Tetrahedron: *Asymmetry* 21 (2010) 2505–2511

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A straightforward access to pyrrolidine-based ligands for asymmetric synthesis

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ARTICLE INFO

Article history:
Received 30 August 2010
Accepted 21 September 2010
Available online 27 October 2010

ABSTRACT

A straightforward and flexible method for the preparation of ligands based on the pyrrolidine scaffold is presented. The synthetic strategy involves a diastereoselective allylation of phenylglycinol-derived imines, followed by a cyclization promoted by a hydrozirconation/halogenation sequence. Enantioselectivities of up to 84% ee in the asymmetric allylic allylation were obtained using these ligands.

1. Introduction

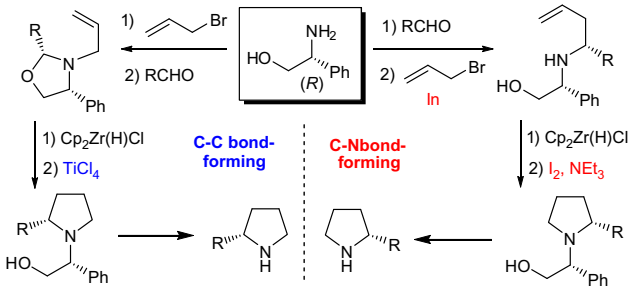
The development of versatile and general asymmetric methods for elaborating upon heterocyclic scaffolds is a key feature in modern ligand design for metal-catalyzed transformations.[1] Although, several *P*,*P*-ligands are known to induce high levels of asymmetric induction on several metal-catalyzed processes, *P*,*N*-ligands occupy a growing place.[2] In fact, the electronic dissymmetry in such ligands has, in some cases, a great impact on the asymmetric course of a reaction.[3] Among *N*-heterocycle-based ligands, the pyrrolidine skeleton has emerged as one the most efficient backbones for generating a discriminative environment around the metal.[4]

We have recently described two strategies for the synthesis of enantiomerically pure 2-substituted pyrrolidines. The first one involves a tandem hydrozirconation/Lewis acid-mediated cyclization applied to *N*-allyloxazolidines.[5] The second, consists of a hydrozirconation/iodination sequence starting from homoallylic amines.[6] These two approaches are general and stereo-complementary leading stereoselectively to enantiomeric pyrrolidines after the removal of the chiral inductor residue (Scheme 1).

Herein we report the synthesis of simple phosphinopyrrolidines prepared according to the C–N bond-forming strategy.

2. Results and discussion

Efficient *P*,*N*-ligands, ferrocene-based amino-phosphines, pyridine-phosphines, and pyrrolidine-phosphines have been proved to afford a high level of asymmetric induction in palladium-catalyzed allylic substitution.[7] Therefore, we decided to prepare different ligands combining a 2-substituted pyrrolidine and a phosphine moiety. Access to these ligands was envisioned by linking the phosphine unit to the 1 or the 2-position of the pyrrolidine. The pyrrolidine precursors would be prepared by applying the sequential hydrozirconation/iodination methodology to enantiomerically pure homoallylic amines. The configuration of the homoallylic amines could be controlled by the diastereoselective allylmetallation of the corresponding (*R*)-phenylglycinol-derived imine (Fig. 1).



Scheme 1.

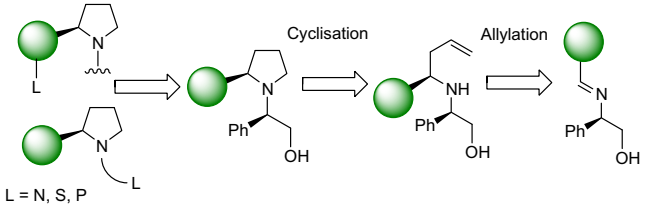


Figure 1.

The diastereoselective allylation of chiral imines has been widely described in the literature and can be carried out either with Grignard reagents or under Barbier conditions with several metals.[8] Among the chiral auxiliaries, phenylglycinol appears to be one of the more efficient ones in terms of stereoselectivity.[9]

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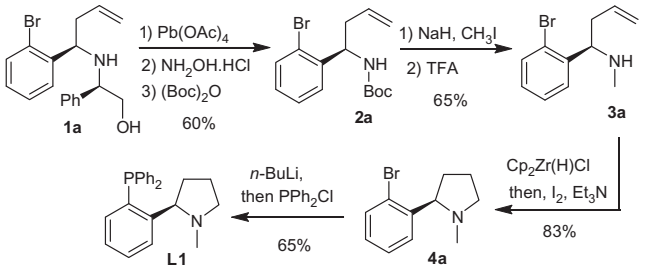
doi:10.1016/j.tetasy.2010.09.015

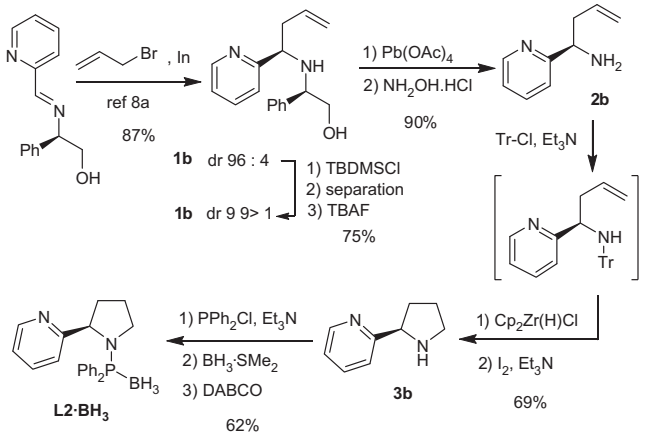
Moreover, different conditions could be employed to remove the chiral auxiliary residue.

We first decided to prepare a simple pyrrolidine bearing a 2-diphenylphosphinyl group at the 2-position of the heterocycle. We have previously reported the preparation of a pyrrolidine bearing 2-bromophenyl at the required position, which prompted us to incorporate the diphenylphosphine via a bromine/lithium exchange. However, the synthetic strategy had to be slightly modified with respect to that described in Scheme 1. In fact, the removal of the chiral auxiliary could not be achieved through hydrogenolysis, but under oxidative conditions prior to cyclization, using $Pb(OAc)_4$. The corresponding amine was isolated in its *N*-Boc protected form **2a** to facilitate purification.[10] Subsequent N-methylation and Boc removal gave the amine intermediate **3a** which underwent the hydrozirconation/iodination-sequence to afford the desired pyrrolidine **4a**. Further bromine/lithium exchange, followed by the addition of chlorodiphenylphosphine, afforded the expected ligand **L1** (Scheme 2).



Scheme 2.

The preparation of a ligand containing the 2-pyridinyl entity was planned next. In this case, the protection of the amine function with a labile group was necessary. However, a deactivating protection had to be avoided, since detrimental pyridine quaternarisation would occur instead. Thus, we chose the *N*-trityl protection strategy by preparing **2b**. In this case, the free pyrrolidine **3b** was directly obtained in 69% yield after aqueous work-up.[11] Additional coupling with PPh_2Cl followed by BH_3 trapping afforded phosphino-pyridine **L2·BH₃** (Scheme 3).

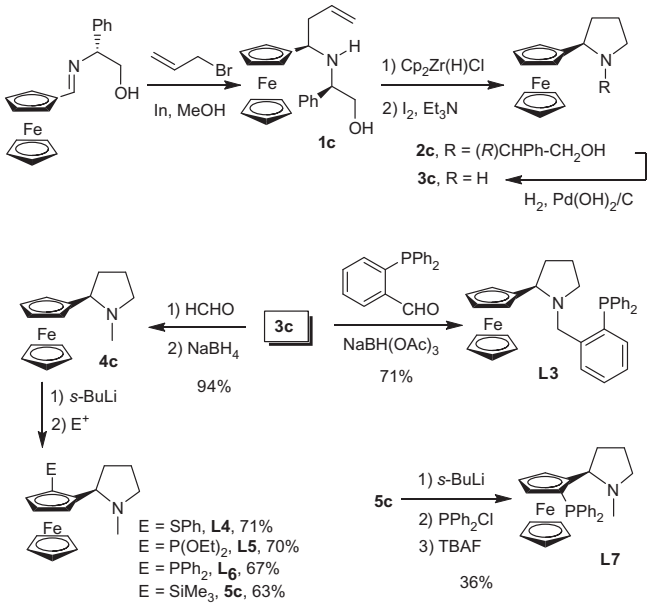


Scheme 3.

From the efficient ligands, ferrocenylphosphines have been proven to induce a high level of asymmetric induction in catalytic transformations.[7a,b] For that reason, we decided to prepare a pyrrolidine containing the ferrocenyl unit at the 2-position. The synthesis started with the stereodetermining allylmetallation of the corresponding (*R*)-phenylglycinol-derived imine. At this stage, whereas the use of allylmagnesium bromide as an allyl promotor resulted in a mixture of diastereomers, the use of indium in Barbier conditions led to the single stereoisomer **1c** in good yield. The hydrozirconation/iodination conditions were applied to afford the expected pyrrolidine **2c**. Subsequent hydrogenolysis gave the *N*-free pyrrolidine **3c** which constitutes the scaffold for the ligand design. The reductive amination applied to **3c** and 2-(diphenylphosphinyl) benzaldehyde in the presence of $NaBH(OAc)_3$ provides **L3**.

We next focused our attention on the functionalization of the ferrocenyl fragment by the stereodirected lithiation of pyrrolidine **4c**, prepared from **2c**. Based on the pioneering work of Ugi,[12] several diastereoselective metallation procedures of the ferrocenyl moiety were reported to provide *P*,*P*-,[13] *P*,*S*-,[14] and *P*,*N*-ligands.[15] Among them, Guiry et al. described the preparation of *N*,*O*-ferrocenyl pyrrolidine ligands via the diastereoselective lithiation of **4c** using *sec*-BuLi as the base and trapping with symmetrical ketones.[16] A highly diastereoselective preparation of ligand **L6** has been mentioned,[17] however no details are given.

According to this procedure, PhSSPh, $(EtO)_2PCl$, and Ph_2PCl were employed as electrophiles. The reaction typically proceeded with a 4:1 diastereomeric ratio. The major isomers were isolated in a pure form after column chromatography, providing the corresponding *S*-*N* ligand and *P*-*N* ligands, **L4**, **L5**, and **L6**, respectively (Scheme 4). Finally, in order to obtain the opposite planar configuration, the locking of the first metallation position with a silyl group was achieved prior to the phosphine incorporation. Thus, TMSCl was employed as the first electrophile to give **5c**. The addition of a second equivalent of the base and reaction with PP_2Cl afforded the desired ligand **L8** after TBAF-mediated silyl removal.

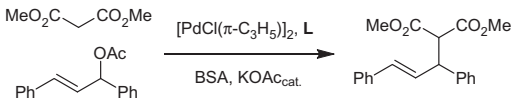


Scheme 4.

With these ligands in hand, the palladium-catalyzed asymmetric allylic substitution was tested next. This reaction is widely described in the literature and has emerged as one of the most powerful C–C, C–N, and C–O asymmetric bond-forming processes.[18] The asymmetric allylic substitution of dimethyl malonate with *rac*-1,3-diphenylpropen-1-yl acetate was then investigated, in the presence of allylpalladium-chloride dimer as the palladium source and ligands **L1**–**L7** (Table 1).

By using these ligands, a complete substrate conversion was achieved within 4 h at room temperature with a catalyst loading

Table 1
Palladium-catalyzed asymmetric allylic alkylation



Entry[a]	Ligand	Time (h)	*T* (°C)	Conversion (%)	ee[b] (%)
1	**L1**	4	20	100	63 (*R*)
2	**L2**[c]	8	20	100	84 (*S*)
3	**L2**[d]	8	20	90	84 (*S*)
5	**L3**	4	20	100	58 (*R*)
6	**L4**	72	20	100	77 (*R*)
7	**L5**	4	20	100	75 (*R*)
8	**L6**	4	20	100	78 (*R*)
9	**L6**	8	0	100	78 (*R*)
10	**L7**	4	20	100	32 (*R*)

[a] The reaction was conducted under Ar at rt using 2 equiv of methyl malonate, 2.5 equiv of BSA, and was initiated by adding a catalytic amount of KOAc.
[b] Determined by HPLC using OD-H-chiralpak column.
[c] **L2** was generated in situ by treating **L2·BH$_3$** with DABCO (1 equiv) for 6 h at 80 °C in toluene prior to the catalytic reaction.
[d] **L2** was generated in situ from **L2·BH$_3$** using $Pd(OAc)_2$ as the palladium source.

of 5 mol % (entries 1–5 and 7–10), except in the case of an *N*,*S*-ligand **L4**, which required 72 h for going to completion. Moderate to good enantioselectivities of up to 84% (ligand **L2**, entries 2 and 3) were observed. In the case of ferrocene-containing ligands, a more efficient discrimination was observed when combining the (*R*)-configuration at the pyrrolidine junction to (*p*-*R*)-configuration of the ferrocenyl fragment, **L3**, **L4**, **L5**, and **L6** versus **L7** (entries 5–9 vs entry 10).

In the cases of the *P*,*N*-ligands, the nucleophilic attack is known to occur predominantly at the allylic termini *trans* to the phosphorus of the allyl–palladium complex.[19]

Therefore, we assumed the predominant formation and reactivity of the allyl–palladium complex **B** over **A** (Fig. 2) to account for the observed enantioselectivity when using **L2** as the ligand. Firstly, **A** suffers from steric interactions, thus favouring the formation of **B**. Secondly, the difference in reactivity may be deduced from the more pronounced congestion in the palladium–olefin complex **A**′ deriving from **A**, favoring the rotation of the allyl fragment from **B** to **B**′,[20] a precursor of the (*S*)-enantiomer.

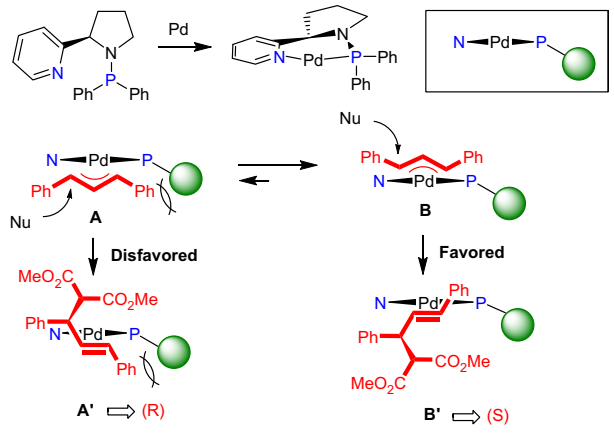


Figure 2.

3. Conclusion

In conclusion, a series of bidentate ligands, based on the 2-pyrrolidine scaffold, have been synthesized. The pyrrolidine framework was built via a sequential hydrozirconation/halogenation sequence. The flexibility of the method allows the incorporation of arylic, pyridinic, or ferrocenic unit at the 2-position of the pyrrolidine and subsequent functionalization providing *N*,*S*- and *N*,*P*-ligands. Tested in an asymmetric allylic substitution, this series of ligands gives moderate to good enantioselectivities, although the methodology offers various opportunities for ligand design in the asymmetric catalysis.

4. Experimental

All the reactions were conducted under an atmosphere of argon. Prior to use, THF and Et_2O were distilled under argon from sodium benzophenone, ketyl, Et_3N, and CH_2Cl_2 were distilled under argon from CaH_2, $Cp_2Zr(H)Cl$ was prepared according to known procedure,[21] reagents were used as received. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$, unless specified, on a Brucker AC-250. Mass spectra were recorded on a Micromass Q-TOF micro MS spectrometer.

4.1. General procedure for the preparation of homoallylic amines (Procedure A)

To a solution of (*R*)-phenylglycinol-derived imine (1 mmol) and allylbromide (260 μL, 3 mmol) in MeOH (5 mL) were added small amounts of In (113 mg, 1 mmol) at rt. The reaction mixture was stirred at rt for 6 h and then a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in AcOEt (30 mL), washed with H_2O (10 mL), dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a mixture of PE/AcOEt to give the corresponding amine **1**.

4.1.1. (*R*)-[(*R*)-1-(2-Bromophenyl)but-3-enylamino)-2-phenyle- thanol 1a

Yield = 77%. Orange oil; $[\alpha]_D^{20} = -37.2$ (*c* 1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ 7.46 (1H, d, J = 7.9 Hz), 7.40–7.19 (7H, m), 7.10 (H, m), 7.03 (1H, d, J = 7.8 Hz), 5.75 (1H, m), 5.08 (d, J = 19.0 Hz, 1H), 5.06 (1H, d, J = 9.1 Hz), 4.32 (1H, t, J = 6.4 Hz), 3.82–3.70 (1H, m), 3.58 (1H, dd, J = 10.0, 5.5 Hz), 2.46 (2H, m), 2.14 (1H, br s); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 142.2, 141.0, 134.5, 132.6, 128.30, 128.25, 128.20, 127.30, 127.25, 127.1, 123.7, 117.8, 65.1, 61.5, 58.4, 40.6; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{21}BrNO$: 346.0807; found: 346.0814.

4.1.2. (*R*)-[(*R*)-1-Ferrocenylbut-3-enylamino)-2-phenylethanol 1c

Yield = 91%. Red oil. $[\alpha]_D^{20} = -57.0$ (*c* 1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ 7.40–7.20 (5H, m), 5.67 (1H, m), 5.02–5.08 (2H, m), 3.95–4.15 (9H, m), 3.88 (1H, dd, J = 8.2, 4.3 Hz), 3.62–3.72 (2H, m), 3.46 (1H, t, J = 5.2 Hz), 2.43 (2H, m), 1.75 (2H, br s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 141.0, 135.1, 128.6, 127.6, 127.1, 116.8, 92.3, 68.2, 67.2, 67.0, 66.6, 66.1, 65.7, 61.1, 53.0, 39.8; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for: $C_{22}H_{26}NOFe$: 376.1364; found: 376.1374.

4.1.3. (*R*)-2-Phenyl-[(*R*)-1-(pyrydin-2-yl)but-3-enylamino]-ethanol 1b[8a]

To a solution of (*R*)-phenylglycinol-derived imine (3.43 g, 15.2 mmol) and allylbromide (2.2 mL, 25 mmol) in MeOH (65 mL) were added small amounts of In (1.6 g, 14 mmol) at rt. The reaction mixture was stirred at rt for 6 h and then a saturated aqueous solution of $NaHCO_3$ (25 mL) was added. The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in AcOEt (50 mL),

washed with H_2O (20 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude **1b** (3.54 g, 87%, dr 96:4) was diluted into CH_2Cl_2 (50 mL), then Et_3N, (2.4 mL, 17 mmol) and TBDMSCl (2.30 g, 15.2 mmol) were added successively at rt. After 6 h of stirring, water (25 mL) was added. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/AcOEt (90:10) to give OTBDMS protected **1b′** (4.37 g, 75%) as a pale yellow oil. $[\alpha]_D^{20} = +15.5$ (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.42 (1H, d, *J* = 4.1 Hz), 7.42 (1H, td, *J* = 7.7, 1.5 Hz), 7.21–7.09 (6H, m), 6.97 (1H, m), 5.68 (1H, m), 5.07 (1H, d, *J* = 17.2 Hz), 5.02 (1H, d, *J* = 10.2 Hz), 3.84 (2H, m), 3.72–3.58 (2H, m), 2.71 (1H, br s), 2.56 (2H, t, *J* = 6.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.4, 148.6, 141.2, 135.7, 134.8, 127.85, 127.80, 126.9, 122.0, 121.3, 117.8, 67.7, 63.5, 61.7, 40.1, 25.8, 18.2, −5.45, −5.50; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{21}N_2O$: 269.1654; found: 269.1649. To a solution of **1b′** (4.26 g, 11.1 mmol) in THF (30 mL) was added TBAF·H_2O (5.19 g, 16 mmol) and the resulting mixture was stirred overnight at rt. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/AcOEt (50:50) to give **1b** (2.65 g, 88%) as a pale yellow oil. $[\alpha]_D^{20} = -10.0$ (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.37 (1H, d, *J* = 4.4 Hz), 7.50 (1H, td, *J* = 7.9, 1.7 Hz), 7.10 (5H, m), 7.06 (2H, m), 5.71 (1H, ddt, *J* = 17.1, 10.0, 7.0 Hz), 5.00–5.08 (2H, m), 3.86–3.78 (2H, m), 3.74 (1H, dd, *J* = 10.6, 5.5 Hz), 3.58 (1H, dd, *J* = 10.6, 7.6 Hz), 2.93 (1H, br s), 2.56 (2H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.4, 149.0, 141.0, 136.1, 134.8, 128.3, 127.4, 127.2, 122.3, 121.8, 117.6, 66.1, 62.8, 61.3, 40.5; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{21}N_2O$: 269.1654; found: 269.1649.

4.1.4. (*R*)-*tert*-Butyl 2-(2-bromophenyl)-but-3-enylcarbamate 2a

To a solution of **1a** (1.56 g, 4.5 mmol) in a mixture of CH_2Cl_2/MeOH (1:1, 50 mL) was added in one portion $Pb(OAc)_4$ (2.18 g, 4.9 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then NH_4OH·HCl (3.2 g, 45 mmol) was added and the stirring was continued for 30 min at 0 °C, after which the solvent was removed under reduced pressure. The residue was taken up with CH_2Cl_2 (50 mL) and the solid was filtered off. To the filtrate were added Et_3N (1.25 mL) and Boc_2O (1.07 g, 4.9 mmol) and the resulting mixture was stirred at rt for 2 h. Next, H_2O (20 mL) was added, and the organic layer was washed with HCl (1 M, 10 mL), then Na_2CO_3 (10%, 10 mL) dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a mixture of PE/CH_2Cl_2 (1:1) to give the compound **2a** (880 mg, 60%) as a white solid. Mp 97 °C. $[\alpha]_D^{20} = +5.7$ (*c* 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.52 (1H, d, *J* = 8.0 Hz), 7.27 (2H, m), 7.09 (1H, m), 5.70 (1H, m), 5.17–5.10 (4H, m), 2.54 (1H, m), 2.43 (1H, m), 1.41 (9H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 154.9, 141.4, 133.5, 133.1, 128.4, 127.3, 127.1, 122.6, 118.5, 79.6, 53.4, 39.5, 28.2.

4.1.5. (*R*)-1-(2-Bromophenyl)-*N*-methylbut-3-en-1-amine 3a

To a suspension of NaH (192 mg, 8 mmol) in DMF (6 mL) was added a solution of **2a** (934 mg, 2.86 mmol) in DMF (2 mL) at 0 °C. After 1 h of stirring, MeI (0.37 mL, 5.4 mmol) was added and the resulting mixture was stirred overnight at rt. Water (10 mL) and AcOEt (15 mL) were added. The aqueous layer was extracted with AcOEt (2 × 15 mL). The organic phases were combined, washed with H_2O (5 × 5 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue (762 mg, 2.2 mmol) was diluted into CH_2Cl_2 (22 mL), then TFA (2.2 mL) was added slowly at 0 °C. After 4 h of stirring at rt, the solvent, and the excess of TFA were removed under reduced pressure. The residue was diluted into CH_2Cl_2 (25 mL) and washed with a saturated aqueous solution of Na_2CO_3 (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/AcOEt (80:20) to give **3a** (446 mg, 65%) as a yellow oil. $[\alpha]_D^{20} = +8.6$ (*c* 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.67 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.60 (1H, dd, *J* = 7.8, 1.6 Hz), 7.45 (1H, dt, *J* = 7.8, 1.3 Hz), 7.23 (1H, dt, *J* = 7.5, 1.3 Hz), 5.92 (1H, m), 5.24 (2H, m), 4.08 (1H, dd, *J* = 8.2, 4.7 Hz), 2.63 (2H, m), 2.40 (3H, s), 1.73 (1H, br s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 142.4, 135.5, 133.3, 128.7, 128.5, 128.0, 124.7, 118.3, 62.8, 41.6, 34.8; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for $C_{11}H_{15}NBr$: 240.0388; found: 240.0384.

4.1.6. (*R*)-(2-Bromophenyl)-1-methylpyrrolidine 4a

To a solution of **3a** (415 mg, 1.7 mmol) in CH_2Cl_2 (5 mL) was added $Cp_2Zr(H)Cl$ (580 mg, 2.2 mmol) in one portion at rt until complete dissolution (ca 1 h). Next, Et_3N (0.3 mL, 1.2 mmol) and I_2 (431 mg, 1.7 mmol) were added and the resulting mixture was stirred for 1 h. Then CH_2Cl_2 (10 mL) and HCl (1 M, 5 mL) were added. The organic phase was washed with HCl (1 M, 5 mL), a saturated aqueous solution of Na_2CO_3 (5 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with a mixture of PE/AcOEt (95:5) to give compound **2a** (300 mg, 72%). $[\alpha]_D^{20} = +89.8$ (*c* 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.59 (1H, dd, *J* = 7.8, 1.6 Hz), 7.50 (1H, dd, *J* = 7.8, 1.6 Hz), 7.31 (1H, t, *J* = 7.5 Hz), 7.08 (1H, t, *J* = 7.6 Hz), 3.55 (1H, t, *J* = 8.3 Hz), 3.25 (1H, t, *J* = 8.2 Hz), 2.39 (2H, m), 2.22 (3H, s), 1.87 (2H, m), 1.53 (1H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 142.2, 132.9, 128.6, 128.4, 128.1, 123.6, 69.7, 57.3, 41.1, 33.9, 23.1; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for $C_{11}H_{15}Br$: 240.0388; found: 240.0385.

4.1.7. (*R*)-1-Methyl-(2-diphenylphosphinophenyl)pyrrolidine L1

To a solution of **4a** (140 mg, 0.6 mmol) in Et_2O (5 mL) was added *n*-BuLi (2.5 M in hexanes, 0.5 mL, 1.25 mmol) at 0 °C. The resulting mixture was stirred for 2 h at rt, then a solution of PPh_2Cl (0.24 mL, 1.3 mmol) in Et_2O (2 mL) was added. The reaction mixture was stirred for 4 h at rt. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (2 × 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/AcOEt (95:5) to give **L1** (135 mg, 65%) as a white solid. $[\alpha]_D^{20} = +26.3$ (*c* 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.59 (1H, ddd, *J* = 7.7, 4.2, 1.3 Hz), 7.30–7.13 (11H, m), 7.02 (1H, td, *J* = 7.5, 1.2 Hz), 6.65 (1H, ddd *J* = 7.7, 4.3, 1.2 Hz), 3.84 (1H, q, *J* = 7.8 Hz), 3.08 (1H, td, *J* = 8.4, 1.6 Hz), 2.13 (1H, m), 1.96 (3H, s), 1.80 (2H, m), 1.60 (1H, m), 1.42 (1H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 148.7 (d, *J* = 21.6 Hz), 137.8 (d, *J* = 11.1 Hz), 137.5 (d, *J* = 10.3 Hz), 136.1 (d, *J* = 13.6 Hz), 134.7, 134.5, 134.4, 134.2, 133.6, 129.9, 129.1, 129.0, 128.9, 127.2, 68.4 (d, *J* = 23.5 Hz), 57.2, 40.7, 35.3, 23.2; ^{31}P{^{1}H} (101.2 MHz, $CDCl_3$): δ −15.9; HRMS-ESI: *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{25}NP$: 346.1725; found: 346.1717.

4.1.8. (*R*)-1-(Pyridin-2-yl)but-3-enamine 2b

To a solution of homoallylic amine **1b** (2.61 g, 9.7 mmol) in a mixture of CH_2Cl_2/MeOH (1:1, 70 mL) was added in one portion $Pb(OAc)_4$ (5.00 g, 4.9 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min, then NH_4OH·HCl (6.75 g, 97 mmol) was added, and the stirring was continued for 30 min at 0 °C, after which the solvent was removed under reduced pressure. The residue was taken up with CH_2Cl_2 (50 mL), and the solid was filtered off. The filtrate was washed with Na_2CO_3 (10%, 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with a mixture of AcOEt/MeOH (9:1) to give **2b** (1.28 g, 90%) as a

yellow oil. $[\alpha]_D^{20} = +47.3$ (c 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.56 (1H, d, J = 6.2 Hz), 7.64 (1H, td, J = 7.8, 1.7 Hz), 7.14 (1H, dd, J = 6.2, 4.9 Hz), 5.77 (1H, dddd, J = 18.5, 10.7, 7.8, 6.6 Hz), 5.10 (1H, d, J = 18.5 Hz), 5.08 (1H, d, J = 10.7 Hz), 4.04 (1H, dd, J = 7.9, 5.3 Hz), 2.59 (1H, dt, J = 13.7, 6.4 Hz), 2.39 (1H, dt, J = 13.7, 7.9 Hz), 1.81 (2H, br s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.9, 148.9, 136.2, 135.0, 121.7, 120.7, 117.6, 56.3, 43.1; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_9H_{13}N_2$: 149.1079; found: 149.1082.

4.1.9. 2-[(*R*)-Pyrrolidin-2-yl]pyridine 3b

To a solution of **2b** (1.28 g, 8.6 mmol) and Et_3N (1.3 mL) in CH_2Cl_2 (20 mL) was added TrCl (2.4 g, 8.6 mmol). The reaction mixture was stirred for 12 h at rt. Water (5 mL) was added and the organic layer was washed with $NaHCO_3$ (10%, 5 mL), dried over $MgSO_4$, and concentrated under vacuum to give the protected amine which was used in the next step without purification. To a solution of the crude amine (3.36 g, 8.6 mmol) in CH_2Cl_2 (30 mL) was added $Cp_2Zr(H)Cl$ (2.45 g, 9.5 mmol) in two portions and the reaction mixture was stirred until complete dissolution (ca 1 h). Next, Et_3N (1.35 mL) and I_2 (2.18 g, 8.6 mmol) were successively added and the stirring was continued for 4 h. Water (10 mL) was added and the heterogeneous mixture was vigorously stirred for 1 h. The organic phase was extracted with water (3 × 10 mL). The aqueous phases were combined and concentrated to 10 mL, saturated with Na_2SO_4, then extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum to give **3b** (0.89 g, 69%). $[\alpha]_D^{20} = +78.4$ (c 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.52 (1H, d, J = 4.2 Hz), 7.64 (1H, td, J = 7.8, 1.6 Hz), 7.34 (1H, d, J = 7.8 Hz), 7.15 (1H, dd, J = 6.7, 6.2 Hz), 4.30 (1H, t, J = 7.1 Hz), 3.70 (1H, br s), 3.20 (1H, dt, J = 10.5, 6.5 Hz), 3.02 (1H, dt, J = 10.5, 7.2 Hz), 2.25 (1H, m), 1.93–1.73 (3H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.2, 148.9, 136.5, 122.0, 121.5, 63.2, 47.0, 33.7, 25.8. $[\alpha]_D^{20} = +78$ (c 1, CH_2Cl_2). HRMS-ESI: m/z $[M+H]^+$ calcd for $C_9H_{13}N_2$: 149.1079; found: 149.1080.

4.1.10. 2-[(*R*)-1-(Diphenylphosphinoborane)pyrrolidin-2-yl]pyridine L2·BH$_3$

To a solution of **3b** (0.88 g, 5.9 mmol) and Et_3N (0.89 ml, 6.5 mmol) in THF (20 mL) was added PPh_2Cl (1.13 mL, 5.9 mmol) at 0 °C and the resulting solution was stirred for 4 h at rt. The solid was filtered off under Ar. To the filtrate was added a solution of $BH_3{\cdot}SMe_2$ (2 M in THF, 3 mL, 6 mmol) and the reaction mixture was stirred for 2 h at rt, after which water (10 mL) was added. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude material was diluted into CH_2Cl_2 (20 mL), then DABCO (662 mg, 5.9 mmol) was added. The solution was stirred overnight at rt. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/AE (9:1) to give **L2·BH$_3$**. (1.27 g, 62%) as a white solid. Mp 82 °C; $[\alpha]_D^{20} = +81.0$ (c 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.16–1.60 (3H, br m), 1.90 (2H, m), 2.06 (1H, m), 2.39 (1H, dq, J = 11.3, 8.4 Hz), 3.37 (1H, m), 3.52 (1H, m), 5.07 (1H, ddd, J = 8.6, 6.2, 2.3 Hz), 7.01 (1H, dd, J = 6.8, 5.4 Hz), 7.09 (1H, d, J = 7.8 Hz), 7.29–7.68 (11H, m), 8.42 (1H, d, J = 4.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 24.7 (d, J = 5.3 Hz), 34.8 (d, J = 5.2 Hz), 49.3, 64.9 (d, J = 4.6 Hz), 132.0 (d, J = 10.3 Hz), 128.1 (d, J = 9.8 Hz), 128.3 (d, J = 9.5 Hz), 129.1 (d, J = 23.2 Hz), 130.9, 132.3 (d, J = 10.4 Hz), 135.8, 148.6, 163.8; ^{31}P NMR {^{1}H} (101.2 MHz, $CDCl_3$): δ 56.4; HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{21}H_{24}BN_2PNa$: 369.1668; found: 369.1663.

4.1.11. (*R*)-2-Phenyl-2-[(*R*)-2-ferrocenylpyrrolidin-1-yl]ethanol 2c

To a solution of **1c** (1.67 g, 4.5 mmol) in CH_2Cl_2 (15 mL) under an atmosphere of argon, was added $Cp_2Zr(H)Cl$ (2.42 g, 9.38 mmol) in one portion and the resulting mixture was stirred until complete dissolution. Then Et_3N (0.68 mL, 4.9 mmol) and I_2 (1.14 g, 4.5 mmol) were added and the reaction mixture was stirred for 2 h. Next, CH_2Cl_2 (10 mL) was added and the organic phase was washed with HCl (1 M, 2 × 3 mL), Na_2CO_3 (10%, 2 × 3 mL) dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a mixture of PE/AcOEt (80:20) to give **2c** (1.4 g, 83%) as a red oil. $[\alpha]_D^{20} = +14.0$ (c 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.75 (2H, m), 2.20 (2H, q, J = 6.9 Hz), 2.50 (1H, br s), 2.68 (2H, t, J = 6.8 Hz), 3.60–3.65 (3H, m), 3.74 (1H, t, J = 6.1 Hz), 3.96–4.12 (9H, m), 7.05–7.25 (5H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 23.0, 33.0, 50.6, 57.9, 62.7, 64.8, 66.7, 66.8, 68.2, 68.4, 69.4, 89.8, 127.2, 128.0, 128.7, 139.2; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{22}H_{26}NOFe$: 376.1364; found: 376.1358.

4.1.12. (2*R*)-Pyrrolidin-2-ylferrocene 3c

A mixture of **2c** (2.96 g, 7.89 mmol) and $Pd(OH)_2/C$ (20%, 500 mg) in MeOH (80 mL) was stirred under an atmosphere of H_2 at rt for 8 h. The reaction mixture was filtered through a pad of Celite and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with a gradient of AcOEt→AcOEt/Et_2NH (98:2) to give **3c** as a red oil (1.9 g, 99%). $[\alpha]_D^{20} = +28.5$ (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.69–2.00 (3H, m), 2.09–2.26 (1H, m), 2.77–2.95 (1H, m), 3.04–3.21 (1H, m), 3.84 (1H, t, J = 7.3 Hz), 4.10–4.26 (9H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 23.5, 30.9, 44.5, 57.4, 66.9, 67.2, 67.3, 67.4, 67.6, 80.0; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{14}H_{18}NFe$: 256.0723; found: 256.0720.

4.1.13. (*R*)-1-[2-(Diphenylphosphino)benzyl-2-ferrocenylpyrrolidine L4

To a solution of **3c** (375 mg, 1.7 mmol) and 2-diphenylphosphonobenzaldehyde (485 mg, 1.67 mmol) in DCE (10 mL) was added $NaBH(OAc)_3$ (550 mg, 2.64 mmol). After 18 h of stirring, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/AcOEt (95:5) to give **L4** (628 mg, 71%) as a yellow foam. $[\alpha]_D^{20} = +81.1$ (c 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.89 (2H, m), 2.11 (3H, app q, J = 8.1 Hz), 2.58 (1H, td, J = 8.3, 4.6 Hz), 3.36 (1H, t, J = 7.1 Hz), 3.62 (1H, dd, J = 13.4, 2.6 Hz), 3.74 (1H, d, J = 13.6 Hz), 4.01–4.10 (9H, m), 6.81 (1H, dd, J = 6.8, 4.2 Hz), 7.09 (1H, t, J = 7.3 Hz), 7.18–7.31 (12H, m), 7.38 (1H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 22.4, 31.8, 52.4, 55.8 (d, J = 18.5 Hz), 62.6, 66.4, 67.0, 67.9, 68.3, 69.8, 88.7, 126.6 (2C), 128.5 (2C), 128.7 (d, J = 5.3 Hz), 133.65 (d, J = 19.8 Hz), 133.70 (d, J = 19.8 Hz), 134.0 (2C), 134.2, 135.8 (d, J = 14.7 Hz), 137.7 (d, J = 10.5 Hz), 137.9 (d, J = 10.5 Hz), 145.0 (d, J = 22.8 Hz); ^{31}P{^{1}H} (101.2 MHz, $CDCl_3$): δ −15.5; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{33}H_{33}FeNP$: 530.1700; found: 530.1696.

4.1.14. *N*-Methyl-(2*R*)-pyrrolidin-2-ylferrocene 4c

To a solution of **3c** (538 mg, 2.1 mmol) in MeOH (10 mL) was added formaldehyde (37% in water, 4.7 mL, 63 mmol). The resulting mixture was stirred for 30 min, then $NaBH_4$ (800 mg, 21 mmol) was added in small portions at 0 °C, and the stirring was continued for 3 h at rt. Next, CH_2Cl_2 (40 mL) was added after which H_2O (10 mL) was successively added. The organic phase was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with AcOEt to give **4c** (519 mg, 92%) as a red oil. $[\alpha]_D^{20} = +89.2$ (c 1, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.69–1.98 (2H, m), 1.98–2.13 (1H, m), 2.17 (3H, s), 2.19–2.34 (2H, m), 2.89 (1H, t, J = 8.1 Hz), 3.03–3.14 (1H, m), 4.02–4.26 (9H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 88.4, 70.2, 68.82, 68.79, 67.7, 66.2, 65.9,

57.9, 40.4, 32.5, 22.8; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{22}H_{26}NOFe$: 270.0951; found: 270.0942.

4.2. General method for functionalisation of 4c

To a solution of **4c** (269 mg, 1 mmol) in Et_2O (3 mL) was added dropwise *sec*-butyllithium (1.3 M in hexanes, 1.15 mL) at −78 °C under Ar. The reaction mixture was stirred for 3 h at −78 °C, then 1 h at 0 °C. The electrophilic reagent was added (1.5 mmol) and the stirring was maintained for 1 h at rt before adding a saturated aqueous solution of $NaHCO_3$ (3 mL). The aqueous layer was extracted with Et_2O (2 × 3 mL), and the organic phases were combined, dried over Na_2SO_4 filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/AcOEt.

4.2.1. 2-[(2*R*)-*N*-Methylpyrrolidin-2-yl]-(1p*R*)-phenylthiolferrocene L4

Yield = 71%, yellow oil; $[\alpha]_D^{20} + 211.9$ (c 1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ 1.14–1.35 (1H, m), 1.40–1.74 (2H, m), 1.76–1.95 (1H, m), 2.24 (1H, dd, J = 17.7, 9.2 Hz), 2.66 (3H, s), 3.03–3.15 (1H, m), 3.28 (1H, t, J = 8.2 Hz), 4.21 (5H, s), 4.32 (1H, t, J = 2.4 Hz), 4.40–4.47 (2H, m), 6.97–7.19 (5H, m); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 22.1, 34.9, 42.4, 57.9, 64.2, 67.6, 67.9, 70.3, 72.0, 75.7, 94.9, 124.4, 125.3, 128.3,140.8; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{21}H_{24}FeNS$: 378.0979; found: 378.0980.

4.2.2. 2-[(2*R*)-*N*-Methylpyrrolidin-2-yl]-(1p*R*)-diethylphosphiteferrocene L5

Yield = 62%, yellow oil; $[\alpha]_D^{20} = +222.3$ (c 1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ 1.14 (3H, t, J = 7.0 Hz), 1.38 (3H, t, J = 7.0 Hz), 1.49–1.88 (3H, m), 2.10–2.36 (2H, m), 2.57 (3H, s), 3.14 (1H, t, J = 7.6 Hz), 3.25 (1H, t, J = 8.0 Hz), 3.44–3.61 (1H, m), 3.69–3.87 (1H, m), 3.96–4.11 (2H, m), 4.18 (5H, s), 4.29 (1H, t, J = 2.3 Hz), 4.37 (1H, m), 4.49 (1H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 17.2 (d, J = 3.5 Hz), 17.9 (d, J = 6.6 Hz), 22.6, 36.8 (d, J = 4.7 Hz), 42.5, 58.5, 59.8, 64.5 (d, J = 21.9 Hz), 64.8 (d, J = 5.0 Hz), 68.4, 69.5 (d, J = 4.3 Hz), 69.9 (2C), 75.5 (d, J = 20.9 Hz), 96.4 (d, J = 22.4 Hz); ^{31}P NMR $\{^1H\}$ (101.2 MHz, $CDCl_3$): δ 155.4; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{19}H_{28}FeNO_2P$: 390.1285; found: 390.1290.

4.2.3. 2-[(2*R*)-*N*-Methylpyrrolidin-2-yl]-(1p*R*)-diphenylphosphinoferrocene L6

Yield = 67%, yellow solid, mp 108–112 °C; $[\alpha]_D^{20} = +255.5$ (c 1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ 1.48–1.83 (4H, m), 2.22 (1H, q, J = 8.1 Hz), 2.51 (3H, s), 3.03 (1H, t, J = 7.6 Hz), 3.30 (1H, t, J = 7.7 Hz), 3.89 (1H, s), 3.96 (5H, s), 4.30 (1H, s), 4.46 (1H, s), 7.18–7.22 (5H, m), 7.37 (3H, m), 7.57 (2H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 22.4, 36.0 (d, J = 6.0 Hz), 42.2, 58.0, 64.7 (d, J = 5.2 Hz), 68.5, 69.5 (d, J = 8.9 Hz), 69.6 (2C), 71.2 (d, J = 4.7 Hz), 97.5 (d, J = 22.9 Hz), 127.6 (d, J = 8.2 Hz), 127.7, 127.9 (d, J = 7.9 Hz), 129.0, 132.5 (d, J = 18.2 Hz), 135.3 (d, J = 21.7 Hz), 138.1 (d, J = 8.5 Hz), 140.5 (d, J = 8.5 Hz); ^{31}P NMR $\{^1H\}$ (101.2 MHz, $CDCl_3$): δ −23.5; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{27}H_{29}NPFe$: 454.1387; found: 454.1386.

4.2.4. 2-[(2*R*)-*N*-Methylpyrrolidin-2-yl]-(1p*R*)-trimethylsilylferrocene 5c

Prepared according to the above procedure. 83%, yellow oil; $[\alpha]_D^{20} = +89.0$ (c 0.4, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ 0.25 (9H, s), 1.29–1.49 (1H, m), 1.51–1.85 (2H, m), 1.98–2.15 (1H, m), 2.24 (1H, dd, J = 17.6, 9.3 Hz), 2.64 (3H, s), 2.99–3.20 (2H, m), 4.01 (1H, dd, J = 2.1, 1.3 Hz), 4.04–4.11 (5H, m), 4.25 (1H, t, J = 2.2 Hz), 4.41 (1H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 0.7, 22.3, 36.8, 42.6, 58.2, 65.2, 67.8, 68.7, 68.8, 68.9, 73.7, 97.7; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{18}H_{28}NFeSi$: 342.1340; found: 342.1346.

4.2.5. 2-[(2*R*)-*N*-Methylpyrrolidin-2′-yl]-(1p*S*)-diphenylphosphinoferrocene L7

To a solution of **5c** (121 mg, 0.35 mmol) in Et_2O (1.3 mL) was added dropwise *sec*-butyllithium (1.3 M in hexanes, 0.48 mL) at −78 °C under Ar. The reaction mixture was stirred for 3h at −78 °C, then 1h at 0 °C. PPh_2Cl (100 μL, 0.52 mmol) was added and the stirring was maintained for 1h at rt before adding a saturated aqueous solution of $NaHCO_3$ (3 mL). The aqueous layer was extracted with Et_2O (2 × 3 mL), the organic phases were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel eluting with a mixture of PE/Et_2O (98:2) to give 2-[(2R)-*N*-Methylpyrrolidin-2′-yl]-3-trimethylsilyl-(1p*S*)-diphenylphosphinoferrocene (89 mg, 82%) to which was added TBAF (1M IN THF, 4 mL). The resulting mixture was heated to reflux for 3 days. Water (4 mL) was then added. The aqueous layer was extracted with AcOEt (2 × 4 mL), and the organic phases were combined, washed with 6 mL of brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using a mixture of AcOEt/Et_2NH (98:2) to give **L7** (34 mg, 44%) as a red oil. $[\alpha]_D^{20} = -339.0$ (c 0.6, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): δ 1.78–2.01 (2H, m), 2.20 (2H, m), 2.34–2.54 (1H, m), 2.97–3.17 (1H, m), 3.36 (1H, dt, J = 8.3, 3.5 Hz), 3.92 (5H, s), 4.00 (1H, m), 4.40 (1H, t, J = 2.3 Hz), 4.57 (1H, m), 7.18–7.42 (8H, m), 7.56–7.67 (2H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 22.5, 35.4, 40.3, 57.7, 63.2 (d, J = 10.0 Hz), 69.3 (d, J = 4.3 Hz), 69.4, 70.2, 70.8 (d, J = 4.6 Hz), 75.2 (d, J = 9.1 Hz), 127.8, 127.9, 128.0, 129.0, 132.7 (d, J = 18.7 Hz), 135.2 (d, J = 22.1 Hz), 138.0 (d, J = 8.1 Hz), 139.8 (d, J = 8.3 Hz), 1C is missing; ^{31}P NMR $\{^1H\}$ (101.2 MHz, $CDCl_3$): δ −25.9; HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{27}H_{29}NPFe$: 454.1387; found: 454.139.

Acknowledgments

Financial support of this work by CNRS and the Ministère de l'Enseignement Supérieur et de la Recherche is gratefully acknowledged.

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