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Chiral Phosphanylferrocenecarboxamides with Amino Acid Pendant Groups as Ligands for Cu-Mediated Asymmetric Conjugate Additions of Diethylzinc to Chalcones – Structural Characterisation of Precursors to the Cu Catalyst

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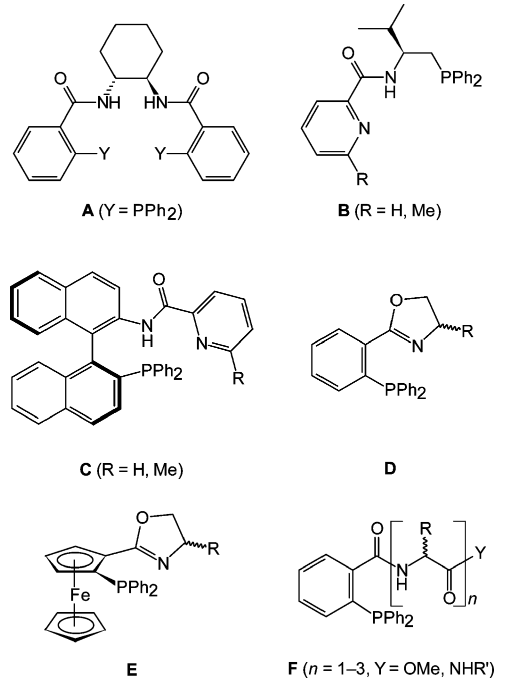
A series of chiral phosphanylferrocenecarboxamides was prepared by treatment of either 1′-(diphenylphosphanyl)ferrocene-1-carboxylic acid (Hdpf) or its planar-chiral 1,2-isomers with amino acid methyl esters in the presence of peptide coupling agents. The compounds were characterised by spectroscopic methods, and the crystal structure of one representative was determined by X-ray diffraction. Catalytic testing of these donors in Cu-catalysed asymmetric conjugate additions of diethylzinc to chalcones revealed that the reaction outcomes were highly sensitive to the ligand structure and the reaction conditions (copper source and solvent), whereas the chalcone substituents (Me, MeO, or Cl in positions 4 or 4′) had a less pronounced influence. Compounds based on Hdpf proved to be better ligands than their planar-chiral analogues. Under optimised conditions, the reaction with L-valine–Hdpf conjugate, (*S*)-$Ph_2PfcCONHCH(CHMe_2)CO_2Me$ (fc = ferrocene-1,1′-diyl) and unsubstituted chalcone gave the alkylation product with complete conversion (20 °C/4 h) and in 87 % *ee*. The catalytic behaviour of the amidophosphane ligands was correlated to the results of a model coordination study and the crystal structure of $[Cu(Ph_2PfcCONHCH_2CO_2Me)_2](CF_3SO_3)\cdot 2CHCl_3$.

Introduction

Asymmetric conjugate additions of carbon nucleophiles to acceptor-activated double bonds represent an attractive tool for the stereoselective formation of C–C bonds. Their practical implementation was recently facilitated by the discovery of metal-catalysed processes that allow for controlled use of highly reactive organometals and require the presence of only catalytic amounts of a metal precursor and a chiral ligand.[1]

In this regard, copper-mediated conjugate additions of diorganozinc reagents to α,β-unsaturated ketones have attracted particular synthetic interest and have dominated the field since their discovery in the 1990s.[2] This is very probably due to the efficient acceleration of this reaction through the use of Cu/L* catalysts (typically generated in situ), allowing in turn for fine-tuning of the course of the reaction. In addition, organozinc reagents react rather selectively and tolerate a variety of functional groups,[3] which further broadens the field of application of these reactions. On the other hand, careful attention has to be paid to the design of chiral donors for any enantioselective variant of these reactions because the chiral ligands are the only source of chirality in this process and thus have crucial impact on the reaction outcomes.[1]

During our studies on phosphanylferrocenecarboxamides,[4,5] we noticed that these donors have a structural similarity with some ligands utilised (though with varying success) in conjugate additions of organometals. Prominent examples of such ligands, combining phosphane and carboxamide moieties, are Trost's chiral bis(amide) (**A** in Scheme 1),[6] some C- and axial-chiral amidophosphanes



Scheme 1.

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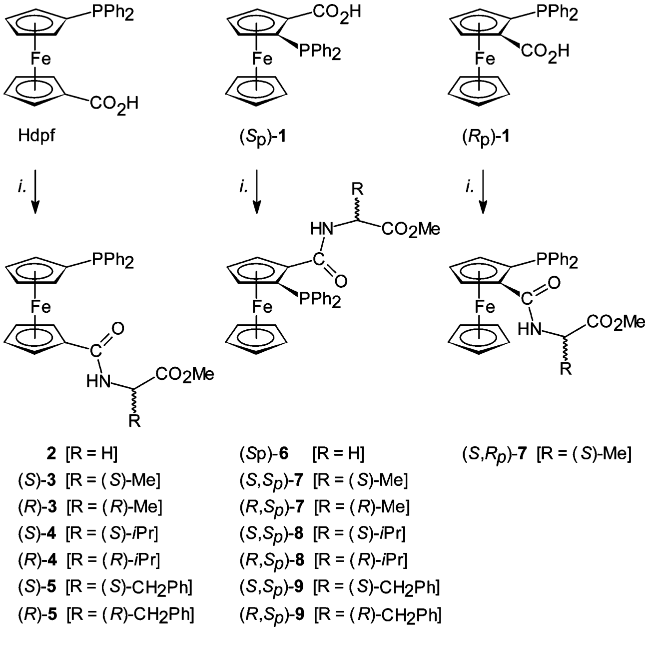
(e.g., **B** and **C**),[7] phosphanyloxazolines (**D** and **E**)[8] and, mainly, the highly versatile amino-acid- and peptide-based phosphanes [**F**; R and chirality depend on the amino acid(s) used].[9,10]

In view of this similarity and of the successful applications of phosphanylferrocene ligands in asymmetric conjugate additions,[1,6,11] we decided to extend our work directed towards the design, coordination properties and catalytic utilisation of phosphanylferrocene–glycine donors Ph_2P-fcC(O)NHCH$_2$C(O)Y (fc = ferrocene-1,1′-diyl; Y = OH, OMe, NH_2)[4a] to their chiral analogues. Here we describe the preparation of a library of phosphanylferrocenecarboxamides with stereogenic carbon atoms in their amide side chains and/or planar chirality at their ferrocene units, together with the results of their testing as ligands for copper-catalysed asymmetric conjugate additions of diethylzinc to chalcones.

Results and Discussion

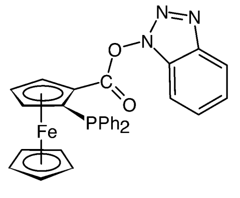
Synthesis and Characterisation of the Ligands

The series of amino acid amides (Scheme 2) was designed to incorporate compounds featuring either a chirality centre in the amino acid or a chirality plane, as well as their analogues with combined chirality. Accordingly, the amides were prepared from 1′-(diphenylphosphanyl)ferrocene-1-carboxylic acid (Hdpf)[12] or its planar-chiral isomers (S_p)- and (R_p)-**1**,[13] and from glycine or C-chiral (L- or D-)amino acids. Amino acid methyl esters, which were used throughout this study in order to avoid undesired reactions at the carboxyl group, were generated in situ from the corresponding hydrochlorides – [$H_3NCH(R)CO_2Me$]Cl (R = H, Me, *i*Pr, and CH_2Ph) – and triethylamine.



Scheme 2. Preparation of the amidophosphane ligands **2**–**9**. Reagents and conditions: (i) 1-hydroxybenzotriazole and *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide in dry dichloromethane (0 °C/30 min); then addition of an [$H_3NCH(R)CO_2Me$]Cl/NEt_3/CH_2Cl_2 mixture and stirring at room temp. overnight.

All amides were obtained by standard amide coupling in the presence of 1-hydroxybenzotriazole and a carbodiimide reagent[14] and were isolated by column chromatography, typically in the forms of orange amorphous solids. It should be noted that, whereas the reactions with L-amino acids proceeded with excellent yields for all phosphanylcarboxylic acids, those involving (S_p)-**1** *and* D-amino acids did not reach completion, with limited amounts of the intermediate active ester 1-hydroxybenzotriazolyl (S_p)-2-(diphenylphosphanyl)ferrocene-1-carboxylate [(S_p)-**10**] also being isolated. This can be explained by a chirality mismatch, resulting in steric crowding and making the coupling reaction more difficult.



(S_p)-**10**

The presence of amide and ester moieties in **3**–**9** is manifested in their IR spectra through the strong bands due to $\nu_{C=O}$ (ester; 1740–1751 cm^{-1}), amide I (1624–1656 cm^{-1}) and amide II (1517–1532 cm^{-1}) vibrations. In addition to signals attributable to the functional substituents, ^{1}H NMR spectra of the Hdpf-based amides each displayed eight resonances due to diastereotopic ferrocene protons, whereas compounds derived from the acid **1** each showed a sharp singlet and three characteristic multiplets of the unsubstituted C_5H_5 ring and the C_5H_3 protons, respectively. Notably, the signals of the amide protons and the CH (or CH_2) groups bonding to the amide nitrogen atom in the planar-chiral amides were observed as ^{31}P-coupled multiplets (confirmed by ^{1}H{^{31}P} NMR). This interaction, resulting in relatively high coupling constants (ca. 13 Hz for the NH protons), seems to reflect the mutual orientation of the interacting moieties and possible N–H···P contacts (vide infra).

The ^{13}C{^{1}H} NMR spectra confirmed the formulation by combining the signals of the PPh_2-substituted ferrocene units and the amide pendants, with two C=O resonances being of particular diagnostic value (Hdpf-based compounds: $\delta_C \approx 170$ ppm for CONH and $\delta_C \approx 173$ ppm for CO_2Me; compounds based on **1**: $\delta_C = 170.6$–173.7 ppm for CO_2Me, and a ^{31}P-coupled doublet at $\delta_C \approx 170$ ppm for CONH). Finally, the ^{31}P{^{1}H} NMR spectra displayed single resonances at $\delta_P \approx -17$ ppm for the Hdpf derivatives and at $\delta_P \approx -20$ ppm for their planar-chiral analogues.

Circular dichroism (CD) spectra of isomeric amides bearing alanine pendants (Figure 1) show several Cotton effects in the regions of ferrocene d–d and CT transitions.[15] The spectra of (*R*)- and (*S*)-**3** demonstrate the expected enantiomeric relationship. Those of the planar-chiral isomers suggest a dominant contribution of planar chirality to the CD response.

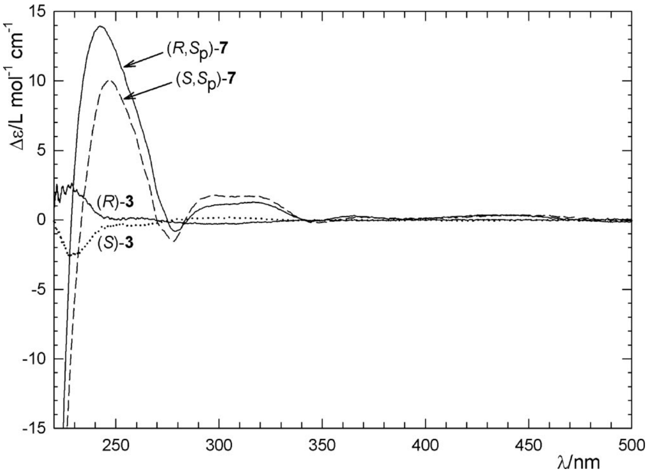


Figure 1. CD spectra of the isomeric compounds (S)-**3** (dotted line), (R)-**3**, (S,S_p)-**7** (dashed line) and (R,S_p)-**7** ($c \approx 1$ mM in MeOH).

In addition to the spectroscopic characterisation, the crystal structure of (S,S_p)-**9** (Figure 2) was determined, corroborating both the expected connectivity and chirality. The geometric data for (S,S_p)-**9** compare well with those for the achiral donor **2**[4a] and for amides prepared from the acid (S_p)-**1**.[4g] The ferrocene cyclopentadienyl rings (Cp) in (S,S_p)-**9** are practically coplanar and assume a near-to-eclipsed conformation. However, the substituents are bonded somewhat asymmetrically. Whereas the P–C2–C1/C3 angles differ by less than 2°, the difference in the C11–C1–C2/C5 angles is 10.5°, because the C1–C11 bond is bent away from the PPh_2 group. This bending occurs without any notable torsion, however, as indicated by the P–C2–C1–C11 angle of 2.5(2)°. The amide group (C11,O1,N) is nearly coplanar with its parent Cp ring [dihedral angle 5.4(2)°] and is oriented with the N–H bond pointing towards the phosphorus atom.[16]

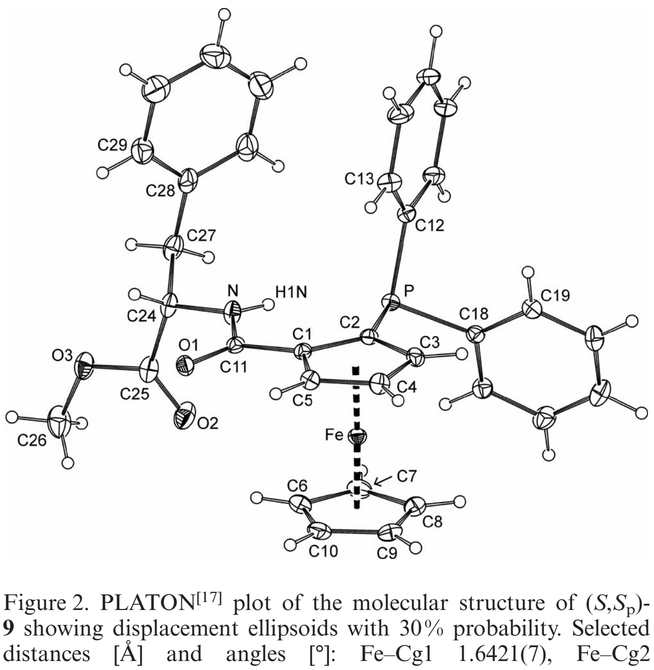
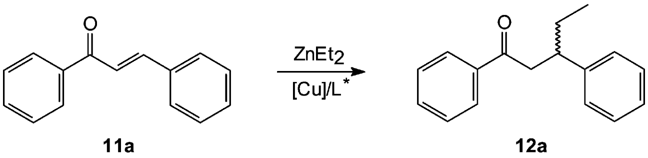


Figure 2. PLATON[17] plot of the molecular structure of (S,S_p)-**9** showing displacement ellipsoids with 30% probability. Selected distances [Å] and angles [°]: Fe–Cg1 1.6421(7), Fe–Cg2 1.6527(7), ∠Cp1,Cp2 2.84(9); C1–C11 1.492(2), C11–O1 1.228(2), C11–N 1.350(2), N–C24 1.449(2), C24–C25 1.520(2), C25–O2 1.196(2), C25–O3 1.342(2), O3–C26 1.451(3), C24–C27 1.537(2), C27–C28 1.512(3), C2–P 1.817(2), P–C12 1.830(1), P–C18 1.833(2); O1–C11–N 121.8(1), C11–N–C24 120.5(1), O2–C25–O3 124.3(2), C25–O3–C26 115.7(1), C–P–C angles 101.84(7)–103.13(7). Definitions: Cp1 = C(1–5), Cp2 = C(6–10); Cg1 and Cg2 are the corresponding ring centroids.

Catalytic Tests

The catalytic potential of the amidophosphane ligands was examined in the copper-catalysed conjugate addition of diethylzinc to *trans*-chalcone (**11a**) to give the ketone **12a** (Scheme 3). The initial screening reactions were performed with (S)-**3**, possessing only central chirality. Particular attention was paid to finding the optimal reaction conditions (Table 1).



Scheme 3. Conjugate addition of diethylzinc to chalcone (**11a**) to give **12a**.

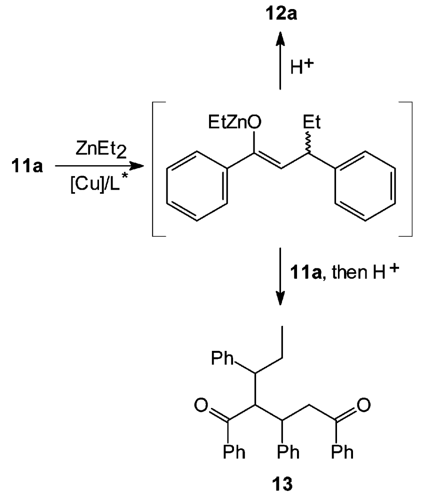
All reactions proceeded cleanly, affording either pure alkylation product or, in cases of incomplete conversion, its mixtures with unreacted chalcone. No 1,3-diphenylpent-1-en-3-ol, the product of direct attack of diethylzinc on the carbonyl group, was detected. However, the crude reaction mixtures typically contained traces of 1,3,5-triphenyl-2-(1-phenylpropyl)pentane-1,5-dione (**13**). This compound, presumably arising from a side-reaction of an intermediate zinc enolate (Scheme 4),[18] was found to crystallise preferentially from the product mixture and was structurally characterised (see the Supporting Information). The amounts of isolated pure alkylation products were always high: a 91% yield of analytically pure **12a**, for instance, was isolated by flash column chromatography from the reaction presented as Entry 1 in Table 1 (conversion 98%).

The results summarised in Table 1 demonstrate that the reaction course (conversion and *ee*) changes strongly both with the metal source and with the solvent. In donor media the reaction became slow (in MeCN it stopped entirely) and less selective. However, even the similar halogenated solvents proved to give different results (cf. Entries 1, 10, 11). On the other hand, the initial oxidation state of copper did not play any important role, whereas the counterions (Entries 1, 3–8), possibly influencing the solubility (etc.) of the copper source, had a pronounced impact. The selectivity was also strongly affected by the Cu/L ratio (Entries 1 and 2). Out of the conditions tested, the combination of a catalyst prepared in situ from $(CuOTf)_2$·PhMe (3 mol-% Cu)

Table 1. Initial optimisation of the reaction conditions with the ligand (*S*)-**3**.[a]

Entry	Metal salt	Solvent	*T* [°C] (*t* [h])	Conversion [%]	*ee* [%][c]
1	$(CuOTf)_2\cdot PhMe$	CH_2Cl_2	0 (4)	98	+70
2	$(CuOTf)_2\cdot PhMe$[b]	CH_2Cl_2	0 (4)	92	+20
3	$Cu(OTf)_2$	CH_2Cl_2	0 (4)	94	+57
4	CuCl	CH_2Cl_2	0 (4)	91	+39
5	CuBr	CH_2Cl_2	0 (4)	87	+40
6	CuI	CH_2Cl_2	0 (4)	79	+35
7	$CuBr\cdot SMe_2$	CH_2Cl_2	0 (4)	40	+33
8	$Cu_2(OAc)_4\cdot 2H_2O$	CH_2Cl_2	0 (4)	93	+35
9	$(CuOTf)_2\cdot PhMe$	PhMe	0 (4)	98	+38
10	$(CuOTf)_2\cdot PhMe$	$CHCl_3$	0 (4)	81	+64
11	$(CuOTf)_2\cdot PhMe$	$(ClCH_2)_2$	0 (4)	75	+48
12	$(CuOTf)_2\cdot PhMe$	*t*BuOMe	0 (4)	100	+49
13	$(CuOTf)_2\cdot PhMe$	Et_2O	0 (4)	100	+42
14	$(CuOTf)_2\cdot PhMe$	THF	0 (4)	57	+13
15	$(CuOTf)_2\cdot PhMe$	$(MeOCH_2)_2$	0 (4)	10	+8
16	$(CuOTf)_2\cdot PhMe$	MeCN	0 (4)	0	–

[a] All reactions were carried out with **11a** (0.50 mmol) and diethylzinc (0.75 mmol, 1 M heptane solution) in the presence of 15 µmol of "copper" (3.0 mol-%) and 18 µmol of ligand (*S*)-**3** (3.6 mol-%), in 3 mL of the solvent stated. The results are averages of two independent runs. [b] Reaction performed at Cu/L = 1:2.4 (molar ratio). [c] *ee* = {[(*R*)] – [(*S*)]}/{[(*R*)] + [(*S*)]}; positive values indicate that the (*R*) isomer dominates.



Scheme 4. Plausible reaction pathway leading to the side-product **13**.

and 1.2 equiv. of ligand in dichloromethane as the solvent gave the best results and was therefore used in all subsequent reactions.

Having established the optimal reaction conditions, we continued with the assessment of the influence of the ligand structure on the reaction course (Table 2). The application of all of the Hdpf-based ligands (Entries 1–6) resulted in good levels of conversion and enantioselectivity. However, a distinct positive effect of the size of the amino acid substituent on the *ee* was noted: ligands bearing bulkier groups gave better results. Accordingly, the best results were obtained with the valine-based donors (*S*)-**4** and (*R*)-**4**, which gave rise to active catalysts affording the alkylation products with complete conversion at 0 °C within 4 h and with *ee* values of +83 or –84% depending on the configurations of the amino acid chirality centres.

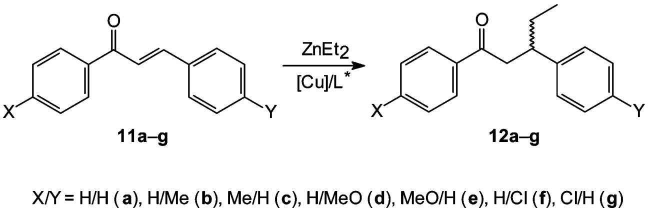
Table 2. Survey of the ligands.[a]

Entry	Ligand	*T* [°C] (*t* [h])	Conversion [%]	*ee* [%][c]
1	(*S*)-**3**	0 (4)	98	+70
2	(*R*)-**3**	0 (4)	97	–68
3	(*S*)-**4**	0 (4)	100	+83
4	(*R*)-**4**	0 (4)	100	–84
5	(*S*)-**5**	0 (4)	92	+79
6	(*R*)-**5**	0 (4)	91	–80
7	(S_p)-**6**	0 (4)	86	–72
8	(S_p)-**6**[b]	0 (4)	87	–59
9	(S,S_p)-**7**	0 (4)	20	–39
10	(R,S_p)-**7**	0 (4)	14	–12
11	(S,R_p)-**7**	0 (4)	13	+11
12	(S,S_p)-**8**	0 (4)	10	–9
13	(R,S_p)-**8**	0 (4)	32	–13
14	(S,S_p)-**9**	0 (4)	16	–8
15	(R,S_p)-**9**	0 (4)	23	–3

[a] All reactions were carried out with **11a** (0.50 mmol) and diethylzinc (0.75 mmol, 1 M heptane solution) in the presence of $(CuOTf)_2\cdot PhMe$ (7.5 µmol, 3.0 mol-% Cu) and ligand (*S*)-**3** (18 µmol, 3.6 mol-%) in CH_2Cl_2 (3 mL). The results are averages of two runs. [b] Reaction performed at Cu/L molar ratio = 1:2.4. [c] *ee* = {[(*R*)] – [(*S*)]}/{[(*R*)] + [(*S*)]}.

Quite unexpectedly, the planar chiral amides proved to be rather poor ligands, with the single exception of the sterically least congested (S_p)-**6** (Entry 7). No improvement was observed when the amount of ligand was increased to 2.4 equiv. (Entry 8). This is rather surprising in view of the high efficiency of the related (non-amino acid) ligands in Pd-catalysed asymmetric allylic alkylations[4g,5] and of the successful application of C- *and* planar-chiral ferrocenediyldiphosphanes in Cu-catalysed conjugate additions of Grignard reagents to enones.[1f,1j]

Another series of catalytic tests was performed with ligand (*S*)-**4** in order to establish possible effects of the reaction temperature and chalcone substituents. The former parameter was varied in the model system involving **11a**. For the latter purpose, six additional substituted chalcones **11b**–**g** were included in the testing, each bearing a substituent (Cl, Me, or MeO) in the 4- or 4′-position, where its influence can be expected to be limited mainly to electronic effects (Scheme 5).



Scheme 5. Conjugate additions of diethylzinc to ring-substituted chalcones.

As indicated by the results in Table 3, the lowering of the reaction temperature to –20 °C did not decrease the reaction rates (conversion) considerably but, surprisingly, had a negative effect on enantioselectivity.[19] At –40 °C the reactions became not only rather slow but also even less selective (Entries 5 and 6). On the other hand, the alkylation performed at 20 °C was complete within 4 h and produced **12a** with 87% *ee* (Entry 2). An increase in the reaction temperature by another 20 °C (Entry 1) finally led to a lower *ee* value.

Table 3. Influence of the reaction temperature and remote substituents.[a]

Entry	Substrate	*T* [°C] (*t* [h])	Conversion [%]	*ee* [%][c]
1	**11a**	+40 (4)	100	+82
2	**11a**	+20 (4)	100	+87
3[b]	**11a**	0 (4)	100	+83
4	**11a**	–20 (4)	100	+79
5	**11a**	–40 (4)	41	+70
6	**11a**	–40 (23)	100	+64
7	**11b**	0 (4)	100	(90)[d]
8	**11c**	0 (4)	100	(87)[d]
9	**11d**	0 (4)	100	(90)[d]
10	**11e**	0 (4)	100	(89)[d]
11	**11f**	0 (4)	100	(83)[d]
12	**11g**	0 (4)	100	(85)[d]

[a] The reactions were performed with the corresponding chalcone (0.50 mmol) and diethylzinc (0.75 mmol, 1 M heptane solution) in the presence of $(CuOTf)_2$·PhMe (7.5 µmol, 3.0 mol-% Cu) and ligand (*S*)-**4** (18 µmol, 3.6 mol-%) in dry CH_2Cl_2 (3 mL). The results are averages of two independent runs. [b] This entry from Table 2 is included for comparison. [c] *ee* = {[(*R*)] – [(*S*)]}/{[(*R*)] + [(*S*)]}. [d] The configuration was not determined.

Previous studies on the influence of remote substituents in conjugate additions to chalcones had given diverse results.[20] In the present case, the introduction of a substituent at the 4- or 4′-position in the substrate (Table 3, Entries 3 and 7–12) influenced the stereoselectivity only marginally, irrespective of the point of attachment. Nonetheless, the substrates with electron-donating groups (Me and MeO) consistently afforded better results than those bearing chlorine as an electron-withdrawing substituent.

Coordination Study

In attempts to interpret the catalytic results, the interaction of copper(I) triflate with **2** as a model donor in solution and in the solid state was studied. ^1H and $^{31}P\{^1H\}$ NMR spectra recorded in CD_2Cl_2 for a mixture of **2** and $(CuOTf)_2$·PhMe at a Cu/L molar ratio of 1:0.9 indicated the presence of two species with chemical shifts δ_P = –10.8 and –4.2 ppm (Figure 3). The signal due to free ligand (δ_P = –17.1 ppm) was not observed. With a change in the Cu/L ratio to 1:2 the high-field signal became dominant (δ_P = –11.0 ppm), and a minor resonance tentatively attributed to ligand phosphane oxide[4a] appeared (δ_P = +32.2 ppm). Electrospray mass spectra of both mixtures revealed the presence of ions attributable to $[\mathbf{2} + H]^+$ (*m*/*z* = 486), $[\mathbf{2} + Na]^+$ (*m*/*z* = 508), $[\mathbf{2} + K]^+$ (*m*/*z* = 524), $[\mathbf{2} + Cu]^+$ (*m*/*z* = 548) and $[(\mathbf{2})_2 + Cu]^+$ (*m*/*z* = 1033).

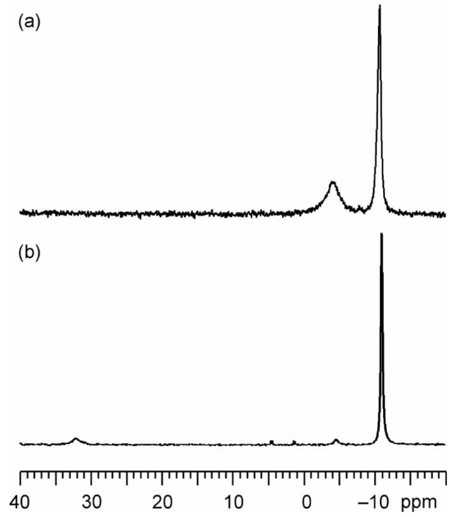


Figure 3. $^{31}P\{^1H\}$ NMR spectra of $(CuOTf)_2$·PhMe/**2** mixtures as recorded in CD_2Cl_2 at 25 °C and (a) 1:0.9, or (b) 1:2 Cu/L molar ratios.

Addition of hexane to a solution of $(CuOTf)_2$·PhMe and **2** (Cu/L = 1:1, *sic!*) in CH_2Cl_2 afforded yellow crystals of the solvated complex $[Cu(\mathbf{2})_2](TfO)$. Unfortunately, these crystals readily decomposed by desolvation, and the determined structure suffered from severe disorder. With a change in the solvent to $CHCl_3$, the same complex was isolated as a slightly more stable $CHCl_3$ solvate, $[Cu(\mathbf{2})_2](TfO)$·$2CHCl_3$ (**14**). Even in this case, the solvent and the counterion are disordered in the solid state, but the better quality and higher stability of the crystals allowed for the collection of good-quality diffraction data and, consequently, for obtaining a reliable structural model.

A view of the cation in the structure of **14** is shown in Figure 4 (for a "full" view, see the Supporting Information). Selected geometric data are presented in Table 4. The copper(I) ion is surrounded by two phosphorus atoms and two *amide* oxygen atoms making up a distorted tetrahedron. The Cu–donor distances are quite uniform and somewhat longer than those reported for a Cu^I complex with a doubly $(2\text{-}Ph_2\mathit{P}C_6H_4)NHC\mathit{O}CH_2$-functionalised calix[4]arene forming an identical donor set.[21] On the other hand, the interligand angles span a rather wide range (ca. 85–124°) and clearly reflect steric demands of the donor moieties: the O11–Cu–O21 angle is the most acute, whereas the P1–Cu–P2 angle represents the maximum.

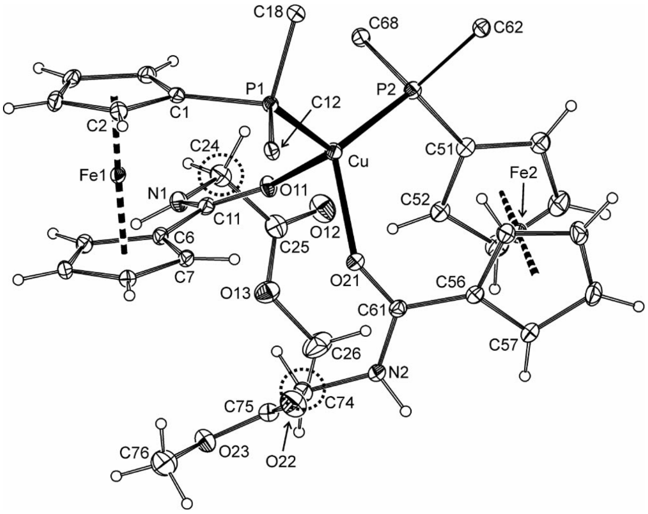


Figure 4. PLATON[17] plot of the cation in the structure of **14** showing atom labelling. (Note: The ligand "molecules" are labelled analogously. Atomic labels for "ligand 2" are obtained by adding 50 for the carbon atoms or by changing the first digit to 2 for other heavy atoms.) Displacement ellipsoids correspond to 20% probability level. For clarity, only pivotal carbon atoms in the phenyl rings and one orientation of the disordered phenyl ring C(62–67) are shown. Carbon atoms that are stereogenic (i.e., substituted) in *chiral* ligands are circled (C24 and C74).

Table 4. Selected distances [Å] and angles [°] for the cation in the structure of complex **14**.[a]

Cu–P1	2.244(1)	Cu–P2	2.275(1)
Cu–O11	2.201(2)	Cu–O21	2.135(2)
P1–Cu–P2	124.38(4)	O11–Cu–O21	84.72(9)
P1–Cu–O11	113.74(8)	P2–Cu–O21	115.77(8)
P1–Cu–O21	113.52(8)	P2–Cu–O11	94.98(7)
C11–O11	1.251(4)	C61–O21	1.248(3)
C11–N1	1.332(5)	C61–N2	1.326(3)
O11–C11–N1	120.7(4)	O21–C61–N2	122.0(2)
C25–O12	1.197(6)	C75–O22	1.198(5)
C25–O13	1.327(5)	C75–O23	1.337(5)
Fe–Cg^P(1)	1.642(2)	Fe–Cg^P(2)	1.640(2)
Fe–Cg^C(1)	1.646(2)	Fe–Cg^C(2)	1.642(2)
∡Cp^P(1),Cp^C(1)	4.2(2)	∡Cp^P(2),Cp^C(2)	1.5(2)
τ(1)	69.5	τ(2)	68.4
ϕ(1)	16.0(5)	ϕ(2)	15.0(3)

[a] Definitions: Cp^P and Cp^C are PPh$_2$- and amide-substituted Cp rings, respectively; Cg^P and Cg^C denote their ring centroids; τ(1/2) = torsion angles C(1/51)–Cg^P(1/2)–Cg^C(1/2)–C(6/56); ϕ = dihedral angles of the Cp^C and amide planes (N1–C11–O11 and N2–C61–O21).

The geometry of the ferrocene units in **14** is regular (cf. Fe–Cg distances and tilt angles). The chelate coordination of **2** is facilitated by a synclinal eclipsed orientation of the donor substituents (cf. ideal value: τ = 72°) and by an inclination of the amide oxygen atom towards the copper atom (see ϕ angles). Notably, the amide C=O distances in **14** are only very slightly elongated in relation to that found for uncoordinated Ph$_2$PfcCONHCH$_2$CO$_2$*t*Bu [1.235(2) Å].[4a]

The complex was also characterised in solution. The NMR spectra recorded for [Cu(**2**)$_2$](OTf) generated in situ indicate that the O,P-coordination remains intact, showing the ^{31}P NMR signal ($\Delta\delta_P \approx +6$ ppm) and the amide resonance [$\Delta\delta_C$(CONH) ≈ +2 ppm] shifted to lower fields. Furthermore, IR spectra of a solid sample suggest a coordinated C=O group (the amide $\nu_{C=O}$ band is shifted by ca. 40 cm^{-1} to lower energies vs. that of free **2**; the ester $\nu_{C=O}$ band remains practically unaffected) and corroborate the presence of the triflate anion (strong bands at 1165–1295 and 1029 cm^{-1}).[22] Electrospray mass spectra confirm the formulation, showing the [Cu(**2**)$_2$]$^+$ ion at *m*/*z* = 1033 with the corresponding accurate mass and isotopic patterns.

Conclusions

Phosphanylferrocenecarboxamides with amino acid pendant groups, readily available in extensive libraries from phosphanylferrocenecarboxylic acids and amino acids as a common chiral pool, were shown to be efficient ligands for copper-catalysed asymmetric conjugate additions of diethylzinc to chalcones. In the series of ligands tested, the donors based on Hdpf proved to be superior to their planar-chiral 1,2-counterparts, providing both high reactivity and enantioselectivity under convenient reaction conditions. The alkylation of unsubstituted chalcone (**11a**) in the presence of L-valine–Hdpf conjugate (*S*)-**4**, for instance, afforded the alkylation product with 100% conversion (20 °C/4 h; 3 mol-% Cu) and 87% *ee*. With **11d** as the substrate, the same catalytic system also achieved the highest selectivity (*er* 95:5 at 0 °C/4 h).

The particular combination of hard and soft donor atoms allows the phosphanyl amides to bind (principally) to both metal atoms involved in the reaction (Cu and Zn) and to act as O,P-chelate ligands. It is the chelate coordination that plays a key role in determining catalytic efficacy, because it results in the formation of rigid structures and brings the ligand's chirality into proximity to the catalytically active metal centre. Furthermore, the data suggest that the addition of the phosphanyl amide ligands to copper(I) triflate affords an equilibrium mixture of cationic species of the type [CuL$_n$]$^+$ (n = 0–2), the exact composition of which changes with the Cu/L molar ratio. Whereas the [CuL$_2$]$^+$ cation is probably the most stable (isolable), the [CuL]$^+$ species appears to be a likely precursor to the catalytically active species. On the other hand, the available data do not allow for any conclusion with regard to the nature of the true catalytic species or substrate–catalyst interactions.

Experimental Section

Materials and Methods: All syntheses were performed under argon and with exclusion of direct daylight. Hdpf,[12a] (S_p)-**1**,[13a] (R_p)-**1**,[13b] **2**[4a] and **11b**–**g**[23] were prepared by literature procedures.

Amino acid methyl ester hydrochlorides – $[H_3NCH(R)CO_2Me]Cl$ (R = H, Me, *i*Pr, CH_2Ph) – were obtained by treatment of the amino acid in question with methanol and thionyl chloride (see the Supporting Information).[24] The racemic ketones **12a**–**g** used for optimisation of the HPLC conditions were synthesised as described in the literature.[25] Anhydrous acetonitrile and *t*BuOMe were purchased from Fluka. Other solvents (Lach-Ner) were dried by standing over appropriate drying agents (CH_2Cl_2, $CHCl_3$, and $ClCH_2CH_2Cl$: K_2CO_3; diethyl ether, 1,2-dimethoxyethane, THF, and toluene: sodium) and distilled under argon. Other chemicals were obtained from commercial sources (Fluka, Aldrich, Alfa) and were used as received. NMR spectra were measured with a Varian UNITY Inova 400 spectrometer (^1H, 399.95; ^{13}C, 100.58; ^{31}P, 161.90 MHz) at 298 K. Chemical shifts (δ/ppm) are given relative to internal tetramethylsilane (^1H and ^{13}C) or to external 85% aqueous H_3PO_4 (^{31}P). IR spectra were recorded with a Nicolet 7600 FTIR spectrometer (Thermo Fisher Scientific) in the 400–4000 cm^{-1} range. Electron impact mass spectra (EI MS), including high-resolution (HR) measurements, were performed with a GCT Premier (Waters) spectrometer. Electrospray mass spectra (ESI MS) were obtained with an Esquire 3000 (Bruker; low resolution) or an LTQ Orbitrap XL instrument (Thermo Fisher Scientific; high resolution). CD spectra were recorded with a JASCO J-815 spectrometer (ca. 1 mM solutions in methanol, *d* = 1 mm). Optical rotations were determined with an Autopol III (Rudolph Research) automatic polarimeter at room temperature.

Preparation of the Ligands

General Procedure for the Preparation of Amides 2–9: A two-necked flask fitted with a gas inlet and containing a stirrer bar was charged with the appropriate acid (1.0 equiv.) and 1-hydroxybenzotriazole (HOBt, 1.2 equiv.). The reaction vessel was flushed with argon and sealed with a septum. Dry dichloromethane (10 mL per 1.0 mmol of the acid) was introduced, and the mixture was stirred for 5 min in an ice bath. Neat *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide (EDC, 1.2 equiv.) was added, and the reaction mixture was stirred in an ice bath for another 30 min. Another mixture, prepared separately by mixing the corresponding amino acid methyl ester hydrochloride (1.2 equiv.), dry triethylamine (ca. 1.4 equiv.) and dichloromethane (10 mL per 1.0 mmol of the hydrochloride), was then introduced. After stirring at room temperature overnight, the reaction mixture was washed successively with aqueous citric acid (10%), saturated $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, and the solvents were removed under vacuum. The residue was purified by column chromatography on silica gel with dichloromethane/methanol (20:1) as the eluent. In the cases of (R,S_p)-**6**, (R,S_p)-**7** and (R,S_p)-**8**, the crude reaction product was contaminated with unreacted (S_p)-**10**. This ester was easily separated from the amide (major component) by column chromatography on silica gel (dichloromethane/methanol, 50:1).

1-(Diphenylphosphanyl)-1′-{*N*-[(*S*)-1-(methoxycarbonyl)ethyl]carbamoyl}ferrocene [(*S*)-3]: The General Procedure, starting with Hdpf (414 mg, 1.0 mmol), HOBt (165 mg, 1.20 mmol), EDC (0.21 mL, 1.20 mmol), (*S*)-$[H_3NCH(CH_3)CO_2Me]Cl$ (170 mg, 1.20 mmol) and Et_3N (0.20 mL, 1.42 mmol), afforded the amide (*S*)-**3** as an orange solid (474 mg, 95%). $[\alpha]_D$ = +10 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.47 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3CH), 3.75 (s, 3 H, OMe), 4.09 (dq, *J* = 1.2, 3.2 Hz, 1 H, fc), 4.21 (m, 2 H, fc), 4.24 (dq, *J* = 1.2, 3.2 Hz, 1 H, fc), 4.44 (dt, *J* = 1.2, 2.4 Hz, 1 H, fc), 4.47 (dt, *J* = 1.2, 2.4 Hz, 1 H, fc), 4.55 (dt, *J* = 1.3, 2.6 Hz, 1 H, fc), 4.62 (dt, *J* = 1.3, 2.6 Hz, 1 H, fc), 4.69 (p, $^3J_{H,H}$ = 7.3 Hz, 1 H, CH_3C*H*), 6.31 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, NH), 7.30–7.41 (m, 10 H, PPh_2) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 18.57 (CH_3CH), 48.01 (CH_3*C*H), 52.42 (OMe), 69.50 (*C*H fc), 71.76 (d, $J_{P,C}$ = 1 Hz, *C*H fc), 71.82 (d, $J_{P,C}$ = 1 Hz, *C*H fc), 72.90 (d, $J_{P,C}$ = 4 Hz, *C*H fc), 73.05 (d, $J_{P,C}$ = 4 Hz, *C*H fc), 74.30 (d, $J_{P,C}$ = 13 Hz, *C*H fc), 74.44 (d, $J_{P,C}$ = 15 Hz, *C*H fc), 75.97 (*C*CONH fc), 128.26 (d, $^3J_{P,C}$ = 7 Hz, *C*H PPh_2), 128.70 (*C*H PPh_2), 128.72 (*C*H PPh_2), 133.36 (d, $^2J_{P,C}$ = 3 Hz, *C*H PPh_2), 133.55 (d, $^2J_{P,C}$ = 3 Hz, *C*H PPh_2), 138.35 (d, $^1J_{P,C}$ = 10 Hz, C_{ipso} PPh_2), 138.49 (d, $^1J_{P,C}$ = 10 Hz, C_{ipso} PPh_2), 169.53 (CONH), 173.65 (CO_2Me) ppm; the signal due to *C*P of fc was not found. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –17.0 (s) ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 3325 (s, ν_{NH}), 1743 (vs., ν_{CO}), 1632 (vs., amide I), 1530 (vs., amide II), 1305 (s), 1266 (w), 1214 (m), 1193 (m), 1175 (m), 1161 (m), 1055 (w), 1027 (m), 834 (w), 743 (s), 697 (s), 569 (w), 488 (m), 451 (w) cm^{-1}. EI MS: *m*/*z* (%) = 499 (15) $[M]^{+\cdot}$, 412 (5) $[M - CH(Me)CO_2Me]^+$, 321 (4) $[Fe(C_5H_4PPh_2)O]$, 305 (2), 279 (9), 256 (5), 201 (9) $[Ph_2PO]^+$, 183 (5) $[Ph_2P - 2 H]^+$, 167 (8), 149 (30), 129 (5), 111 (5), 105 (11), 83 (100), 73 (10) $[CH_2CO_2Me]^+$, 69 (24), 57 (32). HR MS: calcd. for $C_{27}H_{26}NO_3PFe$ 499.0999; found 499.1008.

1-(Diphenylphosphanyl)-1′-{*N*-[(*R*)-1-(methoxycarbonyl)ethyl]carbamoyl}ferrocene [(*R*)-3]: The above procedure, starting with Hdpf (207 mg, 0.50 mmol), HOBt (82 mg, 0.60 mmol), EDC (0.11 mL, 0.60 mmol), (*R*)-$[H_3NCH(CH_3)CO_2Me]Cl$ (97 mg, 0.69 mmol) and Et_3N (0.11 mL, 0.80 mmol), gave the amide (*R*)-**3** as an orange solid (225 mg, 90%). The NMR spectroscopic data for (*R*)-**3** were identical to those of the corresponding (*S*) isomer. $[\alpha]_D$ = –9 (*c* = 0.5, $CHCl_3$).

1-(Diphenylphosphanyl)-1′-{*N*-[(*S*)-1-(methoxycarbonyl)-2-methylprop-1-yl]carbamoyl}ferrocene [(*S*)-4]: The General Procedure, starting with Hdpf (414 mg, 1.0 mmol), HOBt (170 mg, 1.26 mmol), EDC (0.22 mL, 1.20 mmol), (*S*)-$[H_3NCH(CHMe_2)CO_2Me]Cl$ (203 mg, 1.21 mmol) and Et_3N (0.21 mL, 1.49 mmol), provided (*S*)-**4** as an orange solid (496 mg, 94%). $[\alpha]_D$ = –5 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 0.97 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH*Me*$_2$), 1.0 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH*Me*$_2$), 2.24 (d of sept, $^3J_{H,H}$ = 4.9, 6.8 Hz, 1 H, C*H*Me_2), 3.72 (s, 3 H, OMe), 4.11 (dq, *J* = 1.2, 3.1 Hz, 1 H, fc), 4.22 (m, 2 H, fc), 4.25 (dq, *J* = 1.2, 3.1 Hz, 1 H, fc), 4.43 (dt, *J* = 1.2, 2.4 Hz, 1 H, fc), 4.47 (dt, *J* = 1.2, 2.4 Hz, 1 H, fc), 4.55 (dt, *J* = 1.5, 2.2 Hz, 1 H, fc), 4.60 (dt, *J* = 1.5, 2.3 Hz, 1 H, fc), 4.66 (dd, $^3J_{H,H}$ = 4.9, 8.8 Hz, 1 H, NHC*H*), 6.25 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, NH), 7.29–7.41 (m, 10 H, PPh_2) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 17.99 (CH*Me*$_2$), 19.21 (CH*Me*$_2$), 31.17 (*C*HMe_2), 52.15 (OMe), 56.98 (NHCH), 69.25 (*C*H fc), 69.69 (d, $J_{P,C}$ = 1 Hz, *C*H fc), 71.79 (d, $J_{P,C}$ = 1 Hz, *C*H fc), 71.83 (d, $J_{P,C}$ = 1 Hz, *C*H fc), 72.92 (d, $J_{P,C}$ = 3 Hz, *C*H fc), 73.12 (d, $J_{P,C}$ = 4 Hz, *C*H fc), 74.13 (d, $J_{P,C}$ = 13 Hz, *C*H fc), 74.43 (d, $J_{P,C}$ = 15 Hz, *C*H fc), 76.25 (*C*CONH fc), 128.24 (2 × d, $^3J_{P,C}$ = 7 Hz, *C*H PPh_2), 128.68 (*C*H PPh_2), 128.74 (*C*H PPh_2), 133.34 (d, $^2J_{P,C}$ = 7 Hz, *C*H PPh_2), 133.54 (d, $^2J_{P,C}$ = 7 Hz, *C*H PPh_2), 138.30 (d, $^1J_{P,C}$ = 9 Hz, C_{ipso} PPh_2), 138.49 (d, $^1J_{P,C}$ = 9 Hz, C_{ipso} PPh_2), 169.99 (CONH), 172.72 (CO_2Me) ppm; the *C*P of fc was not found. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –17.1 (s) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3335 (m, ν_{NH}), 1742 (vs., ν_{CO}), 1652 (vs., amide I), 1521 (vs., amide II), 1434 (s), 1309 (m), 1259 (w), 1193 (m), 1163 (s), 1093 (w), 1067 (w), 1027 (m), 999 (w), 833 (m), 744 (s), 697 (s), 492 (m), 451 (w) cm^{-1}. EI MS: *m*/*z* (%) = 527 (26) $[M]^{+\cdot}$, 496 (3) $[M - OMe]^+$, 412 (41) $[M - CH(CHMe_2)CO_2Me]^+$, 397 (4) $[M - NHCH(CHMe_2)CO_2Me]^+$, 321 (20) $[Fe(C_5H_4PPh_2)O]$, 305 (6), 250 (4), 226 (4), 201 (29) $[Ph_2PO]^+$, 183 (7) $[Ph_2P - 2 H]^+$, 171 (9), 121 (5) $[Fe(C_5H_5)]^+$, 83 (100). HR MS: calcd. for $C_{29}H_{30}NO_3PFe$ 527.1313; found 527.1300.

1-(Diphenylphosphanyl)-1′-{*N*-[(*R*)-1-(methoxycarbonyl)-2-methylprop-1-yl]carbamoyl}ferrocene [(*R*)-4]: When treated according to the General Procedure, Hdpf (207 mg, 0.50 mmol), HOBt (81 mg, 0.60 mmol), EDC (0.10 mL, 0.60 mmol), (*R*)-[$H_3NCH(CHMe_2)CO_2Me$]Cl (117 mg, 0.70 mmol) and Et_3N (0.11 mL, 0.80 mmol) afforded (*R*)-**4** as an orange solid (251 mg, 95%). The NMR spectroscopic data for (*R*)-**4** were identical with those for (*S*)-**4**. $[a]_D$ = +4 (*c* = 0.5, $CHCl_3$).

1-(Diphenylphosphanyl)-1′-{*N*-[(*S*)-1-(methoxycarbonyl)-2-phenylethyl]carbamoyl}ferrocene [(*S*)-5]: The amide (*S*)-**5** was prepared according to the General Procedure from Hdpf (414 mg, 1.0 mmol), HOBt (169 mg, 1.25 mmol), EDC (0.22 mL, 1.25 mmol), (*S*)-[$H_3NCH(CH_2Ph)CO_2Me$]Cl (262 mg, 1.21 mmol) and Et_3N (0.20 mL, 1.42 mmol), and was isolated as an orange solid (541 mg, 94%). $[a]_D$ = –3 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 3.13 (dd, $^3J_{H,H}$ = 7.1, $^2J_{H,H}$ = 14.0 Hz, 1 H, CH_2Ph), 3.22 (dd, $^3J_{H,H}$ = 5.6, $^2J_{H,H}$ = 14.0 Hz, 1 H, CH_2Ph), 3.72 (s, 3 H, OMe), 3.96 (dq, *J* = 1.2, 3.1 Hz, 1 H, fc), 4.15 (dq, *J* = 1.2, 3.2 Hz, 1 H, fc), 4.17 (m, 2 H, fc), 4.28 (dt, *J* = 1.2, 2.4 Hz, 1 H, fc), 4.34 (dt, *J* = 1.2, 2.4 Hz, 1 H, fc), 4.45 (dt, *J* = 1.3, 2.6 Hz, 1 H, fc), 4.54 (dt, *J* = 1.3, 2.6 Hz, 1 H, fc), 4.99 (ddd, $^3J_{H,H}$ = 5.5, 7.1, 7.9 Hz, 1 H, NHC*H*), 6.18 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, N*H*CH), 7.18–7.35 (m, 15 H, CH_2Ph + PPh_2) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 37.96 (CH_2Ph), 52.33 (OMe), 52.91 (NH*C*H), 64.06 (*C*H fc), 69.68 (d, $J_{P,C}$ = 1 Hz, *C*H fc), 71.80 (d, $J_{P,C}$ = 1 Hz, *C*H fc), 71.82 (d, $J_{P,C}$ = 1 Hz, *C*H fc), 72.84 (d, $J_{P,C}$ = 4 Hz, *C*H fc), 73.07 (d, $J_{P,C}$ = 4 Hz, *C*H fc), 74.07 (d, $J_{P,C}$ = 13 Hz, *C*H fc), 74.41 (d, $J_{P,C}$ = 15 Hz, *C*H fc), 75.96 (*C*CONH fc), 127.18 (*C*H CH_2Ph), 128.19 (d, $^3J_{P,C}$ = 1 Hz, *C*H PPh_2), 128.26 (d, $^3J_{P,C}$ = 2 Hz, *C*H PPh_2), 128.66 (*C*H PPh_2), 128.67 (*C*H CH_2Ph), 128.71 (*C*H PPh_2), 129.21 (*C*H CH_2Ph), 133.34 (d, $^2J_{P,C}$ = 10 Hz, *C*H PPh_2), 133.53 (d, $^2J_{P,C}$ = 10 Hz, *C*H PPh_2), 136.11 (C_{ipso} CH_2Ph), 138.30 (d, $^1J_{P,C}$ = 9 Hz, C_{ipso} PPh_2), 138.47 (d, $^1J_{P,C}$ = 9 Hz, C_{ipso} PPh_2), 169.70 (CONH), 172.28 (CO_2Me) ppm; the signal due to *C*P of fc was not found. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –17.2 (s) ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 3325 (s, ν_{NH}), 1743 (vs., ν_{CO}), 1633 (vs., amide I), 1532 (vs., amide II), 1305 (m), 1216 (m), 1196 (m), 1161 (m), 1094 (w), 1027 (s), 834 (m), 743 (vs), 698 (vs), 491 (s) cm^{-1}. EI MS: *m*/*z* (%) = 575 (48) $[M]^{+\cdot}$, 544 (5) $[M – OMe]^+$, 516 (5) $[M – CO_2Me]^+$, 412 (100) $[M – CH(CH_2Ph)CO_2Me]^+$, 397 (12) $[M – NHCH(CH_2Ph)CO_2Me]^+$, 374 (37) $[M – Ph_2PO]^+$, 321 (69) $[Fe(C_5H_4PPh_2)O]^+$, 305 (28), 264 (27), 226 (14), 201 (81) $[Ph_2PO]^+$, 183 (20) $[Ph_2P – 2H]^+$, 171 (33), 133 (13), 121 (32) $[Fe(C_5H_5)]^+$, 109 (15), 93 (33), 65 (25). HR MS: calcd. for $C_{33}H_{30}NO_3PFe$ 575.1313; found 575.1319.

1-(Diphenylphosphanyl)-1′-{*N*-[(*R*)-1-(methoxycarbonyl)-2-phenylethyl]carbamoyl}ferrocene [(*R*)-5]: Treatment of Hdpf (207 mg, 0.50 mmol), HOBt (81 mg, 0.60 mmol), EDC (0.10 mL, 0.60 mmol), (*R*)-[$H_3NCH(CH_2Ph)CO_2Me$]Cl (151 mg, 0.70 mmol) and Et_3N (0.11 mL, 0.80 mmol) according to the General Procedure provided (*R*)-**5** as an orange solid (280 mg, 97%). The NMR spectroscopic data for (*R*)-**5** were identical to those for (*S*)-**5**. $[a]_D$ = +3 (*c* = 0.5, $CHCl_3$).

(S_p)-1-(Diphenylphosphanyl)-2-{*N*-[(methoxycarbonyl)methyl]carbamoyl}ferrocene [(S_p)-6]: The above procedure, starting with (S_p)-Hpfc (414 mg, 1.0 mmol), HOBt (163 mg, 1.20 mmol), EDC (0.21 mL, 1.20 mmol), ($H_3NCH_2CO_2Me$)Cl (151 mg, 1.20 mmol) and Et_3N (0.20 mL, 1.42 mmol), yielded the amide (S_p)-**6** as an orange solid (354 mg, 73%). $[a]_D$ = –177 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 3.75 (s, 3 H, OMe), 3.87 (m, 1 H, C_5H_3), 3.95 (ddd, $J_{P,H}$ = 0.8, $^3J_{H,H}$ = 4.9, $^2J_{H,H}$ = 18.2 Hz, 1 H, $NHCH_2$), 4.18 (s, 5 H, C_5H_5), 4.30 (ddd, $J_{P,H}$ = 1.3, $^3J_{H,H}$ = 6.2, $^2J_{H,H}$ = 18.2 Hz, 1 H, $NHCH_2$), 4.49 (dt, *J* = 0.5, 2.6 Hz, 1 H, C_5H_3), 5.16 (dt, *J* = 1.6, 2.6 Hz, 1 H, C_5H_3), 7.10–7.65 (m, 10 H, PPh_2), 7.73 (apparent dt, $J_{P,C}$ ≈ 12, $^3J_{H,H}$ ≈ 6 Hz, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 41.31 ($NHCH_2$), 52.22 (OMe), 70.97 (*C*H C_5H_5), 71.75 (*C*H C_5H_3), 73.41 (d, $J_{P,C}$ = 2 Hz, *C*H C_5H_3), 74.61 (d, $J_{P,C}$ = 4 Hz, *C*H C_5H_3), 75.48 (d, $^1J_{P,C}$ = 11 Hz, *C*P C_5H_3), 79.82 (d, $^2J_{P,C}$ = 20 Hz, *C*CONH C_5H_3), 128.21 (*C*H PPh_2), 128.24 (d, $^3J_{P,C}$ = 7 Hz, *C*H PPh_2), 128.37 (d, $^3J_{P,C}$ = 7 Hz, *C*H PPh_2), 129.71 (*C*H PPh_2), 131.98 (d, $^2J_{P,C}$ = 17 Hz, *C*H PPh_2), 135.22 (d, $^2J_{P,C}$ = 21 Hz, *C*H PPh_2), 136.15 (d, $^1J_{P,C}$ = 6 Hz, C_{ipso} PPh_2), 138.18 (d, $^1J_{P,C}$ = 7 Hz, C_{ipso} PPh_2), 170.61 (CO_2Me), 170.73 (d, $^3J_{P,C}$ = 4 Hz, CONH) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –20.2 (s) ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 3330 (m, ν_{NH}), 1750 (vs., ν_{CO}), 1640 (vs., amide I), 1532 (vs., amide II), 1434 (vs), 1410 (w), 1366 (s), 1279 (m), 1199 (s), 1178 (s), 1107 (m), 1094 (w), 1019 (m), 1003 (m), 987 (w), 940 (w), 844 (w), 821 (m), 744 (s), 698 (s), 563 (w), 486 (s), 463 (w) cm^{-1}. EI MS: *m*/*z* (%) = 485 (40) $[M]^{+\cdot}$, 454 (5) $[M – OMe]^+$, 420 (100) $[M – C_5H_5]^+$, 412 (58) $[M – CH_2CO_2Me]^+$, 397 (8) $[M – NHCH_2CO_2Me]^+$, 362 (35), 346 (26), 291 (14), 226 (13), 201 (90) $[Ph_2PO]^+$, 183 (21) $[Ph_2P – 2 H]^+$, 170 (38), 152 (11), 121 (45) $[Fe(C_5H_5)]^+$, 55 (15). HR MS: calcd. for $C_{26}H_{24}NO_3PFe$ 485.0843; found 485.0834.

(S_p)-1-(Diphenylphosphanyl)-2-{*N*-[(*S*)-1-(methoxycarbonyl)ethyl]carbamoyl}ferrocene [(*S*,S_p)-7]: The General Procedure, starting with (S_p)-**1** (414 mg, 1.0 mmol), HOBt (163 mg, 1.20 mmol), EDC (0.21 mL, 1.20 mmol), (*S*)-[$H_3NCH(CH_3)CO_2Me$]Cl (170 mg, 1.20 mmol) and Et_3N (0.20 mL, 1.42 mmol), afforded the amide (*S*,S_p)-**7** (orange solid; 379 mg, 76%). $[a]_D$ = –176 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.29 (d, $^3J_{H,H}$ = 7.3 Hz, 3 H, CH_3CH), 3.80 (s, 3 H, OMe), 3.80 (dt, *J* = 1.2, 2.8 Hz, 1 H, C_5H_3), 4.21 (s, 5 H, C_5H_5), 4.46 (dt, *J* = 0.5, 2.6 Hz, 1 H, C_5H_3), 4.63 (dp, $^3J_{H,H}$ = 7.3, $J_{P,H}$ = 2.1 Hz, 1 H, CH_3C*H*), 5.14 (dt, *J* = 1.6, 2.6 Hz, 1 H, C_5H_3), 7.13–7.60 (m, 10 H, PPh_2), 7.82 (dd, $^3J_{H,H}$ = 7.7, $J_{P,C}$ = 12.9 Hz, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 17.87 (CH_3CH), 48.04 (CH_3*C*H), 52.35 (OMe), 70.96 (*C*H C_5H_5), 71.51 (*C*H C_5H_3), 73.41 (d, $J_{P,C}$ = 2 Hz, *C*H C_5H_3), 74.55 (d, $J_{P,C}$ = 2 Hz, *C*H C_5H_3), 75.57 (d, $^1J_{P,C}$ = 10 Hz, *C*P C_5H_3), 79.83 (d, $^2J_{P,C}$ = 20 Hz, *C*CONH C_5H_3), 128.33 (d, $^3J_{P,C}$ = 6 Hz, *C*H PPh_2), 128.41 (d, $^3J_{P,C}$ = 5 Hz, *C*H PPh_2), 128.47 (*C*H PPh_2), 129.71 (*C*H PPh_2), 132.20 (d, $^2J_{P,C}$ = 18 Hz, *C*H PPh_2), 135.07 (d, $^2J_{P,C}$ = 21 Hz, *C*H PPh_2), 135.77 (d, $^1J_{P,C}$ = 6 Hz, C_{ipso} PPh_2), 137.65 (d, $^1J_{P,C}$ = 7 Hz, C_{ipso} PPh_2), 170.00 (d, $^3J_{P,C}$ = 4 Hz, CONH), 173.78 (CO_2Me) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –20.0 (s) ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 3290 (w, ν_{NH}), 1742 (vs., ν_{CO}), 1652 (vs., amide I), 1521 (vs., amide II), 1434 (vs), 1340 (w), 1309 (w), 1264 (m), 1215 (m), 1195 (s), 1165 (m), 1107 (m), 1094 (w), 1069 (w), 1001 (m), 985 (w), 845 (w), 819 (m), 744 (vs), 697 (vs), 545 (w), 498 (s), 484 (s), 456 (m) cm^{-1}. EI MS: *m*/*z* (%) = 499 (26) $[M]^{+\cdot}$, 468 (4) $[M – OMe]^+$, 434 (66) $[M – C_5H_5]^+$, 412 (73) $[M – CH(Me)CO_2Me]^+$, 397 (8) $[M – NHCH(Me)CO_2Me]^+$, 374 (42), 346 (43), 291 (10), 226 (10), 201 (100) $[Ph_2PO]^+$, 183 (18) $[Ph_2P – 2 H]^+$, 170 (37), 152 (6), 133 (8), 121 (38) $[Fe(C_5H_5)]^+$, 115 (6), 100 (6), 83 (38), 77 (8), 56 (17). HR MS: calcd. for $C_{27}H_{26}NO_3PFe$ 499.0999; found 499.0981.

(S_p)-1-(Diphenylphosphanyl)-2-{*N*-[(*R*)-1-(methoxycarbonyl)ethyl]carbamoyl}ferrocene [(*R*,S_p)-7]: The amide (*R*,S_p)-**7** was prepared as described above, from (S_p)-**1** (207 mg, 0.50 mmol), HOBt (81 mg, 0.60 mmol), EDC (0.11 mL, 0.60 mmol), (*R*)-[$H_3NCH(CH_3)CO_2Me$]Cl (84 mg, 0.60 mmol) and Et_3N (0.10 mL, 0.71 mmol). Isolation by column chromatography afforded (*R*,S_p)-**7** as an orange solid (170 mg, 68%). Some (S_p)-**10** was also isolated. Analytical data for (*R*,S_p)-**7**. $[a]_D$ = –153 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.46 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3CH), 3.60 (s, 3 H, OMe), 3.81 (m, 1 H, C_5H_3), 4.16 (s, 5 H, C_5H_5), 4.45 (dt, *J* = 0.5, 2.6 Hz, 1 H, C_5H_3), 4.71 (dp, $^3J_{H,H}$ = 7.3, $J_{P,H}$ = 1.5 Hz, 1 H, CH_3C*H*), 5.06 (dt, *J* = 1.4, 2.8 Hz, 1 H, C_5H_3), 7.14–7.60 (m, 11

H, N*H* + P*Ph*$_2$) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 18.75 (CH$_3$CH), 48.19 (CH$_3$*C*H), 52.21 (OMe), 70.92 (*C*H C$_5$H$_5$), 71.42 (*C*H C$_5$H$_3$), 73.05 (d, $J_{P,C}$ = 2 Hz, *C*H C$_5$H$_3$), 74.53 (d, $J_{P,C}$ = 5 Hz, *C*H C$_5$H$_3$), 76.25 (d, $^1J_{P,C}$ = 12 Hz, *C*P C$_5$H$_3$), 80.24 (d, $^2J_{P,C}$ = 18 Hz, *C*CONH C$_5$H$_3$), 128.18 (*C*H PPh$_2$), 128.21 (d, $^3J_{P,C}$ = 6 Hz, *C*H PPh$_2$), 128.31 (d, $^3J_{P,C}$ = 7 Hz, *C*H PPh$_2$), 129.54 (*C*H PPh$_2$), 132.18 (d, $^2J_{P,C}$ = 18 Hz, *C*H PPh$_2$), 135.19 (d, $^2J_{P,C}$ = 21 Hz, *C*H PPh$_2$), 136.65 (d, $^1J_{P,C}$ = 9 Hz, C_{ipso} PPh$_2$), 138.50 (d, $^1J_{P,C}$ = 7 Hz, C_{ipso} PPh$_2$), 169.71 (d, $^3J_{P,C}$ = 4 Hz, CONH), 173.33 (*C*O$_2$Me) ppm. ^{31}P{^{1}H} NMR (CDCl$_3$): δ = –20.0 (s) ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 3325 (w, ν_{NH}), 1746 (vs., ν_{CO}), 1624 (vs., amide I), 1521 (vs., amide II), 1265 (w), 1193 (m), 1155 (s), 1106 (w), 1050 (w), 1002 (w), 909 (w), 819 (m), 743 (vs), 698 (vs), 489 (s), 466 (w) cm^{-1}. EI MS: *m/z* (%) = 499 (21) [M]$^{+\cdot}$, 468 (5) [M – OMe]$^+$, 434 (69) [M – C$_5$H$_5$]$^+$, 412 (64) [M – CH(Me)CO$_2$Me]$^+$, 397 (8) [M – NHCH(Me)CO$_2$Me]$^+$, 374 (38), 346 (33), 291 (8), 247 (8), 226 (8), 201 (84) [Ph$_2$PO]$^+$, 183 (14) [Ph$_2$P – 2 H]$^+$, 170 (25), 149 (21), 121 (36) [Fe(C$_5$H$_5$)]$^+$, 111 (19), 97 (34), 81 (44), 69 (95), 57 (100). HR MS: calcd. for $C_{27}H_{26}NO_3PFe$ 499.0999; found 499.1010.

(*R*$_p$)-1-(Diphenylphosphanyl)-2-{*N*-[(*S*)-1-(methoxycarbonyl)ethyl]-carbamoyl}ferrocene [(*S*,*R*$_p$)-7]: The amide (*R*,*S*$_p$)-**7** was prepared as described above, from (*R*$_p$)-**1** (69 mg, 0.17 mmol), HOBt (27 mg, 0.20 mmol), EDC (0.03 mL, 0.20 mmol), (*S*)-[H$_3$NCH(CH$_3$)CO$_2$Me]Cl (30 mg, 0.22 mmol) and Et$_3$N (0.03 mL, 0.25 mmol). Yield: 52 mg (63%) of an orange solid. The NMR spectroscopic data were identical to those for (*R*,*S*$_p$)-**7**. [a]$_D$ = +156 (*c* = 0.5, CHCl$_3$).

(*S*$_p$)-1-(Diphenylphosphanyl)-2-{*N*-[(*S*)-1-(methoxycarbonyl)-2-methylprop-1-yl]carbamoyl}ferrocene [(*S*,*S*$_p$)-8]: The General Procedure, with (*S*$_p$)-**1** (207 mg, 0.50 mmol), HOBt (81 mg, 0.60 mmol), EDC (0.11 mL, 0.60 mmol), (*S*)-[H$_3$NCH(CHMe$_2$)CO$_2$Me]Cl (101 mg, 0.60 mmol) and Et$_3$N (0.10 mL, 0.71 mmol), yielded the amide (*S*,*S*$_p$)-**8** as an orange solid (198 mg, 75%). [a]$_D$ = –195 (*c* = 0.5, CHCl$_3$). ^{1}H NMR (CDCl$_3$): δ = 0.64 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH*Me*$_2$), 0.83 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH*Me*$_2$), 2.17 (dsept, $^3J_{H,H}$ = 4.5, 6.9 Hz, 1 H, C*H*Me$_2$), 3.77 (m, 1 H, C$_5$H$_3$), 3.80 (s, 3 H, OMe), 4.22 (s, 5 H, C$_5$H$_5$), 4.47 (t, *J* = 2.6 Hz, 1 H, C$_5$H$_3$), 4.63 (ddd, $J_{P,H}$ = 2.2, $^3J_{H,H}$ = 4.9, 8.8 Hz, 1 H, NHC*H*), 5.20 (dt, *J* = 1.5, 2.7 Hz, 1 H, C$_5$H$_3$), 7.11–7.60 (m, 10 H, PPh$_2$), 7.88 (dd, $J_{P,H}$ = 13.6, $^3J_{H,H}$ = 8.7 Hz, 1 H, NH) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 17.60 (d, $^7J_{P,C}$ = 2 Hz, CH*Me*$_2$), 18.85 (CH*Me*$_2$), 30.66 (*C*HMe$_2$), 52.11 (OMe), 57.43 (NHCH), 70.91 (*C*H C$_5$H$_5$), 71.63 (*C*H C$_5$H$_3$), 73.83 (d, $J_{P,C}$ = 2 Hz, *C*H C$_5$H$_3$), 74.57 (d, $J_{P,C}$ = 4 Hz, *C*H C$_5$H$_3$), 74.83 (d, $^1J_{P,C}$ = 9 Hz, *C*P C$_5$H$_3$), 80.08 (d, $^2J_{P,C}$ = 18 Hz, *C*CONH C$_5$H$_3$), 128.31 (d, $^3J_{P,C}$ = 6 Hz, *C*H PPh$_2$), 128.36 (*C*H PPh$_2$), 128.41 (d, $^3J_{P,C}$ = 9 Hz, *C*H PPh$_2$), 129.81 (*C*H PPh$_2$), 132.07 (d, $^2J_{P,C}$ = 17 Hz, *C*H PPh$_2$), 135.22 (d, $^2J_{P,C}$ = 21 Hz, *C*H PPh$_2$), 135.56 (d, $^1J_{P,C}$ = 6 Hz, C_{ipso} PPh$_2$), 137.40 (d, $^1J_{P,C}$ = 6 Hz, C_{ipso} PPh$_2$), 170.70 (d, $^3J_{P,C}$ = 4 Hz, CONH), 172.86 (*C*O$_2$Me) ppm. ^{31}P{^{1}H} NMR (CDCl$_3$): δ = –20.0 (s) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3315 (m, ν_{NH}), 1740 (vs., ν_{CO}), 1653 (vs., amide I), 1517 (vs., amide II), 1310 (m), 1274 (w), 1193 (m), 1160 (m), 1107 (w), 1028 (m), 1001 (m), 845 (w), 820 (m), 743 (s), 697 (s), 543 (w), 484 (s) cm^{-1}. EI MS: *m/z* (%) = 527 (31) [M]$^{+\cdot}$, 496 (3) [M – OMe]$^+$, 462 (100) [M – C$_5$H$_5$]$^+$, 412 (64) [M – CH(CHMe$_2$)CO$_2$Me]$^+$, 402 (51), 397 (10) [M – NHCH(CHMe$_2$)CO$_2$Me]$^+$, 346 (43), 303 (7), 291 (6), 247 (6), 226 (10), 201 (85) [Ph$_2$PO]$^+$, 183 (15) [Ph$_2$P – 2 H]$^+$, 170 (28), 149 (11), 121 (30) [Fe(C$_5$H$_5$)]$^+$, 97 (10), 83 (14), 73 (20), 55 (39). HR MS: calcd. for $C_{29}H_{30}NO_3PFe$ 527.1313; found 527.1306.

(*S*$_p$)-1-(Diphenylphosphanyl)-2-{*N*-[(*R*)-1-(methoxycarbonyl)-2-methylprop-1-yl]carbamoyl}ferrocene [(*R*,*S*$_p$)-8]: The General Procedure, starting with (*S*$_p$)-**1** (207 mg, 0.50 mmol), HOBt (81 mg, 0.60 mmol), EDC (0.11 mL, 0.60 mmol), (*R*)-[H$_3$NCH(CHMe$_2$)-CO$_2$Me]Cl (101 mg, 0.60 mmol) and Et$_3$N (0.10 mL, 0.71 mmol), afforded amide (*R*,*S*$_p$)-**8** (orange solid; 169 mg, 64%). Some unreacted (*S*$_p$)-**10** was also isolated. Analytical data for (*R*,*S*$_p$)-**8**. [a]$_D$ = –151 (*c* = 0.5, CHCl$_3$). ^{1}H NMR (CDCl$_3$): δ = 1.03 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH*Me*$_2$), 1.06 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CH*Me*$_2$), 2.27 (dsept, $^3J_{H,H}$ = 4.8, 6.8 Hz, 1 H, C*H*Me$_2$), 3.43 (s, 3 H, OMe), 3.85 (m, 1 H, C$_5$H$_3$), 4.13 (s, 5 H, C$_5$H$_5$), 4.46 (dt, *J* = 0.5, 2.6 Hz, 1 H, C$_5$H$_3$), 4.63 (ddd, $J_{P,H}$ = 2.0, $^3J_{H,H}$ = 4.8, 8.6 Hz, 1 H, NHC*H*), 5.15 (dt, *J* = 1.6, 3.0 Hz, 1 H, C$_5$H$_3$), 7.12–7.60 (m, 11 H, N*H* + P*Ph*$_2$) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 18.10 (CH*Me*$_2$), 19.31 (CH*Me*$_2$), 30.88 (*C*HMe$_2$), 51.71 (OMe), 57.56 (NHCH), 70.80 (*C*H C$_5$H$_5$), 71.59 (*C*H C$_5$H$_3$), 73.64 (d, $J_{P,C}$ = 2 Hz, *C*H C$_5$H$_3$), 74.50 (d, $J_{P,C}$ = 4 Hz, *C*H C$_5$H$_3$), 75.45 (d, $^1J_{P,C}$ = 11 Hz, *C*P C$_5$H$_3$), 80.72 (d, $^2J_{P,C}$ = 20 Hz, *C*CONH C$_5$H$_3$), 128.16 (*C*H PPh$_2$), 128.19 (d, $^3J_{P,C}$ = 6 Hz, *C*H PPh$_2$), 128.33 (d, $^3J_{P,C}$ = 9 Hz, *C*H PPh$_2$), 129.68 (*C*H PPh$_2$), 132.06 (d, $^2J_{P,C}$ = 17 Hz, *C*H PPh$_2$), 135.24 (d, $^2J_{P,C}$ = 21 Hz, *C*H PPh$_2$), 136.26 (d, $^1J_{P,C}$ = 7 Hz, C_{ipso} PPh$_2$), 138.26 (d, $^1J_{P,C}$ = 7 Hz, C_{ipso} PPh$_2$), 170.24 (d, $^3J_{P,C}$ = 4 Hz, CONH), 172.01 (*C*O$_2$Me) ppm. ^{31}P{^{1}H} NMR (CDCl$_3$): δ = –20.0 (s) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3305 (m, ν_{NH}), 1745 (vs., ν_{CO}), 1656 (vs., amide I), 1525 (vs., amide II), 1435 (vs), 1311 (m), 1267 (m), 1206 (m), 1161 (m), 1107 (w), 1093 (w), 1069 (w), 1027 (m), 1003 (m), 823 (s), 752 (vs), 699 (vs), 666 (w), 646 (w), 613 (w), 501 (s), 485 (s), 461 (m) cm^{-1}. EI MS: *m/z* (%) = 527 (26) [M]$^{+\cdot}$, 496 (10) [M – OMe]$^+$, 481 (10), 462 (27) [M – C$_5$H$_5$]$^+$, 412 (18) [M – CH(CHMe$_2$)-CO$_2$Me]$^+$, 402 (16), 397 (4) [M – NHCH(CHMe$_2$)CO$_2$Me]$^+$, 346 (11), 201 (23) [Ph$_2$PO]$^+$, 183 (7) [Ph$_2$P – 2 H]$^+$, 170 (8), 165 (16), 149 (13), 121 (12) [Fe(C$_5$H$_5$)]$^+$, 97 (22), 83 (100), 69 (53), 57 (81). HR MS: calcd. for $C_{29}H_{30}NO_3PFe$ 527.1313; found 527.1321.

(*S*$_p$)-1-(Diphenylphosphanyl)-2-{*N*-[(*S*)-1-(methoxycarbonyl)-2-phenylethyl]carbamoyl}ferrocene [(*S*,*S*$_p$)-9]: Treatment of (*S*$_p$)-**1** (207 mg, 0.50 mmol), HOBt (81 mg, 0.60 mmol), EDC (0.11 mL, 0.60 mmol), (*S*)-[H$_3$NCH(CH$_2$Ph)CO$_2$Me]Cl (131 mg, 0.61 mmol) and Et$_3$N (0.10 mL, 0.71 mmol) according to the General Procedure gave (*S*,*S*$_p$)-**9** as an orange solid (204 mg, 71%). Single crystals suitable for X-ray diffraction analysis were grown from acetone/diethyl ether at +4 °C. [a]$_D$ = –198 (*c* = 0.5, CHCl$_3$). ^{1}H NMR (CDCl$_3$): δ = 3.02 (dd, $^3J_{H,H}$ = 7.6, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Ph), 3.12 (dd, $^3J_{H,H}$ = 5.2, $^2J_{H,H}$ = 14.0 Hz, 1 H, C*H*$_2$Ph), 3.78 (s, 3 H, OMe), 3.86 (m, 1 H, C$_5$H$_3$), 4.09 (s, 5 H, C$_5$H$_5$), 4.46 (dt, *J* = 1.0, 2.6 Hz, 1 H, C$_5$H$_3$), 4.95 (dddd, $J_{P,H}$ = 2.3, $^3J_{H,H}$ = 5.3, 7.7, 7.7 Hz, 1 H, NHC*H*), 5.14 (dt, *J* = 1.6, 2.7 Hz, 1 H, C$_5$H$_3$), 6.96–7.61 (m, 15 H, CH$_2$*Ph* + P*Ph*$_2$), 7.91 (dd, $^3J_{H,H}$ = 7.8, $J_{P,H}$ = 12.8 Hz, 1 H, N*H*CH) ppm. ^{13}C{^{1}H} NMR (CDCl$_3$): δ = 37.97 (*C*H$_2$Ph), 52.27 (OMe), 53.86 (NH*C*H), 70.90 (*C*H C$_5$H$_5$), 71.89 (*C*H C$_5$H$_3$), 73.64 (d, $J_{P,C}$ = 2 Hz, *C*H C$_5$H$_3$), 74.62 (d, $J_{P,C}$ = 4 Hz, *C*H C$_5$H$_3$), 75.02 (d, $^1J_{P,C}$ = 11 Hz, *C*P C$_5$H$_3$), 79.97 (d, $^2J_{P,C}$ = 20 Hz, *C*CONH C$_5$H$_3$), 126.77 (*C*H CH$_2$Ph), 128.08 (*C*H PPh$_2$), 128.24 (d, $^3J_{P,C}$ = 5 Hz, *C*H PPh$_2$), 128.35 (*C*H CH$_2$Ph), 128.35 (d, $^3J_{P,C}$ = 9 Hz, *C*H PPh$_2$), 129.16 (*C*H CH$_2$Ph), 129.81 (*C*H PPh$_2$), 131.85 (d, $^2J_{P,C}$ = 17 Hz, *C*H PPh$_2$), 135.36 (d, $^2J_{P,C}$ = 21 Hz, *C*H PPh$_2$), 136.14 (d, $^1J_{P,C}$ = 6 Hz, C_{ipso} PPh$_2$), 136.17 (C_{ipso} CH$_2$Ph), 138.36 (d, $^1J_{P,C}$ = 6 Hz, C_{ipso} PPh$_2$), 170.34 (d, $^3J_{P,C}$ = 4 Hz, CONH), 172.54 (*C*O$_2$Me) ppm. ^{31}P{^{1}H} NMR (CDCl$_3$): δ = –20.6 (s) ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 3290 (w, ν_{NH}), 1751 (vs., ν_{CO}), 1647 (vs., amide I), 1524 (s, amide II), 1410 (w), 1308 (m), 1269 (m), 1217 (m), 1203 (w), 1193 (m), 1153 (m), 1106 (m), 1090 (w), 1034 (w), 999 (w), 985 (w), 845 (w), 818 (w), 747 (s), 699 (s), 502 (m), 484 (s), 457 (w) cm^{-1}. EI MS: *m/z* (%) = 575 (23) [M]$^{+\cdot}$, 544 (5) [M – OMe]$^+$, 510 (27) [M – C$_5$H$_5$]$^+$, 450 (31), 412 (74) [M – CH(CH$_2$Ph)CO$_2$Me]$^+$, 397 (11) [M – NHCH(CH$_2$Ph)CO$_2$Me]$^+$, 374 (12) [M – Ph$_2$PO]$^+$, 346 (44), 291 (14), 226 (12), 201 (100) [Ph$_2$PO]$^+$, 183 (20) [Ph$_2$P –

2 H]$^+$, 170 (35), 133 (8), 121 (42) [Fe(C_5H_5)]$^+$, 91 (25), 69 (9), 57 (14). HR MS: calcd. for $C_{33}H_{30}NO_3PFe$ 575.1313; found 575.1295.

(S_p)-1-(Diphenylphosphanyl)-2-{*N*-[(*R*)-1-(methoxycarbonyl)-2-phenylethyl]carbamoyl}ferrocene [(*R*,S_p)-9]: Treatment of (S_p)-**1** (207 mg, 0.50 mmol), HOBt (81 mg, 0.60 mmol), EDC (0.11 mL, 0.60 mmol), (*R*)-[$H_3NCH(CH_2Ph)CO_2Me$]Cl (129 mg, 0.60 mmol) and Et_3N (0.10 mL, 0.71 mmol) according to the General Procedure gave the amide (*R*,S_p)-**9** (orange solid; 178 mg, 62%) and also some (S_p)-**10**. $[\alpha]_D$ = –125 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 3.10 (dd, $^3J_{H,H}$ = 8.3, $^2J_{H,H}$ = 14.1 Hz, 1 H, CH_2Ph), 3.27 (dd, $^3J_{H,H}$ = 5.2, $^2J_{H,H}$ = 14.1 Hz, 1 H, CH_2Ph), 3.45 (s, 3 H, OMe), 3.81 (m, 1 H, C_5H_3), 3.90 (s, 5 H, C_5H_5), 4.41 (dt, *J* = 0.5, 2.6 Hz, 1 H, C_5H_3), 5.01 (m, 2 H, NHC*H* + C_5H_3), 7.11–7.56 (m, 16 H, N*H*CH + CH_2Ph + PPh_2) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 37.97 (CH_2Ph), 52.05 (OMe), 53.57 (NH*C*H), 70.80 (*C*H C_5H_5), 71.58 (*C*H C_5H_3), 73.04 (d, $J_{P,C}$ = 4 Hz, *C*H C_5H_3), 74.44 (d, $J_{P,C}$ = 4 Hz, *C*H C_5H_3), 75.82 (d, $^1J_{P,C}$ = 11 Hz, *C*P C_5H_3), 80.04 (d, $^2J_{P,C}$ = 20 Hz, *C*CONH C_5H_3), 127.17 (*C*H CH_2Ph), 128.12 (*C*H PPh_2), 128.14 (d, $^3J_{P,C}$ = 10 Hz, *C*H PPh_2), 128.32 (d, $^3J_{P,C}$ = 7 Hz, *C*H PPh_2), 128.73 (*C*H CH_2Ph), 129.32 (*C*H CH_2Ph), 129.65 (*C*H PPh_2), 132.05 (d, $^2J_{P,C}$ = 17 Hz, *C*H PPh_2), 135.21 (d, $^2J_{P,C}$ = 22 Hz, *C*H PPh_2), 136.38 (d, $^1J_{P,C}$ = 7 Hz, C_{ipso} PPh_2), 136.70 (C_{ipso} CH_2Ph), 138.42 (d, $^1J_{P,C}$ = 7 Hz, C_{ipso} PPh_2), 170.22 (d, $^3J_{P,C}$ = 4 Hz, CONH), 172.05 (CO_2Me) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –20.5 (s) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3300 (w, ν_{NH}), 1743 (vs., ν_{CO}), 1651 (vs., amide I), 1522 (vs., amide II), 1436 (s), 1276 (m), 1218 (m), 1178 (m), 1107 (w), 1028 (w), 1002 (w), 911 (w), 822 (m), 748 (vs), 699 (vs), 666 (w), 548 (w), 485 (s) cm^{-1}. FAB MS : *m*/*z* (%) = 576 (100) [M + H]$^{+\cdot}$, 544 (4) [M – OMe]$^+$, 510 (14) [M – C_5H_5]$^+$, 498 (9), 481 (7), 450 (5), 412 (13) [M – $CH(CH_2Ph)CO_2Me$]$^+$, 397 (29) [M – $NHCH(CH_2Ph)CO_2Me$]$^+$, 346 (9), 277 (15), 226 (11), 201 (6) [Ph_2PO]$^+$, 183 (24) [Ph_2P – 2 H]$^+$, 170 (12), 154 (17), 136 (21), 121 (18) [Fe(C_5H_5)]$^+$, 105 (9), 91 (19), 77 (16), 69 (13), 55 (24). HR MS (FAB): calcd. for $C_{33}H_{31}NO_3PFe$ [M + H]$^+$ 576.1391; found 576.1401.

(S_p)-1-({[2-(Diphenylphosphanyl)-1-ferrocenyl]carbonyl}oxy)-1*H*-benzotriazole [(S_p)-10]: The active ester (S_p)-**10** was isolated from amidation reactions between (S_p)-**1** and (*R*)-amino acid methyl esters in the presence of HOBt/EDC as an orange solid after column chromatography on silica gel with dichloromethane/methanol (50:1) as the eluent. $[\alpha]_D$ = –209 (*c* = 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 4.02 (ddd, *J* = 0.9, 1.6, 2.5 Hz, 1 H, C_5H_3), 4.46 (s, 5 H, C_5H_5), 4.73 (dt, *J* = 0.6, 2.7 Hz, 1 H, C_5H_3), 5.36 (ddd, *J* = 0.9, 1.6, 2.6 Hz, 1 H, C_5H_3), 6.96 (dt, *J* = 1.1, 8.1 Hz, 1 H, C_6H_4), 7.20–7.55 (m, 10 H, PPh_2), 7.35–7.40 (m, 2 H, C_6H_4), 8.02 (dt, *J* = 1.0, 8.3 Hz, 1 H, C_6H_4) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 68.08 (d, $^2J_{P,C}$ = 16 Hz, *C*CONH C_5H_3), 72.04 (*C*H C_5H_5), 73.76 (*C*H C_5H_3), 74.60 (*C*H C_5H_3), 77.24 (d, $J_{P,C}$ = 5 Hz, *C*H C_5H_3), 81.90 (d, $^1J_{P,C}$ = 20 Hz, *C*P C_5H_3), 108.32 (*C*H C_6H_4), 120.27 (*C*H C_6H_4), 124.54 (*C*H C_6H_4), 128.40 (*C*H C_6H_4), 128.42 (2 × d, $^3J_{P,C}$ = 5 Hz, *C*H PPh_2), 128.47 (*C*H PPh_2), 128.74 (*C* C_6H_4), 129.42 (*C*H PPh_2), 132.44 (d, $^2J_{P,C}$ = 20 Hz, *C*H PPh_2), 134.85 (d, $^2J_{P,C}$ = 21 Hz, *C*H PPh_2), 137.03 (d, $^1J_{P,C}$ = 13 Hz, C_{ipso} PPh_2), 138.61 (d, $^1J_{P,C}$ = 13 Hz, C_{ipso} PPh_2), 143.41 (*C* C_6H_4), 167.97 (d, $^3J_{P,C}$ = 4 Hz, CO) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = –17.5 (s) ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 1777 (vs., ν_{CO}), 1321 (w), 1247 (m), 1237 (m), 1155 (w), 1107 (w), 1086 (s), 1019 (m), 926 (m), 905 (m), 829 (w), 741 (vs), 697 (s), 500 (m), 484 (m), 464 (m) cm^{-1}. FAB MS: *m*/*z* (%) = 532 (20) [M + H]$^{+\cdot}$, 521 (5), 446 (5), 429 (15), 414 (12), 397 (25) [M – OBt]$^+$, 369 (3) [M – CO_2Bt]$^+$, 277 (11), 257 (6), 226 (5), 215 (12), 201 (18) [Ph_2PO]$^+$, 185 (55), 183 (9) [Ph_2P – 2 H]$^+$, 149 (5), 121 (5) [Fe(C_5H_5)]$^+$, 110 (27), 93 (100), 75 (22), 57 (25). ESI MS: *m*/*z* (%) = 554 [M + Na]$^+$, 570 [M + K]$^+$. HR MS (FAB): calcd. for $C_{29}H_{23}N_3O_2PFe$ [M + H]$^+$ 532.0877; found 532.0888.

Catalytic Tests: The ligand (18 µmol) and the copper salt (15 µmol of Cu) were mixed with dry dichloromethane (3 mL) and stirred at room temperature for 20 min. The mixture was cooled in ice, and (*E*)-1,3-diphenylprop-2-en-1-one (**11a**; 104 mg, 0.50 mmol) was added. After the mixture had been stirred for another 10 min, a solution of Et_2Zn in heptane (0.75 mL of 1 M solution, 0.75 mmol) was introduced, and the stirring was continued at 0 °C for 4 h. The reaction mixture was washed with saturated aqueous NH_4Cl (2 × 5 mL) and extracted with diethyl ether. The organic layers were dried ($MgSO_4$) and concentrated under vacuum. Subsequent purification by column chromatography (silica gel; hexane/diethyl ether, 1:1) afforded the alkylation product **12a** or, in cases of incomplete conversion, its mixture with unreacted substrate. Levels of conversion were determined from ^1H NMR spectra. Enantiomeric excesses were established by HPLC analysis: Daicel Chiralcel OD-H column (250 mm × 4.6 mm), hexane/*i*PrOH (99:1), flow rate 0.75 mL min^{-1}; t_R[(*R*)-**12a**] = 20.3, t_R[(*S*)-**12a**] = 23.0 min. Spectroscopic data for the alkylation product were in accordance with literature. The configuration was assigned on the basis of optical rotation.[26] Reactions with the substituted chalcones **11b**–**g** were performed similarly. The products were analysed by NMR spectroscopy and HPLC[20b,20e] (see the Supporting Information).

Model Complexation Experiments: Ligand **2** (6.6 mg/13.5 µmol or 14.6 mg/30 µmol) and $(CuOTf)_2\cdot PhMe$ (3.9 mg, 15 µmol Cu) were mixed with CD_2Cl_2 (1 mL). The mixture was sonicated for ca. 5 min and filtered through a pad of Celite to eliminate traces of paramagnetic Cu^{II}, and the filtrate was analysed by NMR spectroscopy. The crystalline complex **14** resulted when the reagents [15 µmol of **2** and 7.5 µmol of $(CuOTf)_2\cdot PhMe$] were mixed in chloroform (ca. 1 mL), and the solution was layered with hexane. Analytical data for **14** are available in the Supporting Information.

X-ray Crystallography

Crystallographic Data for (*S*,S_p)-9: $C_{33}H_{30}FeNO_3P$, *M* = 575.40, orange prism, 0.40 × 0.55 × 0.55 mm; orthorhombic, space group $P2_12_12_1$, *a* = 11.6754(1), *b* = 11.7822(1), *c* = 20.1930(2) Å; *V* = 2777.79(4) Å^3, *Z* = 4. Diffraction data were collected with a Nonius KappaCCD instrument (Mo-K_α radiation, λ = 0.71073 Å) at 150(2) K and were corrected for absorption [μ(Mo-K_α) = 0.636 mm^{-1}; transmission factors: 0.718–0.835]. A total of 48591 diffractions was measured (θ_{max} = 27.5°), of which 6361 were unique (R_{int} = 4.2%) and 6068 observed with $I > 2\sigma(I)$. The structure was solved by direct methods (SIR97[27]) and refined by full-matrix least squares on F^2 (SHELXL97[28]). Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms, except for the amide hydrogen atom, were placed in their calculated positions and refined as riding atoms with U_{iso}(H) assigned to a multiple of U_{eq} of their bonding carbon atom. The amide hydrogen atom, H1N, was identified on a difference Fourier map and refined similarly. The refinement converged ($\Delta/\sigma_{max} \leq$ 0.001, 354 parameters) to *R* = 2.37% for observed, and *R* = 2.61%, *wR* = 6.21%, GOF = 1.053 for all diffractions; $\Delta\rho$ = 0.51, –0.23 e·Å^{-3}. The Flack enantiomorph parameter[29] was determined to be –0.012(8).

Crystallographic Data for 14: $C_{55}H_{50}Cl_6CuF_3Fe_2N_2O_9P_2S$, *M* = 1421.91, yellow prism, 0.20 × 0.23 × 0.35 mm; triclinic, space group $P\bar{1}$, *a* = 13.0920(3), *b* = 14.4847(3), *c* = 17.6069(4) Å; α = 97.023(1), β = 97.085(1), γ = 112.233(1)°; *V* = 3014.2(1) Å^3, *Z* = 2. Diffraction data were collected as described above; absorption was neglected [μ(Mo-K_α) = 1.243 mm^{-1}]. A total of 59208 diffractions was measured (θ_{max} = 27.5°), of which 13796 were unique (R_{int} = 4.2%)

and 9588 observed with $I > 2\sigma(I)$. The structure was solved and refined as described for (S,S_p)-**9**, except that one of the phenyl rings (C62–C67), the triflate anion and one chloroform molecule had to be refined over two positions due to disorder. The refinement converged ($\Delta/\sigma_{max} \leq 0.001$, 734 parameters) to R = 5.23% for observed, and R = 8.42%, wR = 14.8%, GOF = 1.065 for all diffractions; $\Delta\rho$ = 1.12, –1.20 e Å^{-3}.

CCDC-767197 [(S,S_p)-**9**] and -767199 (**14**) contain 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.

Supporting Information (see footnote on the first page of this article): Details on the preparation of the starting amino acid methyl ester hydrochlorides, the crystal structure of **13**, a full view of the crystal structure of **14**, characterisation data for the complex [Cu(**2**)$_2$](TfO), and analytical data for the alkylation products **12a**–**g**.

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