CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200800359

Supramolecular Bidentate Ligands by Metal-Directed in situ Formation of Antiparallel β-Sheet Structures and Application in Asymmetric Catalysis

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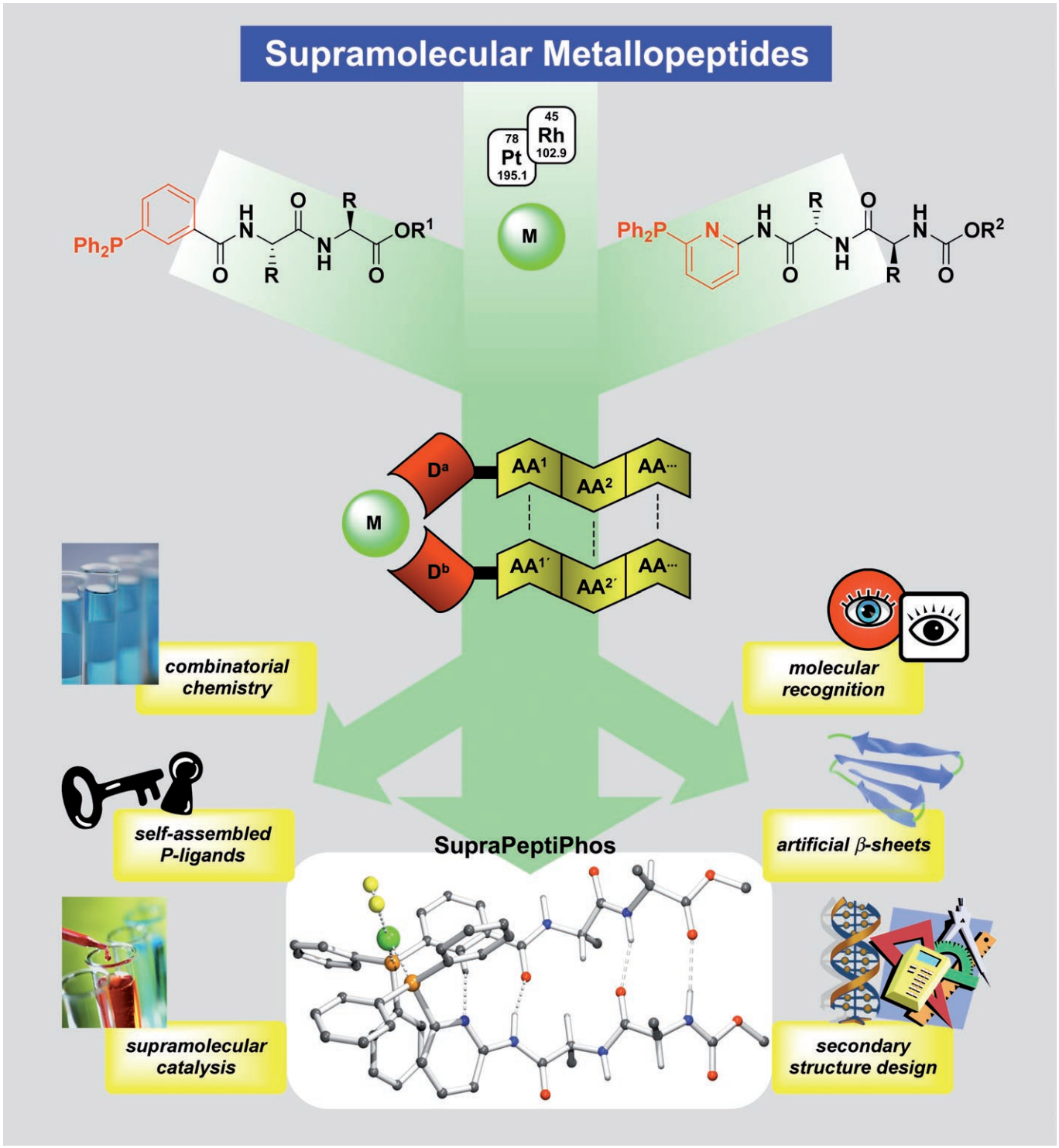
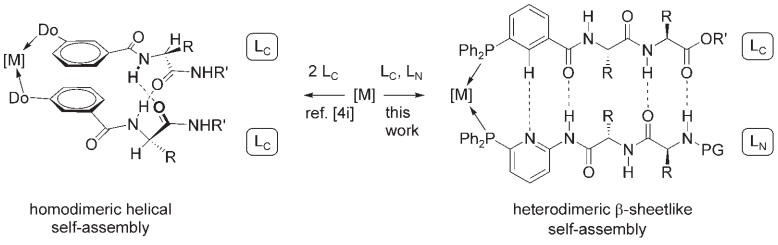


Abstract: The principles of protein structure design, molecular recognition, and supramolecular and combinatorial chemistry have been applied to develop a convergent metal-ion-assisted self-assembly approach that is a very simple and effective method for the de novo design and the construction of topologically predetermined antiparallel β-sheet structures and self-assembled catalysts. A new concept of in situ generation of bidentate P-ligands for transition-metal catalysis, in which two complementary, monodentate, peptide-based ligands are brought together by employing peptide secondary structure motif as constructing tool to direct the self-assembly process, is achieved through formation of stable β-sheet motifs and subsequent control of selectivity. The supramolecular structures were studied by ^{1}H, ^{31}P, and ^{13}C NMR spectroscopy, ESI mass spectrometry, X-ray structure ana1ysis, and theoretical calculations. Our initial catalysis results confirm the close relationship between the self-assembled sheet conformations and the catalytic activity of these metallopeptides in the asymmetric rhodium-catalyzed hydroformylation. Good catalyst activity and moderate enantioselectivity were observed for the selected combination of catalyst and substrate, but most importantly the concept of this new methodology was successfully proven. This work presents a perspective interface between protein design and supramolecular catalysis for the design of β-sheet mimetics and screening of libraries of self-organizing supramolecular catalysts.

Keywords: asymmetric catalysis · beta sheets · combinatorial chemistry · metallopeptides · self-assembly · supramolecular chemistry

Introduction

Spontaneous assembly of molecules through noncovalent complementary interactions and metal coordination is a fundamental process in nature (e.g., enzymes and receptors).[1,2] While it is known that amino acids and peptides have a high propensity for association, they are, surprisingly, not among the most commonly used self-complementary hydrogen-bonding units for the construction of noncovalent self-assembled systems[3] and catalysts.[4,5] We have previously reported a new concept for the in situ generation of heterobidentate ligand libraries based on a nature-analogous A·T base-pair motif and self-assembly through hydrogen bonding of different monodentate ligands in the coordination sphere of a metal.[4b,e–g] Recently we have extended our biomimetic concept and have shown the metal-templated self-assembly of peptide-based P-ligands (L_C) that spontaneously tend to form homodimeric helical peptide structures in the presence of Pt^{II} and Rh^{I} ions (Scheme 1, left-hand side).[4i] Such "PhanePhos"-analogous self-assembling catalyst systems gave excellent enantioinduction in asymmetric hydrogenation of benchmark substrates. We now wondered whether one could use self-assembly based on peptidic structures as a new platform to generate heterodimeric complexes selectively, which would enable a new combinatorial approach to novel chelation emulating ligand libraries for metal complex catalysis. Thus, a peptidyl ligand complementary to the C-linked peptide-based ligand L_C could be a N-linked peptidic system, such as L_N (Scheme 1, right-hand side). Molecular modeling suggested that complementary hydrogen bonding between the amide functions of both systems might occur and induce the formation of an antiparallel β-sheet structure.



Scheme 1. Expanding the concept of self-assembly of monodentate ligands through formation of secondary structures: two complementary metal binding sites with two otherwise flexible appended peptide chains are directed to form a conformationally stable folded β-sheet upon coordination of a metal ion.

Self-assembly with concomitant formation of β-sheet structures is an important aspect on its own, since it is crucial to protein folding and design.[6–9] Many β-sheet models based on covalent molecular templates in order to enforce preorientation of adjacent peptide strands and initiate noncovalent interactions between them have been studied.[6b,10–13] Conversely, relatively little is known about β-

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strand mimics generated through noncovalent self-assembling approaches.[14,15]

Most frequently, peptidomimetics and protein structural motif analogues have been studied for medicinal chemistry purposes,[6a,16] and to give a greater insight into peptide folding.[6b,10a] Much less is known about the application of secondary peptide structural elements as a chiral microenvironment for catalysis. Notable are the pioneering works of Gilbertson, Miller and Hoveyda.[17–22] However, in these cases the catalyst was either covalently linked to an unfolded peptide used purely as a source of chirality or the metal center was embedded into a *preformed* peptidic environment with defined secondary structure, which differs substantially from our approach representing a metal-coordination-induced β-sheet self-assembly process.

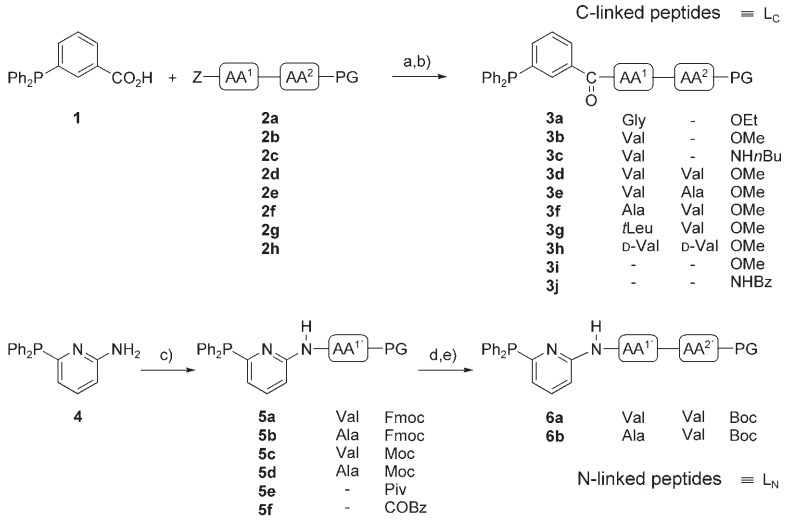
Results and Discussion

Ligand synthesis: Inspection of molecular models suggested that phosphane-functionalized peptides of the general structures **3**, **5** and **6** might be suitable candidates for the envisioned self-assembly process (Schemes 1 and 2). As complementary metal-binding units, 3-diphenylphosphanyl-benzoic acid (**1**, *m*-DPPBA) and 6-diphenyl-phosphanyl-2-aminopyridine (**4**, 6-DPPAP) were selected. Both templates provide complementary functional handles (CO_2H and NH_2) for the attachment of C- and N-terminal peptide residues, respectively. The dimensions of the template were selected such that the pendant peptide chains could be brought into hydrogen-bonding registry. Starting from **1** the peptidyl side chains were introduced by standard peptide coupling methods [4-dimethylaminopyridine (DMAP)/*N*,*N*-dicyclohexylcarbodiimide (DCC) or *N*,*N*-diisopropylcarbodiimide (DIC)] to give the phosphanes **3a**–**h** in good to excellent yields.[4i,22e] The complementary N-linked peptide ligands were prepared starting from aminopyridine **4** by employing conventional solution-phase peptide synthesis procedures utilizing a fragment condensation strategy (Scheme 2, steps c–e).[23]

To demonstrate the importance of the self-assembled β-sheet structure and to probe the nature of the folding peptide residues, we also synthesized a small set of non-peptidic ligands as a control experiment (**3i**,**j**, **5e**,**f**).

Conformational studies in solution: The first objective was to explore whether self-assembly through β-sheet formation is possible. Therefore, solution conformational analysis in aprotic solvents such as $CDCl_3$ was performed by ^1H, ^{31}P, ^{13}C NMR spectroscopy and ESI mass spectrometry. In absence of the metal ion, the peptide ligands did not self-associate and remained unfolded. Next, self-assembly of 1:1 mixtures of complementary C-peptidyl (L_C: **3**) and N-peptidyl ligands (L_N: **5**, **6**) in the presence of, for example, *cis*-[$PtCl_2$(cod)] (cod = 1,5-cyclooctadiene) was probed. Platinum(II) was chosen for its ability to form very stable complexes and to obtain a diamagnetic compound, which easily allows NMR spectroscopic investigation of the supramolecular structure.[4b,24] ESI mass spectrometry allowed the detection of the ion of the heterodimeric self-assembled complex *cis*-[$PtCl_2(L_C{\cdot}L_N)$] $[M-Cl]^+$ and thus provided evidence for the formation of the desired square-planar mononuclear metallopeptides in all cases.[23] Furthermore, ^{31}P NMR spectroscopy confirmed the selective formation of the heterodimeric complex (Figure 1). The detected AB spin systems with a $^2J_{P,P}$ coupling constant of 12.8–16.7 Hz prove in all cases the coordination of two non-equivalent phosphorous atoms to a single platinum center.[24] The $^1J_{P,Pt}$ coupling constants were all larger than 3000 Hz, as is typical for *cis*-diphosphane Pt^{II} complexes.[25] Small quantities of the L_C-homodimer were always observable in the NMR spectra, whereas the L_N-homodimer was also formed, but its signals were not detectable due to line broadening.

Product distributions were analyzed by integration of the resonances and revealed in the best case for *cis*-[$PtCl_2$(**3e**·**5b**)] a 98.3:1.7 mixture of heterodimer and L_C-homodimer at 300 K (Table 1, entry 13). This ratio corresponds to a heterodimer/homodimer equilibrium constant K of $3.23\times10^3\,M^{-1}$ and a statistically corrected free-energy difference ΔG of $-4.0\,kcal\,mol^{-1}$ ($\Delta G = -RT\ln(K/4)$). Such a significant devia-



Scheme 2. Synthesis of C- and N-linked peptide-based phosphane ligands. a) H_2 (1 atm), Pd-C (cat.), MeOH, RT (95–99%); b) DIC or DCC, DMAP, CH_2Cl_2, RT (64–96%); c) amino acid chloride, py, CH_2Cl_2, 0 °C→RT (82–93%); d) Et_2NH, THF, RT (quant); e) DIC, HOBt, CH_2Cl_2, RT (60–80%). Abbreviations: AA = amino acid; Z = benzyloxycarbonyl; PG = protecting group; Bz = benzyl; Piv = pivaloyl; Fmoc = 9-fluorenylmethoxycarbonyl; Moc = methoxycarbonyl.

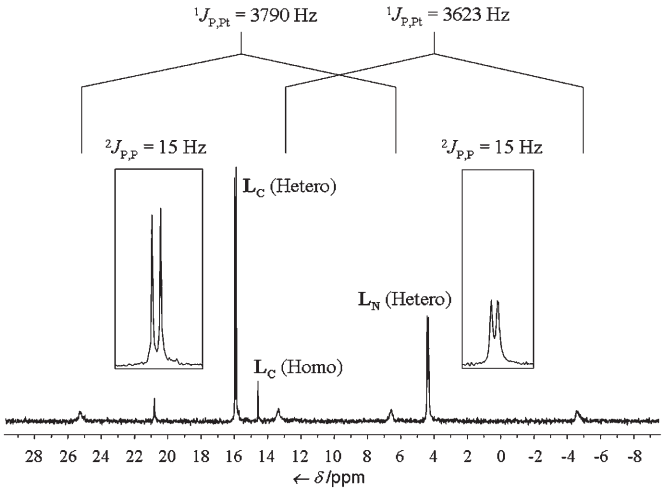


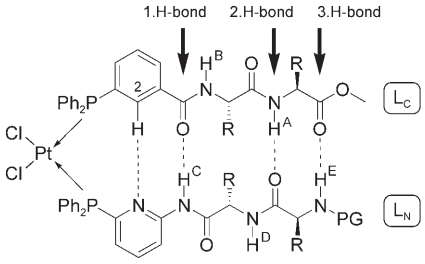
Figure 1. ^{31}P NMR spectrum (202 MHz) of an equimolar mixture of **3e**, **6b**, and *cis*-$PtCl_2$(cod) in $CDCl_3$ (37.5 mM) at 300 K. The AB system belongs to the heterodimeric self-assembled phosphane–phosphane Pt complex *cis*-[$PtCl_2$(**3e·6b**)].

tion from the statistical 50:25:25 mixture, expected for the equilibrium mixture of the heterodimeric and the two homodimeric complexes, was congruent with metal-induced self-assembly based on complementary ligand–ligand interactions, such as interstrand hydrogen bonding. Subtle perturbations in the sequence of these small peptide ligands can influence these equilibria dramatically (Table 1).[23] Thus, higher selectivities for heterodimer formation were obtained when combining sterically more demanding amino acids (AAs: *t*Leu, Val) with smaller AAs (Ala; Table 1, entries 5 vs. 6, 7 vs. 8, 15 vs. 16). A related steric effect is seen on combination of L- and unnatural D-configured AAs, in which interstrand AA side chains point in different directions which minimizes steric interactions and thus allows a closer interstrand contact (entry 9 vs. 10). Also, increasing the number of potential hydrogen-bonding donor and acceptor groups increased the selectivity towards heterodimer formation. Moreover, the terminal protecting groups (PG) play an important role as well, as some of them were capable of increasing the heterodimer stability, presumably by hydrophobic interactions (entry 13 (Fmoc) vs. 14 (Moc)).

Metal coordination is immediately evident from characteristic changes in the ^{1}H NMR spectra of the Pt^{II} complexes in $CDCl_3$ (Figure 2a, that is, signals for NH_C and aromatic 2-H protons) compared to the free ligands. In all cases the signals in the spectra of the complexes remained extremely sharp and the resonances of individual residues are well resolved. The proton NMR spectra are concentration independent at concentrations below 40 mM. This rules out the formation of large, disordered aggregates and suggests the formation of well-defined monomeric supramolecular species.

Significant low-field shifts of the resonances of the amide hydrogen atoms were observed upon complex formation (NH_A $\Delta\delta = 1.28$ ppm, NH_C $\Delta\delta = 2.38$ ppm), which indicates their involvement in hydrogen-bonding (see Table 2, entry 1 vs. 3).[26] Moreover, comparison with the helical homodimeric complexes showed that significant low-field positions of the amide protons of the AA residues that undergo hydrogen-bond formation were not just induced by metal coordination, but a consequence of interstrand hydrogen bonding and β-sheetlike folding (Table 2, entry 2 vs. 3). The magnitude of the vicinal coupling constant $^3J_{NH,C\alpha H}$ is related to the dihedral angles ϕ in peptides.[27] Rather large $^3J_{NH,C\alpha H}$ coupling constants (9.8, 7.8, and 9.7 Hz, see Table 2, entry 3) were monitored for the heterodimeric Pt-complex *cis*-[$PtCl_2$(**3d·5a**)], which is typical for a β-sheetlike conformational situation ($\phi \sim -120°$).[28]

Table 1. ^{1}H NMR spectroscopic and thermodynamic data for the in situ generated *cis*-[$PtCl_2$(L_C·L_N)] complexes.[23]



Entry	L_C·L_N	ArH CH···N [ppm]	NH 1.H-bond [ppm]	NH 2.H-bond [ppm]	NH 3.H-bond [ppm]	hetero/ homodimer ratio[a]	K [b] [M^{-1}]	ΔG [c] [kcal·mol^{-1}]
1	**3i·5e**	n.d.[d]	7.62	–	–	79.1 : 20.9	14	−0.8
2	**3j·5f**	8.91	9.31	–	–	80.7 : 19.3	17	−0.9
3	**3a·5a**	8.48	9.30	–	–	87.6 : 12.4	50	−1.5
4	**3b·5a**	8.58	9.13	–	–	70.2 : 29.8	6	−0.2
5	**3c·5a**	9.42	10.61	7.53	–	92.8 : 7.2	167	−2.2
6	**3c·5b**	9.57	10.78	7.61	–	97.7 : 2.3	1802	−3.6
7	**3g·5a**	9.48	10.59	7.96	–	93.8 : 6.2	228	−2.4
8	**3g·5b**	9.58	10.68	7.98	–	96.8 : 3.2	915	−3.2
9	**3d·5a**	9.47	10.61	7.53	–	94.9 : 5.1	339	−2.6
10	**3h·5a**	9.65	10.91	7.88	–	97.2 : 2.8	1228	−3.4
11	**3d·5b**	9.59	10.71	7.88	–	96.7 : 3.3	856	−3.2
12	**3e·5c**	9.45	10.55	7.98	–	95.7 : 4.3	501	−2.9
13	**3e·5b**	9.59	10.75	7.96	–	98.3 : 1.7	3229	−4.0
14	**3e·5d**	9.59	10.74	8.07	–	96.6 : 3.4	801	−3.2
15	**3d·6a**	9.46	10.56	8.51	5.58	93.6 : 6.4	215	−2.4
16	**3e·6b**	9.61	10.78	8.60	5.38	96.3 : 3.7	685	−3.1

[a] Determined by NMR integration. [b] $K = [\text{Hetero}]^2/([\text{C-Homo}][\text{N-Homo}])$. [c] $\Delta G = -RT\ln(K/4)$. [d] n.d. = not determined.

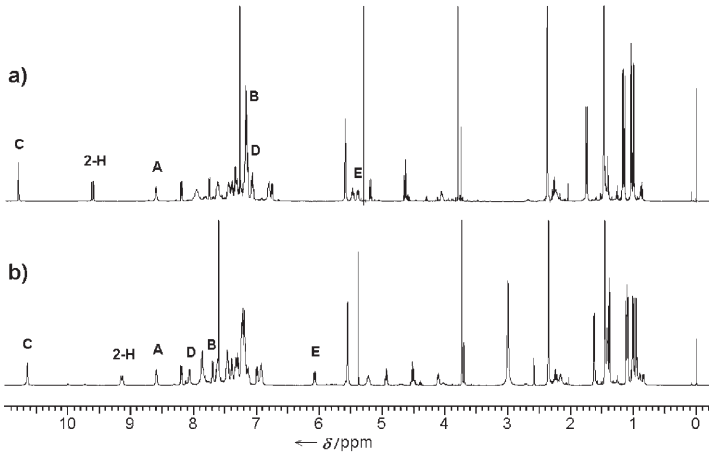
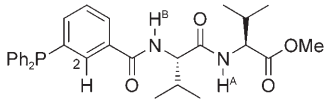
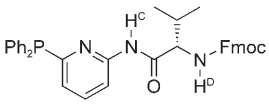


Figure 2. ^{1}H NMR spectra (500 MHz) of *cis*-[$PtCl_2$(**3e·6b**)] in a) $CDCl_3$ (37.5 mM) at 300 K and b) after addition of 20 vol% [D_6]DMSO. For signal assignments (A-E and 2-H) see Table 1.

Table 2. Comparison of relevant ^{1}H NMR proton shifts and coupling constants of free ligand and the homo- and heterodimeric Pt^{II} complexes of **3d** and **5a** in $CDCl_3$.[a]





Entry	Species	2-H	H^A	H^B	H^C	H^D
1	free ligand	7.72	6.56 (8.7)	6.71 (8.7)	8.23	5.34 (brs)
2	homodimer	7.60	6.71 (8.3)	8.14 (6.9)	7.70	5.40 (7.4)
3	heterodimer	9.47	7.84 (7.8)	6.92 (9.8)	10.61	5.70 (9.7)

[a] Chemical shifts in ppm, and corresponding coupling constants in parenthesis in Hz.

Evidence for interstrand interactions was also obtained from dimethylsulfoxide (DMSO) titration experiments (Figure 2b). The ^{1}H NMR spectrum obtained upon addition of [D_6]DMSO to a solution of *cis*-[$PtCl_2$(**3e·6b**)] in $CDCl_3$ showed that, with increasing amounts of [D_6]DMSO, the signals of amide protons B, D, and E are shifted downfield dramatically ($\Delta\delta = 0.53$, 0.95 and 0.69 ppm, respectively), indicative of their exposure to solvent, whereas the signals of amide protons A and C exhibited small upfield shifts ($\Delta\delta =$ 0 and 0.13 ppm, respectively). These results suggest that in a low dielectric solvent like $CDCl_3$, the amide protons A and C are solvent shielded due to the formation of strong, linear, intermolecular, hydrogen bonds.[26] Although amide proton E presumably is involved in a hydrogen bond in $CDCl_3$, proton acceptor solvents such as DMSO disrupt this interstrand interaction. This hydrogen bond might be weaker because of a higher conformational flexibility of the peptide chain ends.

Unambiguous assignment of the ^{1}H NMR resonances for *cis*-[$PtCl_2(L_C{\cdot}L_N)$] in $CDCl_3$ was possible by using a combination of DQF-COSY, edHSQC-N, 2D TOCSY, and 2D ROESY spectra. The 2D ROESY spectrum for *cis*-[$PtCl_2$-(**3e·6b**)] displayed 17 structurally relevant ROE correlations that were utilized to make sequence specific resonance assignments for the peptide chain, and the intrastrand ROE cross-peaks were consistent with extended β-strand conformations of the peptide strands.[29] 2D ROE connectivity also revealed ten interstrand contacts between the adjacent peptide strands attached to the same metal center. The cross-strand ROEs reflected the close proximity of two different ligands, as well as the folded conformation of the peptide strands and established that the peptides fold with the proposed strand alignment shown in Figure 3.[28,29b] The close proximity of two complementary ligands at the same metal center induced intermolecular hydrogen bonding between the neighboring peptide chains and thus lead to the formation of a stable, two-stranded, antiparallel, β-sheet structure.

To probe whether this assembly process is transferable from a platinum(II) to a rhodium(I) center, complexation studies of representative phosphane ligands **3** and **5** with [$Rh(cod)_2$]BF_4 were undertaken. Thus, treatment of [Rh-($cod)_2$]BF_4 with 1:1 mixture of representative ligand **3d** and **5a** in $CDCl_3$ furnished the corresponding self-assembled complex [Rh(cod)(**3d·5a**)]BF_4 exclusively. In the ^{31}P NMR the expected ABX system was monitored at $\delta = 16.0$ and 31.8 ppm ($^1J_{P,Rh} = 145.7$ Hz and 150.6 Hz, $^2J_{P,P} = 30.7$ Hz).[24,30] Moreover, ESI MS data indicated the exclusive formation of the self-assembled heterodimeric complex [Rh(cod)-(**3d·5a**)]BF_4 ($[M-BF_4]^+$ at $m/z = 1328.4$).[23] Hence, the self-assembly process with a rhodium(I) center is similar to that of platinum(II).

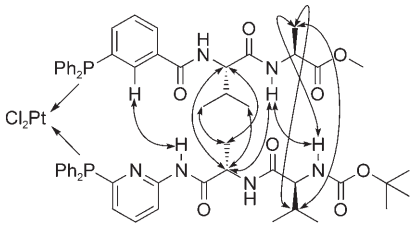


Figure 3. Detected interstrand ROE contacts of *cis*-[$PtCl_2$(**3e·6b**)] in $CDCl_3$ at 500 MHz and 300 K with a 300 ms spin lock time.

DFT calculations: To give a greater insight into the structure of the complex, DFT calculations were performed on a model system closely related to *cis*-[$PtCl_2$(**3e·6b**)], in which Val residues were substituted for Ala (Figure 4; see Supporting Information for full calculational details). Three isomers of this structure, corresponding to different arrangements of the ligands around the metal center, were optimized at the BP86/TZVP level. The resulting structures, which are nearly isoenergetic at this level of theory, all contained a typical two-stranded, antiparallel, β-sheet conformation, in which the AA side chains alternately project up and down as one

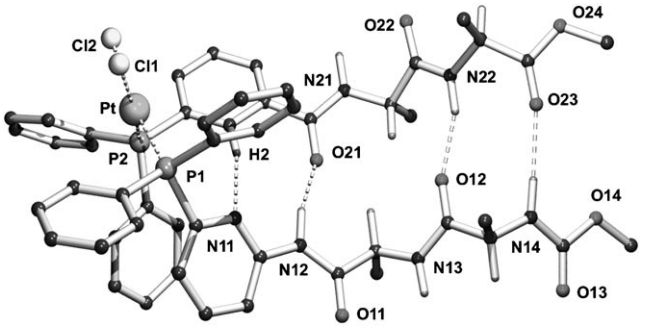


Figure 4. DFT-optimized structure of a slightly simplified model for *cis*-[$PtCl_2$(**3e·6b**)]. Selected interatomic distances (Å) and angles (°): Pt–P1 2.31, Pt–P2 2.30, H2···N11 2.71, N12···O21 2.90, H12···O21 1.90, H22···O12 1.98, H14···O23 2.11; P1–Pt–P2 105.9, C2–H2···N11 165.6, N12–H···O21 161.3, N22–H···O12 158.7, N14–H···O23 172.5.

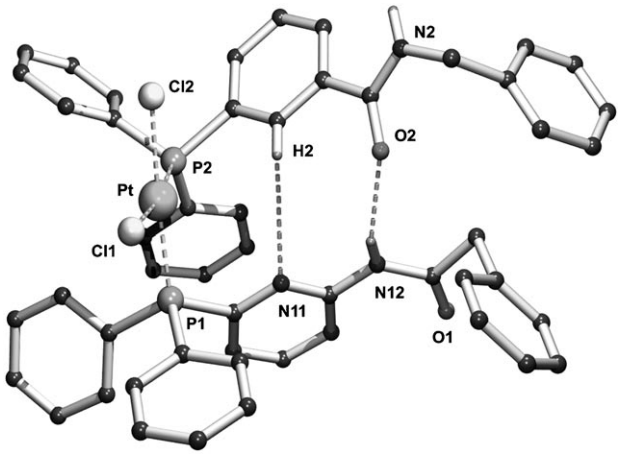


Figure 5. PLATON plot of *cis*-[$PtCl_2$(**3j·5f**)] in the solid-state at 100 K. Selected interatomic distances (Å) and angles (°): Pt–P1 2.238, Pt–P2 2.259, C2···N11 3.572, N12···O2 2.961; P1–Pt–P2 97.9, C–H2···N11 139.7, N12–H···O2 129.7. H atoms bound to C atoms and disordered toluene and $CDCl_3$ solvent molecules in the lattice were omitted for clarity.

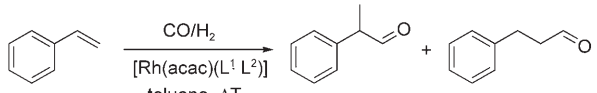
progresses along the strand. The one with the lowest energy of these calculated isomers and its structure is shown in Figure 4.

The experimental ROE contacts of *cis*-[$PtCl_2$(**3e·6b**)] agreed well with the structural parameters of the DFT-calculated structures. Additionally, the model systems suggested the formation of a non-classical hydrogen bond in the template scaffold between 2-H and the aminopyridine ring nitrogen (with C–H···N distances as short as 2.71 Å being seen in the conformers depicted in Figure 4). The formation of such a weak hydrogen bond is also supported by NMR spectroscopic data. Thus, the resonance of 2-H in proton NMR displays an unusual low-field position (ca. 10.55–10.91 ppm, Table 1). Furthermore, ROE studies showed a contact between 2-H and amide proton C, indicating that the template aromatic rings are oriented towards each other. This type of weak hydrogen bond (WHB) has often been observed in solid-state structures, but their detection in solution still remains scarce.[31,32]

X-ray crystal structure: Unfortunately, all efforts to obtain suitable single crystals of heterodimeric complexes employing peptidyl ligands were not successful. However, by using the simplified model ligands **3j** and **5f**, suitable single crystals of the heterodimeric complex *cis*-[$PtCl_2$(**3j·5f**)] could be obtained. The X-ray structure clearly showed that two different *cis*-coordinated phosphane ligands form the expected self-assembled heterodimeric complex (Figure 5).[23] The noncovalent self-organized complex is held together by metal coordination, intermolecular N–H···O and C–H···N hydrogen bonds, and π-stacking between two neighboring aryl groups at the same metal center (PPh_2 aryl group of a C-linked ligand and the pyridine group of a N-linked ligand; compare calculated structure in Figure 4 and X-ray structure in Figure 5). Hence, the metal-templating substructure obtained by X-ray analysis agrees well with the structural parameters of the DFT-calculated structures.

Applications in rhodium(I)-catalyzed asymmetric hydroformylation: The Rh-catalyzed hydroformylation of styrene (**7**) was chosen as an initial test reaction to explore the potential of the self-assembled peptide-based ligands (SupraPeptiPhos) in catalysis (Table 3). Rhodium catalysts were generated in situ through mixing of [$Rh(CO)_2$acac] and the monodentate peptide-based P-ligands. The peptides depicted in

Table 3. Rhodium-catalyzed asymmetric hydroformylation of styrene.[a]



7 **8** **9**

Entry	Ligands	L^1L^2/[Rh]	*T* [°C]	conv.[b] [%]	**8**:**9**[b]	*ee*[c] [%] (*S*)
1	**3d·3d**	5	50	100	92:8	8
2	**5a·5a**	5	50	100	93:7	5
3	**3d·5a**	2.2	50	100	91:9	10
4	**3d·5a**	2.4	50	100	89:11	13
5	**3d·5a**	2.8	50	100	86:14	23
6[d]	**3d·5a**	2.8	50	92	91:9	11
7	**3d·5a**	2.8	40	74	88:12	30
8	**3d·5a**	10	40	47	85:15	38
9[e]	**3d·5a**	10	40	47	85:15	38
10[f]	**3d·5a**	2.8	40	100	92:8	4
11	**3h·5a**	2.8	50	88	88:12	17
12	**3g·5a**	2.8	40	60	87:13	30
13[g]	**3g·5a**	2.8	40	100	86:14	36
14	**3d·5c**	10	40	42	87:13	36
15	**3e·5b**	10	40	45	87:13	23
16	**3d·6a**	2.4	50	73	86:14	27
17[h]	**3d·6a**	2.8	50	100	85:15	34
18[i]	**3d·6a**	2.8	50	54	95:5	11

[a] All reactions were performed in dry toluene (*c* 1.2 mM Rh catalyst) in a 50 mL steel autoclave under a 1:1 mixture of H_2 and CO gas at an initial total pressure of 10 bar for 24 h; c_0 (styrene) 0.6 M, Rh/L^1+L^2/styrene 1:2.2–10:500. [b] Conversion and product distribution were determined by ^{1}H NMR spectroscopy. [c] *ee*'s determined by chiral GC (Hydrodex-β-TBDAc). [d] 20 bar H_2/CO. [e] Catalyst preformation at 40 °C and 10 bar H_2/CO for 1 h. [f] Reaction in THF. [g] *c* (catalyst) 2.3 mM. [h] *c* (catalyst) 5.8 mM. [i] *c* (catalyst) 0.3 mM.

Scheme 2 were used as ligands in this model reaction using 1 mol% of the rhodium precatalyst, 1.1–5.0 mol% of each ligand and 500 mol% of styrene in toluene at 40–60 °C and 10 bar CO/H_2 gas pressure. The reaction course was monitored using ^{1}H NMR spectroscopy by sampling the reaction mixture at appropriate time intervals. Regio- and enantioselectivity were analyzed by ^{1}H NMR spectroscopy and chiral GC (Hydrodex-β-TBDAc), respectively. In all cases the peptide ligands furnished active hydroformylation catalysts. Potential side reactions such as hydrogenation or polymerization of **7** were not observed.

Some general trends were noted. The rhodium complexes based on homocombinations of ligands **3** or **5** (Table 3, entries 1 and 2) showed full conversion, but low enantioselectivities (5–8% enantoimeric excess (*ee*)). Conversely, the rhodium complexes based on the Rh-templated heterobidentate ligand combinations **3·5** and **3·6** (entries 3–9) gave in all cases significantly higher enantioselectivities (up to 38% *ee* entries 8 and 9). These results are in accord with the conformational analysis data and suggest that the self-assembling heterobidentate β-sheetlike motif between ligands L_C/L_N is more efficient than the homodimeric helical arrangement of L_C in terms of enantioinduction in the course of the hydroformylation of styrene.

Conclusion

In summary, this work presents a perspective interface between protein design, supramolecular catalysis, and combinatorial chemistry. A convergent metal-ion-assisted self-assembly process has been designed and implemented that is a simple and effective method for the de novo design and construction of topologically predetermined peptide structures. Thus, mixing of C-linked phosphane-functionalized peptidyl ligands (L_C) with the complementary N-linked phosphane-functionalized peptidyl counterparts (L_N) in the presence of platinum(II) and rhodium(I) transition-metal salts led to the selective formation of heterobidentate complexes [MX_2-(L_C·L_N)]. Detailed conformational analysis studies in solution, theoretical investigations, and X-ray studies show the formation of a two-stranded, antiparallel, β-sheet structure. Factors that influence the equilibria between heterodimeric complexes and homodimeric complexes have been studied in detail. This has given insights into the importance of individual noncovalent interactions. Furthermore, the antiparallel, β-sheet, self-assembly template system has served as basis for the generation of a heterobidentate ligand library, which has been explored in hydroformylation of styrene. From these experiments it became evident that the β-sheet self-assembly template does not only cause the selective formation of heterobidentate ligand arrangements, but although in a remote position relative to the catalytically active center can induce enantioselectivity in the course of a catalytic reaction.

The proof of principle has been achieved, and the concept is now ready to be used to generate β-sheet structures and larger ligand libraries to identify new tailor-made chelation emulating ligands for homogeneous catalysis directed to organic synthesis.

Experimental Section

General remarks: Following starting materials were purchased and used without further purification: glycine ethyl ester hydrochloride (**2a**, Aldrich), Z-L-alanine (ABCR), Z-L-*tert*-leucine (Novartis), L-alanine methyl ester hydrochloride, Boc-L-valine, Fmoc-L-alanine, and Fmoc-L-valine (Fluka), and $[Rh(cod)_2]BF_4$ (BASF). Following protected amino acids were prepared according to literature procedures: Moc-L-alanine, Moc-L-valine,[33] L-valine methyl ester hydrochloride, D-valine methyl ester hydrochloride,[34] Z-L-valine and Z-D-valine,[35] Z-L-valyl-L-valine methyl ester (**2d**),[21e] Z-L-valyl-L-alanine methyl ester (**2e**),[36] Z-L-*tert*-leucyl-L-valine methyl ester (**2g**),[37] Z-D-valyl-D-valine methyl ester (**2h**),[21e] 3-(diphenylphosphanyl)benzoic acid (**1**, *m*-DPPBA),[38] 6-(diphenylphosphanyl)-2-aminopyridine (**4**, 6-DPPAP), and 6-(diphenylphosphanyl)-*N*-pivaloyl-2-aminopyridine (**5e**).[4b] All reactions were carried out in dried glassware under an argon atmosphere (argon 5.0 from Sauerstoffwerk Friedrichshafen GmbH). Air and moisture sensitive liquids and solutions were transferred by syringe. All reagents were commercially available unless otherwise noted. All solvents were dried and distilled by standard procedures. Organic solutions were concentrated under reduced pressure by rotary evaporation. Chromatographic purification of products was accomplished using flash chromatography on a Merck silica gel Si 60® (200–400 mesh). NMR spectra were acquired on a Varian Mercury 300 (300 MHz, 121 MHz and 75 MHz for ^{1}H, ^{31}P and ^{13}C respectively), on a Bruker Avance 400 (400 MHz, 162 MHz and 100 MHz for ^{1}H, ^{31}P and ^{13}C respectively) and on a Bruker Avance 500 (500 MHz, 202 MHz and 125 MHz for ^{1}H, ^{31}P and ^{13}C respectively) spectrometers and are referenced according to residual protio solvent signals [$CDCl_3$: 7.26 ppm (^{1}H), 77.10 ppm (^{13}C)]. Data for ^{1}H NMR are reported as follows: chemical shift (δ in ppm), multiplicity (s, singlet; br, broad signal; d, doublet; t, triplet; q, quartet; m, multiplet; m_c, symmetric multiplet), coupling constant (Hz), integration, assignment (if possible). Data for ^{13}C and ^{31}P NMR are reported in terms of chemical shift (δ in ppm), multiplicity (if not a singlet), coupling constant (Hz), assignment (if possible). High-resolution mass spectra and ESI mass spectra were obtained on a Finnigan MAT 95 instrument and a Finnigan LCQ Advantage respectively. Elementary analysis was performed on an Elementar Vario (Fa. Elementar Analysensysteme GmbH). The enantiomeric excess (*ee*) of the hydroformylation product **8** was determined by chiral GC (Hydrodex-β-TBDAc). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Chromatography solvent ratios are given in *v/v*. Abbreviations: PE = petroleum ether; EE = ethyl ether, Z = benzyloxycarbonyl.

Preparation of dipeptides

*Z-L-Valylbutylamide (**2c**)*: Ethyl chloroformate (0.943 g, 8.69 mmol, 1.0 equiv) was added to a solution of Z-L-valine (2.183 g, 8.688 mmol) and NEt_3 (0.879 g, 8.69 mmol, 1.0 equiv) in dry CH_2Cl_2 (11 mL) at 0 °C. The cooling bath was removed, the mixture was stirred an additional 1 h, then cooled again and a solution of *n*-butylamine (0.960 g, 13.0 mmol, 1.5 equiv) in dry CH_2Cl_2 (2 mL) was added dropwise. After 1 h (TLC control: PE/EE, 1:1) the mixture was acidified with aqueous HCl (1N, 10 mL), washed with H_2O (2×10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was subjected to chromatography twice on silica gel (CH_2Cl_2/EE, 10:1 and 7:1). Trituration with Et_2O afforded compound **2c** as a white solid (1.00 g, 38%, R_f = 0.24 with 5:1). M.p. 139 °C (CH_2Cl_2/Et_2O); $[\alpha]_D^{20}$ −9.9° (c = 0.665 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.0 Hz, 3H; 4′-H_3), 0.92 (d, J = 7.0 Hz, 3H; 4-H_3 or 5-H_3), 0.95 (d, J = 6.7 Hz, 3H; 5-H_3 or 4-H_3), 1.32 (qt, J = 7.3, 7.2 Hz, 2H; 3′-H_2), 1.46 (tt, J = 7.2, 7.0 Hz, 2H; 2′-H_2), 2.11 (m_c, J = 6.6 Hz, 1H; 3-H), 3.23 (m_c, J = 7.0 Hz, 2H; 1′-H_2), 3.89 (dd, J = 8.8, 6.5 Hz, 1H; 2-H), 5.10 (s, 2H; 7-H_2), 6.17 (d, J = 6.9 Hz, 1H; 2-NH), 6.71 (br s, 1H; 1′-NH), 7.29–7.42 ppm (m, 5H; ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 ($C_{4'}$), 18.0, 19.3 (C_4, C_5), 20.1 ($C_{3'}$), 31.0 (C_3), 31.6 ($C_{2'}$),

39.3 ($C_{1'}$), 60.9 (C_2), 67.1 (C_7), 128.1 ($2C_{10}$), 128.3 (C_{11}), 128.6 ($2C_9$), 136.3 (C_8), 157.3 (C_6), 171.1 ppm (C_1); elemental analysis calcd (%) for $C_{17}H_{26}N_2O_3$: C 66.64, H 8.55, N 9.14; found: C 66.33, H 8.63, N 8.97.

*Z-L-Alanyl-L-valine methyl ester (**2f**)*: DMAP (0.274 g, 2.24 mmol, 1.0 equiv) and DCC (0.462 g, 2.24 mmol, 1.0 equiv) were added to a solution of Z-L-alanine (0.500 g, 2.24 mmol) and MeO-L-Val-H·HCl (0.375 g, 2.24 mmol, 1.0 equiv) in dry CH_2Cl_2 (6 mL) at room temperature. The resulting solution was stirred at room temperature for further 18 h. The mixture was filtered through a 2 cm pad of Celite (wetted with CH_2Cl_2), and the filter cake was washed with some CH_2Cl_2. After concentration in vacuo, the residue was dissolved in EE (20 mL), washed with aqueous HCl (2 N, 30 mL) and saturated aqueous $NaHCO_3$ (30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and short filtration over silica gel (PE/EE, 1:1) gave dipeptide **2f** as a white solid (0.736 g, 98%, R_f=0.38). M.p. 83°C (PE/EE); $[\alpha]_D^{20}=-12.5°$ (c=0.760 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87 (d, J=7.0 Hz, 3H; 4-H_3 or 5-H_3), 0.90 (d, J=7.0 Hz, 3H; 5-H_3 or 4-H_3), 1.38 (d, J=7.0 Hz, 3H; 8-H_3), 2.15 (m_c, J=6.9 Hz, 1H; 3-H), 3.73 (s, 3H; OCH_3), 4.28 (dq, J=7.0, 7.0 Hz, 1H; 7-H), 4.52 (dd, J=8.8, 4.8 Hz, 1H; 2-H), 5.12 (s, 2H; 10-H_2), 5.31 (brs, 1H; 7-NH), 6.48 (brs, 1H; 2-NH), 7.28–7.38 ppm (m, 5H; ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ=17.7, 18.4, 19.0 (C_4, C_5, C_8), 31.3 (C_3), 50.6 (C_7), 52.2 (OCH_3), 57.2 (C_2), 67.2 (C_{10}), 128.2 ($2C_{13}$), 128.3 (C_{14}), 128.6 ($2C_{12}$), 136.3 (C_{11}), 156.1 (C_9), 172.2, 172.3 ppm (C_1, C_6); HRMS (EI-MS): m/z: calcd for $C_{17}H_{24}N_2O_5$ [M^+] 336.1685; found: 336.1677.

Synthesis of C-linked phosphane ligands: Under the peptide-coupling conditions applied in the present work no racemization of the amino acid was observed.[39] Control experiment with **3b**: HPLC (Chiralpak AD, *n*-heptane/*i*PrOH 95:5, 1 mL min^{-1}, 252 nm): t_R (min)=16.93 (*S*); 100% *ee*.

*3-(Diphenylphosphanyl)benzoylglycine ethyl ester (**3a**)*: DIC (0.111 g, 0.879 mmol, 1.08 equiv) was added to a solution of **1** (0.250 g, 0.816 mmol), **2a** (0.114 g, 0.816 mmol, 1.0 equiv) and DMAP (0.100 g, 0.816 mmol, 1.0 equiv) in dry CH_2Cl_2 (4.5 mL) at room temperature. The resulting solution was stirred at room temperature for further 27 h, concentrated in vacuo, and subjected to chromatography on silica gel (PE/EE, 3:1) to afford monopeptidyl phosphane **3a** as a colorless, resinous oil (0.307 g, 96%, R_f=0.39 with 1:1). M.p. 63°C (PE/EE); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.29 (t, J=7.1 Hz, 3H; 1-H_3), 4.17 (d, J=5.0 Hz, 2H; 4-H_2), 4.23 (q, J=6.7 Hz, 2H; 2-H_2), 6.62 (brs, 1H; 4-NH), 7.26–7.44 (m, 12H; ArH), 7.76–7.82 ppm (m, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.2 (C_1), 41.2 (C_4), 61.7 (C_2), 127.6 ($C_{6'}$), 128.7 (d, $J_{C,P}$=6.9 Hz, 4ArC_{meta}), 128.9 (d, $J_{C,P}$=5.5 Hz, $C_{5'}$), 129.1 (2ArC_{para}), 132.2 (d, $J_{C,P}$=23.9 Hz, $C_{2'}$), 133.8 (d, $J_{C,P}$=19.9 Hz, 4ArC_{ortho}), 134.1 (d, $J_{C,P}$=7.5 Hz, $C_{1'}$), 136.5 (d, $J_{C,P}$=10.7 Hz, 2ArC_{ipso}), 136.7 (d, $J_{C,P}$=15.8 Hz, $C_{4'}$), 138.6 (d, $J_{C,P}$=13.5 Hz, $C_{3'}$), 167.2, 170.0 ppm (C_3, C_5); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−5.04 ppm (s); HRMS (EI-MS): m/z: calcd for $C_{23}H_{22}NO_3P$ [M^+] 391.1337; found: 391.1336.

*(+)-(3-Diphenylphosphanyl)benzoyl-L-valine methyl ester (**3b**)*: Dry CH_2Cl_2 (3 mL) was added to **2b** (111 mg, 0.654 mmol), **1** (200 mg, 0.653 mmol, 1.0 equiv), DMAP (81.7 mg, 0.668 mmol, 1.02 equiv), and DCC (141 mg, 0.686 mmol, 1.05 equiv). The mixture was stirred at room temperature for 21 h. The reaction mixture was filtered through Celite to remove dicyclohexylurea, and the filter cake was washed with some CH_2Cl_2. The filtrate was concentrated in vacuo and subjected to chromatography on silica gel (PE/EE, 4:1) to afford monopeptidyl phosphane **3b** as a glass foam (194 mg, 71%, R_f=0.61 with 1:1). Additional recrystallization from PE/Et_2O gave analytically pure **3b** as a white solid. M.p. 75°C (PE/Et_2O); $[\alpha]_D^{20}=+31.2°$ (c=0.765 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.92 (d, J=6.9 Hz, 3H; 4-H_3 or 5-H_3), 0.96 (d, J=6.7 Hz, 3H; 4-H_3 or 5-H_3), 2.23 (qqd, J=6.7, 6.7, 5.1 Hz, 1H; 3-H), 3.75 (s, 3H; OCH_3), 4.71 (dd, J=8.5, 4.9 Hz, 1H; 2-H), 6.47 (d, J=8.5 Hz, 1H; NH), 7.27–7.39 (m, 11H; ArH), 7.43 (m_c, 1H; ArH), 7.70 (d, J=7.3 Hz, 1H; ArH), 7.79 ppm (m_c, 1H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.9, 19.0 (C_4, C_5), 31.6 (C_3), 52.3 (OCH_3), 57.5 (C_2), 127.7 ($C_{6'}$), 128.7 (d, $J_{C,P}$=6.9 Hz, 4ArC_{meta}), 128.9 (d, $J_{C,P}$=6.1 Hz, $C_{5'}$), 129.1 (2ArC_{para}), 132.1 (d, $J_{C,P}$=22.2 Hz, $C_{2'}$), 133.8 (d, $J_{C,P}$=19.9 Hz, 2ArC_{ortho}), 133.9 (d, $J_{C,P}$=19.6 Hz, 2ArC_{ortho}), 134.5 (d, $J_{C,P}$=6.9 Hz, $C_{1'}$), 136.5 (d, $J_{C,P}$=10.9 Hz, 2ArC_{ipso}), 136.8 (d, $J_{C,P}$=17.0 Hz, $C_{4'}$), 138.6 (d, $J_{C,P}$=13.5 Hz, $C_{3'}$), 167.1, 172.5 ppm (C_1, C_6); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−5.22 ppm (s); elemental analysis calcd (%) for $C_{25}H_{26}NO_3P$: C 71.59, H 6.25, N 3.34; found: C 71.26, H 6.30, N 3.25.

*(+)-(3-Diphenylphosphanyl)benzoyl-L-valine-n-butylamide (**3c**)*: Pd-C (10%, 10 mg, Fluka) was added to a solution of **2c** (0.500 g, 1.63 mmol) in dry MeOH (8 mL), and the suspension was stirred under H_2 (1 atm) at room temperature for 15 h. The reaction mixture was filtered through Celite and the solvent removed in vacuo to yield the free amine as a viscous oil (0.281 g, 1.63 mmol, quant). The amine was dissolved in dry CH_2Cl_2 (7 mL), and **1** (0.500 g, 1.63 mmol, 1.0 equiv), DMAP (0.199 g, 1.63 mmol, 1.0 equiv) and DIC (0.214 g, 1.70 mmol, 1.04 equiv) were added. The mixture was stirred at room temperature for 19 h, concentrated in vacuo, and the residue was subjected to chromatography on silica gel (PE/EE, 3:1) to give peptidyl phosphane **3c** as a glass foam (0.585 g, 78%, R_f=0.52 with 1:1). M.p. 66°C (PE/EE); $[\alpha]_D^{20}=+0.2°$ (c=0.620 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, J=7.2 Hz, 3H; 10-H_3), 0.95 (d, J=6.7 Hz, 3H; 4-H_3 or 5-H_3), 0.97 (d, J=6.7 Hz, 3H; 4-H_3 or 5-H_3), 1.31 (qt, J=7.2, 7.0 Hz, 2H; 9-H_2), 1.45 (tt, J=7.0, 6.9 Hz, 2H; 8-H_2), 2.15 (dqq, J=6.9, 6.7, 6.7 Hz, 1H; 3-H), 3.18 (m_c, J=7.0 Hz, 1H; 7-H^B), 3.27 (m_c, J=7.0 Hz, 1H; 7-H^A), 4.35 (dd, J=8.4, 7.5 Hz, 1H; 2-H), 6.17 (t, J=5.5 Hz, 1H; 7-NH), 6.71 (d, J=8.5 Hz, 1H; 2-NH), 7.26–7.42 (m, 12H; ArH), 7.70–7.78 ppm (m, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7 (C_{10}), 18.5, 19.4 (C_4, C_5), 20.1 (C_9), 31.4 (C_3), 31.6 (C_8), 39.4 (C_7), 59.2 (C_2), 127.5 ($C_{6'}$), 128.7 (d, $J_{C,P}$=7.2 Hz, 4ArC_{meta}), 128.9 (overlapped d, $C_{5'}$), 129.1 (2ArC_{para}), 132.3 (d, $J_{C,P}$=23.6 Hz, $C_{2'}$), 133.8 (2d, $J_{C,P}$=19.6 Hz, 4ArC_{ortho}), 134.5 (d, $J_{C,P}$=7.2 Hz, $C_{1'}$), 136.5 (2d, $J_{C,P}$=10.7 Hz, 2ArC_{ipso}), 136.8 (d, $J_{C,P}$=15.8 Hz, $C_{4'}$), 138.7 (d, $J_{C,P}$=13.8 Hz, $C_{3'}$), 167.3, 171.0 ppm (C_1, C_6); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−5.25 ppm (s); elemental analysis calcd (%) for $C_{28}H_{33}N_2O_2P$: C 73.02, H 7.22, N 6.08; found: C 72.76, H 7.36, N 6.02.

*(+)-(3-Diphenylphosphanyl)-benzoyl-L-valyl-L-valine methyl ester (**3d**)*: Pd-C (10%, 20 mg, Fluka) was added to a solution of **2d** (1.782 g, 4.890 mmol) in dry MeOH (20 mL); the suspension was stirred under H_2 (1 atm) at room temperature for 15 h. The reaction mixture was filtered through Celite and the solvent removed in vacuo to yield the free amine H-L-Val-L-Val-OMe as a viscous oil (1.13 g, 4.89 mmol, quant). The amine was dissolved in dry CH_2Cl_2 (25 mL), and **1** (1.648 g, 5.379 mmol, 1.1 equiv), DMAP (0.598 g, 4.89 mmol, 1.0 equiv) and DCC (1.112 g, 5.379 mmol, 1.1 equiv) (or DIC) were added at room temperature. The resulting white, chalky solution was stirred at room temperature for further 19 h. The mixture was filtered through a 2 cm pad of Celite (wetted with CH_2Cl_2), and the filter cake was washed with some CH_2Cl_2. After concentration in vacuo, the residue was subjected to chromatography on silica gel (PE/EE, 2:1) to afford dipeptidyl phosphane **3d** as a glass foam (2.368 g, 93%, R_f=0.23). M.p. 172°C (PE/EE); $[\alpha]_D^{20}=+5.5°$ (c=0.945 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.87 (d, J=6.9 Hz, 3H; CH_3), 0.88 (d, J=6.9 Hz, 3H; CH_3), 0.96 (d, J=7.8 Hz, 3H; CH_3), 0.98 (d, J=7.0 Hz, 3H; CH_3), 2.09–2.23 (m, J=6.8 Hz, 2H; 3-H, 8-H), 3.74 (s, 3H; OCH_3), 4.47–4.53 (m, J=8.5, 8.2 Hz, 2H; 2-H, 7-H), 6.56 (d, J=8.7 Hz, 1H; 2-NH), 6.71 (d, J=8.7 Hz, 1H; 7-NH), 7.26–7.42 (m, 12H; ArH), 7.72 (d, J=7.6 Hz, 1H; 2′-H), 7.77 ppm (m_c, 1H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.8, 18.3, 19.0, 19.2 (C_4, C_5, C_9, C_{10}), 31.1, 31.4 (C_3, C_8), 52.2 (OCH_3), 57.4, 58.9 (C_2, C_7), 127.6 (C_6), 128.7 (d, $J_{C,P}$=7.2 Hz, 2ArC_{meta}), 128.8 (d, $J_{C,P}$=7.2 Hz, 2ArC_{meta}), 128.9 (d, $J_{C,P}$=5.5 Hz, $C_{5'}$), 129.1 (ArC_{para}), 129.1 (ArC_{para}), 132.3 (d, $J_{C,P}$=23.3 Hz, $C_{2'}$), 133.8 (d, $J_{C,P}$=19.6 Hz, 2ArC_{ortho}), 133.9 (d, $J_{C,P}$=19.9 Hz, 2ArC_{ortho}), 134.5 (d, $J_{C,P}$=6.9 Hz, $C_{1'}$), 136.5 (d, $J_{C,P}$=10.9 Hz, ArC_{ipso}), 136.6 (d, $J_{C,P}$=10.9 Hz, ArC_{ipso}), 136.8 (d, $J_{C,P}$=15.8 Hz, $C_{4'}$), 138.6 (d, $J_{C,P}$=13.8 Hz, $C_{3'}$), 167.3, 171.2, 172.1 ppm (C_1, C_6, C_{11}); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−5.26 ppm (s); elemental analysis calcd (%) for $C_{30}H_{35}N_2O_4P$: C 69.48, H 6.80, N 5.40; found: C 69.44, H 7.06, N 5.53.

*(+)-(3-Diphenylphosphanyl)benzoyl-L-valyl-L-alanine methyl ester (**3e**)*: Pd-C (10%, 37 mg, Fluka) was added to a solution of **2e** (0.700 g, 2.08 mmol) in dry MeOH (9.5 mL) and CH_2Cl_2 (3 mL), and the suspension was stirred under H_2 (1 atm) at room temperature for 17 h. The reaction mixture was filtered through Celite and the solvent removed in vacuo to yield the free amine H-L-Val-L-Ala-OMe as a viscous oil (quant). The amine was dissolved in dry CH_2Cl_2 (10 mL), and **1** (0.624 g, 2.04 mmol, 1.0 equiv), DMAP (0.249 g, 2.04 mmol, 1.0 equiv) and DIC

(0.257 g, 2.04 mmol, 1.0 equiv) were added at room temperature. The reaction mixture was stirred at room temperature for further 24 h. After concentration in vacuo, the residue was subjected to chromatography on silica gel (PE/EE, 1:1) to afford dipeptidyl phosphane **3e** as a glass foam (0.640 g, 64%, R_f=0.31). M.p. 75°C (PE/EE); $[\alpha]_D^{20}$=+5.1° (c=1.270 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.97 (d, J=6.9 Hz, 3H; 7-H_3 or 8-H_3), 1.00 (d, J=6.7 Hz, 3H; 7-H_3 or 8-H_3), 1.38 (d, J=7.2 Hz, 3H; 3-H_3), 2.16 (m_c, J=6.7 Hz, 1H; 6-H), 3.75 (s, 3H; OCH_3), 4.47 (dd, J=8.5, 6.6 Hz, 1H; 5-H), 4.70 (dq, J=7.3, 7.2 Hz, 1H; 2-H), 6.52 (d, J=7.3 Hz, 1H; 2-NH), 6.68 (d, J=8.5 Hz, 1H; 5-NH), 7.26–7.43 (m, 12H; ArH), 7.70–7.80 ppm (m, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.1, 18.2, 19.2 (C_3, C_7, C_8), 31.7 (C_6), 48.2 (C_2), 52.5 (OCH_3), 58.7 (C_5), 127.6 ($C_{6'}$), 128.7 (d, $J_{C,P}$=6.9 Hz, 4ArC_{meta}), 128.9 (d, $J_{C,P}$=5.8 Hz, $C_{5'}$), 129.1 (2ArC_{para}), 132.3 (d, $J_{C,P}$=23.9 Hz, $C_{2'}$), 133.8 (d, $J_{C,P}$=19.9 Hz, 2ArC_{ortho}), 133.9 (d, $J_{C,P}$=19.9 Hz, 2ArC_{ortho}), 134.5 (d, $J_{C,P}$=7.2 Hz, $C_{1'}$), 136.5 (2d, $J_{C,P}$=10.7 Hz, 2ArC_{ipso}), 136.8 (d, $J_{C,P}$=15.8 Hz, $C_{4'}$), 138.7 (d, $J_{C,P}$=13.5 Hz, $C_{3'}$), 167.3, 170.7, 173.1 ppm (C_1, C_4, C_9); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−5.26 ppm (s); elemental analysis calcd (%) for $C_{28}H_{31}N_2O_4P$: C 68.56, H 6.37, N 5.71; found: C 68.43, H 6.62, N 5.97.

*(−)-(3-Diphenylphosphanyl)-benzoyl-*L*-alanyl-*L*-valine methyl ester (**3f**)*: Pearlman's catalyst (20% Pd(OH)$_2$ on carbon, 31% H_2O, ca. 5 mg) was added to a solution of **2f** (0.275 g, 1.16 mmol) in dry MeOH (5 mL), and the suspension was stirred under H_2 (1 atm) at room temperature for 2 h. The reaction mixture was filtered through Celite and the solvent removed in vacuo to yield the free amine H-L-Ala-L-Val-OMe as a viscous oil (0.235 g, 1.16 mmol, quant). The amine was dissolved in dry CH_2Cl_2 (10 mL), and **1** (0.357 g, 1.16 mmol, 1.0 equiv), HOBt (0.157 g, 1.16 mmol, 1.0 equiv), DMAP (14 mg, 0.12 mmol, 0.1 equiv) and DIC (0.147 g, 1.16 mmol, 1.0 equiv) were added at room temperature. The reaction mixture was stirred at room temperature for further 14 h. After concentration in vacuo, the residue was subjected to chromatography on silica gel (PE/EE, 2:1) to give dipeptidyl phosphane **3f** as a glass foam (0.208 g, 37%, R_f=0.31 with 1:1). M.p. 70°C (PE/EE); $[\alpha]_D^{20}$=−7.3° (c=0.755 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.87 (d, J=6.9 Hz, 3H; 4-H_3 or 5-H_3), 0.88 (d, J=6.9 Hz, 3H; 4-H_3 or 5-H_3), 1.45 (d, J=7.0 Hz, 3H; 8-H_3), 2.17 (m_c, 1H; 3-H), 3.74 (s, 3H; OCH_3), 4.50 (dd, J=8.8, 5.0 Hz, 1H; 2-H), 4.70 (dq, J=7.0, 7.0 Hz, 1H; 7-H), 6.65 (d, J=8.5 Hz, 1H; 2-NH), 6.68 (d, J=7.0 Hz, 1H; 7-NH), 7.26–7.41 (m, 12H; ArH), 7.72–7.79 ppm (m, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.7, 18.1, 19.0 (C_4, C_5, C_8), 31.2 (C_3), 49.3 (C_7), 52.3 (OCH_3), 57.4 (C_2), 127.5 ($C_{6'}$), 128.8 (d, $J_{C,P}$=6.9 Hz, 4ArC_{meta}), 128.9 (d, $J_{C,P}$=5.2 Hz, $C_{5'}$), 129.1 (2ArC_{para}), 132.3 (d, $J_{C,P}$=25.0 Hz, $C_{2'}$), 133.8 (2d, $J_{C,P}$=19.9 Hz, 4ArC_{ortho}), 134.2 (d, $J_{C,P}$=7.8 Hz, $C_{1'}$), 136.5 (2d, $J_{C,P}$=9.8 Hz, 2ArC_{ipso}), 136.8 (d, $J_{C,P}$=14.7 Hz, $C_{4'}$), 138.7 (d, $J_{C,P}$=13.5 Hz, $C_{3'}$), 167.1, 172.1, 172.2 ppm (C_1, C_6, C_9); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−5.16 ppm (s); HRMS (EI-MS): m/z: calcd for $C_{28}H_{31}N_2O_4P$ [M^+] 490.2021; found: 490.2009.

*(+)-(3-Diphenylphosphanyl)benzoyl-*L*-tert-leucyl-*L*-valine methyl ester (**3g**)*: Pd-C (10%, 20 mg, Fluka) was added to a solution of **2g** (0.240 g, 0.634 mmol) in dry MeOH (3 mL), and the suspension was stirred under H_2 (1 atm) at room temperature for 15 h. The reaction mixture was filtered through Celite and the solvent removed in vacuo to yield the free amine H-L-*t*Leu-L-Val-OMe as a viscous oil (quant). The amine was dissolved in dry CH_2Cl_2 (3 mL), and **1** (0.194 g, 0.634 mmol, 1.0 equiv), DMAP (78 mg, 0.63 mmol, 1.0 equiv) and DIC (80 mg, 0.63 mmol, 1.0 equiv) were added at room temperature. The reaction mixture was stirred at room temperature for further 16 h. After concentration in vacuo, the residue was subjected to chromatography on silica gel (PE/EE, 5:1→0:1) to afford dipeptidyl phosphane **3g** as a glass foam (0.274 g, 81%, R_f=0.39 with 2:1). M.p. 82°C (PE/EE); $[\alpha]_D^{20}$=+30.9° (c=0.640 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.89 (d, J=6.9 Hz, 3H; 4-H_3 or 5-H_3), 0.90 (d, J=6.9 Hz, 3H; 5-H_3 or 4-H_3), 1.45 (s, 9H; *t*-Bu), 2.15 (m_c, J=8.4, 4.8 Hz, 1H; 3-H), 3.75 (s, 3H; OCH_3), 4.45 (d, J=9.2 Hz, 1H; 7-H), 4.50 (dd, J=8.4, 4.8 Hz, 1H; 2-H), 6.16 (d, J=8.5 Hz, 1H; 2-NH), 6.67 (d, J=9.1 Hz, 1H; 7-NH), 7.26–7.38 (m, 11H; ArH), 7.42 (m_c, 1H; ArH), 7.66 (d, J=7.0 Hz, 1H; ArH), 7.77 ppm (m_c, 1H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.9, 19.0 (C_4, C_5), 26.7 ($3C_9$), 31.2 (C_3), 35.3 (C_8), 52.2 (OCH_3), 57.4 (C_2), 61.0 (C_7), 127.6 ($C_{6'}$), 128.8 (d, $J_{C,P}$=7.2 Hz, 4ArC_{meta}), 128.9 (d, $J_{C,P}$=6.0 Hz, $C_{5'}$), 129.1 (2ArC_{para}), 132.1 (d, $J_{C,P}$=21.9 Hz, $C_{2'}$), 133.9 (2d, $J_{C,P}$=19.9 Hz, 4ArC_{ortho}), 134.2 (d, $J_{C,P}$=6.9 Hz, $C_{1'}$), 136.6 (2d, $J_{C,P}$=10.7 Hz, 2ArC_{ipso}), 136.8 (d, $J_{C,P}$=17.0 Hz, $C_{4'}$), 138.7 (d, $J_{C,P}$=13.5 Hz, $C_{3'}$), 167.2, 170.5, 172.1 ppm (C_1, C_6, C_{10}); ^{31}P NMR (162 MHz, $CDCl_3$): δ=5.29 ppm (s); elemental analysis calcd (%) for $C_{31}H_{37}N_2O_4P$: C 69.91, H 7.00, N 5.26; found: C 69.72, H 7.19, N 5.23.

*(−)-(3-Diphenylphosphanyl)benzoyl-*D*-valyl-*D*-valine methyl ester (**3h**)*: was prepared as **3d** using Z-D-Val-D-Val-OMe (**2h**) and DIC as coupling reagent to afford phosphane **3h** as a glass foam; $[\alpha]_D^{20}$ −3.5° (c 0.575, $CHCl_3$). NMR data identical to **3d**; HRMS (EI-MS): m/z: calcd for $C_{30}H_{35}N_2O_4P$ [M^+] 518.2334; found: 518.2339.

*3-(Diphenylphosphanyl)benzoic acid methyl ester (**3i**)*: DCC (0.135 g, 0.653 mmol, 1.0 equiv) was added to a solution of **1** (0.200 g, 0.653 mmol) and DMAP (8.8 mg, 0.07 mmol, 0.1 equiv) in dry MeOH (2 mL) at room temperature. The resulting white, chalky solution was stirred at room temperature for further 3 h. The mixture was filtered through a 2 cm pad of Celite (wetted with CH_2Cl_2), and the filter cake was washed with some CH_2Cl_2. After concentration in vacuo, the residue was subjected to chromatography on silica gel (PE/EE, 5:1) and recrystallized from PE/Et_2O (2:1) to give the methyl ester **3i** as a white solid (0.120 g, 57%, R_f=0.71 with 1:1). M.p. 68°C (PE/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.87 (s, 3H; OCH_3), 7.26–7.49 (m, 12H; ArH), 7.98–8.08 ppm (m, 2H; ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.2 (OCH_3), 128.7 (d, $J_{C,P}$=6.9 Hz, 4ArC_{meta}), 129.1 (2ArC_{para}), 129.1 (overlapped d, C_5), 129.9 (C_6), 130.5 (d, $J_{C,P}$=7.5 Hz, C_1), 133.8 (d, $J_{C,P}$=19.9 Hz, 4ArC_{ortho}), 134.9 (d, $J_{C,P}$=23.3 Hz, C_2), 136.6 (d, $J_{C,P}$=10.7 Hz, 2ArC_{ipso}), 137.9 (d, $J_{C,P}$=16.4 Hz, C_4), 138.4 (d, $J_{C,P}$=13.5 Hz, C_3), 166.9 ppm (C=O); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−5.18 ppm (s); HRMS (EI-MS): m/z: calcd for $C_{20}H_{17}O_2P$ [M^+] 320.0966; found: 320.0965; elemental analysis calcd (%) for $C_{20}H_{17}O_2P$: C 74.99, H 5.35; found: C 74.70, H 5.59.

*N-Benzyl-3-(diphenylphosphanyl)-benzamide (**3j**)*: Benzylamine (0.218 g, 2.03 mmol, 1.25 equiv) and DIC (0.208 g, 1.65 mmol, 1.0 equiv) were added to a solution of **1** (0.500 g, 1.63 mmol) and DMAP (0.212 g, 1.73 mmol, 1.06 equiv) in dry CH_2Cl_2 (2 mL) at room temperature . The mixture was stirred at room temperature for further 24 h and filtered through a short plug of silica gel (CH_2Cl_2/EE, 3:1). Concentration in vacuo and trituration with Et_2O gave the benzylamide **3j** as a white solid (0.500 g, 78%, R_f=0.95 with 3:1). M.p. 129°C (Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ=4.59 (d, J=5.7 Hz, 2H; 2-H_2), 6.32 (s, 1H; NH), 7.27–7.42 (m, 17H; ArH), 7.73 (d, J=8.2 Hz, 1H; ArH), 7.79 ppm (m, 1H; ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ=44.2 (C_2), 127.7 ($C_{6'}$, C_6), 127.9 ($2C_5$), 128.7 (d, $J_{C,P}$=7.5 Hz, 4ArC_{meta}), 128.9 ($2C_4$), 129.0 (d, $J_{C,P}$=5.4 Hz, $C_{5'}$), 129.1 (2ArC_{para}), 132.0 (d, $J_{C,P}$=24.7 Hz, $C_{2'}$), 133.8 (d, $J_{C,P}$=20.4 Hz, 4ArC_{ortho}), 134.7 (d, $J_{C,P}$=7.5 Hz, $C_{1'}$), 136.5 (d, $J_{C,P}$=10.1 Hz, 2ArC_{ipso}), 136.6 (d, $J_{C,P}$=15.0 Hz, $C_{4'}$), 138.1 (C_3), 138.5 (d, $J_{C,P}$=12.9 Hz, $C_{3'}$), 167.1 ppm (C_1); ^{31}P NMR (121 MHz, $CDCl_3$): δ=−5.09 ppm (s); HRMS (EI-MS): m/z: calcd for $C_{26}H_{22}NOP$ [M^+] 395.1439; found: 395.1447; elemental analysis calcd (%) for $C_{26}H_{22}NOP$: C 78.97, H 5.61, N 3.54; found: C 78.61, H 5.63, N 3.56.

Synthesis of N-linked phosphane ligands

*(−)-(6-Diphenylphosphanyl)-2-aminopyridinyl-*L*-valyl-Fmoc (**5a**)*: $SOCl_2$ (1.50 mL, 2.44 g, 20.6 mmol, 11 equiv) was added to a suspension of Fmoc-L-valine (0.641 g, 1.89 mmol) in dry CH_2Cl_2 (8 mL) and the resulting mixture was stirred for 1 h at 55–60°C. The clear reaction mixture was concentrated in vacuo and the residue was redissolved in dry CH_2Cl_2 (5 mL). The solvent was removed in vacuo and this procedure was repeated two more times to give Fmoc-L-Val-Cl as a white solid (0.676 g, 1.89 mmol, quant). The amino acid chloride was dissolved in dry CH_2Cl_2 (5 mL) and was added dropwise at 0°C to a solution of **4** (0.500 g, 1.80 mmol, 0.95 equiv) and pyridine (0.165 g, 2.08 mmol, 1.1 equiv) in CH_2Cl_2 (3 mL). The yellow solution was stirred at room temperature for further 23 h, then washed with half-saturated aqueous $KHSO_4$ (6 mL) and saturated aqueous $NaHCO_3$ (6 mL), and dried [$MgSO_4$]. The organic layer was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (PE/EE, 5:1) to afford monopeptidyl phosphane **5a** as a glass foam (0.890 g, 83%, R_f=0.41 with 2:1). M.p. 93°C (PE/EE); $[\alpha]_D^{20}$=−18.5° (c 0.750 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88–1.50 (m, 6H; 4-H_3, 5-H_3), 2.23 (m_c, 1H; 3-H), 4.15–4.25 (m, J=6.0 Hz, 2H; 2-H, 8-H), 4.43 (m_c, J=8.3 Hz, 2H; 7-H_2), 5.34 (br s,

1H; 2-NH), 6.81 (d, J=7.5 Hz, 1H; 5′-H), 7.25–7.42 (m, 14H; ArH), 7.54–7.63 (m, 3H; 4′-H, fluorenyl H), 7.75 (d, J=7.3 Hz, 2H; fluorenyl H), 8.11 (d, J=8.2 Hz, 1H; 3′-H), 8.23 ppm (brs, 1H; 2′-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.6, 19.4 (C_4, C_5), 31.3 (C_3), 47.3 (C_8), 61.2 (C_2), 67.2 (C_7), 112.9 ($C_{3'}$), 120.1 (2 fluorenyl C), 124.5 (d, $J_{C,P}$=12.7 Hz, $C_{5'}$), 125.1 (2 fluorenyl C), 127.2 (2 fluorenyl C), 127.8 (2 fluorenyl C), 128.8 (d, $J_{C,P}$=7.2 Hz, 4 ArC_{meta}), 129.3 (2 ArC_{para}), 134.2 (d, $J_{C,P}$=19.9 Hz, 4 ArC_{ortho}), 135.8 (d, $J_{C,P}$=11.3 Hz, 2 ArC_{ipso}), 138.2 ($C_{4'}$), 141.4 (2 fluorenyl C), 143.8 (fluorenyl C), 143.9 (fluorenyl C), 150.9 (d, $J_{C,P}$=14.1 Hz, $C_{6'}$), 156.7 (C_6), 162.3 ($C_{2'}$), 170.3 ppm (C_1); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−3.90 ppm (s); elemental analysis calcd (%) for $C_{37}H_{34}N_3O_3P$: C 74.11, H 5.71, N 7.01; found: C 73.71, H 6.00, N 6.92.

*(−)-6-(Diphenylphosphanyl)-2-aminopyridinyl-*L*-alanyl-Fmoc* (***5b***): $SOCl_2$ (1.40 mL, 2.24 g, 18.9 mmol, 10 equiv) was added to a suspension of Fmoc-L-alanine (0.587 g, 1.89 mmol) in dry CH_2Cl_2 (11 mL) and the resulting mixture was stirred for 0.5 h at 60 °C. The clear reaction mixture was concentrated in vacuo and the residue was redissolved in dry CH_2Cl_2 (5 mL). The solvent was removed in vacuo and this procedure was repeated two more times to give Fmoc-L-Ala-Cl as a waxy oil (0.622 g, 1.89 mmol, quant). The amino acid chloride was dissolved in dry CH_2Cl_2 (5 mL) and was added dropwise at 0 °C to a solution of **4** (0.500 g, 1.80 mmol, 0.95 equiv) and pyridine (0.165 g, 2.08 mmol, 1.1 equiv) in dry CH_2Cl_2 (3 mL). The yellow solution was stirred at room temperature for further 24 h, then washed with half-saturated aqueous $KHSO_4$ (6 mL) and saturated aqueous $NaHCO_3$ (6 mL), and dried ($MgSO_4$). The organic layer was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (CH_2Cl_2/EE, 20:1) to afford monopeptidyl phosphane **5b** as a glass foam (0.913 g, 89%, R_f=0.62). M.p. 93 °C (CH_2Cl_2/EE); $[\alpha]_D^{20}$=−14.1° (c=0.655 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.45 (d, J=5.4 Hz, 3H; 3-H_3), 4.19 (t, J=6.6 Hz, 1H; 6-H), 4.42 (m, J=6.7 Hz, 3H; 2-H, 5-H_2), 5.39 (brs, 1H; 2-NH), 6.80 (d, J=7.5 Hz, 1H; 5′-H), 7.25–7.43 (m, 14H; ArH), 7.52–7.64 (m, J=8.1 Hz, 3H; 4′-H, fluorenyl H), 7.75 (d, J=7.5 Hz, 2H; fluorenyl H), 8.10 (d, J=8.4 Hz, 1H; 3′-H), 8.44 ppm (brs, 1H; 2′-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.8 (C_3), 47.2 (C_6), 51.6 (C_2), 67.3 (C_5), 113.0 ($C_{3'}$), 120.1 (2 fluorenyl C), 124.5 (d, $J_{C,P}$=12.1 Hz, $C_{5'}$), 125.1 (2 fluorenyl C), 127.2 (2 fluorenyl C), 127.8 (2 fluorenyl C), 128.7 (d, $J_{C,P}$=7.2 Hz, 4 ArC_{meta}), 129.3 (2 ArC_{para}), 134.2 (d, $J_{C,P}$=19.9 Hz, 4 ArC_{ortho}), 135.8 (2d, $J_{C,P}$=10.5 Hz, 2 ArC_{ipso}), 138.2 (d, $J_{C,P}$=1.4 Hz, $C_{4'}$), 141.4 (2 fluorenyl C), 143.8 (fluorenyl C), 143.9 (fluorenyl C), 151.1 (d, $J_{C,P}$=14.1 Hz, $C_{6'}$), 156.0 (C_4), 162.3 (d, $J_{C,P}$=3.7 Hz, $C_{2'}$), 171.1 ppm (C_1); ^{31}P NMR (121 MHz, $CDCl_3$): δ=−4.04 ppm (s); elemental analysis calcd (%) for $C_{35}H_{30}N_3O_3P$: C 73.54, H, 5.29, N 7.35; found: C 73.35, H 5.39, N 7.30.

*(−)-(6-Diphenylphosphanyl)-2-pyridinyl-*L*-valyl-Moc* (***5c***): A catalytic amount of DMF (1–2 drops) and oxalyl chloride (0.225 g, 1.77 mmol, 1.2 equiv) were added to a suspension of Moc-L-valine (0.255 g, 1.45 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C, and the resulting mixture was stirred at room temperature for further 2 h. The clear reaction mixture containing Moc-L-Val-Cl was added dropwise at 0 °C to a solution of **4** (0.400 g, 1.45 mmol, 1.0 equiv) and pyridine (0.30 mL, 0.29 g, 3.7 mmol, 2.5 equiv) in dry CH_2Cl_2 (5 mL). The resulting dark solution was stirred at room temperature for further 25 h, then concentrated in vacuo, and purified by column chromatography on silica gel (PE/EE, 5:1) to give monopeptidyl phosphane **5c** as a glass foam (0.344 g, 55%, R_f=0.60). M.p. 80 °C (PE/EE); $[\alpha]_D^{20}$=−43.3° (c=0.970 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.94 (d, J=6.9 Hz, 3H; CH_3), 1.01 (d, J=6.9 Hz, 3H; CH_3), 2.24 (m_c, J=6.7 Hz, 1H; 3-H), 3.68 (s, 3H; OCH_3), 4.18 (brs, 1H; 2-H), 5.22 (d, J=6.9 Hz, 1H; 2-NH), 6.79 (d, J=7.3 Hz, 1H; 5′-H), 7.28–7.40 (m, 10H; PPh_2), 7.57 (ddd, J=8.4, 8.4, 1.7 Hz, 1H; 4′-H), 8.10 (d, J=8.4 Hz, 1H; 3′-H), 8.29 ppm (brs, 1H; 2′-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.5, 19.5 (C_4, C_5), 31.2 (C_3), 52.7 (OCH_3), 61.1 (C_2), 112.9 ($C_{3'}$), 124.5 (d, $J_{C,P}$=12.7 Hz, $C_{5'}$), 128.8 (d, $J_{C,P}$=7.2 Hz, 4 ArC_{meta}), 129.3 (2 ArC_{para}), 134.2 (d, $J_{C,P}$=19.9 Hz, 4 ArC_{ortho}), 135.8 (d, $J_{C,P}$=10.4 Hz, 2 ArC_{ipso}), 138.2 (d, $J_{C,P}$=1.7 Hz, $C_{4'}$), 151.0 (d, $J_{C,P}$=14.4 Hz, $C_{6'}$), 156.2 (C_6), 162.3 (d, $J_{C,P}$=3.5 Hz, $C_{2'}$), 170.4 ppm (C_1); ^{31}P NMR (121 MHz, $CDCl_3$): δ=−3.97 ppm (s); elemental analysis calcd (%) for $C_{24}H_{26}N_3O_3P$: C 66.20, H 6.02, N 9.65; found: C 65.93, H 6.26, N 9.66.

*(−)-(6-Diphenylphosphanyl)-2-aminopyridinyl-*L*-alanyl-Moc* (***5d***): A catalytic amount of DMF (1–2 drops) and oxalyl chloride (0.316 g, 2.48 mmol, 1.1 equiv) were added to a solution of Moc-L-alanine (0.333 g, 2.26 mmol) in dry CH_2Cl_2 (4.5 mL) at 0 °C, and the resulting mixture was stirred at room temperature for further 2 h. The clear reaction mixture containing Moc-L-Ala-Cl was added dropwise at 0 °C to a solution of **4** (0.600 g, 2.15 mmol, 1.0 equiv) and pyridine (0.200 g, 2.49 mmol, 1.1 equiv) in dry CH_2Cl_2 (3 mL). The resulting dark solution was stirred at room temperature for further 21 h, then washed with half-saturated aqueous $KHSO_4$ (7 mL) and saturated aqueous $NaHCO_3$ (7 mL), and dried (Na_2SO_4). The organic layer was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (PE/EE, 4:1→3:2) to afford monopeptidyl phosphane **5d** as a glass foam (0.640 g, 73%, R_f=0.20 with 2:1). M.p. 74 °C (PE/EE); $[\alpha]_D^{20}$=−30.6° (c=0.700 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.45 (d, J=7.2 Hz, 3H; 3-H_3), 3.67 (s, 3H; OCH_3), 4.39 (brs, 1H; 2-H), 5.27 (brs, 1H; 2-NH), 6.78 (d, J=7.3 Hz, 1H; 5′-H), 7.28–7.42 (m, 10H; PPh_2), 7.57 (ddd, J=8.1, 8.1, 1.8 Hz, 1H; 4′-H), 8.09 (d, J=8.4 Hz, 1H; 3′-H), 8.49 ppm (brs, 1H; 2′-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=18.8 (C_3), 51.6 (C_2), 52.6 (OCH_3), 113.0 ($C_{3'}$), 124.4 (d, $J_{C,P}$=12.1 Hz, $C_{5'}$), 128.8 (d, $J_{C,P}$=7.2 Hz, 4 ArC_{meta}), 129.3 (2 ArC_{para}), 134.2 (2d, $J_{C,P}$=19.8 Hz, 4 ArC_{ortho}), 135.8 (2d, $J_{C,P}$=10.4 Hz, 2 ArC_{ipso}), 138.2 ($C_{4'}$), 151.1 (d, $J_{C,P}$=14.4 Hz, $C_{6'}$), 156.6 (C_4), 162.2 (d, $J_{C,P}$=4.3 Hz, $C_{2'}$), 170.3 ppm (C_1); ^{31}P NMR (121 MHz, $CDCl_3$): δ=−4.09 ppm (s); HRMS (EI-MS): m/z: calcd for $C_{22}H_{22}N_3O_3P$ [M^+] 407.1398; found: 407.1397.

6-(Diphenylphosphanyl)-N-phenylacetyl-2-aminopyridine (***5f***): NEt_3 (0.600 g, 5.93 mmol, 5.5 equiv) was added to a solution of **4** (0.300 g, 1.08 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C, followed by the dropwise addition phenylacetyl chloride (0.200 g, 1.29 mmol, 1.2 equiv); the resulting mixture was stirred at room temperature for further 24 h. The resulting white, chalky solution was washed with half-saturated aqueous $KHSO_4$ (7 mL) and saturated aqueous $NaHCO_3$ (7 mL), and dried (Na_2SO_4). The organic layer was concentrated in vacuo, and the waxy residue crystallized after 1 h. Trituration with Et_2O/CH_2Cl_2 (9:1) afforded compound **5f** as a yellow solid (0.320 g, 75%, R_f=0.60 with PE/EE 2:1). M.p. 167 °C (Et_2O/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.70 (s, 2H; 2-H_2), 6.77 (d, J=7.5 Hz, 1H; 5′-H), 7.25–7.40 (m, 15H; ArH), 7.55 (ddd, J=8.4, 7.5, 1.8 Hz, 1H; 4′-H), 7.92 (brs, 1H; NH), 8.10 ppm (d, J=8.4 Hz, 1H; 3′-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=45.0 (C_2), 112.8 ($C_{3'}$), 124.3 (d, $J_{C,P}$=12.7 Hz, $C_{5'}$), 128.7 (d, $J_{C,P}$=7.2 Hz, 4 ArC_{meta}), 129.1 (2C_5), 129.2 (2 ArC_{para}), 129.5 (2C_4), 134.0 (C_3), 134.2 (2d, $J_{C,P}$=19.6 Hz, 4 ArC_{ortho}), 135.9 (2d, $J_{C,P}$=10.4 Hz, 2 ArC_{ipso}), 138.1 (d, $J_{C,P}$=1.7 Hz, $C_{4'}$), 151.4 (d, $J_{C,P}$=14.4 Hz, $C_{6'}$), 161.9 (d, $J_{C,P}$=4.6 Hz, $C_{2'}$), 169.6 ppm (C_1); ^{31}P NMR (121 MHz, $CDCl_3$): δ=−4.10 ppm (s); HRMS (EI-MS): m/z: calcd for: $C_{25}H_{21}N_2OP$ [M^+] 396.1391; found: 396.1399.

*(−)-(6-Diphenylphosphanyl)-2-aminopyridinyl-*L*-valyl-*L*-valine-Boc* (***6a***): Et_2NH (0.50 mL, 0.35 g, 4.8 mmol, 19 equiv) was added to a solution of **5a** (0.150 g, 0.251 mmol) in dry THF (2 mL) and the resulting mixture was stirred at room temperature for 2 h (TLC control: PE/EE, 2:1). Evaporation in vacuo followed by addition of dry CH_2Cl_2 (2 mL) and reevaporation (repeat 2–3 times) gave a waxy oil (94 mg, 0.251 mmol, quant). The free amine was dissolved in dry CH_2Cl_2 (3 mL) and treated successively with Boc-L-valine (54 mg, 0.25 mmol, 1.0 equiv), HOBt (34 mg, 0.25 mmol, 1.0 equiv) and DIC (32 mg, 0.25 mmol, 1.0 equiv) at room temperature. The resulting solution was stirred at room temperature for further 20 h and concentrated in vacuo. The residue was subjected to chromatography on silica gel (CH_2Cl_2→CH_2Cl_2/EE, 7:1) to afford dipeptidyl phosphane **6a** as a white solid (115 mg, 80%, R_f=0.52 with 5:1). M.p. 121 °C (CH_2Cl_2/EE); $[\alpha]_D^{20}$=−27.9° (c=0.875 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.90 (d, J=6.7 Hz, 3H; CH_3), 0.91 (d, J=6.6 Hz, 3H; CH_3), 0.95 (d, J=6.9 Hz, 3H; CH_3), 0.98 (d, J=6.9 Hz, 3H; CH_3), 1.42 (s, 9H; *t*-Bu), 2.04–2.30 (m, J=6.5 Hz, 2H; 3-H, 8-H), 3.91 (dd, J=8.4, 6.7 Hz, 1H; 7-H), 4.48 (dd, J=8.4, 5.9 Hz, 1H; 2-H), 5.10 (brs, 1H; 7-NH), 6.57 (d, J=8.5 Hz, 1H; 2-NH), 6.79 (d, J=7.5 Hz, 1H; 5′-H), 7.30–7.40 (m, 10H; PPh_2), 7.55 (dd, J=9.2, 8.4 Hz, 1H; 4′-H), 8.07 (d, J=8.2 Hz, 1H; 3′-H), 8.39 ppm (brs, 1H; 2′-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.8, 18.0, 19.4 (2C) (C_4, C_5, C_9, C_{10}), 28.4 ($3C_{13}$), 30.5, 31.2 (C_3, C_8), 59.1 (C_7), 60.4 (C_2), 80.1 (C_{12}), 112.9 ($C_{3'}$), 124.5 (d, $J_{C,P}$=13.2 Hz, $C_{5'}$), 128.7 (d, $J_{C,P}$=7.2 Hz, 4 ArC_{meta}), 129.2 (2 ArC_{para}),

134.2 (2d, $J_{C,P}=19.7$ Hz, 4 ArC_{ortho}), 135.8 (d, $J_{C,P}=10.7$ Hz, 2 ArC_{ipso}), 138.1 ($C_{4'}$), 151.0 (d, $J_{C,P}=13.8$ Hz, $C_{6'}$), 156.2 (C_{11}), 162.3 ($C_{2'}$), 170.0, 172.1 ppm (C_1, C_6); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta=-3.93$ ppm (s); elemental analysis calcd (%) for $C_{32}H_{41}N_4O_4P$: C 66.65, H 7.17, N 9.72; found: C 66.39, H 7.45, N 9.68.

*(−)-(6-Diphenylphosphanyl)-2-aminopyridinyl-L-alanyl-L-valine-Boc (**6b**)*: Et_2NH (0.70 mL, 6.7 mmol, 19 equiv) was added to a solution of **5b** (0.200 g, 0.350 mmol) in dry THF (2 mL) and the resulting mixture was stirred at room temperature for 3.5 h (TLC control: PE/EE, 2:1). Evaporation in vacuo gave a waxy oil (quant). The free amine was dissolved in dry CH_2Cl_2 (3 mL) and treated successively with Boc-L-valine (76 mg, 0.35 mmol, 1.0 equiv), HOBt (47 mg, 0.35 mmol, 1.0 equiv) and DIC (44 mg, 0.35 mmol, 1.0 equiv) at room temperature. The resulting solution was stirred at room temperature for further 20 h and concentrated in vacuo. The residue was subjected to chromatography on silica gel (CH_2Cl_2/EE, 10:1) to afford dipeptidyl phosphane **6b** as a glass foam (0.115 g, 60%, $R_f=0.47$ with 5:1). M.p. 95 °C (CH_2Cl_2/EE); $[\alpha]_D^{20}=-31.0°$ ($c=1.200$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.87$ (d, $J=6.7$ Hz, 3H; 7-H_3 or 8-H_3), 0.90 (d, $J=7.0$ Hz, 3H; 7-H_3 or 8-H_3), 1.42 (s, 9H; *t*-Bu), 1.43 (overlapped d, $J=7.2$ Hz, 3H; 3-H_3), 2.08 (m_c, $J=6.5$ Hz, 1H; 6-H), 3.94 (dd, $J=7.2$, 7.0 Hz, 1H; 5-H), 4.66 (dq, $J=7.2$, 7.0 Hz, 1H; 2-H), 5.13 (brs, 1H; 5-NH), 6.67 (d, $J=7.0$ Hz, 1H; 2-NH), 6.78 (d, $J=7.5$ Hz, 1H; 5′-H), 7.29–7.38 (m, 10H; PPh_2), 7.56 (dd, $J=8.1$, 7.8 Hz, 1H; 4′-H), 8.06 (d, $J=8.4$ Hz, 1H; 3′-H), 8.57 ppm (brs, 1H; 2′-NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=17.9$, 19.4 (C_7, C_8), 18.4 (C_3), 28.4 ($3C_{11}$), 31.0 (C_6), 49.8 (C_2), 60.0 (C_5), 80.0 (C_{10}), 112.9 ($C_{3'}$), 124.4 (d, $J_{C,P}=13.3$ Hz, $C_{5'}$), 128.7 (d, $J_{C,P}=7.2$ Hz, 4 ArC_{meta}), 129.2 (2 ArC_{para}), 134.2 (2d, $J_{C,P}=19.8$ Hz, 4 ArC_{ortho}), 135.9 (2d, $J_{C,P}=10.4$ Hz, 2 ArC_{ipso}), 138.1 ($C_{4'}$), 151.1 (d, $J_{C,P}=13.8$ Hz, $C_{6'}$), 156.0 (C_9), 162.2 (d, $J_{C,P}=3.6$ Hz, $C_{2'}$), 170.9, 171.8 ppm (C_1, C_4); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta=-4.09$ ppm (s); HRMS (EI-MS): *m/z*: calcd for: $C_{30}H_{37}N_4O_4P$ [M^+] 548.2552; found: 548.2562.

General procedure for the generation of homo- and heterodimeric platinum(II) complexes: Ligand 1 (30.0 μmol, 1.0 equiv), a complementary ligand 2 (30.0 μmol, 1.0 equiv) and *cis*-[$PtCl_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv) were dissolved in $CDCl_3$ (0.8 mL, 37.5 mM) at room temperature and analyzed by NMR (^1H; ^{31}P, ^{13}C) spectroscopy and ESI-MS. For other characterization experiments, an appropriate amount of the complex was dissolved in CH_2Cl_2 and stirred for 10 min at room temperature. The solvent was removed in vacuo and the residue was washed with *n*-pentane. The remaining white solid was dried in vacuo. In most of the cases the N-homodimer signals in the ^{31}P NMR spectra were broad or not detectable due to line broadening. Thus, heterodimer/C-homodimer ratios were determined by integration of corresponding signals in the ^{31}P and/or ^{13}C NMR spectra.

*cis-[PtCl$_2$(**3d**·**3d**)]*: Following the general procedure this compound was obtained from *cis*-[$PtCl_2$(cod)] (11.3 mg, 30.0 μmol) and **3d** (31.6 mg, 60.9 μmol, 2.0 equiv) in $CDCl_3$ (0.8 mL). ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.94$ (d, $J=6.9$ Hz, 3H; 4-H_3 or 5-H_3), 0.96 (d, $J=6.9$ Hz, 3H; 4-H_3 or 5-H_3), 1.00 (d, $J=6.8$ Hz, 3H; 9-H_3 or 10-H_3), 1.02 (d, $J=6.8$ Hz, 3H; 9-H_3 or 10-H_3), 2.15–2.25 (m, $J=6.8$, 6.6, 5.4 Hz, 2H; 3-H, 8-H), 3.75 (s, 3H; OCH_3), 4.24 (dd, $J=8.5$, 8.3 Hz, 1H; 7-H), 4.56 (dd, $J=8.7$, 5.1 Hz, 1H; 2-H), 6.71 (d, $J=8.3$ Hz, 1H; 2-NH), 6.99 (dd, $J=7.5$, 7.5 Hz, 1H; 5′-H), 7.22 (dd, $J=7.2$, 7.1 Hz, 2H; ArH_{meta}), 7.28 (dd, $J=7.4$, 7.1 Hz, 2H; ArH_{meta}), 7.34–7.42 (m, 2H; ArH_{para}), 7.45 (dd, $J=9.2$, 8.8 Hz, 1H; 4′-H), 7.54 (d, $J=7.8$ Hz, 1H; 6′-H), 7.58–7.66 (m, 3H; 2′-H, ArH_{ortho}), 7.69 (dd, $J=11.4$, 7.8 Hz, 2H; ArH_{ortho}), 8.14 ppm (d, $J=6.9$ Hz, 1H; 7-NH); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=18.0$, 19.0 (C_4, C_5), 19.6, 19.7 (C_9, C_{10}), 30.2, 31.2 (C_3, C_8), 52.2 (OCH_3), 57.5 (C_2), 61.1 (C_7), 127.5 ($C_{5'}$), 128.0 (2 ArC_{meta}), 128.1 (2 ArC_{meta}), 128.5 ($C_{6'}$), 128.9 (d, $J_{C,P}=65.7$ Hz, ArC_{ipso}), 129.2 (d, $J_{C,P}=65.7$ Hz, ArC_{ipso}), 129.8 (d, $J_{C,P}=63.3$ Hz, ArC_{ipso}), 131.3 (ArC_{para}), 131.5 (ArC_{para}), 133.3 ($C_{2'}$), 133.6 (ArC), 135.5 (2 ArC_{ortho}), 135.7 (2 ArC_{ortho}), 136.2 ($C_{4'}$), 165.8, 172.0, 172.7 ppm (C_1, C_6, C_{11}); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta=14.79$ ppm (d, $^1J_{P,Pt}=3658.7$ Hz); MS (ESI, 5 kV, calcd for: $C_{60}H_{70}Cl_2N_4O_8P_2Pt$): *m/z* (%): 1267.2 (100) [M^+ −Cl].

*cis-[PtCl$_2$(**5a**·**5a**)]*: Following the general procedure this compound was obtained from *cis*-[$PtCl_2$(cod)] (11.2 mg, 30.0 μmol) and **5a** (36.8 mg, 60.0 μmol, 2.0 equiv) in $CDCl_3$ (0.8 mL). ^1H NMR (500 MHz, $CDCl_3$): $\delta=0.95$ (d, $J=6.2$ Hz, 3H; 4-H_3 or 5-H_3), 0.99 (d, $J=6.0$ Hz, 3H; 4-H_3 or 5-H_3), 2.13 (m_c, 1H; 3-H), 4.04 (m_c, 1H; 2-H), 4.20 (dd, $J=6.9$, 6.7 Hz, 1H; 8-H), 4.37 (dd, $J=9.1$, 7.1 Hz, 1H; 7-H^B), 4.50 (dd, $J=10.6$, 6.9 Hz, 1H; 7-H^A), 5.40 (d, $J=7.4$ Hz, 1H; 2-NH), 7.15–7.47 (m, 12H; ArH), 7.57 (d, $J=7.2$ Hz, 2H; ArH), 7.61–7.83 (m, 6H; ArH), 7.70 (overlapped s, 1H; 2′-NH), 7.91 ppm (d, $J=7.7$ Hz, 1H; 3′-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=17.8$, 19.4 (C_4, C_5), 31.1 (C_3), 47.2 (C_8), 61.0 (C_2), 67.3 (C_7), 115.2 ($C_{3'}$), 120.08 (fluorenyl C), 120.10 (fluorenyl C), 125.0 (fluorenyl C), 125.1 (fluorenyl C), 126.5 (d, $J_{C,P}=22.7$ Hz, $C_{5'}$), 127.2 (2 fluorenyl C), 127.8 (m, 6 ArC), 131.1 (ArC), 131.3 (ArC), 135.5 (2 ArC), 135.9 (2 ArC), 137.7 (d, $J_{C,P}=8.2$ Hz, $C_{4'}$), 141.4 (2 fluorenyl C), 143.71 (fluorenyl C), 143.72 (fluorenyl C), 150.2 (d, $J_{C,P}=17.9$ Hz, $C_{6'}$), 153.2 (d, $J_{C,P}=86.6$ Hz, $C_{2'}$), 156.5 (C_6), 170.3 ppm (C_1); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta=12.60$ ppm (d, $^1J_{P,Pt}=3702.7$ Hz); MS (ESI, 5 kV, calcd for: $C_{74}H_{68}Cl_2N_6O_6P_2Pt$): *m/z* (%): 1429.4 (100) [M^+−Cl].

*cis-[PtCl$_2$(**3i**·**5e**)]*: Following the general procedure this compound was obtained from *cis*-[$PtCl_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3i** (9.7 mg, 30 μmol, 1.0 equiv), and **5e** (10.9 mg, 30.0 μmol, 1.0 equiv). ^{31}P NMR (121 MHz, $CDCl_3$): $\delta=11.59$ (dd, $^1J_{P,Pt}=3519.5$ Hz, $^2J_{P,P}=15.6$ Hz, amide **5e**), 14.44 ppm (dd, $^1J_{P,Pt}=3687.1$ Hz, $^2J_{P,P}=15.6$ Hz, ester **3i**); MS (ESI, 5 kV, calcd for: $C_{42}H_{40}Cl_2N_2O_3P_2Pt$): *m/z* (%): 955.1 (42) [M^+−Cl] (**5e** homodimer), 913.1 (100) [M^+−Cl] (heterodimer), 876.2 (49) [M^+−Cl] (**3i** homodimer); heterodimer/C-homodimer ratio = 79.1:20.9.

*cis-[PtCl$_2$(**3j**·**5f**)]*: Following the general procedure this compound was obtained from *cis*-[$PtCl_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3j** (12.0 mg, 30 μmol, 1.0 equiv), and **5f** (12.0 mg, 30.0 μmol, 1.0 equiv). M.p. 135 °C (toluene/$CDCl_3$); ^{31}P NMR (202 MHz, $CDCl_3$): $\delta=9.32$ (d and brs, $^1J_{P,Pt}=3788.4$ Hz, $^2J_{P,P}$ not detectable, **5f**), 14.49 ppm (dd overlapped with C-homodimer signal, $^1J_{P,Pt}=3674.4$ Hz, $^2J_{P,P}<19$ Hz, **3j**); MS (ESI, 5 kV, calcd for: $C_{51}H_{43}Cl_2N_3O_2P_2Pt$): *m/z* (%): 1022.1 (100) [M^+−Cl], 985.2 (16) [M^+−Cl−HCl]; elemental analysis calcd (%) for $C_{51}H_{43}Cl_2N_3O_2P_2Pt$: C 57.91, H 4.10, N 3.97; found: C 57.62, H 4.31, N 3.72; heterodimer/C-homodimer ratio = 80.7:19.3. Colorless plate-like crystals suitable for single-crystal X-ray diffraction analysis were obtained from a solution of the complex in toluene/$CDCl_3$ (5:2), which was allowed to stand at room temperature for two weeks.

*cis-[PtCl$_2$(**3a**·**5a**)]*: Following the general procedure this compound was obtained from *cis*-[$PtCl_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3a** (11.7 mg, 30.0 μmol, 1.0 equiv), and **5a** (18.0 mg, 30.0 μmol, 1.0 equiv). ^{31}P NMR (121 MHz, $CDCl_3$): $\delta=10.61$ (dd, $^1J_{P,Pt}=3691.0$ Hz, $^2J_{P,P}=12.8$ Hz, N-peptide **5a**), 14.83 ppm (dd overlapped with C-homodimer signal, $^1J_{P,Pt}=3658.1$ Hz, $^2J_{P,P}=14.5$ Hz, C-peptide **3a**); MS (ESI, 5 kV, calcd for $C_{60}H_{56}Cl_2N_4O_6P_2Pt$): *m/z* (%): 1429.2 (10) [M^+−Cl] (**5a** homodimer), 1221.2 (100) [M^+−Cl] (heterodimer), 1011.9 (10) [M^+−Cl] (**3a** homodimer); heterodimer/N-homodimer ratio = 87.6:12.4.

*cis-[PtCl$_2$(**3b**·**5a**)]*: Following the general procedure this compound was obtained from *cis*-[$PtCl_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3b** (12.6 mg, 30.0 μmol, 1.0 equiv), and **5a** (18.0 mg, 30.0 μmol, 1.0 equiv). ^{31}P NMR (121 MHz, $CDCl_3$): $\delta=10.02$ (dd, $^1J_{P,Pt}=3716.6$ Hz, $^2J_{P,P}=16.7$ Hz, N-peptide **5a**), 15.06 ppm (dd, $^1J_{P,Pt}=3685.4$ Hz, $^2J_{P,P}=15.6$ Hz, C-peptide **3b**); MS (ESI, 5 kV, calcd for $C_{62}H_{60}Cl_2N_4O_6P_2Pt$): *m/z* (%): 1429.3 (40) [M^+−Cl] (**5a** homodimer), 1249.2 (100) [M^+−Cl] (heterodimer); heterodimer/C-homodimer ratio = 70.2:29.8.

*cis-[PtCl$_2$(**3c**·**5a**)]*: Following the general procedure this compound was obtained from *cis*-[$PtCl_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3c** (13.8 mg, 30.0 μmol, 1.0 equiv), and **5a** (18.0 mg, 30.0 μmol, 1.0 equiv). ^{31}P NMR (121 MHz, $CDCl_3$): $\delta=5.81$ (dd, $^1J_{P,Pt}=3647.6$ Hz, $^2J_{P,P}=16.2$ Hz, N-peptide **5a**), 15.77 ppm (dd, $^1J_{P,Pt}=3777.3$ Hz, $^2J_{P,P}=16.7$ Hz, C-peptide **3c**); MS (ESI, 5 kV, calcd for: $C_{65}H_{67}Cl_2N_5O_5P_2Pt$): *m/z* (%): 1290.3 (100) [M^+−Cl]; heterodimer/C-homodimer ratio = 92.8:7.2.

*cis-[PtCl$_2$(**3c**·**5b**)]*: Following the general procedure this compound was obtained from *cis*-[$PtCl_2$(cod)] (8.4 mg, 22.5 μmol, 1.0 equiv), **3c** (10.4 mg, 22.5 μmol, 1.0 equiv), and **5b** (12.9 mg, 22.5 μmol, 1.0 equiv). ^{31}P NMR (202 MHz, $CDCl_3$): $\delta=4.58$ (dd, $^1J_{P,Pt}=3647.4$ Hz, $^2J_{P,P}=16.7$ Hz, N-peptide **5b**), 16.20 ppm (dd, $^1J_{P,Pt}=3775.3$ Hz, $^2J_{P,P}=16.2$ Hz, C-peptide **3c**); MS (ESI, 5 kV, calcd for: $C_{63}H_{63}Cl_2N_5O_5P_2Pt$): *m/z* (%): 1373.2 (5) [M^+

−Cl] (**5b** homodimer), 1262.2 (100) [M^+−Cl] (heterodimer); heterodimer/C-homodimer ratio = 97.7:2.3.

*cis-[PtCl$_2$(**3g**·**5a**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (8.4 mg, 22.5 μmol, 1.0 equiv), **3g** (12.0 mg, 22.5 μmol, 1.0 equiv), and **5a** (13.5 mg, 22.5 μmol, 1.0 equiv). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 4.89 (dd, $^1J_{P,Pt}$ = 3649.8 Hz, $^2J_{P,P}$ = 16.2 Hz, N-peptide **5a**), 15.87 ppm (dd, $^1J_{P,Pt}$ = 3799.6 Hz, $^2J_{P,P}$ = 14.8 Hz, C-peptide **3g**); MS (ESI, 5 kV, calcd for: $C_{68}H_{71}Cl_2N_5O_7P_2Pt$): *m/z* (%): 1362.3 (100) [M^+−Cl]; heterodimer/C-homodimer ratio = 93.8:6.2.

*cis-[PtCl$_2$(**3g**·**5b**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (8.4 mg, 22.5 μmol, 1.0 equiv), **3g** (12.0 mg, 22.5 μmol, 1.0 equiv), and **5b** (12.9 mg, 22.5 μmol, 1.0 equiv). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 4.46 (dd, $^1J_{P,Pt}$ = 3648.7 Hz, $^2J_{P,P}$ = 16.7 Hz, N-peptide **5b**), 16.33 ppm (dd, $^1J_{P,Pt}$ = 3812.4 Hz, $^2J_{P,P}$ = 14.8 Hz, C-peptide **3g**); MS (ESI, 5 kV, calcd for: $C_{66}H_{67}Cl_2N_5O_7P_2Pt$): *m/z* (%): 1334.3 (100) [M^+−Cl]; heterodimer/C-homodimer ratio = 96.8:3.2.

*cis-[PtCl$_2$(**3d**·**5a**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3d** (15.6 mg, 30.0 μmol, 1.0 equiv), and **5a** (18.0 mg, 30.0 μmol, 1.0 equiv). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 5.02 (dd, $^1J_{P,Pt}$ = 3652.0 Hz, $^2J_{P,P}$ = 16.2 Hz, N-peptide **5a**), 15.89 ppm (dd, $^1J_{P,Pt}$ = 3802.9 Hz, $^2J_{P,P}$ = 16.2 Hz, C-peptide **3d**); MS (ESI, 5 kV, calcd for: $C_{67}H_{69}Cl_2N_5O_7P_2Pt$): *m/z* (%): 1348.1 (100) [M^+−Cl]; heterodimer/C-homodimer ratio = 94.9:5.1.

*cis-[PtCl$_2$(**3h**·**5a**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3h** (15.6 mg, 30.0 μmol, 1.0 equiv), and **5a** (18.0 mg, 30.0 μmol, 1.0 equiv). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 4.67 (dd, $^1J_{P,Pt}$ = 3668.7 Hz, $^2J_{P,P}$ = 16.2 Hz, N-peptide **5a**), 15.63 ppm (dd, $^1J_{P,Pt}$ = 3799.9 Hz, $^2J_{P,P}$ = 16.2 Hz, C-peptide **3h**); MS (ESI, 5 kV, calcd for $C_{67}H_{69}Cl_2N_5O_7P_2Pt$): *m/z* (%): 1348.3 (100) [M^+−Cl]; elemental analysis calcd (%) for $C_{67}H_{69}Cl_2N_5O_7P_2Pt$: C 58.13, H 5.02, N 5.06; found: C 58.13, H 5.21, N 4.77; heterodimer/C-homodimer ratio = 97.2:2.8.

*cis-[PtCl$_2$(**3d**·**5b**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (8.4 mg, 22.5 μmol, 1.0 equiv), **3d** (11.7 mg, 22.5 μmol, 1.0 equiv), and **5b** (12.9 mg, 22.5 μmol, 1.0 equiv). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 4.47 (dd, $^1J_{P,Pt}$ = 3647.6 Hz, $^2J_{P,P}$ = 16.2 Hz, N-peptide **5b**), 16.28 ppm (dd, $^1J_{P,Pt}$ = 3804.1 Hz, $^2J_{P,P}$ = 16.2 Hz, C-peptide **3d**); MS (ESI, 5 kV, calcd for $C_{65}H_{65}Cl_2N_5O_7P_2Pt$): *m/z* (%): 1320.3 (100) [M^+−Cl]; heterodimer/C-homodimer ratio = 96.7:3.3.

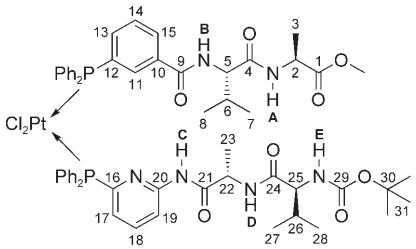
*cis-[PtCl$_2$(**3e**·**5c**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (8.4 mg, 22.5 μmol, 1.0 equiv), **3e** (11.0 mg, 22.5 μmol, 1.0 equiv), and **5c** (9.8 mg, 22 μmol, 1.0 equiv). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 5.59 (dd, $^1J_{P,Pt}$ = 3670.4 Hz, $^2J_{P,P}$ = 16.2 Hz, N-peptide **5c**), 15.82 ppm (dd, $^1J_{P,Pt}$ = 3779.6 Hz, $^2J_{P,P}$ = 16.7 Hz, C-peptide **3e**); MS (ESI, 5 kV, calcd for $C_{52}H_{57}Cl_2N_5O_7P_2Pt$): *m/z* (%): 1156.1 (100) [M^+−Cl] (heterodimer), 1101.2 (29) [M^+−Cl] (**5c** homodimer); heterodimer/C-homodimer ratio = 95.7:4.3.

*cis-[PtCl$_2$(**3e**·**5b**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3e** (14.7 mg, 30 μmol, 1.0 equiv), and **5b** (17.1 mg, 30.0 μmol, 1.0 equiv). M.p. 150 °C (CH_2Cl_2); $[\alpha]_D^{21}$ = −40.0° (*c* = 0.700 in $CHCl_3$); ^{31}P NMR (202 MHz, $CDCl_3$): δ = 4.56 (dd, $^1J_{P,Pt}$ = 3660.9 Hz, $^2J_{P,P}$ = 16.2 Hz, N-peptide **5b**), 16.17 ppm (dd, $^1J_{P,Pt}$ = 3797.9 Hz, $^2J_{P,P}$ = 16.2 Hz, C-peptide **3e**); MS (ESI, 5 kV, calcd for $C_{63}H_{61}Cl_2N_5O_7P_2Pt$): *m/z* (%): 1373.1 (34) [M^+−Cl] (**5b** homodimer), 1292.1 (100) [M^+−Cl] (heterodimer); elemental analysis calcd (%) for $C_{63}H_{61}Cl_2N_5O_7P_2Pt$: C 56.97, H 4.63, N 5.27; found: C 57.03, H 4.72, N 5.13; heterodimer/C-homodimer ratio = 98.3:1.7.

*cis-[PtCl$_2$(**3e**·**5d**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3e** (14.8 mg, 30.0 μmol, 1.0 equiv), and **5d** (12.3 mg, 30.0 μmol, 1.0 equiv). M.p. 145–147 °C (CH_2Cl_2); $[\alpha]_D^{21}$ = −37.4° (*c* = 0.620 in $CHCl_3$); ^{31}P NMR (202 MHz, $CDCl_3$): δ = 4.24 (dd, $^1J_{P,Pt}$ = 3647.4 Hz, $^2J_{P,P}$ = 14.8 Hz, N-peptide **5d**), 15.91 ppm (dd, $^1J_{P,Pt}$ = 3775.3 Hz, $^2J_{P,P}$ = 14.8 Hz, C-peptide **3e**); MS (ESI, 5 kV, calcd for $C_{50}H_{53}Cl_2N_5O_7P_2Pt$): *m/z* (%): 1128.0 (100) [M^+−Cl]; elemental analysis calcd (%) for $C_{50}H_{53}Cl_2N_5O_7P_2Pt$: C 51.60, H 4.59, N 6.02; found: C 51.90, H 4.83, N 5.71; heterodimer/C-homodimer ratio = 96.6:3.4.

*cis-[PtCl$_2$(**3d**·**6a**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (11.2 mg, 30.0 μmol, 1.0 equiv), **3d** (15.6 mg, 30.0 μmol, 1.0 equiv), and **6a** (17.3 mg, 30.0 μmol, 1.0 equiv). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 5.30 (dd, $^1J_{P,Pt}$ = 3653.1 Hz, $^2J_{P,P}$ = 16.2 Hz, N-peptide **6a**), 15.99 ppm (dd, $^1J_{P,Pt}$ = 3880.9 Hz, $^2J_{P,P}$ = 16.2 Hz, C-peptide **3d**); MS (ESI, 5 kV, calcd for $C_{62}H_{76}Cl_2N_6O_8P_2Pt$): *m/z* (%): 1383.3 (9) [M^+−Cl] (**6a** homodimer), 1325.3 (100) [M^+−Cl] (heterodimer); elemental analysis calcd (%) for $C_{62}H_{76}Cl_2N_6O_8P_2Pt$: C 54.71, H 5.63, N 6.17; found: C 54.34, H 5.83, N 5.98; heterodimer/C-homodimer ratio = 93.6:6.4.

*cis-[PtCl$_2$(**3e**·**6b**)]*: Following the general procedure this compound was obtained from *cis*-[PtCl$_2$(cod)] (11.3 mg, 30.0 μmol, 1.0 equiv), **3e** (14.8 mg, 30.0 μmol, 1.0 equiv), and **6b** (16.6 mg, 30.0 μmol, 1.0 equiv). M.p. 155 °C (CH_2Cl_2); $[\alpha]_D^{20}$ = −14.0° (*c* = 1.000 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.9 Hz, 3H; 27-H$_3$ or 28-H$_3$), 1.03 (d, *J* = 6.6 Hz, 3H; 27-H$_3$ or 28-H$_3$), 1.14 (d, *J* = 6.9 Hz, 3H; 7-H$_3$ or 8-H$_3$), 1.17 (d, *J* = 6.9 Hz, 3H; 7-H$_3$ or 8-H$_3$), 1.46 (d, *J* = 6.0 Hz, 3H; 3-H$_3$), 1.47 (s, 9H; *t*Bu), 1.74 (d, *J* = 6.9 Hz, 3H; 23-H$_3$), 2.22 (m$_c$, 1H; 26-H), 2.26 (m, *J* = 6.9 Hz, 1H; 6-H), 3.79 (s, 3H; OCH_3), 4.05 (dd, *J* = 6.9, 6.6 Hz, 1H; 25-H), 4.63 (dq, *J* = 7.3, 6.9 Hz, 1H; 2-H), 5.18 (dd, *J* = 9.1, 6.9 Hz, 1H; 5-H), 5.38 (d, *J* = 8.5 Hz, 1H; NH_E), 5.47 (dd, *J* = 7.3, 6.9 Hz, 1H; 22-H), 6.75 (dd, *J* = 7.6, 4.1 Hz, 1H; 17-H), 6.80 (m$_c$, 2H; ArH), 7.03–7.10 (m, 2H; ArH, 13-H), 7.12–7.22 (m, 10H; ArH, 14-H, NH_D, NH_B), 7.23–7.47 (m, 7H; ArH, 18-H), 7.62 (m$_c$, 2H; ArH), 7.74 (dd, *J* = 7.7, 1.1 Hz, 1H; 15-H), 7.95 (m$_c$, 2H; ArH), 8.19 (dd, *J* = 8.3, 2.3 Hz, 1H; 19-H), 8.60 (d, *J* = 6.9 Hz, 1H; NH_A), 9.61 (d, *J* = 14.8 Hz, 1H; 11-H), 10.78 ppm (s, 1H; NH_C); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.9 (C_3, $C_{27/28}$), 18.7, 19.0 (C_7, C_8), 19.5 ($C_{27/28}$), 20.3 (C_{23}), 28.4 ($3C_{31}$), 31.1 (C_{26}), 33.0 (C_6), 48.3 (C_2), 49.7 (C_{22}), 52.3 (OCH_3), 58.2 (C_5), 60.4 (C_{25}), 80.1 (C_{30}), 114.6 (C_{19}), 124.2 (d, $J_{C,P}$ = 16.1 Hz, C_{17}), 127.5 (d, $J_{C,P}$ = 11.8 Hz, 2 ArC_{meta}), 127.6 (d, $J_{C,P}$ = 10.8 Hz, 2 ArC_{meta}), 127.9 (d, $J_{C,P}$ = 10.7 Hz, 2 ArC_{meta}), 128.1 (d, $J_{C,P}$ = 11.8 Hz, 2 ArC_{meta}), 128.3 (d, $J_{C,P}$ = 8.6 Hz, C_{14}), 128.5 (ArC), 128.5 (ArC), 129.4 (d, $J_{C,P}$ = 61.3 Hz, ArC), 130.4 (ArC), 130.6 (ArC), 131.3 (ArC), 131.4 (ArC), 134.4 (d, $J_{C,P}$ = 9.7 Hz, 2 ArC), 134.7 (d, $J_{C,P}$ = 14.0 Hz, ArC), 135.1 (d, $J_{C,P}$ = 10.8 Hz, 2 ArC), 135.2 (d, $J_{C,P}$ = 10.7 Hz, 2 ArC), 137.2 (d, $J_{C,P}$ = 7.5 Hz, C_{18}, 2 ArC), 138.1 (d, $J_{C,P}$ = 21.5 Hz, C_{11}), 151.6 (d, $J_{C,P}$ = 20.4 Hz, C_{20}), 153.9 (d, $J_{C,P}$ = 96.7 Hz, C_{16}), 156.0 (C_{29}), 166.9, 171.2, 171.7, 172.1, 173.2 ppm (C_1, C_4, C_9, C_{21}, C_{24}); ^{31}P NMR (202 MHz, $CDCl_3$): δ = 4.37 (dd, $^1J_{P,Pt}$ = 3622.7 Hz, $^2J_{P,P}$ = 14.8 Hz, N-peptide **6b**), 15.92 ppm (dd, $^1J_{P,Pt}$ = 3790.1 Hz, $^2J_{P,P}$ = 14.8 Hz, C-peptide **3e**); MS (ESI, 5 kV, calcd for $C_{58}H_{68}Cl_2N_6O_8P_2Pt$): *m/z* (%): 1269.2 (100) [M^+−Cl]; elemental analysis calcd (%) for $C_{58}H_{68}Cl_2N_6O_8P_2Pt$: C 53.38, H 5.25, N 6.44; found: C 53.24, H 5.37, N 6.38; heterodimer/C-homodimer ratio = 96.3:3.7. Resonance assignments were based on DQF-COSY, edHSQC, 2D TOCSY and 2D ROESY analysis.



General procedure for the generation of homo- and heterodimeric rhodium(I) complexes: Equal amounts of ligand 1 (30.0 μmol, 1.0 equiv), complementary ligand 2 (30.0 μmol, 1.0 equiv) and [Rh(cod)$_2$]BF_4 (12.2 mg, 30.0 μmol, 1.0 equiv) were dissolved in degassed $CDCl_3$ (37.5 mM) at room temperature and analyzed by NMR (^{1}H, ^{31}P) spectroscopy and ESI MS.

*[Rh(cod)(**3d**·**3d**)]BF_4*: Following the general procedure this compound was obtained from [Rh(cod)$_2$]BF_4 (10.0 mg, 24.6 μmol) and **3d** (25.5 mg, 49.3 μmol, 2.0 equiv) in $CDCl_3$ (0.7 mL). ^{1}H NMR (300 MHz, $CDCl_3$):

$\delta = 0.93$ (2d, $J = 7.3$ Hz, 6H; 4-H_3, 5-H_3), 1.06 (d, $J = 6.5$ Hz, 3H; 9-H_3 or 10-H_3), 1.07 (d, $J = 6.5$ Hz, 3H; 9-H_3 or 10-H_3), 2.22 (m_c, 1H; 3-H), 2.29 (m_c, 1H; 8-H), 3.69 (s, 3H; OCH_3), 4.43 (dd, $J = 8.2$, 8.1 Hz, 1H; 7-H), 4.54 (dd, $J = 8.5$, 5.3 Hz, 1H; 2-H), 7.05 (d, $J = 7.6$ Hz, 1H; 2-NH), 7.15–7.70 (m, 12H; ArH), 7.80 (d, $J = 7.3$ Hz, 1H; ArH), 8.04 (d, $J = 6.7$ Hz, 1H; 7-NH), 8.30 ppm (br s, 1H; ArH); ^{31}P NMR (121 MHz, $CDCl_3$): $\delta =$ 27.28 (d, $^1J_{P,Rh} = 144.8$ Hz); MS (ESI, 5 kV, calcd for $C_{68}H_{82}BF_4N_4O_8P_2Rh$): m/z (%): 1262.7 (41) [M^+_{oxide}−Cl], 1246.8 (100) [M^+−Cl].

*[Rh(cod)(**3d**·**5a**)]BF_4*: Following the general procedure this compound was obtained from [Rh(cod)$_2$]BF_4 (10.8 mg, 26.6 μmol), **3d** (13.9 mg, 26.8 μmol, 1.0 equiv), and **5a** (15.9 mg, 26.5 μmol, 1.0 equiv). ^{1}H NMR (400 MHz, $CDCl_3$, only relevant resonances): $\delta = 8.24$ (d, $J = 9.2$ Hz, 1H; NH_A), 9.49 (d, $J = 14.3$ Hz, 1H; 13-H), 10.68 ppm (s, 1H; NH_C); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 16.04$ (dd, $^1J_{P,Rh} = 145.7$ Hz, $^2J_{P,P} =$ 30.7 Hz, N-peptide **5a**), 31.81 ppm (dd, $^1J_{P,Rh} = 150.6$ Hz, $^2J_{P,P}$ not resolved due to broad line width, C-peptide **3d**); MS (ESI, 7 kV, calcd for $C_{75}H_{81}BF_4N_5O_7P_2Rh$): m/z (%): 1328.4 (100) [M^+−BF_4], 1220.1 (22) [M^+ −BF_4−cod], 811.0 (63).

X-ray crystal structure analysis: A single crystal of *cis*-[$PtCl_2$(**3j**·**5f**)] was submitted for X-ray data collection on a Rigaku R-AXIS SPIDER image plate diffractometer using graphite monochromated $Mo_{K\alpha}$ radiation at 100 K. Structure solution was carried out with SHELXS-97,[40] and refinement against F^2 with SHELXL-97.[41] Crystallographic data of *cis*-[$PtCl_2$-(**3j**·**5f**)] have been deposited to the Cambridge Crystallographic Data Centre. CCDC-650318 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for asymmetric hydroformylation: In an argon atmosphere [Rh(CO)$_2$acac] (1.5 mg, 5.8 μmol, 1 mol%) and the corresponding ligands $\mathbf{L_C}$ (1.1–5 mol%) and $\mathbf{L_N}$ (1.1–5 mol%) were dissolved in dry toluene and stirred for 5–10 min at room temperature. Then, styrene (**7**) was added and the resulting pale yellow solution was transferred into a 50 mL stainless steel autoclave under argon, and subsequently flushed three times with a 1:1 mixture of H_2 and CO gas. An initial total pressure of 10 bar H_2/CO 1:1 gas mixture was finally adjusted, and the autoclave was heated within 5 min to the reaction temperature while the solution was stirred. Reaction samples were taken through a sample valve and analyzed by GC and/or ^{1}H NMR spectroscopy. Conversion and regioselectivity (**8**:**9** ratio) were determined by ^{1}H NMR spectroscopy. Enantiomeric excess of **8** was determined by chiral GC, using a Hydrodex-β-TBDAc column, 25 m × 0.25 mm, 95 °C. t_R (min) = 10.2 [(*R*)-enantiomer], 11.3 [(*S*)-enantiomer].

Acknowledgement

This work was supported by the Fonds der Chemischen Industrie, DFG (Int. Research Training Group GRK 1038), the Alfried Krupp Award for young university teachers of the Krupp Foundation (to B.B.), and BASF. J.M.S. is grateful to the Alexander von Humboldt Foundation for a fellowship. We kindly thank J. "Leo" Leonhardt and B. Ruf for great technical assistance, and Dr. M. Keller for ROE spectroscopy experiments.

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Received: February 27, 2008
Published online: April 30, 2008

