Competition between planar and central chiral control elements in nucleophilic addition to ferrocenyl imine derivatives†

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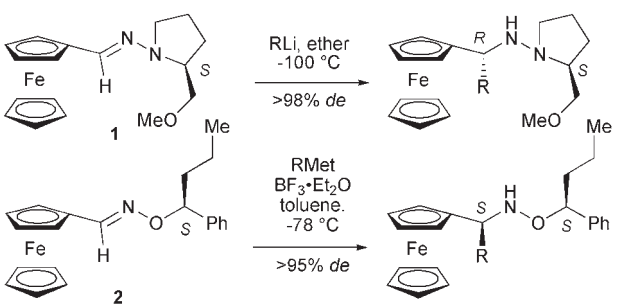
Planar chirality associated with the ferrocene in ferrocenyl oximes and hydrazones bearing chiral auxiliaries effectively competes with or overrides the normally excellent stereocontrol afforded by the auxiliary in determining the diastereoselectivity of addition to the C═N bond.

Chiral ferrocene derivatives, particularly α-ferrocenyl alkylamines, are useful ligands in asymmetric catalysis.[1–6] Most routes to such enantiopure α-ferrocenylalkylamines are either based on chiral ferrocenylalkanols,[7] or on nucleophilic addition to ferrocenyl imine derivatives, FcCH═NR (Scheme 1). For example, addition of organolithium reagents to Enders' SAMP-hydrazone **1** proceeds with excellent stereocontrol to give (*R*)-ferrocenylalkylamine derivatives in good yield,[8,9] whilst our own efforts in this field have centred on the use of chiral oxime ethers,[10] and addition of organolithium or Grignard reagents to the ferrocenyl oxime **2** in the presence of boron trifluoride etherate proceeds with excellent stereocontrol.[11,12] In these and other examples,[13–16] the auxiliary is readily cleaved to give the desired α-ferrocenylalkylamines.

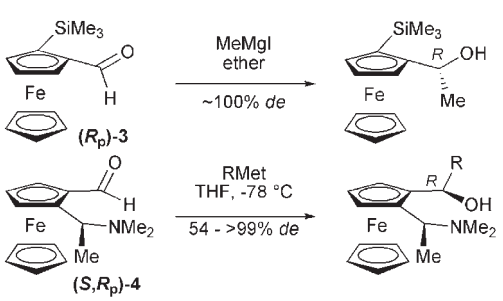
In recent years, attention has turned to ferrocene derivatives that also possess planar chirality, since ligands based on these systems have proved particularly effective in asymmetric catalysis.[1,2,17] The traditional route to such compounds is to use an enantioselective *ortho*-metallation of the Cp-ring.[18] Thus one can start with enantiopure *N*,*N*-dimethylamino ethylferrocene, the so-called Ugi amine, and introduce a second substituent onto the same Cp-ring using directed lithiation.[19] More recently, methods have been developed that start from an achiral ferrocene, and use a sparteine-mediated *ortho*-lithiation to access planar chiral ferrocenes.[20–22] However, an alternative mode of access to such compounds involves exploiting the planar chirality to generate the α-ferrocenyl stereocentre. Originally investigated by Ugi and co-workers, this approach has been relatively little used. Thus in early work, Ugi showed that addition of methylmagnesium iodide to the (S_p)-ferrocene aldehyde **3** was stereospecific (Scheme 2).[23] The reaction has subsequently been investigated by Kagan and co-workers using a wider range of planar chiral ferrocene aldehydes,[24] and by Richards and co-workers,[25] and has been used in the synthesis of novel ferrocenyl ligands.[26] Recently allylzinc reagents have been added to similar planar chiral ferrocene derivatives.[27] In related work, Fukuzawa and co-workers have investigated the addition of organometallic reagents to ferrocene aldehydes that possess both planar and central chirality. Thus, ferrocenyl aldehyde **4** undergoes stereoselective addition of a range of organometallic reagents resulting in formation of a series of (*R*)-alcohols (Scheme 2).[28–31]



Scheme 1

All of the above reactions of planar chiral ferrocene derivatives involve additions to aldehydes, and there appear to be very few reports of corresponding addition to ferrocenyl imine derivatives (*cf.* Scheme 1).[32,33] Therefore in continuation of our interest in enantiopure α-ferrocenylalkylamine derived ureas as chiral receptors for carboxylate binding,[11,12] we have investigated the addition of organometallic reagents to ferrocenyl oximes and hydrazones that possess both planar chirality and a chiral control element on the C═N nitrogen.

In the light of previous results using ferrocenyl ureas as potential enantioselective receptors for chiral carboxylates,[11,12] we were interested in ureas that displayed both central and planar chirality, and how the interplay between the two elements of asymmetry in the diastereomers affected their binding to chiral carboxylates. Therefore we sought to use our chiral oxime ether



Scheme 2

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methodology (ROPHy/SOPHy)[10] to prepare such substrates starting from the known (R_p)-2-methylferrocenecarbaldehyde.[34]

Formation of the (*R*)-oxime ether **5** was followed by addition of benzylmagnesium chloride in the presence of boron trifluoride etherate to give the expected addition product, the hydroxylamine **6a** as a single diastereoisomer in 57% yield after chromatography. Cleavage of the N–O bond gave the corresponding amine that, without purification, was reacted with 4-nitrophenyl isothiocyanate to give the crystalline thiourea **7a** (66% over two steps). Repeating the reaction without isolation and purification of the intermediate hydroxylamine **6a** gave the same thiourea **7a** in 55% yield over the three steps, and with a dr of >97 : 3 as determined by NMR analysis of the thiourea before purification. On the basis of previous work,[10–12] nucleophilic addition of benzylmagnesium chloride to an (*R*)-oxime ether was expected to lead to a hydroxylamine with (*R*)-stereochemistry at the new centre. The absolute configuration of the new stereocentre in thiourea **7a** was established crystallographically by refinement of an absolute structure parameter.[35] Hence, crystallography showed clearly that the new stereocentre in thiourea **7a** has the (*S*)-configuration (Fig. 1a), suggesting that the ferrocene chirality completely overrides the normally excellent stereocontrol exerted by the oxime chiral auxiliary. Unsurprisingly, use of the (*S*)-oxime ether **8** also results in formation of the (*S*)-thiourea **7a** (33% over three steps without purification of hydroxylamine **9**), after cleavage of the N–O bond and reaction with 4-nitrophenyl isothiocyanate, since both stereocontrol elements now reinforce each other. The stereocontrol exerted by the ferrocene extends to the achiral *O*-benzyl oxime **10** that again leads to the (*S*)-thiourea **7a** (67% over three steps without purification of hydroxylamine **11**) (Scheme 3). The sequence of reactions was repeated with *n*-butyllithium as nucleophile with similar results, as summarised in Scheme 3, although the reduced diastereoselectivity (as determined by NMR analysis of the crude thiourea product) in the addition to the (*R*)-oxime implies that the control exerted by the chiral auxiliary is not totally overridden in this case.

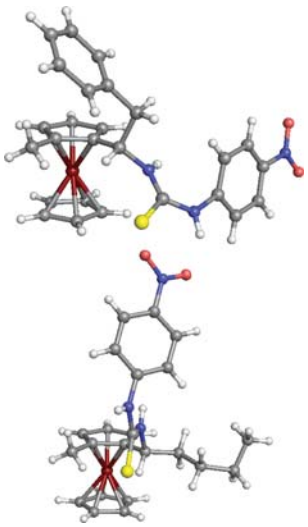
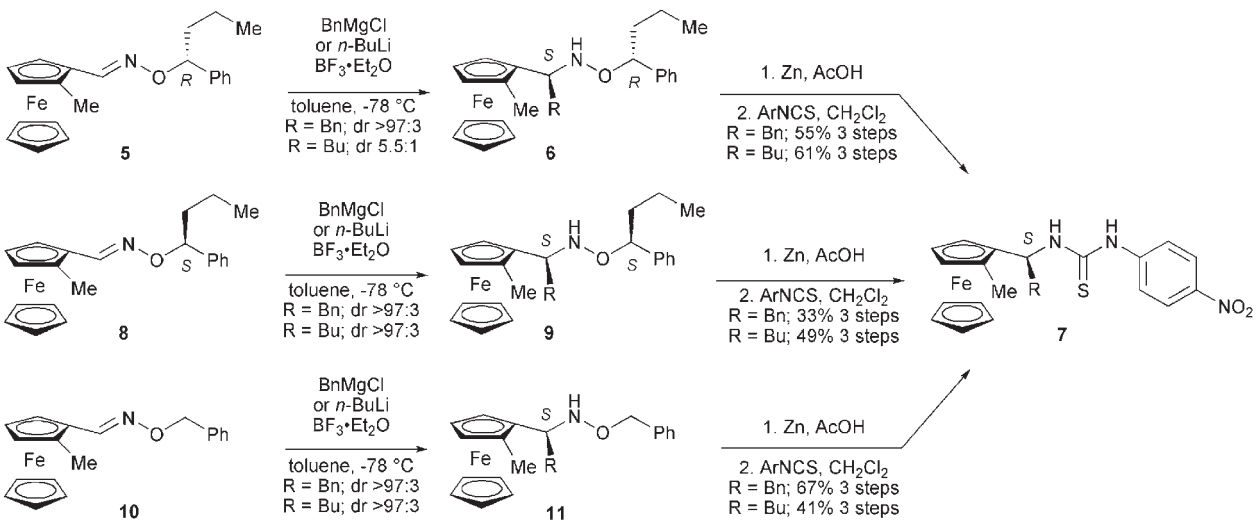


Fig. 1 (a) (Top) X-ray crystal structure of ferrocenyl thiourea **7a**; (b) (bottom) X-ray crystal structure of ferrocenyl thiourea **14**.

With the failure to obtain both diastereoisomers of the desired ferrocenyl ureas using the ROPHy/SOPHy oxime ether methodology, we turned to the Enders RAMP/SAMP hydrazone protocol. These chiral auxiliaries normally provide excellent stereocontrol, not only in ferrocene derivatives,[8,9] but also in a range of other situations.[36] Therefore the SAMP and RAMP hydrazones **12** and **15** of (R_p)-2-methylferrocenecarbaldehyde were prepared along with the hydrazone **17** derived from 1-aminopyrrolidine. In the absence of the element of planar chirality, the SAMP-hydrazone of ferrocenecarbaldehyde undergoes addition of *n*-butyllithium in >98% de, with the new centre having the (*R*)-configuration.[8,9] However, in the present case, the SAMP hydrazone **12** results in poor stereocontrol (dr = 2.1 : 1 determined on the crude thiourea product), although the major isomer of the thiourea **14**, formed by addition of *n*-butyllithium and, without purification of the intermediate hydrazine **13**, cleavage of the N–N bond and reaction with 4-nitrophenyl isothiocyanate, has the (*R*)-configuration, implying that the hydrazone auxiliary performs somewhat better than the oxime-based auxiliary in controlling addition to the C=N bond. Again, the absolute configuration of the new stereocentre in thiourea **14** was established crystallographically (Fig. 1b) by refinement of an absolute structure parameter.[37] When the RAMP hydrazone



Scheme 3 **a**, R = CH_2Ph; **b**, R = *n*-Bu.

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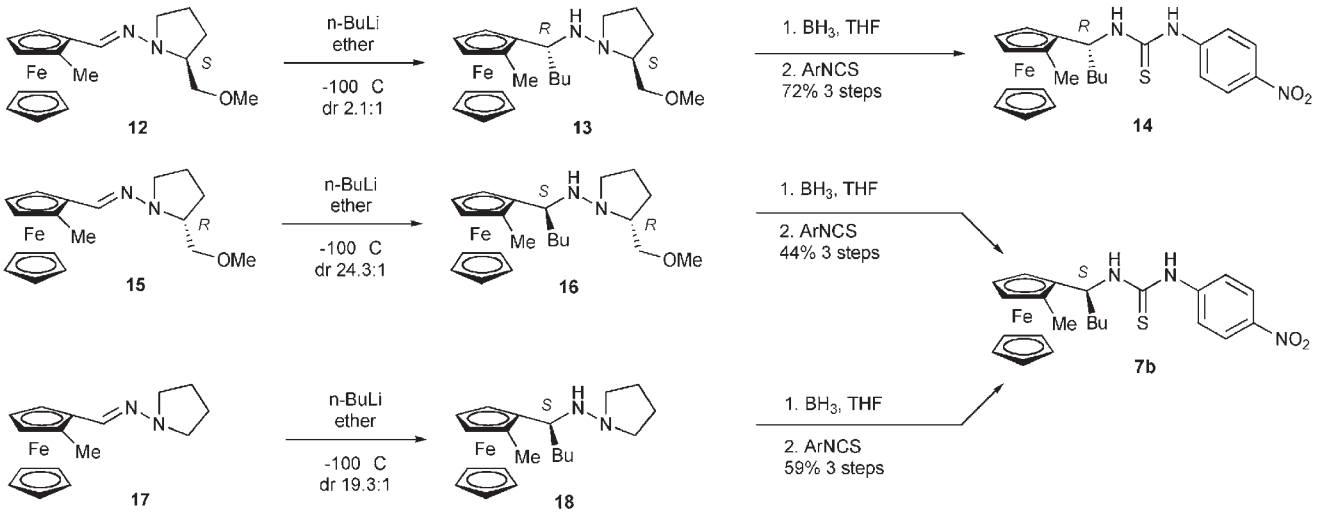

Scheme 4

15 and the achiral hydrazone **17** were used, after cleavage of the N–N bond and reaction with the isothiocyanate, the product thiourea **7b** was formed as the (*S*)-stereoisomer (dr = 24.3 : 1 and 19.3 : 1, respectively as determined on the thiourea before purification) (Scheme 4).

In all cases except the SAMP hydrazone **12**, the major diastereoisomer has the (*S*)-configuration at the newly generated stereocentre, and results from attack on the top face of the C=N bond oriented to minimise steric repulsions. Only in the case of **12** can the chiral auxiliary overcome this preference.

In conclusion we have shown for the first time that in the competition between two asymmetric control elements, the planar chirality associated with the ferrocene system and the central chirality associated with the auxiliary, nucleophilic addition to ferrocenyl imine derivatives is dominated by the ferrocene planar chirality.

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35 *Crystal data for* **7a**. $C_{26}H_{25}FeN_3O_2S$, M = 499.40, monoclinic, a = 7.7541(5), b = 35.144(2), c = 8.9281(6) Å, β = 101.221(1)°, U = 2386.5(3) Å^3, T = 150(2) K, space group $P2_1$ (No. 4), Z = 4, μ(Mo-Kα) = 0.748 mm^{-1}, 10 473 unique reflections measured, corrected for absorption (R_{int} 0.016) and used in all calculations. Final R_1 [9738 $F \geq 4\sigma(F)$] = 0.0414 and wR(all F^2) was 0.106. The absolute structure parameter refined to −0.016(11).
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