2.8\) Hz, 4H, H-arom), 6.79 (dd, \(J = 6.8\) Hz, \(J = 1.8\) Hz, 4H, H-arom), 3.77 (s, 6H, OCH₃), 0.95 (s, 9H, tBu), –0.20 (s, 6H, Si(CH₃)₂); \(^{13}\)C \({\text{\{}}^1\text{H}\) NMR (125 MHz, CDCl₃): δ = 155.2 (CO), 143.2 (CN), 127.7 (CH), 113.9 (CH), 55.3 (OCH₃), 27.6 (C(CH₃)₃), 20.0 (C(CH₃)₃), –2.0 (Si(CH₃)₂); HRMS (FAB+): m/z calcd. for C₂₉H₃₉NO₂Si (M+H⁺): 344.2046; found: 344.2043; anal. calcd. for C₂₀H₂₉NO₂Si: C 69.92, H 8.51, N 4.08; found: C 69.85, H 8.64, N 3.98.

**N-(tert-Butyldimethylsilyl)-bis(3-(diphenylphosphino)-4-methoxyphenyl)amine (12):** TMEDA (4.98 g, 42.9 mmol) was added to n-BuLi (17.2 mL, 2.5 M in hexanes, 42.9 mmol). At –15 °C, a solution of 11 (6.45 g, 20.2 mmol) in diethyl ether (50 mL) was added dropwise. The mixture was allowed to stir at room temperature for 16 h to yield a yellow suspension. At 0 °C, a solution of PPh₂Cl (9.46 g, 42.9 mmol) in hexanes (10 mL) was added dropwise. After being stirred for 4 h at room temperature, the reaction mixture was hydrolyzed with brine (50 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Purification by crystallization (methylene chloride/methanol) gave 12 in 50 % yield (7.21 g) as a white solid. \(^1\)H NMR (500 MHz, CDCl₃): δ = 7.33-7.23 (m, 20H, H-arom), 6.73 (m, 4H, H-arom), 6.33 (dd, \(J = 5.0\) Hz, \(J = 3.0\) Hz, 2H, H-arom), 3.69 (s, 6H, OCH₃), 0.54 (s, 9H, tBu), –0.26 (s, 6H, Si(CH₃)₂); \(^{31}\)P \({\text{\{}}^1\text{H}\) NMR (121 MHz, CDCl₃): δ = –15.76; HRMS (FAB+): m/z calcd. for C₄₄H₄₈NO₂P₂Si (M+H⁺): 712.2946; found: 712.2943; anal. calcd. for C₄₄H₄₆NO₂P₂Si: C 60.39, H 6.93, N 3.34; found: C 60.37, H 6.92, N 3.33.
Bis(3-(diphenylphosphino)-4-methoxyphenyl)amine (4): To a solution of 12 (7.0 g, 9.8 mmol) in THF (80 mL) was added (n-Bu)₃NF·3H₂O (5.3 g, 16.7 mmol) and the reaction mixture was stirred for 20 h at room temperature. Then brine (50 mL) and toluene (80 mL) were added. The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The residue was washed with hexanes and purified by crystallization (methylene chloride/methanol) to give 4 in 62 % yield (3.6 g) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ = 7.33-7.25 (m, 20H, H-arom), 6.90 (d, J = 6.5 Hz, 2H, H-arom), 6.72 (dd, J = 6.8 Hz, J = 4.5 Hz, 2H, H-arom), 6.22 (m, 2H, H-arom), 5.06 (bs, 1H, NH), 3.70 (s, 6H, OCH₃); ¹³C {¹H} NMR (125 MHz, CDCl₃): δ = 155.9 (d, J = 15.2 Hz, CO), 137.8 (CN), 136.8 (d, J = 11.1 Hz, CP), 134.0 (d, J = 19.9 Hz, CH), 128.7 (CH), 128.5 (d, J = 7.2 Hz, CH), 126.8 (d, J = 13.2 Hz, CP), 123.8 (CH), 119.2 (CH), 111.6 (CH), 56.4 (OCH₃); ³¹P {¹H} NMR (121 MHz, CDCl₃): δ = –15.03; IR (KBr, cm⁻¹): 3416 (w), 3050 (w), 3012 (w), 2930 (w), 2831 (w), 1580 (m), 1475 (s), 1433 (s), 1314 (m), 1278 (m), 1180 (m), 1061 (m), 1016 (s), 768 (s), 746 (s), 694 (s); HRMS (FAB+): m/z calcd. for C₃₈H₃₄NO₂P₂ (M+H⁺): 598.2065; found: 598.2061; anal. calcd. for C₃₈H₃₃NO₂P₂: C 76.37, H 5.57, N 2.34; found: C 76.43, H 5.69, N 2.22.

Bis[2-(diphenylphosphino)ethyl]amine hydrochloride (1): This compound was prepared according to a literature procedure. Diphenylphosphine (7.45 g, 40.0 mmol) was added to a suspension of potassium tert-butoxide (7.01 g, 62.5 mmol) in THF (125 mL). The resulting deep red solution was stirred for 5 min and bis(2-chloroethyl)amine hydrochloride (3.57 g, 20.0 mmol) was added. The mixture was refluxed for 16 h, poured into hexanes (200 mL), and washed with 10 % NaOH (75 mL) and brine (75 mL). The organic phase was separated and stirred vigorously with 200 mL of 2 N aqueous HCl-solution, giving a white precipitate. Recrystallization of the collected precipitate from boiling acetonitrile (75 mL) gave 1 in 74 % yield (7.03 g) as a white powder. ¹H NMR (300 MHz, CDCl₃): δ = 10.01 (bs, 2H, NH.HCl), 7.41-7.26 (m, 20H, H-arom), 2.92 (m, 4H, CH₂), 2.58 (m, 4H, CH₂); ¹³C {¹H} NMR (125 MHz, CDCl₃): δ = 135.8 (d, J = 11.6 Hz, PC), 132.6 (d, J = 26.3 Hz, CH₂), 129.2 (CH), 128.7 (d, J = 6.9 Hz, CH), 44.2 (d, J = 26.5 Hz, CH₂), 23.7 (d, J = 15.6 Hz, CH₂); ³¹P {¹H} NMR (121 MHz, CDCl₃): δ = –15.03; IR (KBr, cm⁻¹): 3146 (w), 3050 (w), 2930 (w), 1625 (s), 1475 (s), 1311 (m), 1278 (m), 1180 (m), 1061 (s), 768 (s), 746 (s), 694 (s); HRMS (FAB+): m/z calcd. for C₃₂H₃₄N₂: (M+H⁺): 598.2065; found: 598.2061; anal. calcd. for C₃₂H₃₄N₂: C 80.65, H 5.92; found: C 80.65, H 5.97.

Methyl 4-(bis(2-(diphenylphosphino)ethyl)amino)-4-oxobutanoate (13): To a mixture of 1 (4.0 g, 8.4 mmol) and triethylamine (5.4 mL, 38.5 mmol) in methylene chloride (80 mL) was added methyl 4-chloro-4-oxobutyrate (1.39 g, 9.2 mmol) in methylene chloride (10 mL). The resulting deep red solution was stirred for 16 h at room temperature and subsequently washed with 2 M HCl (2 × 40 mL) and 0.1 M NaOH (40 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. Purification by flash silica gel chromatography (2 % MeOH in CH₂Cl₂) gave 13 in 81 % yield (3.78 g) as a yellowish oil. ¹H NMR (300 MHz, CDCl₃): δ = 7.42-7.30 (m, 20H, H-arom), 3.68 (s, 3H, CH₃), 3.43 (m, 2H, CH₂), 3.29 (m, 2H, CH₂), 2.57 (t, J = 6.6 Hz, 2H, CH₂), 2.29 (m, 6H, CH₂); ¹³C {¹H} NMR (125 MHz, CDCl₃): δ = 173.3 (COO), 170.4 (NCO), 170.4 (NCO), 137.7 (d, J = 12.1 Hz, PC), 137.1 (d, J = 12.2 Hz, PC), 132.5 (d, J = 26.3 Hz, CH), 128.5 (d, J = 6.9 Hz, CH), 128.4 (d, J = 6.9 Hz, CH), 51.5 (OCH₃), 45.1 (d, J = 26.0 Hz, CH₂), 43.7 (d, J = 23.6 Hz, CH₂), 28.9 (CH₂), 27.8 (d, J = 15.6 Hz, CH₂), 27.7 (CH₂), 26.3 (d, J = 15.5 Hz, CH₂); ³¹P {¹H} NMR (121 MHz, CDCl₃): δ = –18.84, –20.35; HRMS
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(FAB+): m/z calcd. for C_{33}H_{36}NO_3P_2 (M+H+): 556.2170; found: 556.2169; anal. calcd. for C_{33}H_{35}NO_3P_2: C 71.34, H 6.35, N 2.52; found: C 71.26, H 6.35, N 2.46.

4-(Bis(2-(diphenylphosphino)ethyl)amino)-4-oxobutanoic acid (14): LiOH·H_2O (0.33 g, 7.9 mmol) in water (10 mL) was added to 13 (2.0 g, 3.6 mmol) in THF (20 mL). After stirring for 1 h additional water (10 mL) was added. The organic solvent was removed under reduced pressure and the remaining solution was treated with 2 M HCl (5 mL). The white precipitate was collected and dried in vacuo, yielding 14 as a white powder (88 %, 1.59 g). 1H NMR (300 MHz, CDCl_3): δ = 7.33-7.17 (m, 20H, H-arom), 3.29 (m, 2H, CH_2), 3.08 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 2.27 (m, 4H, CH_2), 2.06 (m, 2H, CH_2); 13C {1H} NMR (125 MHz, CDCl_3): δ = 175.8 (COO), 172.1 (NCO), 136.9 (m, PC), 136.4 (m, PC), 132.9 (d, J = 18.1 Hz, CH), 129.4 (CH), 129.0 (CH), 128.9 (CH), 45.7 (d, J = 25.3 Hz, CH_2), 44.1 (d, J = 22.0 Hz, CH_2), 29.9 (CH_2), 28.0 (CH_2), 27.9 (d, J = 10.2 Hz, CH_2), 26.1 (d, J = 9.7 Hz, CH_2); 31P {1H} NMR (121 MHz, CDCl_3): δ = –19.09, –20.41.

(S)-Methyl 2-(4-(bis(2-(diphenylphosphino)ethyl)amino)-4-oxobutanamido)-3-methylbutanoate (15): This compound was prepared according to a literature procedure with minor changes.[19] To a solution of diphosphine 14 (0.40 g, 0.74 mmol) in methylene chloride (10 mL) were added L-valine methyl ester hydrochloride (0.12 g, 0.74 mmol), Et_3N (0.21 mL, 1.48 mmol) and EDC (0.21 g, 1.11 mmol). After stirring for 16 h at room temperature, the mixture was washed with brine (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5 % methanol in methylene chloride), to afford 15 as a colorless oil (91 %, 0.44 g). [α]_D^{20} = +8.5 ° (c 1.0, CHCl_3); 1H NMR (300 MHz, CD_2Cl_2): δ = 7.43-7.32 (m, 20H, H-arom), 6.83 (d, J = 8.0 Hz, 1H, NH), 4.46 (m, 1H, Hα), 3.70 (s, 3H, OCH_3), 3.44 (m, 2H, CH_2), 2.50 (t, J = 6.5 Hz, 2H, CH_2), 2.39 (t, J = 6.5 Hz, 2H, CH_2), 2.32 (m, 4H, CH_2), 2.16 (m, 1H, Hβ), 0.95 (d, J = 3.0 Hz, 3H, CH_3), 0.93 (d, J = 3.6 Hz, 3H, CH_3); 13C {1H} NMR (125 MHz, CD_2Cl_2): δ = 172.9 (CO), 172.8 (CO), 171.8 (CO), 138.8 (m, PC), 138.1 (m, PC), 133.2 (d, J = 3.0 Hz, CH), 133.1 (d, J = 3.0 Hz, CH), 129.5 (CH), 129.2 (CH), 128.9 (d, J = 6.8 Hz, CH), 57.7 (Ca), 52.3 (OCH_3), 45.7 (d, J = 26.1 Hz, CH_2), 44.3 (d, J = 24.9 Hz, CH_2), 31.8 (CH_2), 31.6 (Cβ), 29.2 (CH_2), 28.3 (CH_2), 28.2 (CH_2), 26.8 (d, J = 13.9 Hz, CH_2), 19.4 (CH_3), 18.2 (CH_3); 31P {1H} NMR (202 MHz, CD_2Cl_2): δ = –19.67, –20.75; HRMS (FAB+): m/z calcd. for C_{38}H_{42}N_2O_4P_2 (M+H+): 655.2855; found: 655.2858.

Methyl 4-[bis(3-(diphenylphosphino)phenyl)amino]-4-oxobutanoate (16): Sodium hydride (0.12 g, 60 % in mineral oil, 3.0 mmol) was added to a solution of 3 (0.81 g, 1.5 mmol) in THF (30 mL) and the reaction mixture was stirred for 16 h at reflux temperature. The solution was cooled to room temperature and methyl 4-chloro-4-oxobutyrate (0.45 g, 3.0 mmol) was added. The reaction mixture was stirred another 16 h at reflux temperature. After cooling to room temperature, the solution was diluted with toluene (40 mL) and washed with brine (40 mL). The organic layer was dried over MgSO_4 and concentrated under reduced pressure. The obtained yellow oil was washed with hexanes and purification by silica gel column chromatography (4 % MeOH in methylene chloride) gave 16 in 42 %
yield (0.41 g) as a white solid. 1H NMR (300 MHz, CD2Cl2): δ = 7.36-7.28 (m, 28H, H-arom.), 3.43 (s, 3H, OMe), 2.57 (t, J = 6.6 Hz, 2H, CH2), 2.42 (t, J = 6.6 Hz, 2H, CH2); 13C {1H} NMR (75 MHz, CD2Cl2): δ = 173.5 (COO), 171.6 (NCO), 143.2 (m, CN), 137.2 (m, PC), 134.3 (CH), 134.0 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 52.1 (OCH3), 30.9 (CH2), 29.8 (CH2); 31P {1H} NMR (121 MHz, CD2Cl2): δ = −4.18; HRMS (FAB+): m/z calcd. for C41H36NO3P2 (M+H+): 652.2170; found: 652.2171; anal. calcd. for C41H35NO3P2: C 75.57, H 5.41, N 2.15; found: C 75.46, H 5.36, N 2.20.

4-[Bis(3-(diphenylphosphino)phenyl)amino]-4-oxobutanoic acid (17): To a solution of 16 (0.32 g, 0.49 mmol) in THF (5 mL) was added LiOH·H2O (0.023 g, 0.54 mmol) in water (5 mL). The reaction mixture was allowed to stir for 16 h at 60 °C. After cooling to room temperature, additional water (5 mL) was added. THF was removed under reduced pressure and the remaining solution was treated with 2 M HCl (5 mL). The white precipitate was filtered off and purified by silica gel column chromatography (5 % MeOH in CH2Cl2) yielding 17 as a colourless oil (66 %, 0.21 g). 1H NMR (300 MHz, CD2Cl2): δ = 7.65-7.43 (m, 6H, H-arom.), 7.30-7.22 (m, 22H, H-arom), 2.52 (t, J = 6.0 Hz, 2H, CH2), 2.39 (t, J = 6.0 Hz, 2H, CH2); 13C {1H} NMR (75 MHz, CD2Cl2): δ = 175.5 (COO), 172.3 (NCO), 142.9 (m, CN), 137.2 (m, PC), 134.2 (CH), 133.9 (CH), 132.5 (CH), 129.4 (CH), 129.1 (CH), 30.9 (CH2), 30.1 (CH2); 31P {1H} NMR (121 MHz, CD2Cl2): δ = −4.16; HRMS (FAB+): m/z calcd. for C40H34NO3P2 (M+H+): 638.2014; found: 638.2018.

(S)-Methyl-2-[4-(bis(3-(diphenylphosphino)phenyl)amino)-4-oxobutanamido]-3-methylbutanoate (18): Following the procedure as described for the synthesis of compound 15, diphosphine 18 was obtained starting from 17 (0.32 g, 0.50 mmol) and L-valine methyl ester hydrochloride (84 mg, 0.50 mmol). Purification by silica gel column chromatography (2 % methanol in methylene chloride) gave 18 in 78 % yield (0.29 g) as a white solid. [α]D20 = +3.4 ° (c 1.0, CHCl3); 1H NMR (500 MHz, CD2Cl2): δ = 7.36-7.19 (m, 28H, H-arom.), 6.37 (d, J = 8.5 Hz, 1H, NH), 4.46 (dd, J = 9.0 Hz, J = 5.5 Hz, 1H, Ha), 3.70 (s, 3H, OCH3), 2.49 (m, 4H, CH2), 2.12 (m, 1H, Hβ), 0.93 (d, J = 6.5 Hz, 3H, CH3), 0.90 (d, J = 6.5 Hz, 3H, CH3); 13C {1H} NMR (125 MHz, CD2Cl2): δ = 172.9 (CO), 172.3 (CO), 143.4 (m, CN), 137.3 (m, PC), 134.3 (CH), 134.1 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 57.7 (Ca), 52.4 (OCH3), 31.9 (CH2), 31.7 (CH2), 31.6 (Cβ), 19.3 (CH3), 18.2 (CH3); 31P {1H} NMR (121 MHz, CD2Cl2): δ = −4.11; HRMS (FAB+): m/z calcd. for C60H53N2O5P2 (M+H+): 751.2855; found: 751.2846; anal. calcd. for C60H52N2O5P2: C 73.59, H 5.91, N 3.73; found: C 73.32, H 5.78, N 3.59.

Methyl 4-[bis(3-(diphenylphosphino)-4-methoxyphenyl)amino]-4-oxobutanoate (19): Sodium hydride (0.066 g, 60 % in mineral oil, 1.66 mmol) was added to a solution of 4 (0.49 g, 0.82 mmol) in THF (20 mL) and the reaction mixture was stirred for 2 h at reflux temperature. The solution was cooled to room temperature and methyl 4-chloro-4-oxobutyrate (0.25 g, 1.64 mmol) was added. The reaction mixture was stirred another 2 h at reflux temperature. After cooling to room temperature, the solution was diluted with toluene (10 mL) and washed with brine (10 mL). The organic phase was dried over MgSO4 and concentrated under reduced pressure. The obtained yellow oil was washed with hexanes. Purification by silica gel column chromatography (40 % ethyl acetate in light petroleum)
gave 19 in 81% yield (0.47 g) as a white solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.30-7.18$ (m, 20H, H-arom), 6.98 (m, 1H, H-arom), 6.79 (m, 2H, H-arom), 6.31 (m, 2H, H-arom), 3.76 (bs, 3H, OCH$_3$), 3.71 (bs, 3H, OCH$_3$), 3.63 (s, 3H, OCH$_3$), 2.53 (t, $J = 7.0$ Hz, 2H, CH$_2$), 2.31 (t, $J = 7.0$ Hz, 2H, CH$_2$); $^{13}$C $^1$H NMR (125 MHz, CDCl$_3$): $\delta = 173.1$ (COO), 171.3 (NCO), 160.0 (d, $J = 12.6$ Hz, CO), 158.7 (d, $J = 15.2$ Hz, CO), 136.1 (m, CN, CP), 133.7 (m, CH), 133.1 (CH), 131.8 (d, $J = 10.1$ Hz, CH), 130.9 (CH), 129.9 (CH), 128.9 (CH), 128.4 (m, CH), 128.0 (CH), 125.8 (d, $J = 10.9$ Hz, CP), 110.9 (CH), 110.2 (CH), 56.0 (OCH$_3$), 51.7 (OCH$_3$), 30.1 (CH$_2$), 29.4 (CH$_2$); $^{31}$P $^1$H NMR (121 MHz, CDCl$_3$): $\delta = –14.97, –15.71$; IR (KBr, cm$^{-1}$): 3050 (w), 2998 (w), 2944 (w), 2838 (w), 1738 (s), 1670 (s), 1586 (m), 1479 (s), 1434 (s), 1404 (s), 1284 (m), 1240 (m), 1175 (m), 1067 (m), 1023 (s), 743 (s); HRMS (FAB+): m/z calcd. for C$_{43}$H$_{40}$NO$_5$P$_2$ (M+H$^+$): 712.2382; found: 712.2387; anal. calcd. for C$_{43}$H$_{39}$NO$_5$P$_2$: C 72.56, H 5.52, N 1.97; found: C 72.86, H 5.48, N 2.00.  

4-[Bis(3-(diphenylphosphino)-4-methoxyphenyl)amino]-4-oxo-butanic acid (20): To a solution of compound 19 (0.35 g, 0.49 mmol) in THF (5 mL) was added LiOH·H$_2$O (0.023 g, 0.54 mmol) in water (2 mL). After stirring for 1 h additional water (2 mL) was added. THF was removed under reduced pressure and the remaining solution was treated with 2 M HCl (5 mL). The white precipitate was filtered off and purified by silica gel column chromatography (ethyl acetate) yielding 20 as a white solid (46%, 0.16 g). $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.32-7.20$ (m, 20H, H-arom), 6.97 (m, 1H, H-arom), 6.80 (m, 2H, H-arom), 6.29 (m, 1H, H-arom), 3.75 (bs, 3H, OCH$_3$), 3.71 (bs, 3H, OCH$_3$), 2.57 (t, $J = 6.5$ Hz, 2H, CH$_2$), 2.33 (t, $J = 6.5$ Hz, 2H, CH$_2$); $^{13}$C $^1$H NMR (125 MHz, CDCl$_3$): $\delta = 177.5$ (COO), 171.9 (NCO), 160.3 (d, $J = 12.7$ Hz, CO), 159.1 (d, $J = 15.7$ Hz, CO), 135.9 (m, CN, CP), 133.9 (m, CH), 133.2 (CH), 132.0 (d, $J = 10.6$ Hz, CH), 131.2 (CH), 129.9 (CH), 129.6 (CH), 128.7 (m, CH), 128.2 (CH), 126.2 (d, $J = 10.9$ Hz, CP), 123.8 (CH), 119.2 (CH), 111.2 (CH), 110.5 (CH), 56.1 (OCH$_3$), 30.2 (CH$_2$), 29.9 (CH$_2$); $^{31}$P $^1$H NMR (121 MHz, CDCl$_3$): $\delta = –15.09, –15.31$; HRMS (FAB+): m/z calcd. for C$_{42}$H$_{38}$NO$_5$P$_2$ (M+H$^+$): 698.2225; found: 698.2222.  

(S)-Methyl 2-[4-(bis(3-(diphenylphosphino)-4-methoxy-phenyl)amino)-4-oxobutanamido]-3-methylbutanoate (21): METHOD A. Following the procedure as described for the synthesis of compound 15, diphosphine 21 was obtained starting from 20 (25 mg, 35 μmol) and L-valine methyl ester hydrochloride (5.9 mg, 35 μmol). Crystallization from ethyl acetate/light petroleum afforded 21 in 75% yield (21 mg) as a white solid. METHOD B. Sodium hydride (24 mg, 60% in mineral oil, 0.60 mmol) was added to a solution of 4 (0.18 g, 0.29 mmol) in THF (10 mL) and the reaction mixture was stirred for 2 h at reflux temperature. The solution was cooled to room temperature and a solution of (S)-N-(4-chloro-4-oxobutanoyl)-valine methyl ester (0.15 g, 0.59 mmol), prepared from SOCl$_2$ and valine derivative A, in THF (5 mL) was added. The reaction mixture was stirred another 16 h at reflux temperature. After cooling to room temperature, the solution was diluted with toluene (10 mL) and washed with brine (20 mL). The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure. The obtained yellow oil was washed with hexanes. Purification by silica gel column chromatography (40% ethyl acetate in light petroleum) gave 21 in 80% yield (0.19 g) as a white solid. $[\alpha]_D^{20} = +5.5^\circ$ (c 2.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.30-7.18$ (m, 20H, H-arom), 6.99 (m,
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(5)-N-(3-Carboxypropanoyl)-valine methyl ester (A): This compound was prepared according to a literature procedure used for the synthesis of a phenylalanine derivative.[42] Triethylamine (2.0 mL, 14.34 mmol) was added to a solution of L-valine methyl ester hydrochloride (1.20 g, 7.16 mmol) in CH₃CN (60 mL) at 0 °C, and the solution was left stirring for 15 min. A solution of succinic anhydride (0.76 g, 7.58 mmol) in CH₃CN (40 mL) was added dropwise and the reaction mixture was stirred for 2 h, keeping the temperature at 0 °C. The solvent was then removed under vacuum and the crude material was dissolved in ethyl acetate (60 mL), and washed with 0.5 M citric acid solution (30 mL) and brine (2 × 50 mL). The organic phase was dried over Na₂SO₄ and the solvent removed in vacuo to afford A (1.18 g, 71%) as a colorless oil. \(^1\)H NMR (300 MHz, CDCl₃): δ = 6.50 (d, J = 8.7 Hz, 1H, NH), 4.53 (dd, J = 8.7 Hz, J = 4.8 Hz, 1H, Hα), 3.72 (s, 3H, OCH₃), 2.68 (m, 2H, CH₂), 2.56 (m, 2H, CH₂), 2.23 (m, 1H, Hβ), 0.90 (d, J = 6.9 Hz, 3H, CH₃), 0.87 (d, J = 7.2 Hz, 3H, CH₃); \(^1\)^13C \(^1\)H NMR (75 MHz, CDCl₃): δ = 177.0 (CO), 173.0 (CO), 172.3 (CO), 57.5 (Cα), 52.5 (OCH₃), 31.5 (Cβ), 30.9 (CH₂), 29.7 (CH₂), 29.1 (CH₃), 18.0 (CH₃).

Methyl 4-[4,6-bis(diphenylphosphino)-phenoxazin-10-yl]-4-oxo-butyrate (22): Sodium hydride (0.15 g, 60 % in mineral oil, 3.66 mmol) was added to a solution of 2 (1.0 g, 1.81 mmol) in THF (40 mL) and this solution was stirred for 1 h at reflux temperature. The resulting red solution was cooled to room temperature and methyl 4-chloro-4-oxobutyrate (0.55 g, 3.62 mmol) was added. The solution was stirred another 16 h at reflux temperature. After cooling to room temperature, the resulting yellow solution was diluted with toluene (40 mL) and washed with brine (40 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The obtained yellow oil was washed with hexanes. Purification by crystallization (methylene chloride/methanol) gave 22 in 66 % yield (0.80 g) as a pale yellow solid. \(^1\)H NMR (500 MHz, CDCl₃): δ = 7.50 (d, J = 8.0 Hz, 2H, H-arom), 7.31-7.22 (m, 20H, H-arom.), 7.02 (t, J = 7.7 Hz, 2H, H-arom), 6.58 (dd, J = 7.7 Hz, J = 1.3 Hz, 2H, H-arom), 3.61 (s, 3H, OMe), 2.92 (t, J = 6.7 Hz, 2H, CH₂), 2.69 (t, J = 6.7 Hz, 2H, CH₂); \(^1\)^13C \(^1\)H NMR (125 MHz, CDCl₃): δ = 173.0 (COO), 170.8 (NCO), 153.0 (t, J = 20.2 Hz, CO), 136.1 (t, J = 11.4 Hz, PC), 134.0 (t, J = 21.1 Hz, CH), 131.1 (CH), 128.6 (CH), 128.3 (d, J = 7.2 Hz, CH), 127.3 (t, J = 21.5 Hz, CH), 125.6 (CH), 125.5 (CH), 125.0 (OCH₃), 29.4 (CH₂); \(^3\)P \(^1\)H NMR (121 MHz, CDCl₃): δ = −16.97; IR (KBr, cm⁻¹): 3065 (w), 3053 (w), 3001 (w), 2950 (w), 1743 (s), 1687 (s), 1578 (s), 1460 (s), 1412 (s), 1370 (s), 1318 (s), 1270 (m), 1223 (s), 1176 (m), 1069 (m), 1025 (s), 745 (s), 696 (s); HRMS
Methyl 3-[4,6-bis(diphenylphosphino)-phenoxazin-10-yl]propionate (23): This compound was prepared according to a literature procedure.\textsuperscript{[35]} To a stirred suspension of Nixantphos (1.0 g, 1.81 mmol) and methyl acrylate (3.4 mL, 37.9 mmol) was added a solution of NBu\textsubscript{4}Br (0.079 g, 0.25 mmol) and sodium methoxide (0.015 g, 0.28 mmol) in methanol (1.0 mL). The mixture was heated and stirred under reflux for 16 h. Water (20 mL) was added and the mixture was extracted with methylene chloride (3 × 10 mL). The combined organic phases were dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. Crystallization (methylene chloride/methanol) yielded 0.86 g (75 \%) of 23 as an off-white solid. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ = 7.26-7.21 (m, 20H, H-arom.), 6.71 (t, J = 8.0 Hz, 2H, H-arom), 6.54 (d, J = 8.0 Hz, 2H, H-arom), 6.07 (d, J = 8.0 Hz, 2H, H-arom), 3.92 (t, J = 7.8 Hz 2H, CH\textsubscript{2}), 3.75 (s, 3H, OCH\textsubscript{3}), 2.74 (t, J = 7.8 Hz, 2H, CH\textsubscript{2}); \textsuperscript{13}C {\textsuperscript{1}H} NMR (125 MHz, CDCl\textsubscript{3}): δ = 171.8 (COO), 147.0 (t, J = 21.2 Hz, CO), 136.8 (t, J = 12.7 Hz, PC), 133.8 (t, J = 20.6 Hz, CH), 132.4 (CN), 128.2 (CH), 128.1 (t, J = 6.4 Hz, CH), 125.6 (CH), 125.1 (t, J = 19.4 Hz, Cq), 123.8 (CH), 111.6 (CH), 51.9 (CH\textsubscript{3}), 40.0 (CH\textsubscript{2}), 29.7 (CH\textsubscript{2}); \textsuperscript{31}P {\textsuperscript{1}H} NMR (121 MHz, CDCl\textsubscript{3}): δ = –17.63.

3-[4,6-Bis(diphenylphosphino)phenoxazin-10-yl]propanoic acid (24): To a solution of 23 (0.61 g, 0.96 mmol) in THF (10 mL) was added LiOH·H\textsubscript{2}O (0.044 g, 1.05 mmol) in water (5 mL). After stirring for 1 h, additional water (5 mL) was added. THF was removed under reduced pressure and the remaining solution was treated with 2 M HCl (5 mL). The white precipitate was filtered off and recrystallized from CH\textsubscript{2}Cl\textsubscript{2}/MeOH yielding 24 as a white solid (0.55 g, 92 \%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ = 7.13-7.02 (m, 20H, H-arom), 6.57 (t, J = 8.0 Hz, 2H, H-arom), 6.43 (d, J = 7.5 Hz, 2H, H-arom), 5.90 (dd, J = 8.0 Hz, J = 1.5 Hz, 2H, H-arom), 3.76 (m, 2H, CH\textsubscript{2}), 2.56 (m, 2H, CH\textsubscript{2}); \textsuperscript{13}C {\textsuperscript{1}H} NMR (125 MHz, CDCl\textsubscript{3}): δ = 173.7 (COOH), 147.1 (t, J = 20.7 Hz, CO), 136.1 (t, J = 11.4 Hz, PC), 133.8 (t, J = 20.4 Hz, CH), 132.6 (CN), 128.4 (CH), 128.2 (t, J = 6.8 Hz, CH), 125.5 (CH), 125.1 (t, J = 18.9 Hz, Cq), 124.0 (CH), 111.8 (CH), 40.0 (CH\textsubscript{2}), 29.7 (CH\textsubscript{2}); \textsuperscript{31}P {\textsuperscript{1}H} NMR (121 MHz, CDCl\textsubscript{3}): δ = –16.42; IR (KBr, cm\textsuperscript{-1}): 3070 (w), 2920 (w), 1745 (s), 1580 (s), 1555 (s), 1464 (s), 1420 (s), 1382 (s), 1346 (m), 1280 (m), 1178 (m), 1096 (m), 746 (s), 693 (s); HRMS (FAB+): m/z calcd. for C\textsubscript{39}H\textsubscript{32}NO\textsubscript{3}P\textsubscript{2} (M+H\textsuperscript{+}): 624.1857; found: 624.1843; anal. calcd. for C\textsubscript{39}H\textsubscript{31}NO\textsubscript{3}P\textsubscript{2}: C 75.11, H 5.01, N 2.25; found: C 74.98, H 5.09, N 2.20.

(S)-Methyl 2-[3-(4,6-bis(diphenylphosphino)-phenox-azin-10-yl)propanamido]-3-methylbutanoate (25): Following the procedure as described for the synthesis of compound 15, phenoaxine 25 was obtained starting from diphosphine 24 (0.17 g, 0.27 mmol) and L-valine methyl ester hydrochloride (45 mg, 0.27 mmol). Purification by silica gel column chromatography (2 % methanol in methylene chloride) gave 25 in 45 \% yield (89 mg) as a white solid. [\alpha] 	extsuperscript{20}D = +9.8 \textdegree (c 1.0, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ = 7.33-7.23 (m, 20H, H-arom.), 6.73 (t, J = 8.0 Hz, 2H, H-arom), 6.63 (d, J = 8.0 Hz, 2H, H-arom), 6.18 (d, J = 8.5 Hz, 1H, NH), 6.05 (dd, J = 7.5 Hz, J = 1.5 Hz, 2H, H-arom), 4.55 (dd, J = 8.5 Hz, J = 5.0 Hz, 1H, Ha), 3.94 (m, 2H, CH\textsubscript{2}), 3.72 (s, 3H, OCH\textsubscript{3}), 2.64 (t, J = 7.5 Hz, 2H, CH\textsubscript{2}), 2.14
(m, 1H, Hβ), 0.94 (d, J = 6.5 Hz, 3H, CH₃), 0.92 (d, J = 6.5 Hz, 3H, CH₃); ¹³C {¹H} NMR (125 MHz, CD₂Cl₂): δ = 172.8 (CO), 170.8 (CO), 147.5 (t, J = 21.1 Hz, CO), 137.5 (t, J = 12.7 Hz, PC), 134.4 (t, J = 21.1 Hz, CH), 133.4 (t, J = 3.8 Hz, CN), 129.0 (CH), 128.8 (t, J = 6.7 Hz, CH), 125.9 (CH), 125.4 (t, J = 19.0 Hz, Cq), 124.4 (CH), 112.6 (CH), 57.8 (Ca), 52.6 (OCH₃), 40.9 (CH₂), 32.4 (CH₂), 31.8 (Cβ), 19.2 (CH₃), 18.3 (CH₃); ³¹P {¹H} NMR (121 MHz, CD₂Cl₂): δ = –18.11; HRMS (FAB+): m/z calcd. for C₄₅H₄₃N₂O₄P₂ (M⁺H⁺): 737.2698; found: 737.2695.

2-(1,3-Dioxoisindolin-2-yl)-N,N-bis(2-(diphenylphosphino)ethyl) acetamide (26): To a mixture of diphosphine 1 (0.48 g, 1.0 mmol) and triethylamine (0.65 mL, 4.6 mmol) in methylene chloride (20 mL) was added phthalylglycyl chloride (0.25 g, 1.1 mmol). The reaction mixture was stirred for 16 h at room temperature and then washed with degassed water (10 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (1 % methanol in methylene chloride) to afford 26 in 68 % yield (0.43 g) as an off-white solid. ¹H NMR (500 MHz, CD₂Cl₂): δ = 7.87 (m, 2H, H-arom), 7.76 (m, 2H, H-arom), 7.49-7.33 (m, 20H, H-arom), 4.13 (s, 2H, CH₂), 3.36 (m, 4H, CH₂); ¹³C {¹H} NMR (125 MHz, CD₂Cl₂): δ = 168.3 (CO), 165.4 (CO), 138.6 (d, J = 12.7 Hz, PC), 137.9 (d, J = 12.6 Hz, PC), 134.6 (CH), 133.3 (d, J = 12.3 Hz, CH), 133.1 (d, J = 12.3 Hz, CH), 132.8 (Cq), 129.6 (CH), 129.3 (d, J = 7.2 Hz, CH), 129.2 (CH), 129.1 (d, J = 6.8 Hz, CH), 123.8 (CH), 45.1 (d, J = 26.6 Hz, CH₂), 44.5 (d, J = 24.9 Hz, CH₂), 39.4 (CH₂), 28.4 (d, J = 15.2 Hz, CH₂), 26.6 (d, J = 13.8 Hz, CH₂); ³¹P {¹H} NMR (121 MHz, CD₂Cl₂): δ = –19.28, –20.64; HRMS (FAB+): m/z calcd. for C₃₈H₃₅N₂O₃P₂ (M⁺H⁺): 629.2123; found: 629.2116; anal. calcd. for C₃₈H₃₄N₂O₃P₂: C 72.60, H 5.45, N 4.46; found: C 72.49, H 5.48, N 4.60.

2-Amino-N,N-bis(2-(diphenylphosphino)ethyl)acetamide (27): To a suspension of 26 (0.34 g, 0.54 mmol) in methanol (10 mL) was added hydrazine monohydrate (53 μL, 1.08 mmol). The reaction mixture was stirred for 16 h at room temperature and then concentrated under reduced pressure. To the residue was added methylene chloride (10 mL). The precipitates were filtered off and the filtrate was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (4 % methanol in methylene chloride) to afford 27 in 74 % yield (0.20 g) as a colourless oil. ¹H NMR (500 MHz, CD₂Cl₂): δ = 7.60-7.34 (m, 20H, H-arom), 3.48 (m, 2H, CH₂), 3.23 (m, 2H, CH₂), 3.11 (s, 2H, CH₂), 2.30 (m, 4H, CH₂), 2.30 (m, 4H, CH₂); ¹³C {¹H} NMR (125 MHz, CD₂Cl₂): δ = 172.6 (CO), 138.8 (d, J = 13.1 Hz, PC), 138.0 (d, J = 12.7 Hz, PC), 133.1 (d, J = 19.0 Hz, CH), 129.5 (CH), 129.2 (CH), 129.1 (d, J = 5.2 Hz, CH), 129.0 (d, J = 6.8 Hz, CH), 44.4 (d, J = 26.3 Hz, CH₂), 44.1 (d, J = 24.0 Hz, CH₂), 43.5 (CH₂), 28.2 (d, J = 15.2 Hz, CH₂), 26.8 (d, J = 13.8 Hz, CH₂); ³¹P {¹H} NMR (121 MHz, CD₂Cl₂): δ = –19.47, –20.50; HRMS (FAB+): m/z calcd. for C₃₀H₃₃N₂O₃P₂ (M⁺H⁺): 499.2068; found: 499.2068; anal. calcd. for C₃₀H₃₂N₂O₃P₂: C 72.60, H 5.45, N 4.46; found: C 72.49, H 5.48, N 4.60.

(S)-(9H-Fluorenlyl)methyl 1-(2-(bis(2-(diphenylphosphino)ethyl)amino)-2-oxoethylamino)-1-oxopropan-2-ylcarbamate (28): To a solution of 27 (0.20 g, 0.40 mmol) and Fmoc-Ala-OH (0.15 g, 0.48 mmol) in methylene chloride (10 mL) was added EDC (92 mg, 0.48 mmol). The reaction mixture
was stirred for 16 h at room temperature and then washed with brine (10 mL). The organic phase was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (2% methanol in CH₂Cl₂ to afford 28 in 69% yield (0.22 g) as white solid. \([\alpha]^{20}_{D} = +1.2^\circ \text{ (c 1.0, CHCl}_3\); \(^1\)H NMR (500 MHz, CDCl₃): \(\delta = 7.78 \text{ (d, } J = 7.5 \text{ Hz, 2H, H-arom), 7.62 \text{ (d, } J = 7.5 \text{ Hz, 2H, H-arom), 7.39-7.31 \text{ (m, 24H, H-arom), 6.85 \text{ (bs, 1H, NH), 5.50 \text{ (d, } J = 8.0 \text{ Hz, 1H, Ha), 4.38 \text{ (d, } J = 7.5 \text{ Hz, 2H, CH}_2\), 4.24 \text{ (t, } J = 7.0 \text{ Hz, 2H, CH}_2\), 3.77 \text{ (dq, } J = 17.5 \text{ Hz, 1H, Ha), 3.41 \text{ (m, 2H, CH}_2\), 3.22 \text{ (m, 2H, CH}_2\), 2.25 \text{ (m, 4H, CH}_2\), 1.38 \text{ (d, } J = 7.0 \text{ Hz, 3H, CH}_3\); \(^13\)C \{\^1\}H NMR (125 MHz, CDCl₃): \(\delta = 172.4 \text{ (CO), 167.8 \text{ (CO), 156.3 \text{ (CO), 144.6 \text{ (d, } J = 10.6 \text{ Hz, Cq), 141.8 \text{ (Cq), 138.6 \text{ (d, } J = 13.1 \text{ Hz, PC), 137.8 \text{ (d, } J = 13.4 \text{ Hz, PC), 133.1 \text{ (d, } J = 18.1 \text{ Hz, CH), 129.7 \text{ (CH), 129.3 \text{ (CH), 129.3 \text{ (d, } J = 6.7 \text{ Hz, CH), 129.1 \text{ (d, } J = 6.7 \text{ Hz, CH), 128.2 \text{ (CH), 127.6 \text{ (CH), 125.7 \text{ (CH), 120.5 \text{ (CH), 67.4 \text{ (CH), 51.1 \text{ (CH), 47.8 \text{ (CH), 44.8 \text{ (d, } J = 25.6 \text{ Hz, CH}_2\), 44.2 \text{ (d, } J = 24.5 \text{ Hz, CH}_2\), 41.7 \text{ (CH}_2\), 28.1 \text{ (d, } J = 15.6 \text{ Hz, CH}_2\), 26.6 \text{ (d, } J = 14.5 \text{ Hz, CH}_2\), 19.3 \text{ (CH}_3\); \(^{31}\)P \{\^1\}H NMR (121 MHz, CDCl₃): \(\delta = –19.66, –20.91; \text{ HRMS (FAB+): m/z calcld. for C}_{48}\text{H}_{48}\text{N}_{3}\text{O}_{4}\text{P}_{2} (\text{M+H}): 792.3120; \text{ found: } 792.3124; \text{ anal. calcd. for C}_{48}\text{H}_{47}\text{N}_{3}\text{O}_{4}\text{P}_{2}: C72.81, H 5.98, N 5.31; found: C 72.65, H 5.94, N 5.28.}

(S)-(9H-Fluorenyl)methyl 1-chloro-1-oxopropan-2-ylcarbamate, Fmoc-Ala-Cl (B): Compound B was prepared according to a literature procedure. \[43\] A suspension of \(N\)-Fmoc-L-alanine (1.0 g, 3.2 mmol) in methylene chloride (15 mL) was treated with freshly distilled thionyl chloride (2.0 mL, 27.6 mmol). The mixture was stirred for 2 h at reflux temperature. All volatiles were removed under reduced pressure and the residue was co-evaporated twice with methylene chloride (10 mL) to remove excess of thionyl chloride. Crystallization from a methylene chloride/hexanes mixture gave acid chloride B (0.88 g, 84%) as a white solid. \(^1\)H NMR (300 MHz, CDCl₃): \(\delta = 7.77 \text{ (d, } J = 7.5 \text{ Hz, 2H, H-arom), 7.59 \text{ (dd, } J = 8.5 \text{ Hz, 4.5 Hz, 2H, H-arom), 7.41 \text{ (t, } J = 8.2 \text{ Hz, 2H, H-arom), 7.33 \text{ (t, } J = 8.0 \text{ Hz, 2H, H-arom), 5.21 \text{ (d, } J = 8.0 \text{ Hz, 1H, NH), 4.61 \text{ (t, } J = 7.5 \text{ Hz, 1H, CH), 4.46 \text{ (m, 2H, CH}_2\), 4.23 \text{ (t, } J = 6.6 \text{ Hz, 1H, Ha), 1.55 \text{ (d, } J = 6.9 \text{ Hz, 3H, CH}_3\).}

(S)-(9H-Fluorenyl)methyl 1-(bis(3-(diphenylphosphino)-4-methoxyphenyl)amino)-1-oxopropan-2-ylcarbamate (29): Sodium hydride (0.044 g, 60% in mineral oil, 1.10 mmol) was added to a solution of 4 (0.33 g, 0.55 mmol) in THF (20 mL) and this solution was stirred for 2 h at reflux temperature. After cooling to ambient temperature, a solution of acid chloride B (0.20 g, 0.60 mmol) in THF (10 mL) was added to the reaction mixture. The solution was stirred another 16 h at reflux temperature. After cooling to room temperature, the solution was diluted with toluene (40 mL) and washed with brine (40 mL). The organic phase was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20 → 40% ethyl acetate in light petroleum) to afford 29 in 61% yield (0.30 g) as a white solid. \([\alpha]^{20}_{D} = +68.6^\circ \text{ (c 1.0, CHCl}_3\); \(^1\)H NMR (500 MHz, CDCl₃): \(\delta = 7.77 \text{ (d, } J = 7.5 \text{ Hz, 2H, H-arom), 7.59 \text{ (d, } J = 7.5 \text{ Hz, 2H, H-arom), 7.41 \text{ (t, } J = 7.2 \text{ Hz, 2H, H-arom), 7.33-7.18 \text{ (m, 23H, H-arom), 7.09 \text{ (m, 1H, H-arom), 6.82 \text{ (dd, } J = 8.5 \text{ Hz, 4.5 Hz, 2H, H-arom), 6.37 \text{ (bs, 1H, H-arom), 6.27 \text{ (bs, 1H, H-arom), 5.52 \text{ (d, } J = 8.0 \text{ Hz, 1H, NH), 4.36 \text{ (m, 1H, CH), 4.32 \text{ (m, 2H, CH}_2\), 4.20 \text{ (t, } J = 7.2 \text{ Hz, 1H, Ha), 3.77 \text{ (s, 3H, OCH}_3\), 3.72 \text{ (s, 3H, OCH}_3\), 1.04 \text{ (d, } J = 6.5 \text{ Hz, 3H, CH}_3\); \(^13\)C \{\^1\}H NMR (125 MHz, CDCl₃): \(\delta = 173.3 \text{ (NCO),}
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160.7 (d, $J = 14.3$ Hz, CO), 159.2 (d, $J = 14.7$ Hz, CO), 159.2 (d, $J = 14.7$ Hz, CO), 155.6 (COO), 144.1 (Cq), 141.5 (Cq), 136.0 (m, CN, CP), 134.8 (Cq), 134.0 (CH), 133.9 (CH), 133.7 (CH), 133.4 (CH), 132.1 (d, $J = 11.8$ Hz, CH), 131.1 (CH), 130.4 (CH), 129.2-128.6 (m, CH), 127.9 (CH), 127.3 (CH), 125.4 (CH), 125.4 (CH), 120.2 (CH), 111.4 (CH), 110.6 (CH), 67.2 (CH$_2$), 56.2 (OCH$_3$), 53.6 (Cq), 48.2 (CH), 47.4 (CH), 19.0 (CH$_3$); $^{31}$P $^1$H NMR (202 MHz, CDCl$_3$): $\delta = –15.11, –15.72$; IR (KBr, cm$^{-1}$): 3050 (w), 3001 (w), 2935 (w), 2836 (w), 1720 (s), 1668 (s), 1585 (m), 1478 (s), 1434 (s), 1391 (m), 1240 (s), 1179 (m), 1067 (m), 1025 (s), 815 (m), 742 (s), 696 (s); HRMS (FAB+): m/z calcd. for C$_{56}$H$_{49}$N$_2$O$_5$P$_2$ ($M^+H^+$): 891.3117; found: 891.3114; anal. calcd. for C$_{56}$H$_{48}$N$_2$O$_5$P$_2$: C 75.49, H 5.43, N 3.14; found: C 75.48, H 5.38, N 3.11.

(S)-(9H-Fluorenyl)methyl 1-(bis(2-diphenylphosphinoethyl)amino)-1-oxopropan-2-ylcarbamate (30): To a mixture of diphosphine 1 (0.24 g, 0.50 mmol) and triethylamine (0.32 mL, 2.3 mmol) in methylene chloride (10 mL) was added a solution of acid chloride B (0.18 g, 0.55 mmol) in methylene chloride (2 mL). The reaction mixture was stirred for 16 h at room temperature and subsequently washed with brine (2 × 10 mL). The organic phase was dried over MgSO$_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (CH$_2$Cl$_2$ $\rightarrow$ 3 % MeOH in CH$_2$Cl$_2$) gave 30 in 41 % yield (0.15 g) as a white solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.79$ (d, $J = 7.5$ Hz, 2H, H-arom), 7.64 (t, $J = 6.5$ Hz, 2H, H-arom), 7.46-7.27 (m, 24H, H-arom), 5.79 (d, $J = 7.5$ Hz, 1H, NH), 4.41 (m, 3H, CH$_3$), 4.25 (t, $J = 6.5$ Hz, 1H, CH), 3.61 (m, 1H, CH$_2$), 3.33 (m, 3H, CH$_2$), 2.42 (m, 1H, CH$_2$), 2.31 (m, 3H, CH$_2$), 1.19 (d, $J = 6.5$ Hz, 3H, CH$_3$); $^{13}$C $^1$H NMR (125 MHz, CDCl$_3$): $\delta = 172.3$ (NCO), 155.6 (COO), 141.4 (d, $J = 13.8$ Hz, Cq), 141.4 (Cq), 137.9 (d, $J = 12.3$ Hz, CP), 137.7 (d, $J = 12.2$ Hz, CP), 137.3 (d, $J = 12.3$ Hz, CP), 136.8 (d, $J = 12.3$ Hz, CP), 133.0-132.6 (m, CH), 130.8 (d, $J = 9.7$ Hz, CH), 129.3-128.7 (m, CH), 127.8 (CH), 127.2 (CH), 125.3 (CH), 121.1 (CH), 120.1 (CH), 119.9 (CH), 67.0 (CH$_2$), 47.3 (CH), 47.1 (CH), 45.3 (d, $J = 26.1$ Hz, CH$_2$), 44.0 (d, $J = 24.9$ Hz, CH$_2$), 28.2 (d, $J = 15.6$ Hz, CH$_2$), 26.6 (d, $J = 14.3$ Hz, CH$_2$), 19.3 (CH$_3$); $^{31}$P $^1$H NMR (121 MHz, CDCl$_3$): $\delta = –17.49, –19.50$; HRMS (FAB+): m/z calcd. for C$_{46}$H$_{45}$N$_2$O$_3$P$_2$: C 74.49, H 5.43, N 3.14; found: C 74.48, H 5.38, N 3.11.

General procedure for the asymmetric alkylation of 2-acetylcyclohexanone with cinnamyl acetate. A mixture of [Pd($\eta^3$-C$_3$H$_5$)Cl]$_2$ (1.0 μmol) and ligand (2.2 μmol) in THF (1.0 mL) was stirred for 10 minutes at room temperature. Cinnamyl acetate (0.3 mmol) was added to the solution. After another 10 minutes, the solution was added to a suspension of 2-acetylcyclohexanone (0.2 mmol) and NaH (0.25 mmol) in THF (1.0 mL) at the appropriate temperature. The resulting suspension was stirred at the appropriate temperature for 20 h. After the addition of 1 M aqueous HCl (2.0 mL), the mixture was extracted twice with ethyl acetate (2.0 mL). The combined organic phases were dried over MgSO$_4$. The conversion was determined by GC using a DB-1 (J&W) column. Purification by silica gel flash column chromatography (EtOAc/hexane = 1/3) afforded the product as a colourless oil. The enantiomeric excess of the product was determined by chiral HPLC analysis using a Chiralpak AD-H column (0.46 × 25 cm); with 1 % 2-propanol in n-hexane as eluent; flow rate = 0.5 mL.min$^{-1}$; $\lambda$ = 254 nm; $t_R$ (R) = 16.1 min and $t_R$ (S) = 17.4 min.
References and Notes


[29] Following an alternative route, ligand 21 was synthesized by the acylation of compound 4 with the acid chloride derivative of (S)-N-(3-carboxypropanoyl)-valine methyl ester which was obtained by the reaction of L-valine methyl ester with succinic anhydride (see Experimental Section).


Allylic Alkylation by means of Secondary Interactions


[34] The hydrolysis of the amide bond was not observed in the saponification of related compounds 16 and 19.

[35] Calculations were performed using the CaChe WorkSystem (Fujitsu Ltd.) Pro Version 7.5.0.85, using the MM2 program.


[41] Data is in agreement with the literature: Ref. 28.
