An efficient and highly stereoselective synthesis of new *P*-chiral 1,5-diphosphanylferrocene ligands and their use in enantioselective hydrogenation†

Weiping Chen,‡* Stanley M. Roberts, John Whittall and Alexander Steiner

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An efficient and highly stereoselective synthesis of *P*-chiral 1,5-diphosphanylferrocene ligands has been developed, and the introduction of *P*-chirality in ferrocene-based phosphine ligands enhances the enantioselective discrimination produced by the corresponding catalyst when matching of the planar chirality, the chirality at carbon and the chirality at phosphorus occurs.

Asymmetric catalysis is a powerful tool for producing enantiomerically enriched compounds. In this area, the design and synthesis of chiral phosphine ligands has played a significant role in the development of efficient transition metal-catalysed reactions.[1] However, the search for more practical and efficient ligands in terms of ease of preparation, air-stability, high enantioselectivity and activity remains an important goal in asymmetric catalysis. Since careful matching of the chiral ligand, the reaction type, the catalyst, and the substrate is usually necessary, there is a demand for highly efficient, flexible and modular syntheses of phosphines to allow convenient modification of steric and electronic properties, and hence rapid optimisation of ligand–substrate matches.

Ferrocene-based phosphine ligands are well documented.[2] Recently Knochel and co-workers reported a new type of ferrocene-based 1,5-diphosphine **1a** called Taniaphos,[3] which gave excellent enantioselectivities for various metal-catalysed asymmetric reactions. The nature of the substituent at the α-position in Taniaphos as well its absolute configuration proved to be very important for achieving high degrees of stereocontrol. The second generation of Taniaphos (type **1b**), bearing a methoxy group with the (α*S*)-configuration, proved to be superior for all of the reactions under study.

Taniaphos
First generation: 1a, $R^1 = R^2 = Ph$, $R^3 = H$, $R^4 = NMe_2$
Second generation: 1b, $R^1 = R^2 = Ph$, $R^3 = OMe$, $R^4 = H$

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PingFer

StylaCats Ltd. Chemistry Department, University of Liverpool, Liverpool, UK L69 7ZD

† Electronic supplementary information (ESI) available: Experimental procedures and X-ray crystal structure data for compounds (2′*S*,4′*S*,S_{Fc},R_P)-**10a** and (2′*S*,4′*S*,S_{Fc},R_P)-**10b**. See DOI: 10.1039/b601952h

‡ Present address: Solvias AG, WRO-1055.6.68B, 4002 Basel, Switzerland. Fax: +41 61 68 66 311; Tel: +41 61 68 66 433; E-mail: weiping.chen@solvias.com

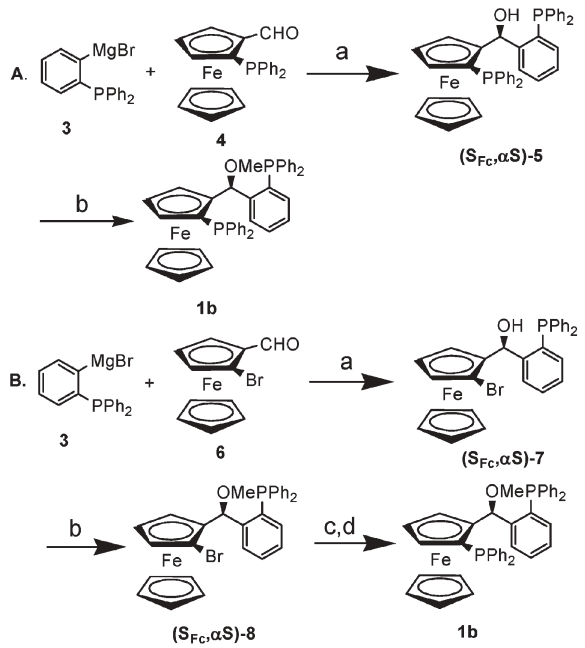
We focused our interest on the new range of phosphine ligands, incorporating several elements of the Taniaphos skeleton but also incorporating a stereogenic centre at phosphorus. In theory, *P*-chiral phosphines are highly likely to provide a superior class of ligands for asymmetric catalysis by virtue of bringing the chiral environment into the closest possible proximity to the catalytic centre. Thus, there are some examples of phosphines wherein the configuration(s) of the stereogenic centre(s) at phosphorus (where different steric and electronic properties are readily tunable) is (are) critical for the attainment of high selectivity in asymmetric catalysis.[4] However, there is only one documented example of *P*-chiral phosphines featuring ferrocenyl groups incorporating carbon-centred stereogenicity,[4(ii)] despite their potential utility as ligands in asymmetric catalysts, doubtless due to the previous difficulties in their synthesis. Herein, we are pleased to describe the efficient and highly stereoselective synthesis of novel *P*-chiral ferrocene-based 1,5-diphosphines **2** (PingFer), and their unprecedented reactivity and selectivity in a portfolio of important asymmetric transformations.

Unlike the synthesis of first generation Taniaphos **1a**, the route to second generation Taniaphos **1b** is non-stereoselective. The key step, namely the reaction of lithiated ferrocenyl sulfoxide with 2-diphenylphosphanylbenzaldehyde, furnished a mixture of two diastereomeric alcohols in the ratio *ca.* 5:4, which were separated only by tedious column chromatography.[3c] Key to our long-term goal, in the initial stages of our work we developed two new, efficient and highly stereoselective routes to Taniaphos **1b**, generating the required α*S* stereochemistry in a highly selective manner.

In the first route (Scheme 1A), reaction of (*S*)-α-(diphenylphosphino)ferrocenecarboxaldehyde **4**[5] with the Grignard reagent **3**, prepared from the readily available (2-bromophenyl)diphenylphosphine,[6] gave the product in 96% yield with a ratio of 9:1 for the α*S*/α*R* diastereomers. Recrystallisation from hexane gave the pure diastereomer (S_{Fc},α*S*)-**5** in 76% yield. Standard methylation of (S_{Fc},α*S*)-**5** afforded **1b** in 91% yield. The physical properties of the sample of **1b** prepared in this way were identical with those reported previously.

In the second route (Scheme 1B), reaction of (*S*)-2-bromoferrocenecarboxaldehyde **6**[5] with the Grignard reagent **3** gave the desired (S_{Fc},α*S*)-**7** in 98% yield as a single diastereomer. Methylation of alcohol (S_{Fc},α*S*)-**7** furnished the ether (S_{Fc},α*S*)-**8**, whereafter exchange of the bromine atom for the diphenylphosphino moiety proceeded without incident to afford Taniaphos **1b** in 92% overall yield.

The difference in the diastereoselectivity for the addition of Grignard reagent **3** to (*S*)-2-bromoferrocenecarboxaldehyde **6** and



Scheme 1 Reagents and conditions: (a) THF, −78 °C–rt, 76% (A); (b) 30% KH, MeI, THF, 0 °C, 91% (A); (c) t-BuLi, THF, −78 °C; (d) Ph_2PCl, −78 °C–rt, 94% (B).

(*S*)-2-(diphenylphosphino)ferrocenecarboxaldehyde **4** can be explained as follows. The lone electron pair on substituent X (Fig. 1) and the oxygen atom of the carbonyl group repel each other, so that the favoured conformation of the 2-substituted ferrocenecarboxaldehyde has the carbonyl group oriented *anti* to the substituent X. Addition of the Grignard reagent to the carbonyl group occurs from the *Si*-face exclusively when X is small (such as Br), while when X is the bulky diphenylphosphino entity, one of the phenyl groups hinders attack by Grignard reagent on the *Si*-face of the aldehyde unit to a minor extent.[7]

Utilising some of this new chemistry, we turned our attention to the preparation of the new family of phosphine ligands **2**. Halogen–lithium exchange on compound (S_{Fc},α*S*)-**8** (−78 °C, 15 min) and reaction with $PhPCl_2$ (−78 °C, 10 min, then rt, 1.5 h) and then *o*-anisyllithium (−78 °C–rt, overnight) gave a single diastereomer (S_{Fc},α*S*,S_P)-**2a** in 91% yield (Scheme 2). Similarly, replacement of *o*-anisyllithium with 1-naphthyllithium afforded **2b** as a mixture of two diastereomers in 90% yield. The ratio of (S_{Fc},α*S*,S_P)-**2b** to (S_{Fc},α*S*,R_P)-**2b** was determined by ^{1}H NMR and ^{31}P NMR spectroscopy to be 9:1. The major diastereomer can be purified very easily by recrystallisation from hexane.

The high diastereoselectivity of the transformation from (S_{Fc},α*S*)-**8** to (S_{Fc},α*S*,S_P)-**2** can be explained by a similar reaction mechanism to that proposed in the synthesis of *P*-chiral phosphines from Ugi's amine (Scheme 3),[8] whereby a seven-membered

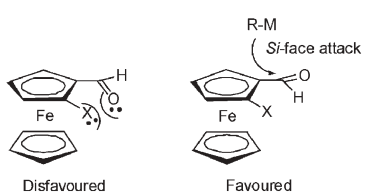
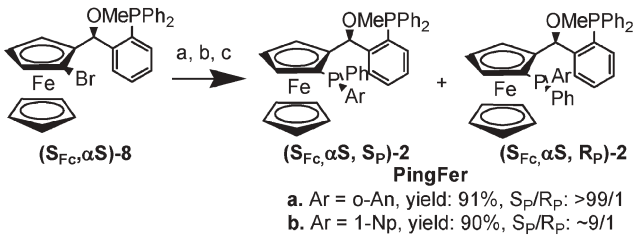
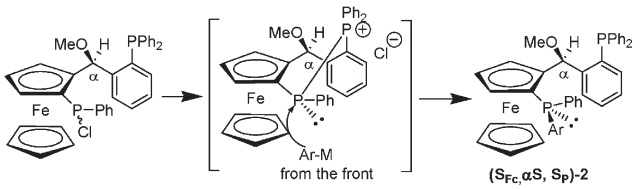


Fig. 1



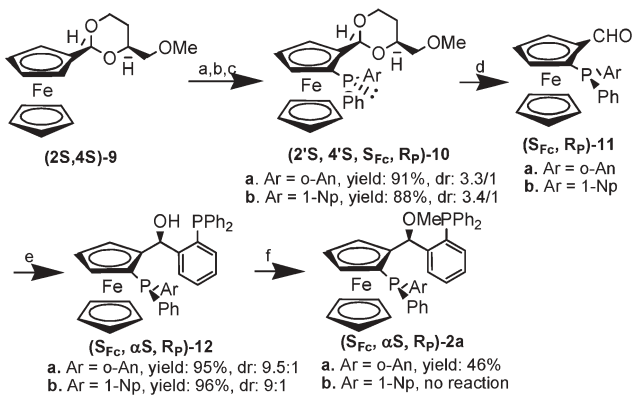
Scheme 2 Reagents and conditions: (a) t-BuLi, THF, −78 °C; (b) $PhPCl_2$, −78 °C–rt; (c) ArLi, −78 °C–rt.



Scheme 3

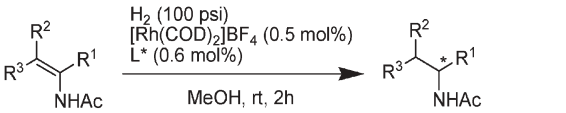
ring, quaternary phosphonium salt intermediate is formed and then the organometallic compound ArM attacks from the front (as portrayed) to give the products observed.

Efforts to make suitable crystals of (S_{Fc},α*S*,S_P)-**2a** or (S_{Fc},α*S*,S_P)-**2b** or (S_{Fc},α*S*,R_P)-**2b** for X-ray diffraction analysis failed. However, the absolute configuration of (S_{Fc},α*S*,R_P)-**2a** was confirmed by employing another synthetic route (Scheme 4). The ferrocenyl dioxane derivative (2*S*,4*S*)-**9**[5] was lithiated with t-BuLi (−78 °C, 10 min, then rt, 1.5 h), and then reacted with $PhPCl_2$ (−78 °C, 10 min, then rt, 1.5 h) followed by the requisite aryllithium (−78 °C–rt, overnight) to afford a mixture of two diastereomers in *ca.* 90% yield. The ratio of the two diastereomers was determined by ^{1}H NMR and ^{31}P NMR spectroscopy to be *ca.* 3.3:1. The major diastereomers (2′*S*,4′*S*,S_{Fc},R_P)-**10a** and (2′*S*,4′*S*,S_{Fc},R_P)-**10b** can be easily separated by a single recrystallization from hexane in about 50% yield; their absolute configuration was confirmed by single-crystal X-ray diffraction analysis.§ Acid hydrolysis of (2′*S*,4′*S*,S_{Fc},R_P)-**10a** afforded the aldehyde (S_{Fc},R_P)-**11a** quantitatively. Reaction of (S_{Fc},R_P)-**11a** with the Grignard reagent prepared from (2-bromophenyl)diphenylphosphine gave the desired product in 96% yield as a mixture of



Scheme 4 Reagents and conditions: (a) t-BuLi, Et_2O, −78 °C–rt; (b) $PhPCl_2$, −78 °C–rt; (c) ArLi, −78 °C–rt, (d) *p*-TsOH, H_2O–CH_2Cl_2, rt, 100%; (e) 2-diphenylphosphinophenylmagnesium bromide, THF, −78 °C–rt; (f) 30% KH, MeI, THF, 0 °C.

Table 1 Asymmetric hydrogenation of α-dehydroamino acid derivatives[a]



Run[b]	Ligand	R^1	R^2	R^3	Ee (%)
1	**1b**	CO_2Me	H	Ph	90.5 (*S*)
2	(S_{Fc},α*S*,S_P)-**2b**	CO_2Me	H	Ph	**99.6** (*S*)
3	(S_{Fc},α*S*,R_P)-**2b**	CO_2Me	H	Ph	69.3 (*S*)
4	(S_{Fc},α*S*,R_P)-**2a**	CO_2Me	H	Ph	10.8 (*S*)
5	**1b**	CO_2Me	H	3-BrPh	97.3 (*S*)
6	(S_{Fc},α*S*,S_P)-**2b**	CO_2Me	H	3-BrPh	>**99.9** (*S*)
7	(S_{Fc},α*S*,R_P)-**2b**	CO_2Me	H	3-BrPh	17.1 (*S*)
8	(S_{Fc},α*S*,R_P)-**2a**	CO_2Me	H	3-BrPh	12.2 (*S*)
9	**1b**	CO_2Me	H	2-BrPh	91.4 (*S*)
10	(S_{Fc},α*S*,S_P)-**2b**	CO_2Me	H	2-BrPh	>**99.9** (*S*)
11	(S_{Fc},α*S*,R_P)-**2b**	CO_2Me	H	2-BrPh	52.4 (*S*)
12	**1b**	Ph	H	H	86.4 (*S*)
13	(S_{Fc},α*S*,S_P)-**2b**	Ph	H	H	**96.3** (*S*)
14[c]	**1b**	Me	CO_2Me	H	92.4 (*S*)
15[c]	(S_{Fc},α*S*,S_P)-**2b**	Me	CO_2Me	H	**96.1** (*S*)

[a] (S_{Fc},α*S*,S_P)-**2a** is not active in this reaction. [b] All reactions went to completion under the conditions except for run 4 (55.4% conversion) and run 8 (61.8% conversion). [c] The hydrogenation reactions were performed under 300 psi hydrogen for 12 h at room temperature.

two diastereomers (ratio of α*S*:α*R* = 9.5:1) whereupon recrystallisation from hexane gave the pure diastereomer (S_{Fc},α*S*,R_P)-**12a** in 73% yield. Subsequent methylation of (S_{Fc},α*S*,R_P)-**12a** afforded (S_{Fc},α*S*,R_P)-**2a** in 46% yield. Etherification of (S_{Fc},α*S*,R_P)-**12b** failed under similar conditions, presumably due to interference by the naphthyl moiety.

The preliminary results of some asymmetric hydrogenation reactions catalysed by PingFer-Rh complexes show that the introduction of *P*-chirality into ferrocene-based phosphine ligands enhances the enantioselective discrimination of the catalyst when synergistic matching of the planar chirality, the chirality of carbon and the chirality on phosphorus exists. Thus the matched new ligand (S_{Fc},α*S*,S_P)-**2b** leads to higher enantioselectivities than Taniaphos **1b** in a wide range of asymmetric hydrogenations. First, we compared the new ligands in the Rh-catalysed asymmetric hydrogenation of α-dehydroamino acid derivatives (Table 1). The ligand (S_{Fc},α*S*,S_P)-**2b** gives products in over 99% ee for the three α-dehydroamino acid derivatives tested. In contrast, when the mismatched (S_{Fc},α*S*,R_P)-**2b** is employed in the same reactions much lower enantioselectivity is observed (17–69% ee).

Similarly, in the Rh-catalysed asymmetric hydrogenations of an enamide (run 12 *vs.* run 13) and an (*E*)-β-dehydroamino acid derivative (run 14 *vs.* run 15), the chiral ligand with matched stereodirecting units (S_{Fc},α*S*,S_P)-**2b** again gave superior results to Taniaphos **1b**.

In summary, we have developed a highly stereoselective synthesis of *P*-chiral 1,5-diphosphanylferrocene ligands. The introduction of *P*-chirality in ferrocene-based phosphine ligands enhances the enantioselective discrimination produced by the corresponding catalyst when matching of the different stereogenic components is achieved. The highly stereoselective, modular synthesis of new phosphine ligands and the excellent enantioselectivities obtained in three important transformations, combine to signpost the potential importance of this new family of chiral ligand.

Notes and references

§ Crystallographic data were recorded on Stoe IPDS (**10a**) and Bruker Smart Apex (**10b**) diffractometers using MoK_α-radiation (λ = 0.71073 Å). Structures were refined by full-matrix least squares against F^2 using all data (SHELX97[9]). Apart from disordered atoms, non-hydrogen atoms were refined anisotropically and hydrogen atoms were fixed geometrically. **10a**: $C_{29}H_{31}FeO_4P$, M = 530.36, T = 213 K, orthorhombic, space group $P2_12_12_1$ (No. 4), a = 8.2767(8), b = 10.7033(12), c = 29.205(3) Å, V = 2587.2(5) Å^3, Z = 4, $\mu(MoK_\alpha)$ = 0.678, 4118 unique reflections (R_{int} = 0.0817), R_1 [$I > 2\sigma(I)$] = 0.0586, wR_2 (all data) = 0.1319; **10b**: $C_{32}H_{31}FeO_3P$, M = 550.39, T = 100 K, monoclinic, space group $P2_1$ (No. 19), a = 9.210(4), b = 7.142(3), c = 20.061(8) Å, β = 94.636(7)°, V = 1315.4(9) Å^3, Z = 2, $\mu(MoK_\alpha)$ = 0.667, 3385 independent reflections (R_{int} = 0.0595), R_1 [$I > 2\sigma(I)$] = 0.0455, wR_2 (all data) = 0.1149. **10a** contains a disordered dioxane group and **10b** a disordered phenyl ring. Disordered atoms were split on two positions and refined isotropically with 0.5 occupancy factors using similar-distance and similar-U restraints. CCDC 604420 and 604421. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b601952h

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