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Cyclic decapeptide gramicidin S derivatives containing phosphines: novel ligands for asymmetric catalysis†‡

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The cyclic peptide gramicidin S was used as a rigid template to provide novel peptide-based bisphosphine ligands for transition metal catalysis. Two bisphosphine-coordinated Rh(I) complexes allowed asymmetric hydrogenation with 10–52% ee and the corresponding Pd(II) analogues catalysed asymmetric allylic alkylation with 13–15% ee.

Introduction

Catalysis is of vital importance for many industrial chemical processes. Still, man-made catalysts do not meet the exceptional selectivity obtained by enzymes in living systems. On the other hand, no enzymes are known to catalyse most of the reactions of industrial interest such as hydroformylation,[1–3] hydrogenation,[4–9] and allylic substitution.[10–14] The design of functional molecules able to catalyse a variety of asymmetric transformations is one of the important challenges in contemporary chemistry.[15] The design of artificial metalloenzymes, where a transition metal is anchored covalently or in a supramolecular fashion to an existing protein,[16] has involved tremendous effort.[17] Several highly enantioselective hybrid catalysts have been reported.[18] Although these artificial metalloenzymes can be further improved using the strength of directed evolution methodologies,[19] there are still practical problems to overcome.[20] Metallopeptides are presented as alternative hybrid catalysts, since they are readily accessible.[16] They are obtained by incorporating a metal complex into a peptide.[21] Gilbertson and co-workers as pioneers of this area made use of a fruitful approach where oligopeptides are used as scaffolds to create a unique asymmetric environment for organo- or transition metal catalysis.[22–25] Of key importance for the design of peptide-based catalysts for bidentate metal chelation is the structure of the oligopeptide and the spatial orientation of its ligands amenable for transition metal complexation,[15] as well as the nonproteinogenic metal coordinating moieties used, which enhance the coordination to metals. Examples with carboxylate-containing side chains,[26] phosphines[27] and pyridines[28] have been described. Phosphines are arguably the most successful ligands in transition metal catalysis.[15]

The natural product gramicidin S (GS) is a promising scaffold for the construction of metal complexes.[29] New hybrid chiral ligands incorporating achiral phosphines into the chiral scaffolds of biomolecules may generate biomimetic molecules with interesting catalytic properties once coordinated to active metals such as palladium, ruthenium or rhodium. GS is a cyclic decameric peptide ((Pro-Val-Orn-Leu-dPhe)$_2$) with C_2-symmetry that adopts a rigid cyclic β-hairpin structure. Because of the cyclic β-hairpin structure the side-chains of the two ornithine (Orn) residues are on the same side of the molecule and have been used for the attachment of ligands for transition metals. Exemplary is the design and synthesis of a GS-tetrakis(2-pyridylmethyl) dinuclear zinc complex that is able to catalyse the hydrolysis of a phosphodiester bond.[30] Several modified-phosphine gramicidin S derivatives **I–III** have been recently reported by our laboratories and presented as potential chiral ligands for catalysts (Fig. 1), maintaining the general β-hairpin secondary structure of the parent GS molecule as confirmed by X-ray crystal structure analysis. It was concluded that there are significant differences between the different GS derivatives, which are found in the shape and size of the linkage between the oligopeptide backbone and the phosphine.

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†Dedicated to an inspiring scientist and friend, Prof. David Cole-Hamilton, for his invaluable contribution to transition metal catalysis, on the occasion of his retirement. "Onwards and upwards" as Geoffrey Wilkinson used to say!

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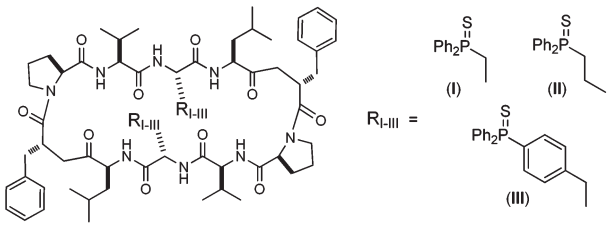

Fig. 1 Schematic representation of sulfur protected diphosphine-functionalized gramicidin derivatives **I–III**.

Preliminary modelling studies indicated that these biphosphine-functionalized gramicidin S derivatives were suitable ligands for transition-metals, favouring the subtle *trans*-bisphosphine coordination with metal over *cis* configuration.[29]

We here report the first asymmetric catalytic hydrogenation and allylic substitution using four new GS derivatives containing phosphines (GS–PP) **3a**, **3b**, **3c** and **3d** (Fig. 2), for the construction of bidentate phosphine metal complexes of palladium and rhodium.

Results and discussion

The synthesis and characterisation of four new bisphosphine-containing cyclic decapeptide derivatives **3a**, **3b**, **3c** and **3d** of gramicidin S are reported (see Fig. 2, also ESI‡). Complexation with rhodium and palladium was studied by ^{31}P NMR spectroscopy and the resulting complexes were evaluated in asymmetric hydrogenation and allylic amination. Several functional groups can be incorporated into gramicidin S by reaction of the free amino groups in the two ornithine residues, which are situated at one side of the β-sheet. For instance, two bis-(pyridylmethyl)amino groups were introduced in place of free amino groups, and it was demonstrated that this system accelerates the cleavage of phosphodiesters in the presence of zinc(II).[30] Most of the hybrid ligands reported[30–33] contain a phosphine modified amino acid which is protected prior to incorporation into the peptide chain, requiring extra deprotection steps and cleavage from the solid support. To avoid extra steps, we followed the method of Christensen and Meldal.[34] Phosphine moieties were incorporated in solution, *via* amide bond formation, to the amino residue of the amino acid ornithine prior to complexation with rhodium(I) or palladium(II).

We have prepared four new GS derivatives following a published method by our laboratories, incorporating *o*-, *m*-, *p*-diphenylphosphinobenzoic acids **1a**, **1b**, **1c** and diphenylphosphinopropanoic acid **1d**, previously activated by reaction with *N*-hydroxysuccinimide in dichloromethane (see Fig. 2).[35] The reaction of the corresponding phosphines GS–PP (**3a**, **3b**, **3c** and **3d**) with [Rh(nbd)$_2$]BF$_4$ leads to the formation of rhodium(I) complexes [Rh(nbd)(**3a–d**)]BF$_4$ (**4a–d**) which were characterised by ^{1}H, ^{31}P NMR spectroscopy and MALDI-TOF MS (see ESI‡).

Phosphorus chemical shifts for complexes **4a–d** and phosphorus–rhodium coupling constants for **4a**, **4b** and **4c** are in the expected range (Table 1). The resonances were found around 30 ppm as expected with J_{Rh-P} of the order of 170 Hz, showing that phosphorus atoms were coordinated to the

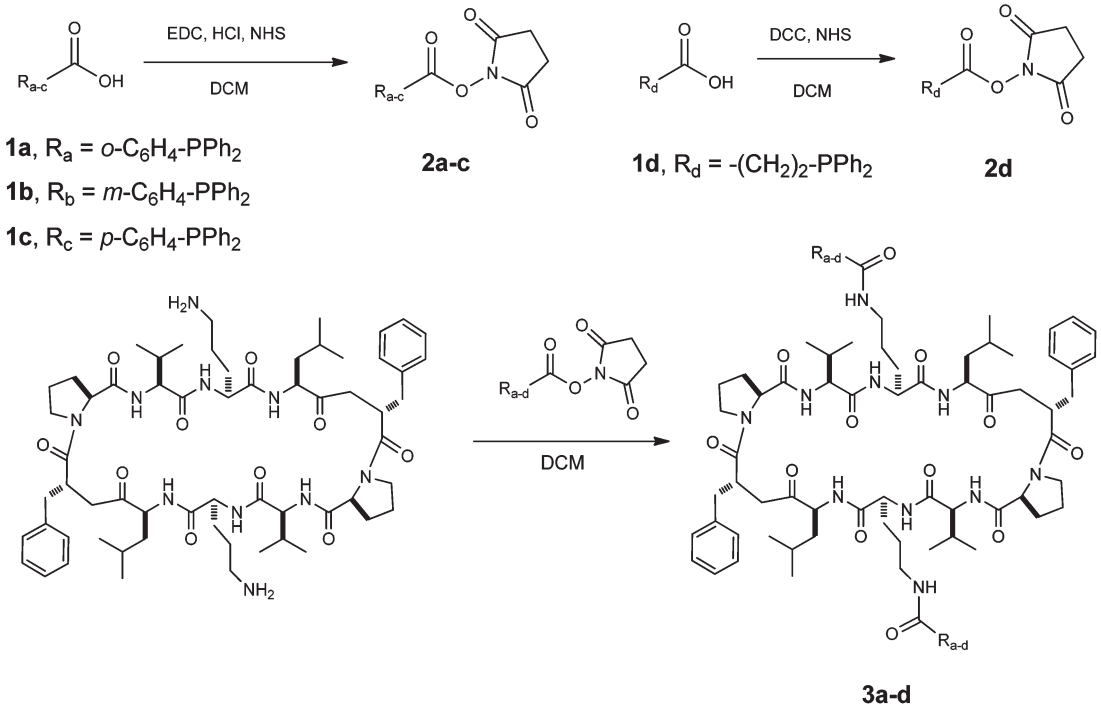

Fig. 2 Synthesis of modified-phosphine GS derivatives, **3a–3d**.

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rhodium centre.[36] The ^{31}P NMR spectrum of **4a** indicates that the metal complex keeps C_2 symmetry, since a doublet was observed. The ^{31}P NMR spectrum of complex **4b** shows a broad signal probably due to coalescence between two different complex structures or two non-equivalent phosphorus atoms, on the other hand, only one species was detected by MALDI-TOF MS.

At the same time, the ^{31}P NMR spectrum of complex **4c** shows two different doublets at 30.9 and 29.1 ppm, which suggests either the presence of two different conformers or one metal complex with two non-equivalent phosphorus nuclei. However, this last possibility was discarded since MALDI-TOF MS of **4c** shows only one species. Similar to **4c**, the ^{31}P NMR spectrum of complex **4d** also shows two doublets almost overlapped, indicating that two conformers are present, since only one species was detected by MALDI-TOF MS.

The coordination chemistry with the palladium dimer [Pd-(η^3-allyl)(μ-Cl)]$_2$ was studied for the ligands *meta*- and *para*-GS–PP, **3b** and **3c** respectively. Reactions were performed by mixing the ligand and the metal precursor in dichloromethane under argon.

The new palladium(II) complexes **5b** and **5c** showed phosphorus resonances at 23.1 and 22.2 ppm, respectively. These chemical shifts are in the typical region for palladium phosphine complexes indicating the coordination of the ligand to the palladium centre. Rh and Pd complexes **4b** and **5b** were fully characterised by including ^{31}P–^{1}H HSQC and TOCSY (see ESI‡).

Table 1 ^{31}P{^{1}H} chemical shifts for the complexes **4a–d**

Complex		δ (ppm), [mult.]	J(Rh–P) Hz
[Rh(nbd)(**3a**)](BF$_4$)	(**4a**)	29.7 [d]	170
[Rh(nbd)(**3b**)](BF$_4$)	(**4b**)	30.7 [*broad*]	—
[Rh(nbd)(**3c**)](BF$_4$)	(**4c**)	30.9 [d], 29.1 [d]	176.8, 161.7
[Rh(nbd)(**3d**)](BF$_4$)	(**4d**)	26.0 [d], 25.9 [d]	172.8, 175.9

We tested the catalytic performance of rhodium(I) complexes of **4a–d** in the asymmetric hydrogenation of substrates **A**, **B** and **C** (Fig. 3). The results are summarised in Table 2.

It can be observed that only metal complexes **4b** and **4c** show catalytic activity. Rhodium complex **4b** containing the phosphine in the *meta* position was found to be more active and selective than **4c** (phosphine in *para* position) for all substrates studied, probably due to the closer proximity of the two phosphines to the chiral scaffold. However, the unexpected inactivity of **4a** breaks this trend. At the same time, metal complex **4d** showed no activity for asymmetric hydrogenation. Preliminary modeling studies comparing three different gramicidin S complexes **4a–c** (containing triphenylphosphine substituted at the *o*-, *m*-, *p*- position) predicted higher enantiomeric induction in the order *o*- > *m*- > *p*- based on the generally accepted quadrant model[4] as the phosphine moieties coordinated to metal that were attached to gramicidin S were directed towards the peptide backbone. Interestingly, **4b** and **4c** produced enantiomers *R* and *S* respectively, showing that the simple variation on the phosphine position has a direct

Table 2 Catalytic hydrogenation results using GS derivatives[a]

Entry	Complex	Substrate	% Conv.	% ee
1	**4a**	A	0	—
2	**4b**	A	57	15 (*R*)
3	**4c**	A	30	13 (*S*)
4	**4d**	A	0	—
5	**4a**	A	0	—
6	**4b**	B	99	43 (*R*)
7	**4c**	B	>99	7 (*S*)
8	**4d**	B	0	—
9	**4a**	C	0	—
10	**4b**	C	73	52 (*R*)
11	**4c**	C	36	10 (*S*)
12	**4d**	C	0	—

[a] Reaction conditions: 48 nmol catalyst [Rh(nbd)(**3a–d**)]BF$_4$ (**4a–d**), substrate : Rh : L = 30 : 1 : 1, solvent: DCM 0.5 mL, P = 20 bar, T = 25 °C, t = 18 h.

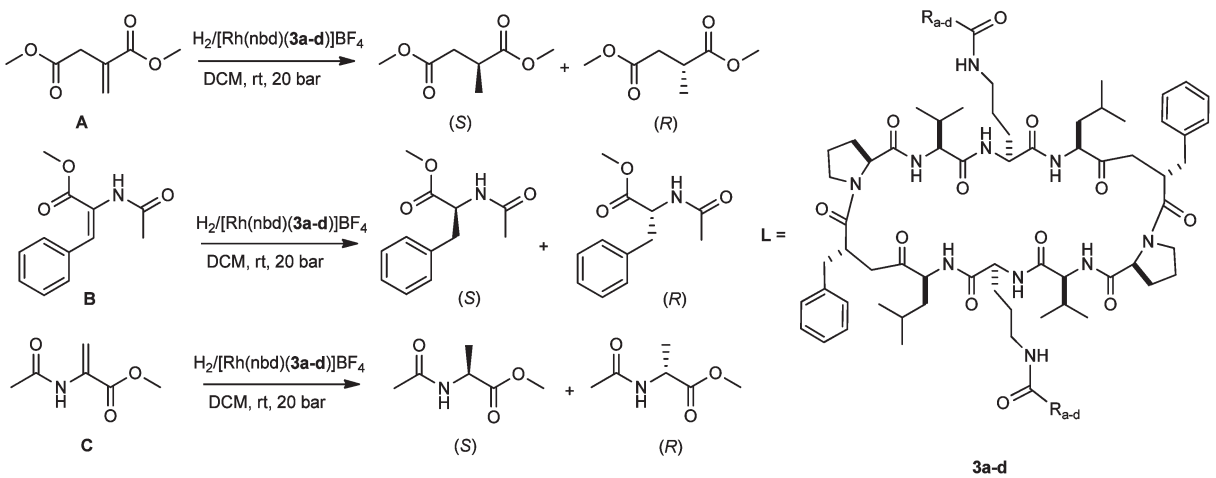

Fig. 3 Substrates utilised in hydrogenation reactions catalysed by Rh complexes of phosphine containing GS derivatives, **3a–d**.

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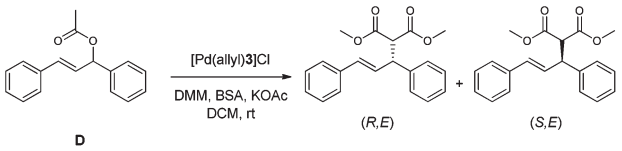

Fig. 4 Asymmetric allylic alkylation of 1,3-diphenylallyl acetate.

Table 3 Catalytic results of asymmetric allylic alkylation[a]

Entry	Complex	Substrate	Nucleophile	% Conv.	% ee
13	[Pd(allyl)(**3b**)]Cl (**5b**)	**D**	DMM	14	15 (*R*)
14	[Pd(allyl)(**3c**)]Cl (**5c**)	**D**	DMM	12	13 (*S*)

[a] Reaction conditions: 58 nmol catalyst [Pd(allyl)(**3b–c**)]Cl (**5b–c**), nucleophile : BSA : allyl acetate : Pd : L = 120 : 120 : 40 : 1 : 1, catalytic amount of KOAc, solvent: DCM 0.5 mL, T = 25 °C, t = 18 h.

influence on the absolute configuration of the products. The best results in terms of activity were found for substrate **B** using complexes **4b** and **4c**, where more than 99% conversion to the desired product was detected by GC. For substrates **A** and **C**, the conversions observed were from moderate to good (30–73%).

This may explain why metal complexes **4b** and **4c**, in which the phosphorus atoms are much closer than in **4d**, yielded higher catalytic activity and enantioselectivity, while metal complex **4a** containing the most sterically hindered phosphine is not active.

Complex **4b** gives the best ee both for methyl 2-acetamidoacrylate **B** (43%), and for methyl-*Z*-α-acetamidocinnamate **C** (52%). These results show that the design of ligands using a biological chiral scaffold is a promising approach.

The palladium(II) complexes **5b** and **5c** have been evaluated in allylic substitution of 1,3-diphenylallyl acetate (**D**) with the anion from dimethyl malonate (DMM) (see Fig. 4). Both complexes gave low conversions and 13 and 15% ee respectively. The results are summarised in Table 3.

An inversion of absolute configuration of the products was observed, as occurred for hydrogenation, since complexes bearing ligands **3b** *m*- and **3c** *p* produced the opposite enantiomers, *S* and *R* respectively.

Conclusions

In summary, unprotected phosphine moieties can be directly incorporated into the cyclic decapeptide gramicidin S *via* amide bond formation avoiding extra steps. The phosphine-containing *m*- and *p*-GS derivatives were found to be active in Rh-catalysed asymmetric hydrogenation with up to 52% ee and in Pd-catalysed allylic substitution with up to 15% ee. Complex **4b** is the most active of the whole series, for all substrates in asymmetric hydrogenation giving the highest ee, probably due to the angle between the phosphines and the metal along with steric environment. Interestingly, an inversion of the absolute configuration of products was observed for **4b** to **4c** in asymmetric hydrogenation and allylic alkylation, which indicates that small changes in the ligand influence tremendously the outcome of the reaction. We are currently expanding the range of phosphorus containing GS derivatives to find active and selective systems for several catalytic reactions.

Shortening the side-chains of the amino acid residue would place the metal closer to the chiral scaffold, which may improve the enantiomeric excess of the reactions.

Experimental

General procedure for hydrogenation reactions

The reactions were carried out in a GC vial, reaction volume 0.5 mL, due to the very small amounts of catalyst required; it was observed that reproducibility of the results critically depends on the care taken in the preparation of the catalytic samples. Dichloromethane was distilled over CaH_2, and degassed prior to use.

Catalytic runs were prepared in GC vials, which were previously purged and flushed with argon three times in a carrousel or a Schlenk vessel under argon. The metal complex stock solution was obtained by adding 0.1 mL of $[Rh(nbd)_2]BF_4$ (2.21 mg, 5.82 μmol) previously dissolved in 1 mL of DCM to a solution of 0.5 mL of DCM of the appropriate ligand (1 mg, 0.582 μmol). The final volume of the metal complex stock solution was 0.6 mL. The solution was stirred at room temperature for 20 min. Stock solutions of the different substrates, dimethyl itaconate, methyl acetamidoacrylate, methyl acetamidocinnamate and decane (internal standard) were prepared in Schlenk vessels which were previously purged and flushed with argon three times, 14.6 μmol of substrate was dissolved in 5 mL of DCM, 7.3 μmol of decane was dissolved in 5 mL of DCM. The GC vials in the carrousel were filled with 1.46 μmol of substrate, 0.73 μmol of decane, and 58.2 nmol of the metal complex. The GC vial was filled with 0.35 mL of DCM to obtain a final reaction volume of 0.5 mL. All GC vials were placed in a stainless steel insert and introduced in a stainless steel autoclave; under argon, all GC vials were punched with a needle. The autoclave was flushed 3 times with 5 bar of H_2 and finally pressurised with 20 bar of H_2 and stirred at room temperature for 18 hours. After the reaction, the 0.5 mL reaction volume of each run was passed through a silica pad, washed with 1 mL of DCM–MeOH (9 : 1) solution prior to GC analysis.

General procedure for allylic alkylation

Catalytic runs were prepared in GC vials, which were previously purged and flushed with argon three times in a carrousel or a Schlenk vessel under argon containing a catalytic amount of KOAc, and the stirring bar. The GC vials were placed in the carrousel. The metal source $[Pd(allyl)Cl]_2$ (1 mg, 2.73 μmol) was dissolved in 1 mL of DCM and 0.273 μmol of this solution was added to the stock solution 0.5 mL of DCM of the appropriate

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ligand (1 mg, 0.582 μmol). The final volume of the stock solution containing the metal complex was 0.6 mL.

Stock solutions of the substrate, 1,3-diphenylallyl acetate, dimethyl malonate, BSA and diphenyl ether (internal standard) were prepared in Schlenk vessels, which were previously purged and flushed with argon three times. To the GC vial containing 300 μL KOAc was added 58.2 nmol of the metal complex, 14.6 μmol of substrate, and the reaction mixture was stirred for 20 min, after this time 6 μmol of dimethyl malonate, 6 μmol of BSA and 7.3 μmol of diphenyl ether in 5 mL of DCM were added. The final reaction volume was 0.5 mL. All GC vials were stirred at room temperature for 18 hours.

To work up the reactions, the mixtures were filtered over a plug of silica and washed with 1 mL of DCM. The solvent was evaporated, and HPLC grade hexane was added. The samples were analysed by HPLC.

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