Large-Scale Synthesis of Chiral Ferrocenyl Imino-Phosphines

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Abstract: A convenient, multigram-scale synthesis of ferrocenyl imino-phosphine ligands, combining planar and central chirality, and featured by a flexible and easy-to-tune molecular structure has been developed.

Key words: imines, ferrocenes, phosphorus, ligands, stereoselective synthesis

Scheme 1

Introduction

The need to develop innovative, sustainable industrial processes for the production of fine chemicals is increasingly pushing chemists to deliver more robust, efficient and selective asymmetric catalysts and, hence, to design optically pure ligands with improved performance parameters.

Chiral bidentate 1,2-substituted ferrocenyl ligands play a fundamental role in asymmetric catalysis.1 Since the pioneering work of Hayashi and co-workers,2 the range of application of such ligands has been steadily growing, and several industrial asymmetric hydrogenation processes based on their use are currently in operation.3 A most important feature of ferrocenyl ligands is their modularity, especially in terms of synthetic approach, which allows a great variety of derivatives to be assembled into a single common structural framework.4 Indeed, a large number of ligands with homo- and mixed-donor atom sets, including the P,N one, have been reported.5,6 Among these, iminophosphines have received particular attention due to their flexible coordination behaviour associated with tunable steric and electronic properties. Most chiral 1,2-ferrocenyl imino-phosphines reported so far are characterised by a tertiary phosphine unit directly linked to the ferrocenyl fragment and by a pendant 1-ethylimino substituent.7 Recently, Knochel has introduced a series of structurally related compounds in which a side-chain carbon stereocentre bearing a phosphorus donor atom and a nitrogen heterocycle are linked in a 1,2 fashion to the ferrocenyl unit.8

In this paper, we provide a detailed account of an easy, multigram synthetic protocol to obtain various stereo-homogeneous 1,2-disubstituted ferrocenyl iminophosphines 4, containing 1-ethylphosphino and N-ferrocenylidene groups (Scheme 1). The main synthetic procedure to these optically pure ligands has been recently communicated, together with a preliminary study of Pd-catalysed asymmetric allylic alkylations.9

Scope and Limitations

The synthetic procedure developed to synthesise the new ferrocenyl iminophosphate ligands is illustrated in Scheme 1. The stereoconservative side-chain nucleophilic substitution of the bromo ferrocenylamine 10 with diarylphosphines [Ar = Ph; 3,5-(CF3)2C6H3] in AcOH gave the bromo-diarylphosphine compounds 2 in high yields.11 Treatment of 2 with n-BuLi/DMF afforded the formyl derivatives (R)-1-[(S)-2-formylferrocenyl]ethyl-diarylphosphine 3. Compounds 3 are the key precursors to the optically pure iminophosphine ligands 4aa–ae and 4bd, which were obtained in multigram-scale and in 88–
99% yields by treatment with the appropriate amine. The purification of compounds 4 was effectively performed by flash chromatography on neutral alumina in order to avoid the possible hydrolysis of the imino bond.

The absolute configuration of each stereocenter in the P,N-ligands was assigned on the basis of the solid-state structure of the borane adduct 5 obtained by a single-crystal X-ray diffraction analysis. The compound 5 was prepared by reacting the formylferrocenyl compound 3a with BH₃(SMe₂) (Scheme 2). The adduct 5 can be easily handled, stored in the air and purified by standard chromatographic techniques; moreover 5 regenerates 3a quantitatively by treatment with N,N,N',N'-tetramethyl-ethylenediamine.

Scheme 2

Key intermediates in the overall synthesis of the ferrocenyl iminophosphines are therefore the optically pure formylferrocenyl derivatives 3, which may be used as a chiral precursor to a variety of derivatives through the intrinsic reactivity of the formyl functional group.

All manipulations were performed under a pure N₂ atmosphere unless otherwise stated. C₅H₅ and THF were distilled over Na/benzophenone. Toluene, n-pentane and n-hexane were distilled over sodium. CH₂Cl₂ was distilled over CaH₂. N,N-Dimethylformamide (DMF) was distilled from K₂CO₃ under high vacuum and stored on activated 4 Å molecular sieves. MeOH was distilled over Mg/I₂ and stored on activated 3 Å molecular sieves. Unless otherwise stated, all the other chemicals were obtained from commercial suppliers and were used as received without further purification.

1H and 13C NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer operating at 161.98 MHz. Chemical shifts are relative to external 85% H₃PO₄ with downfield values reported as positive. 1H NMR (400 MHz, 294 K, CDCl₃): δ = 6.14 (s, 1 H, C=O), 7.57 (s, 1 H, PhH), 7.48 (s, 3 H, PhH), 7.21 (m, 1 H, PhH), 7.72 (m, 2 H, PhH), 7.01 (m, 2 H, PhH), 4.60 (m, 1 H, HCP), 4.55 (m, 1 H, HCP), 4.53 (m, 1 H, HCP), 4.25 (s, 5 H, HCP'), 3.86 (m, 1 H, HCP), 1.62 (s, 6 H, CH₃). 13C NMR (100.61 MHz, 294 K, CDCl₃; selected data): δ = 168.23 (s, C=O), 162.98 (m, 1 H, HCP), 156.81 (m, 1 H, HCP), 128.07 (m, 1 H, CHMe), 126.32 (m, 1 H, CH), 123.40 (m, 1 H, CHMe), 122.04 (m, 1 H, HCP), 115.42 (m, 1 H, HCP), 115.27 (m, 1 H, HCP), 114.89 (m, 1 H, HCP). 31P{1H} NMR (161.98 MHz, 294 K, CDCl₃): δ = 7.68 (s, PhP).


(3S)-2-(Bromoformyl)ethyl-3,5-trifluoromethyl-diphenylphosphine (2a)

To a solution of 1 (0.133 g, 0.396 mmol) and HP[H₂(CF₃)₂]₂ (0.200 g, 0.435 mmol) in AcOH (1 mL) was stirred at 110 °C under a N₂ atmosphere for 5 h. The solvent was then removed in vacuo and the crude product was purified via flash chromatography (CH₂Cl₂–n-pentane–Et₂O = 9:1:2) under N₂ to afford a yellow-orange semi-solid compound (0.264 g, 89% yield).

(3S)-2-Formylferroceny lethyl-3,5-trifluoromethyl-diphenylphosphine (2b)

To a solution of 1 (0.133 g, 0.396 mmol) and HP[H₂(CF₃)₂]₂ (0.200 g, 0.435 mmol) in AcOH (1 mL) was stirred at 110 °C under a N₂ atmosphere for 5 h. The solvent was then removed in vacuo and the crude product was purified via flash chromatography (CH₂Cl₂–n-pentane–Et₂O = 9:1:2) under N₂ to afford a yellow-orange semi-solid compound (0.264 g, 89% yield).

(3S)-2-Formylferrocenyl ethyl-3,5-trifluoromethyl-diphenylphosphine (3a)

To a solution of 1 (0.133 g, 0.396 mmol) and HP[H₂(CF₃)₂]₂ (0.200 g, 0.435 mmol) in AcOH (1 mL) was stirred at 110 °C under a N₂ atmosphere for 5 h. The solvent was then removed in vacuo and the crude product was purified via flash chromatography (CH₂Cl₂–n-pentane–Et₂O = 9:1:2) under N₂ to afford a yellow-orange semi-solid compound (0.264 g, 89% yield).

PRACTICAL SYNTHETIC PROCEDURES

gel under N₂ (gradient of elution: n-pentane–EtOAc = 95:5 → 60:40) to afford a red-orange compound (0.70 g, 67% yield).

1H NMR (400 MHz, 294 K, CDCl₃): δ = 9.66 (s, 1 H, CH=O), 8.21 (m, 2 H, ArH), 8.06 (m, 1 H, ArH), 7.82 (m, 1 H, ArH), 7.43 (m, 2 H, ArH), 4.65 (m, 1 H, HCP), 4.63 (m, 2 H, HCP), 4.43 (s, 5 H, HCP), 4.41 (m, 1 H, CHMe), 1.70 (dd, J_HH = 7.2 Hz, J_HP = 14.5 Hz, 3 H, CH₃).

13C{1H} NMR (100 MHz, 294 K, CDCl₃): δ = 162.35 (s, 2 H, Ph), 171.82 (s, 1 H, CH=O), 136.53 (d, J = 15.6 Hz, CHMe), 130.38 (d, J = 16.3 Hz, CH₂), 129.30 (d, J = 15.6 Hz, CH₂), 128.45 (d, J = 15.2 Hz, CPh), 127.58 (d, J = 15.4 Hz, CHMe), 126.79 (d, J = 15.5 Hz, CH₂), 122.22 (s, CPh), 118.93 (s, CH₂), 113.30 (s, CH₂), 112.94 (d, J = 9.49 Hz, CH₂), 112.60 (d, J = 9.37 Hz, CH₂), 110.40 (d, J = 9.63 Hz, CPh), 72.08 (d, J = 11.9 Hz, CH₂), 71.30 (s, CH₂), 69.32 (s, C₅H₅), 69.10 (s, CH₃), 68.79 (s, CH₃), 56.30 (s, 2 CH₃), 38.72 (s, N=CH₂).

Anal. Calcd for C₂₅H₂₆BFeO (440.11): C, 68.23; H, 5.95. Found: C, 74.77; H, 5.98; N, 2.49.

(R)-1-(S)-(2)-Ferrocenylideneamine[ethylidiphosphine (4ab)

Phosphine (4aa)

The reaction was carried out following the same procedure described above for 4aa, using aniline instead of 2,6-dimethylaniline. The crude product was rapidly purified via flash chromatography over neutral aluminium oxide (n-pentane–EtOAc, 90:10) to afford a red-orange product (88% yield); [α]_D ~ 247° (c = 1.23, CHCl₃).

IR (nujol): 1620 (C=O) cm⁻¹.

1H NMR (400 MHz, 294 K, CDCl₃): δ = 7.31 (s, 1 H, CH=N), 7.61 (m, 1 H, PhH), 7.52–6.86 (m, 13 H, PhH), 4.79 (s, 1 H, HCP), 4.49 (s, 1 H, HCP), 4.42 (s, 5 H, HCP), 3.79 (m, 1 H, CHMe), 1.63 (dd, J_HH = 6.2 Hz, J_HP = 12.6 Hz, 3 H, CH₃).

13C{1H} NMR (100 MHz, 294 K, CDCl₃): δ = 159.70 (s, 2 C₅H₅), 79.43 (s, C₅H₅), 69.73 (s, HCP), 69.56 (s, CH₃), 69.53 (s, CH₃), 67.32 (s, CH₃), 29.87 (d, J = 17.1 Hz, CH₃CH₂), 18.80 (d, J = 23.0 Hz, CH₂CH₃).

1P{1H} NMR (161.98 MHz, 294 K, CDCl₃): δ = 9.87 (s, PhPH). Anal. Calcd for C₃₃H₂₈FeNP (539.13): C, 74.26; H, 5.63; N, 2.79. Found: C, 74.13; H, 5.52; N, 2.29.

(R)-1-(S)-(2)-Ferrocenylidenechloroethylamine[ethylidiphosphine (4ac)

Cyclohexylamine (0.241 mL, 2.11 mmol) was added to a solution of 3a (0.180 g, 0.422 mmol), in anhyd toluene (2.5 mL). The reaction mixture was treated with AcOH (10 µL) and stirred at 60 °C for 3 h. The solution was filtered through a cotton pad and the solvent was removed in vacuo to give an orange pure oil which was used without further purification (0.205 g, 96% yield); [α]_D ~ 650° (c = 0.88, CHCl₃).

IR (nujol): 1635 (C=O) cm⁻¹.

1H NMR (400 MHz, 294 K, CDCl₃): δ = 7.68 (m, 1 H, CH=CH₂), 7.52 (m, 2 H, PhH), 7.43 (m, 3 H, PhH), 7.19 (m, 1 H, PhH), 7.12 (m, 2 H, PhH), 6.98 (m, 2 H, PhH), 4.68 (m, 1 H, PhCH₂), 4.33 (m, 1 H, PhH), 4.24 (m, 1 H, HCP), 4.11 (s, 5 H, HCP), 3.72 (quint, J_HH = J_HP = 6.8 Hz, 1 H, CH₂), 2.66 (m, 2 H, N-CH₂), 1.69 (m, 2 H, CyH), 1.55 (m, 2 H, CyH), 1.59 (dd, J_HH = 7.0 Hz, J_HP = 14.1 Hz, 3 H, CH₃), 1.48–1.16 (m, 6 H, CyH).

13C{1H} NMR (100.61 MHz, 294 K, CDCl₃, selected data): δ = 156.44 (s, 2 C₅H₅), 93.06 (d, J = 16.3 Hz, CP), 78.74 (s, CP), 70.35 (s, CP), 69.49 (s, C₅H₅), 68.71 (s, HCP), 66.89 (s, HCP), 38.72 (s, N- Cy), 34.90 (s, Cy), 34.10 (s, Cy), 29.54 (d, J = 13.8 Hz, CHMe), 25.68 (s, 24 Cy), 24.97 (s, Cy), 24.84 (s, Cy), 18.70 (d, J = 18.5 Hz, CH₃).

1P{1H} NMR (161.98 MHz, 294 K, CDCl₃): δ = 7.89 (s, PhPH).

Anal. Calcd for C₃₃H₃₄FeNP (570.44): C, 73.38; H, 6.75; N, 2.76. Found: C, 73.26; H, 6.61; N, 2.69.

(R)-1-(S)-(2)-Ferrocenylidene-aminoethyl[ethylidiphosphine (4ad)

A mixture of 3a (0.270 g, 0.613 mmol), ethylamine (5 mL) and AcOH (10 µL) was stirred at 40 °C for 6 h. The excess of amine was evaporated under a stream of N₂ to give a brown-orange compound. The crude product was rapidly purified under a N₂ atmosphere via flash chromatography over neutral aluminium oxide (petroleum ether–EtOAc, 90:10) to afford the pure compound in quantitative yield; [α]_D ~ 387° (c = 1.06, CHCl₃).

IR (nujol): 1639 (C=O) cm⁻¹.

1H NMR (400 MHz, 294 K, CDCl₃): δ = 7.51 (m, 2 H, PhH), 7.48 (s, 1 H, CH=CH₂), 7.44 (m, 3 H, PhH), 7.16 (m, 1 H, PhH), 7.12 (m, 2 H, PhH), 6.94 (m, 2 H, PhH), 4.66 (m, 1 H, HCP), 4.45 (t, J_HH = 305.13 Hz, J_HP = 15.1 Hz, 2 H, CH₂).
References


