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Asymmetric Synthesis of Chiral α-Ferrocenylalkylamines and Their Use in the Preparation of Chiral Redox-Active Receptors

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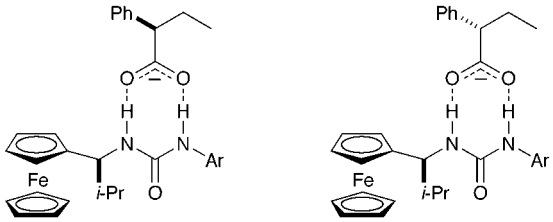
ABSTRACT



A new strategy for the asymmetric synthesis of chiral primary α-ferrocenylalkylamines has been utilized to generate homochiral redox-active receptors that bind chiral carboxylate anions with moderate enantioselectivity and undergo a redox response to complexation

Chiral ferrocenes have been utilized in a number of processes, most notably in asymmetric synthesis and in catalysis.[1] Nonracemic ferrocenes are normally prepared via resolution methods, and examples of their preparation via asymmetric synthesis are still relatively rare.[2] Of those ferrocene compounds with central chirality, the resolvable tertiary α-ferrocenylalkylamines are particularly important, since they are useful precursors for ferrocenes that display both planar and central chirality and for primary α-ferrocenylalkylamines that may be used as chiral ligands and auxiliaries.[1,2] We reasoned that primary α-ferrocenylalkylamines may also serve as useful precursors to homochiral redox-active receptors. Such compounds could enable the electrochemical readout of enantioselective recognition as an alternative to other methods of enantioselective sensing that involve changes in the optical properties of the receptor.[3] A number of chiral receptors for organic molecules are now known, for example, those that bind carboxylic acids and carboxylates.[4] However, among the growing number of redox-active receptors for charged or neutral species,[5] as far as we are aware, there is only one example of a homochiral redox-active receptor that participates in enantioselective

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recognition.[5e] Here we report a convenient route to primary α-ferrocenylalkylamines that is based on the stereoselective addition to the C═N bond in a chiral ferrocenyl oxime derivative,[6,7] and we demonstrate how such compounds can be used to prepare novel homochiral redox-active receptors for binding chiral carboxylate anions.

The starting oxime **1** was readily prepared in 93% yield by reaction of ferrocenecarboxaldehyde with (*S*)-*O*-(1-phenylbutyl)-hydroxylamine, the (*E*)-geometry being confirmed by X-ray crystallography (Figure 1). In line with our

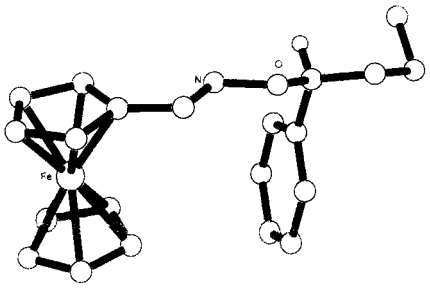


Figure 1. X-ray structure of ferrocenyl oxime **1**.

previous work on *O*-(1-phenylbutyl)aldoximes,[8] the oxime **1** underwent highly diastereoselective addition of organometallic reagents in the presence of boron trifluoride diethyl etherate in toluene at low temperature. Thus, addition of isopropylmagnesium chloride, *n*-butyllithium, and allylmagnesium bromide gave the corresponding hydroxylamines **2** (70−85%) formed in >95% diastereomeric excess, as determined by ^{1}H NMR spectroscopy (Supporting Information). On the basis of previous work, the configuration at the new chiral center was expected to be (*S*), and this was confirmed by X-ray crystallographic analysis of the benzyl carbamate **3** (Figure 2), formed by zinc−acetic acid cleavage

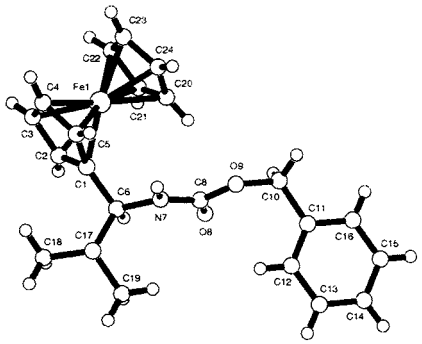
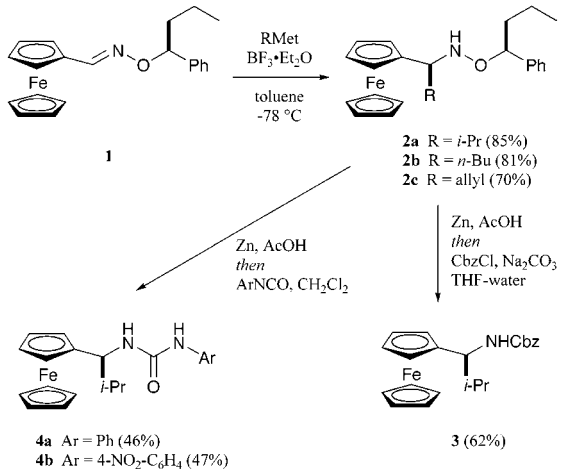


Figure 2. X-ray structure of the (*S*)-ferrocenyl carbamate **3**.

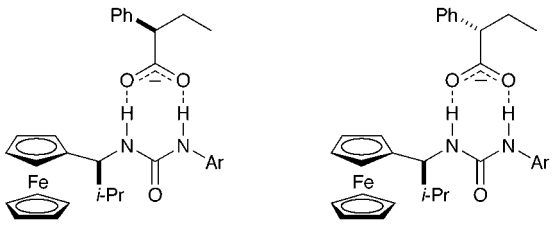
(under sonication) of the N−O bond, followed by reaction with benzyl chloroformate (Scheme 1). To investigate the binding of carboxylates to chiral ferrocene derivatives, a urea-based receptor was chosen. Hence the hydroxylamine **2a** was converted into the ureas **4** by cleavage of the N−O bond (as above) followed by reaction with the corresponding aryl isocyanate (Scheme 1).

Scheme 1



Both **4a** and **4b** bind carboxylate ions in CD_3CN solution, as evidenced by changes to the ^{1}H NMR spectrum of each host (ca. 7 mM) upon addition of aliquots of a racemic mixture of tetrabutylammonium 2-phenylbutyrate, **5**. As expected, large downfield shifts (ca. +4 ppm) in the resonances for the urea NH protons were observed (Supporting Information), which confirmed the urea moiety as the binding site, with Job plots (Supporting Information) establishing the stoichiometry as 1:1 (Scheme 2).

Scheme 2



Titration data were used[9a] to establish the binding constant between **4a** and racemic **5** as 2080 M^{-1} (±10%) at 293 K.

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The increased acidity of the urea protons in **4b** due to the electron-withdrawing nitrophenyl moiety meant that the binding strength with **5** was too high for the binding constant to be determined at NMR concentrations. However, the nitrobenzene chromophore[9b] allowed the binding process to be followed at much lower concentrations (ca. 0.05 mM) in DMSO by UV−vis spectroscopy, as shown in Figure 3.

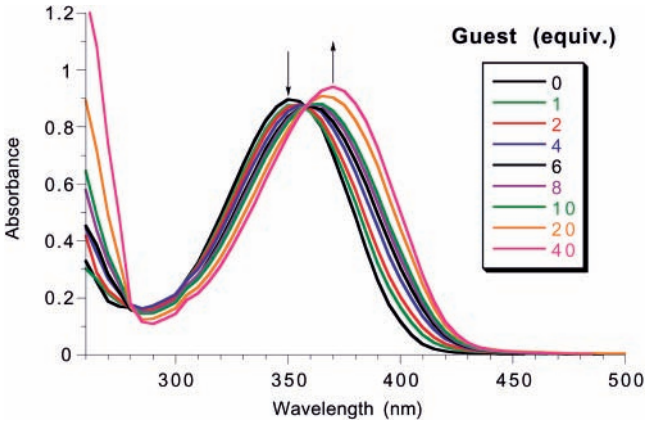

Figure 3. Changes to the UV−vis spectrum of **4b** in DMSO upon addition of aliquots of racemic **5** at 293 K.

The increase in absorption intensity at 408 nm was monitored, and the data were subjected to a Benesi−Hildebrand plot (Figure 4),[10] giving a binding constant

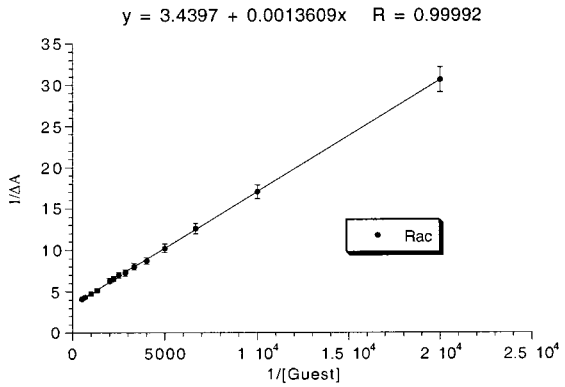

Figure 4. Benesi−Hildebrand plot with **4b** of $1/\Delta A$ at 408 nm vs 1/[(*rac*)**5**].

between **4b** and racemic **5** of 2530 M^{-1} (±10%) at 293 K, which is higher than the value for **4a**, even though a more polar solvent was used.

Studies were then repeated with the enantiopure forms of **5**, giving binding constants of 2350 M^{-1} (±10%) and 2910 M^{-1} (±10%) for the (*S*) and (*R*) forms, respectively. As expected, these values lie on either side of the value for racemic **5**. The difference in binding strength between the two enantiomers is only moderate but is comparable to related systems.[4,5e] These results are not unexpected because, although the chiral center in **4b** lies in close proximity to the urea binding site, the receptor framework is not restrained and the chiral centers of the host and guest are not particularly close to one another in the complex.

Cyclic voltammetry experiments[11] revealed that both receptors undergo a reversible oxidation in dry CH_3CN at 298 K [E = 0.48 and 0.49 V vs decamethylferrocene internal reference, for **4a** and **4b**, respectively, where $E = (E_{pa} + E_{pc})/2$]. Upon addition of an excess amount of racemic **5** to a solution of receptor **4b**, a significant cathodic shift of −70 (±5) mV in the redox couple of **4b** was observed (Figure 5). Therefore, as found with related metallocene binders of

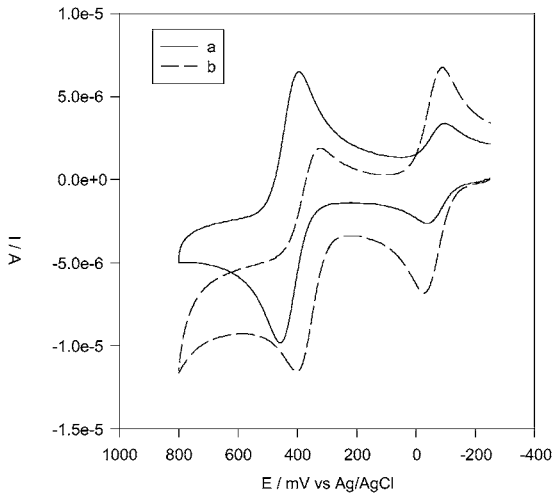

Figure 5. Cyclic voltammograms of (a) **4b** (0.5 mM) and decamethylferrocene (ca. 0.2 mM) and (b) **4b** (0.5 mM) and decamethylferrocene (ca. 0.5 mM) in the presence of 5 molar equiv of racemic **5**.

achiral carboxylic acids and carboxylates,[5c,f] complexation affects the redox potential of the ferrocene unit, which enables these chiral compounds to be electrochemically sensed. However, it is interesting to note that, as found in the one previous attempt at electrochemical readout of enantioselective recognition,[5e] no significant differences between the redox response of **4b** to complexation of racemic and enantiopure forms of **5** were observed.

In conclusion, we have established a convenient and versatile synthetic route to enantiopure chiral metallocene

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(11) Conditions: reference electrode, Ag/AgCl; counter electrode, Pt wire; working electrode, glassy carbon; scan rate, 100 mV/s; supporting electrolyte, TBAP (0.1 M); concentration of **4a** and **4b** = 0.5 mM.

receptors that locates the chiral center in close proximity to the binding site. The fact that enantioselectivity is only moderate means that the electrochemical readout of enantioselectivity remains elusive. However, the ease of the synthesis and the significant redox response to complexation makes these systems ideal starting points for the design of related chiral redox-active receptors with improved enantioselectivities.

Acknowledgment. We thank the EPSRC for support of this work.

Supporting Information Available: Synthetic procedures for the preparation of **4a** and **4b**, crystallographic data for **1** and **3**, and carboxylate binding data for **4a** and **4b** (Job Plots, NMR, and UV/vis titrations). This material is available free of charge via the Internet at http://pubs.acs.org.

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