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# The synthesis of new planar chiral heterobidentate chelate ligands for asymmetric catalysis

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**Abstract**—A series of new heterobidentate N,S; N,O and N,P chelate ligands have been synthesised where the sole source of chirality is derived from a planar chiral ferrocene unit and have been shown to give up to 79% ee (*R*) in the palladium catalysed allylic substitution reaction, suggesting that they may be suitable in other palladium catalysed processes.


## 1. Introduction

As part of an ongoing research programme into new chiral ligands for asymmetric catalysis,[1] we have synthesised and investigated some new heterobidentate chelate ligands where the sole source of chirality is derived from a planar chiral ferrocene unit.[2,3] Planar chiral ferrocene ligands[4] have been shown to be efficient stereocontrol elements in many metal centred asymmetric catalytic reactions due to their stability, ease of introduction of planar chirality and interesting electronic properties of the ferrocene unit.[5] Most ferrocene ligands contain both planar and central or axial chirality. Investigations of these ligands have shown that the planar chirality can reinforce chiral induction,[6] but in other systems has a negligible effect,[7] leaving the remaining chiral element (centre or axis of chirality) to dictate stereocontrol. We have been interested in synthesising new heterobidentate chelate ligands based on ferrocene that possess only planar chirality in order to develop simple and efficient ligand systems.[8] Herein we report the synthesis of some new planar chiral heterobidentate chelate ligands and our investigations using the popular test reaction involving the palladium catalysed substitution of 1,3-diphenyl-2-propenyl acetate with dimethylmalonate.[9]

## 2. Results and discussion

In our previous work concerning the synthesis of planar chiral ferrocenyl 1,3-diamines and 1,3-amino ethers, we found that the conventional planar chiral ferrocene building block *N*,*N*-dimethyl-1-ferrocenyl ethylamine introduced by Ugi and co-workers[5a,10] was unsuitable for the introduction of *O* and *N* functionality directly onto the cyclopentadienyl ring.[8] The directed *ortho* metallation route from *N*,*N*-diisopropyl ferrocenecarboxamide with *n*-BuLi and TMEDA or (−)-sparteine developed by Sniekus and co-workers was the most convenient route to synthesis novel combinations of N, O, S and P heterobidentate ferrocenyl ligands for this study.[5c,g] Herein racemic ligands were synthesised with the view that only those that showed some catalytic efficiency would then be prepared enantiomerically pure.

Treatment of *N*,*N*-diisopropyl ferrocenecarboxamide **1** with *n*-BuLi and TMEDA and quenching with various electrophiles led to *ortho*-substituted products **2a**,**c** and **d** in high yield in accord with the literature (Scheme 1).[5g] Quenching with dimethyldisulfide led to the novel sulfide **2b** in 97% yield. Amides **2a**–**c** were converted into potential N,S (**3a** and **b**) and N,P (**3c**) chelate ligands by reduction of the amide with $LiAlH_4$. Introduction of an oxygen substituent was carried out from the iodide **2d** according to our published procedure[8] and subsequent reduction gave the potential N,O-chelate ligand **3d**. We have also shown that iodide **2d** can be used to introduce a primary amine.[8] Unfortunately reduction of this compound with $LiAlH_4$ to give the corresponding potential N,N-chelate ligand was thwarted by our inability to purify the diamine satisfactorily.

Several literature reports have documented the poor chelating ability of the diisopropylamine group.[11] In

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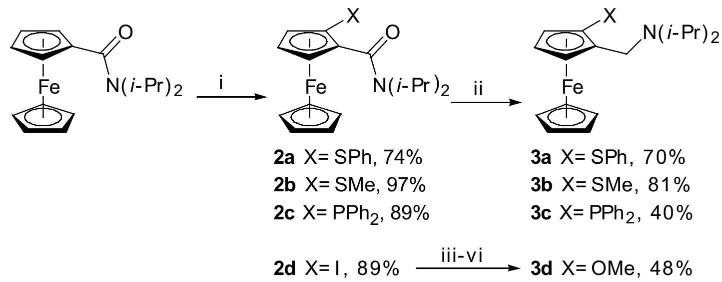
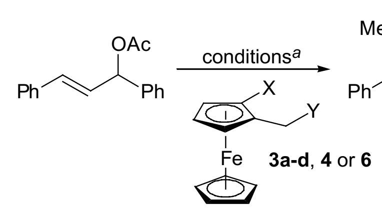



**Scheme 1.** Reagents and conditions: (i) *n*-BuLi, TMEDA, $Et_2O$,–78 °C; **2a** $S_2Ph_2$, **2b** $S_2Me_2$, **2c** $ClPPh_2$, **2d** $I_2$; (ii) $LiAlH_4$, $Et_2O$, 35 °C, 14 h; (iii) AcOH, $Cu_2O$, MeCN, 85%; (iv) aq NaOH, EtOH, 88%; (v) NaH, MeI, THF, 80%; (vi) $LiAlH_4$, $Et_2O$, 35 °C, 14 h, 81%.

order to maximise the ability of our heterobidentate ligands to coordinate effectively, we attempted to exchange the diisopropylamine group for a dimethylamine group (Scheme 2). Standard quaternisation of the diisopropylamine of **3d** with MeI followed by treatment with dimethylamine gave ligand **4**.[12] This method proved unsuccessful with the more nucleophilic S and P *ortho*-substituted diisopropylamines **3a–c**. However amines **3a** and **b** could be treated with acetic anhydride to give acetates **5a** and **b** in high yield,[12] but only the *ortho*-SMe acetate gave the desired amine **6** upon treatment with dimethylamine in 35% yield. Formation of acetate **5a** took four times longer than for **5b** which indicated steric hindrance from the thiophenyl group. We therefore assume the failure of the subsequent substitution reaction of **5a** with dimethylamine to be due to steric hindrance. The dimethylamine analogue of **3c** could not be prepared by these routes, although it has been prepared in enantiomerically pure form by resolution.[13]

The novel racemic ligands **3a–d**, **4** and **6** were tested against $PPh_3$ in the standard palladium catalysed substitution of 1,3-diphenyl-2-propenyl acetate with the nucleophile derived from the reaction of dimethylmalonate and *N*,*O*-bis-trimethylsilyl)acetamide (BSA) and potassium acetate (Eq. 1), to see which did not impede the reaction.[14] Only N,S-chelate ligands **3b** and **6** and N,P-chelate ligand **3c** were effective ligands for this reaction (Table 1). Of these three ligands only the N,P-chelate system had a similar relative rate to $PPh_3$ (compare entries 1 and 7). The failure of the *ortho*-SPh ligand system could be due to the sulfur lone pair being conjugated with both a cyclopentadienyl and phenyl ring.

**Table 1.** Efficiency of planar chiral ligands in Eq. 1[a]

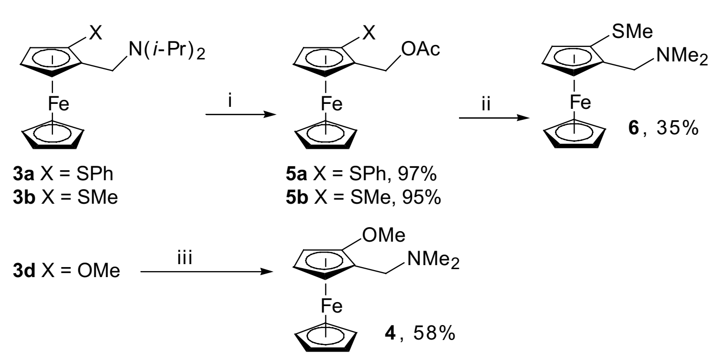



(1)

| Entry | Ligand | X | Y | Yield (%)[b] | Time (h) | Ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | $PPh_3$ | — | — | 86 | 2.5 | — |
| 2 | **3a** | SPh | N(*i*-Pr)$_2$ | — | — | — |
| 3 | **3b** | SMe | N(*i*-Pr)$_2$ | 81 | 48 | 1.3[d] |
| 4 | **6** | SMe | $NMe_2$ | 84 | 18 | 59[e] |
| 5 | **3d** | OMe | N(*i*-Pr)$_2$ | — | — | — |
| 6 | **4** | OMe | $NMe_2$ | — | — | — |
| 7 | **3c** | $PPh_2$ | N(*i*-Pr)$_2$ | 89 | 3 | 79[f] |

[a] Reagents and conditions: 1.0 mmol scale in $CH_2Cl_2$ at rt, allylic acetate (1 equiv), dimethylmalonate (3 equiv), BSA (3 equiv), KOAc (3 mol%), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), ligand (5 mol%).
[b] Isolated yield.
[c] Determined by HPLC on a Chiralcel OD–H column.[17]
[d] Reaction using (*R*)-**3b**.
[e] Reaction using (*R*)-**6**.
[f] Reaction using (*R*)-**3c**.

The *ortho*-SMe ligand, possessing a diisopropylamine donor group **3b**, was much slower than the corresponding dimethylamine ligand **6**. Either extra steric hindrance from the diisopropylamine group retards the reaction or ligand **6** gives a more efficient reaction due to an enhanced ability to chelate the palladium catalyst.




**Scheme 2.** Reagents and conditions: (i) $Ac_2O$, 80 °C; (ii) $HNMe_2$, MeOH, rt; (iii) MeI, MeCN, $HNMe_2$, rt.