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# Versatile reagents: ferrocenyl azolium compounds as auxiliary ligands for the Heck reaction and potential antifungal agents

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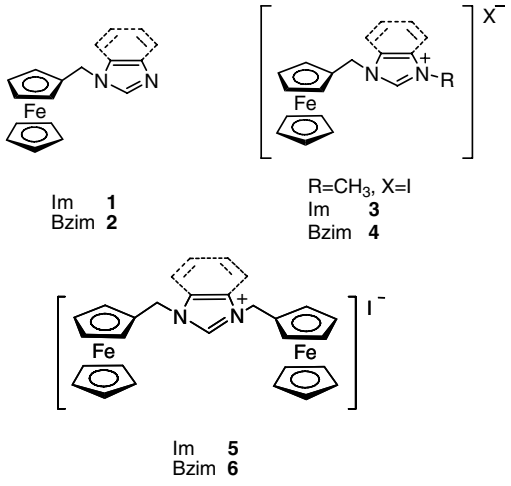
**Abstract**—We report the synthesis, catalytic, and biological properties of new bridged and cyclic ferrocenyl azolium compounds.


The azole system arguably represents one of the most ubiquitous classes of heterocyclic species. Their many wide-ranging applications vary from medicinal use as pharmaceuticals to being some of the building blocks necessary for life. They are also used in numerous more technical applications, such as electrolytes, components in supramolecular structures, and in polymers.[1] One particular area in which the application of azoles, in particular imidazoles, has been expanding is that of transition-metal catalysis, as imidazolium salts are becoming increasingly recognized as stable alternatives to triarylphosphines as auxiliary ligands.[2]

Studies by us into the application and derivatization of azolium salts focused on their ability to act as potential anion receptors[3] and their biological activity.[4] The ionic azolium structure has been introduced into ferrocene, tripodal, and cyclophane imidazole systems, which have then been evaluated as anion receptors and antimicrobial agents. Previously prepared compounds include the ferrocenyl azoles **1** and **2** and ferrocenyl azolium salts, for example, **3**–**6** (Im = imidazolium, Bzim = benzimidazolium).[3,4]

Herein, we report on the synthesis of a new series of acyclic and cyclic ferrocenyl azole/azolium compounds and their application as auxiliary ligands in transition-metal catalysis, anion receptors, and bioactive agents. Following our previous studies, we focused on the preparation of a new generation of ferrocenyl azolium systems **7** and **8** containing two azolium and four centers, respectively.




Such compounds could be potentially used as both carbene ligands and anion receptors. Compounds **7** and **8** contain a cavity, which we believe would aid the preorganization of the imidazolium groups to enhance anion binding selectivity.[5] The acyclic ferrocenyl azolium system may have the potential to form a cleft with a specific geometry and topology to offer greater selectivity for anion recognition.

Outlined in Scheme 1 is the synthetic strategy employed to prepare **7**. A facile way of introducing two azolium centers was to link two monosubstituted ferrocenyl

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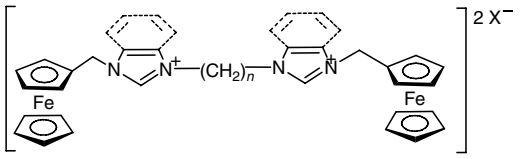
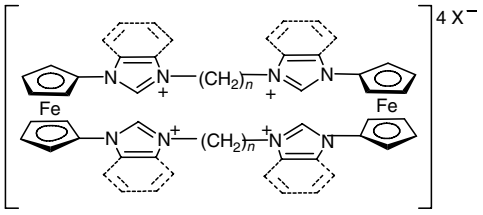


7



8

azole systems[3] to create a [1-(1-ferrocenylmethyl)-3-alkylazolium]-3-(1-ferrocenylmethyl) azolium salt with a four-atom spacer as the linker group. Precursors **1** and **2** were treated with 1,4-diidobutane to obtain the corresponding azolium iodide salt. A further aliquot of the ferrocenyl azole yielded the bridged bisazolium ferrocenyl iodide salt systems **10** and **12**. In this way, both the imidazolium and benzimidazolium analogues were prepared.

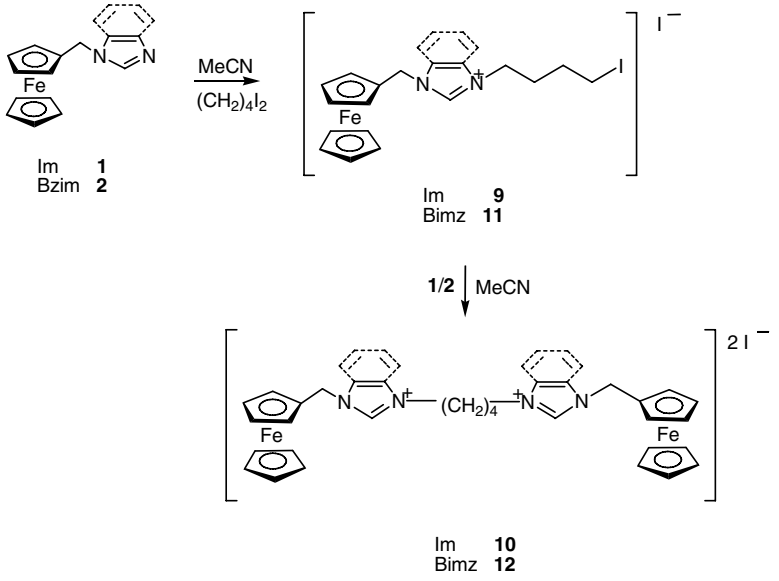
The syntheses were facile and moderately high yielding; for the imidazolium derivatives, the overall yields were 50% for **10** and 55% for **12**. However, it should be noted that purification of these compounds proved to be more difficult than for the intermediate monosubstituted ferrocenyl azolium salts. Both **10** and **12** proved to be sparingly soluble in dimethyl sulfoxide (DMSO) and insoluble in dichloromethane, chloroform, methanol, and acetonitrile. Thus, they could not be purified by column chromatography. However, they were characterized and shown to be sufficiently pure by NMR spectroscopic and elemental analysis.

The preparation of the macrocyclic structure **8** with four azolium centers linking two ferrocene units was successfully carried out by using the same synthetic route as that for the preparation of the linear bridged bisazolium ferrocenyl salts **10** and **12** (Scheme 2). 1,4-Diiodobutane was reacted with 1,1′-bis(1-methylbenzimidazole)ferrocene **13**, obtained from the reaction of benzimidazole with a disubstituted ferrocenyl quaternary ammonium salt,[6] to yield the intermediate benzimidazolium diiodide **14**. Reaction of this compound with a further aliquot of **13** gave the final macrocycle **15** in 60% yield.

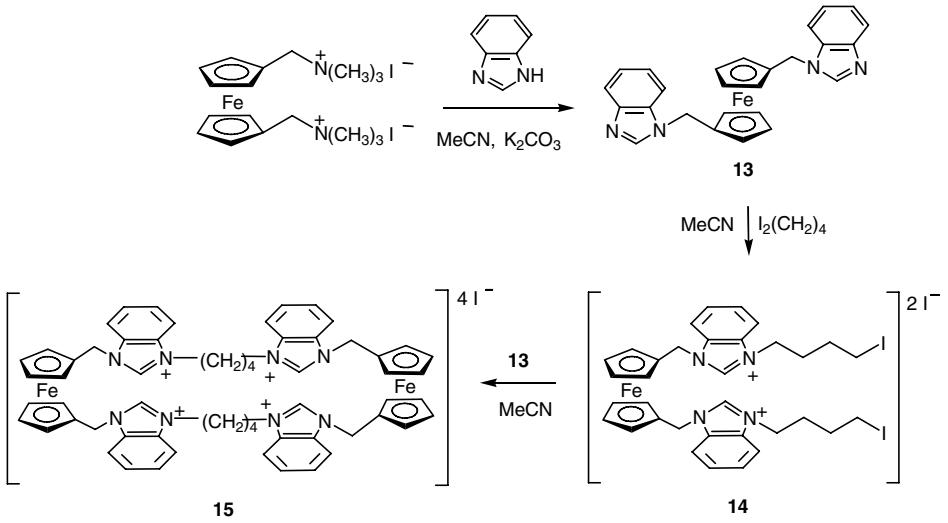
Both the intermediate **13** and the product **15** were insoluble in most solvents, being only sparingly soluble in DMSO and dimethylformamide (DMF), so further purification by column chromatography or crystallization was not possible. However, **15** could be reprecipitated from DMF/$CHCl_3$ and was characterized by NMR spectroscopy and elemental analysis (see Supplementary data for details).

Modeling experiments show that **15** may exist as different rotameric isomers. There are several possible rotatomers of this compound, in which the contortion of the benzimidazolium moieties and the butyl spacer groups leads to different cavity shapes. MM+ and PM3 optimizations predicted two different projected geometries (Fig. 1) for **8**, and a space-filling computer modeling projection shows four possible rotatomers (Fig. 2). We believe the poorly resolved $^1$H NMR spectrum of **12** confirms the presence of rotational isomers (see the Supplementary data).

Further derivatives of these compounds were prepared. Reaction of **13** with methyl iodide or *n*-butyl iodide provided bisbenzimidazolium salts **16** and **17** in yields of 60% and 75%, respectively (Scheme 3). Compound **18** was prepared by the treatment of 1,1′-ferrocenyldimethanol with CDI[7] in 71% yield (Scheme 4).



**Scheme 1.** The synthetic strategy to introduce two azolium centers.




**Scheme 2.** The synthetic strategy to introduce four azolium centers for the preparation of cyclophane **15**.

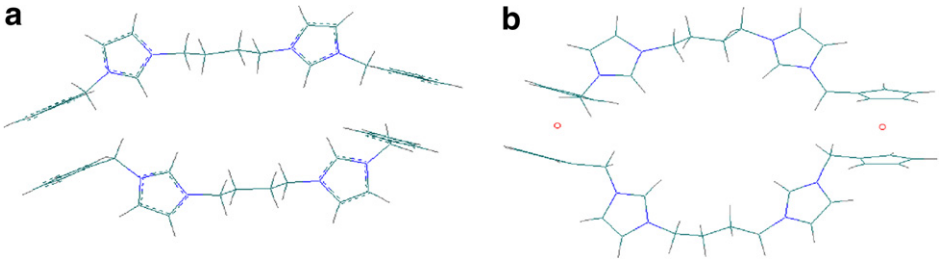



**Figure 1.** (a) MM+ optimization of a model of the structure of **8**. The Fe atoms are removed, showing the Cp rings to be constrained 3.32 Å apart. The cavity is asymmetric; ca. 5.5 × 8.5 Å (aspect ratio 1:1.55). (b) PM3 optimization of **8** (starting at MM+ opt geometry; using no constraints) showing an asymmetric cavity; ca. 8.5 × 10.5 Å (aspect ratio 1:1.24).

To investigate the catalytic properties of the ferrocenyl azolium salts, a simple Heck reaction system was chosen and a range of salts were employed as auxiliary ligands; a mixture of the monosubstituted and disubstituted imidazolium/benzimidazolium salts was used. As shown previously, preparation of the carbene metal complex beforehand was unnecessary.[8] Therefore, the active complex should form in situ from an azolium salt/palladium system. We tested our new compounds in the reaction of ethyl acrylate with 4-nitrobromobenzene at 120 °C under nitrogen for 24 h with sodium acetate as the base (1.25 equiv), DMF as the solvent, and $Pd(OAc)_2$ (1 mol %) as the catalyst precursor (Table 1).

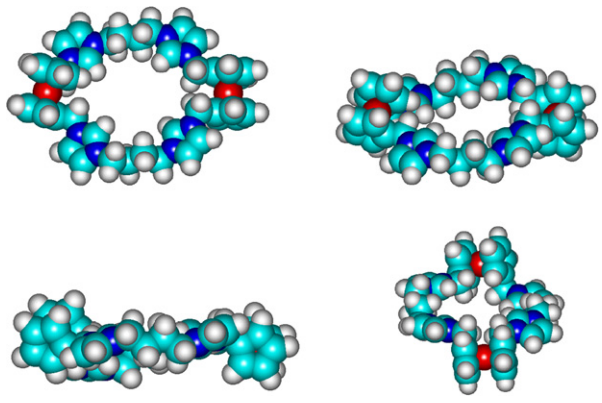
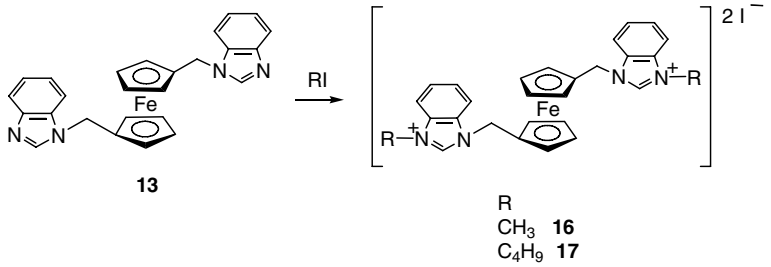


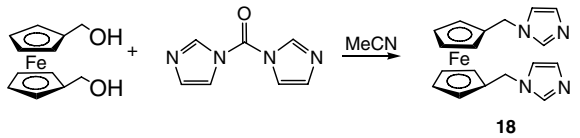
**Figure 2.** Computer modeling projections of the four predicted rotamers of **8** using PM3 optimization.

These compounds successfully aided catalysis of this Heck reaction with the product being formed in very high yields in some cases. This result adds to the growing, albeit still small, evidence of benzimidazolium salts acting as effective ligands in such reactions.[9] Therefore, there is considerable potential in the application of these compounds in transition-metal catalysis. Further derivatization should build on this performance so that substrate scope and increased yields can be obtained and so that they can be applied to other transition-metal catalysis reactions.

The performance of **15** as an anion receptor was evaluated by $^1$H NMR titration experiments in DMSO-$d_6$ by monitoring the change in chemical shift of the H-2 proton of the imidazolium groups. We were limited to DMSO as the solvent due to the poor solubility of **15** in organic solvents. Preliminary results indicated that **15** binds with acetate, chloride and fluoride, however, the chemical shift continued to increase even after the addition of 5 M equiv of anion. These results indicate that **15** does not behave as a typical receptor.[10]

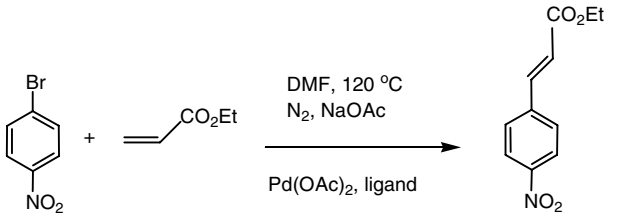



**Scheme 3.** Preparation of ferrocenyl bisbenzimidazolium salts through alkylation.




**Scheme 4.** The preparation of ferrocenyl bisimidazole analogue **18**.

**Table 1.** The use of ferrocenyl azolium salts as the auxiliary ligand in the Heck reaction




| Compound | Yield (%) |
|---|---|
| **3** | 74 |
| **4** | 89 |
| **5** | 91 |
| **10** | 94 |
| **12** | 85 |
| **15** | 36 |
| **16** | 78 |
| **17** | 91 |
| No auxiliary ligand | 20 |

The antimicrobial activities of a representative selection of the ferrocenyl azole/azolium compounds were investigated for their antibiotic capabilities, as the previously prepared ferrocenyl azole/azolium compounds had shown considerable promise.[4] The compounds were screened against a yeast, *Candida albicans*, and a Gram-negative bacterium, *Pseudomonas aeruginosa*. Both of these microbes form biofilms that are resistant to antimicrobial agents and have been recognized as opportunistic pathogens that infect immunocompromised human hosts.[11]

Ferrocenyl azolium compounds **5** and **12** showed antifungal activity with $LD_{50}$ values of 175 and 84 μg $ml^{-1}$. However, all the compounds tested gave very poor responses as antibacterial agents. It is interesting to note that both **5** and **12** are bisferrocenyl azolium derivatives. It would appear that both the neutral and charged ferrocenyl monoazole compounds showed little bioactivity. The presence of two ferrocene units seems to be essential for bioactivity. Perhaps the ferrocene groups are playing an electrochemical role, as has been observed with ferrocenyl antimalarials.[4] To better understand the bioactivity of both **5** and **12**, a series of structural modifications are currently being developed from which a new pharmacophore can be generated.

In summary, a series of acyclic and cyclic linked ferrocene and azolium units have been prepared that show much promise in transition-metal catalysis and as antifungal agents. Further derivatization of these structures would aid the development of highly efficient reagents.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.179.

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