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Design and Synthesis of a New Type of Ferrocene-Based Planar Chiral DMAP Analogues. A New Catalyst System for Asymmetric Nucleophilic Catalysis†

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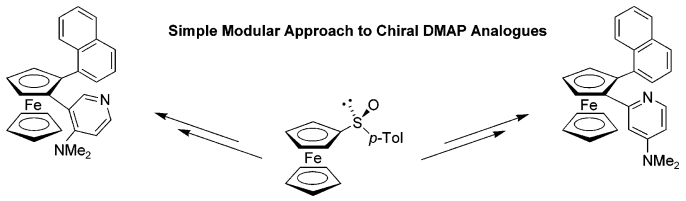

A new first-generation catalyst system for nucleophilic catalysis has been developed. It is based on a planar chiral ferrocene skeleton with either the potent nucleophile 4-(dimethylamino)pyridine (DMAP) or the related 4-nitropyridine *N*-oxide attached in either the 2- or the 3-position. The syntheses are short, efficient, and enantioselective and X-ray crystal structures of both DMAP-derived catalysts are presented. The DMAP-based catalysts were tested in asymmetric reactions and the 3-derivative **14** showed good activity and a moderate level of enantioselectivity. The sense of induction (selectivity) was studied using molecular modeling and the results pointed at new directions for future generations of catalysts based on this design.

Introduction

Due to the widespread array of reactions subject to catalysis by nucleophiles,[1] the recent years have seen an increasing interest toward the development of generic asymmetric catalyst systems for these processes. Reactions which may be catalyzed by asymmetric nucleophiles include important examples such as kinetic resolution of secondary alcohols,[2−8] desymmetrization of *meso*-diols[4,9] and cyclic *meso*-anhydrides,[10,11] addition of alcohols to ketenes,[12] β-lactam formation by reaction of ketenes and imines,[13,14] and, last but not least, the rearrangement reactions of azlactones,[15,16] oxindoles, and benzofuranones[17−19] to generate quaternary stereocenters. 4-(Dimethylamino)pyridine (DMAP) is a powerful acylation catalyst[20−23] and is probably the most

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frequently used nucleophilic catalyst in general and displays high activity in a broad range of reactions, Although attempts at making chiral variants of DMAP for asymmetric catalysis have, until recently, been notably rare.[24−26] A growing interest in the subject of asymmetric nucleophilic catalysis has, at the same time, led to the discovery of a number of powerful chiral nucleophiles based on, e.g., phosphines, stable carbenes, and the well-known imidazole which are all very good alternatives to the DMAP-based systems.[5−7] As is evident, significant progress has recently been made and, in some instances, the developed catalysts and asymmetric processes may even be industrially viable. Many of the catalysts, however, suffer from drawbacks, e.g. tedious preparations such as multiple synthetic steps and separation of the enantiomers by chiral HPLC or instability. As a consequence there is still ample room for improvement regarding these concerns.

Since its discovery in 1951, ferrocene has increasingly established itself as an efficient and generally applicable backbone in chiral ligands and catalysts due to the possibility of introducing and exploiting both central and planar chirality.[27,28] A principal advantage of planar chirality as a control element is that it does not racemize as compared to, for example, axial chirality seen in the classic biarylic systems, and today, several efficient methods exist for introducing planar chirality onto the ferrocene backbone.[29] The development of an asymmetric nucleophilic catalyst system based on planar chiral ferrocene has been reported by Fu et al.[25] and has been shown to perform well for a variety of reactions.

Here, we wish to report the development of a first-generation catalyst system which show promise for future generations based on the design of a DMAP attached to a planar chiral ferrocene backbone. The synthetic sequence involves planar chiral 4-nitropyridine *N*-oxides as intermediates, which may show nucleophilic catalytic activity themselves.[30]

Results and Discussion

Catalyst Design and Synthesis. The purpose of the present study was to design, prepare, and test new asymmetric nucleophilic catalysts. In light of the activity shown by DMAP and pyridine *N*−oxide as nucleophilic catalysts and the promising results shown, especially by chiral analogues of DMAP,[8,24,25] it seemed sensible to embark on the task of designing a catalyst system that met the following criteria: (1) it should be *modular*, i.e. a structure easily modified for preparing analogues, (2) it should be stable and easily synthesized, i.e. high yielding in few steps, (3) it should have enantioselective synthesis, i.e. no need for resolution by use of chiral HPLC, and (4) it should be cost-effective to prepare. To meet these criteria we envisioned an analogue of DMAP or pyridine *N*-oxide attached to a chiral ferrocene skeleton, the general structure of which is shown in Figure 1 for DMAP.

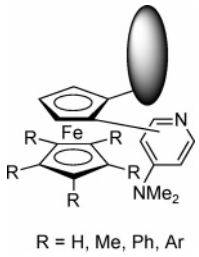
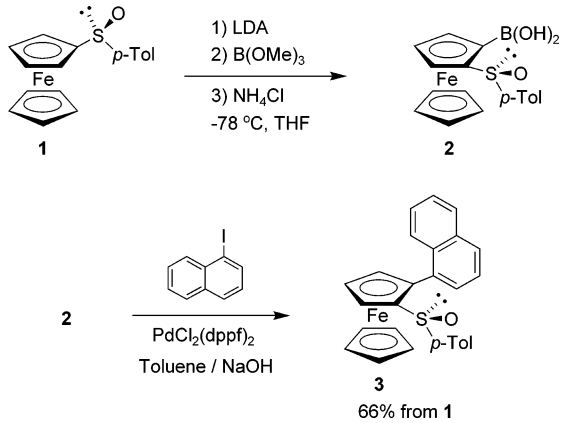


FIGURE 1. Catalyst design. Changing the order of attachment of the two groups on the upper ferrocene ring gives the enantiomer.

The selectivity of the catalyst is dependent on the chiral environment around the pyridine unit and it is, first and foremost, desirable to develop a modular synthesis in which it is possible to easily change this. The catalytic activity will largely depend on the substitution of the pyridine ring. Previous studies on chiral DMAP analogues have shown the nucleophilic activity of DMAP analogues to be highly diminished upon incorporation of substituents in the pyridine 2-position.[8,24] However, locked variants of 2-substituted DMAP have, on the other hand, also been proven to be quite active.[14,25,31]

The synthesis of our novel asymmetric nucleophilic catalysts commences with the introduction of planar chirality onto the ferrocene backbone. This was accomplished using methodology developed by Kagan et al. with enantiopure ferrocene sulfoxide **1** as the starting material.[32] Following this methodology, a diastereoselective *o*-lithiation allows for preparation of boronic acid **2** which could be coupled directly with 1-iodonaphthalene under conditions developed by our group.[33] Initially we believed that the incorporation of a 1-naphthyl group would provide a sufficiently asymmetric environment for the catalyst (Scheme 1).

SCHEME 1. Introduction of Planar Chirality



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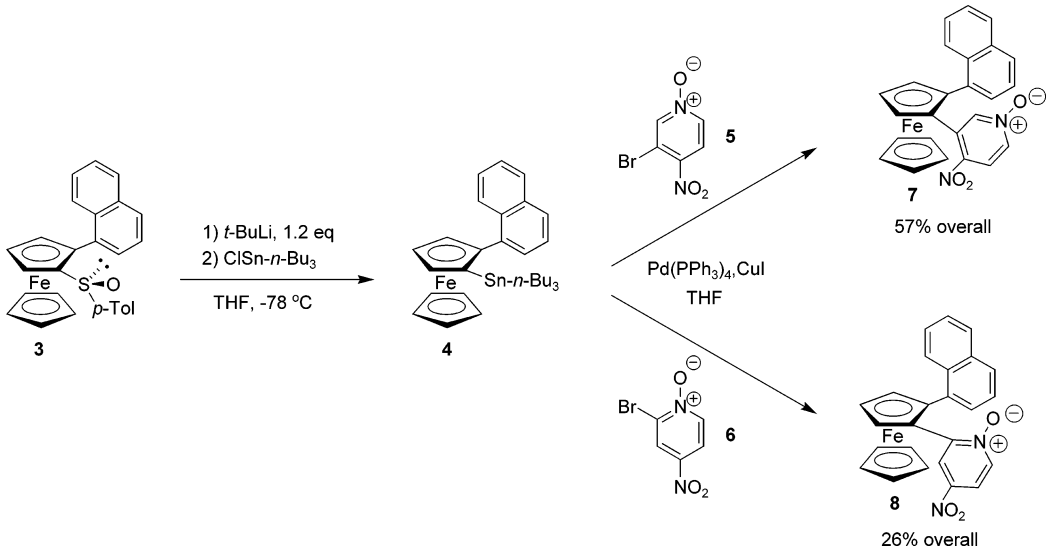
SCHEME 2. Synthesis of 7 and 8 via Stille Cross Coupling

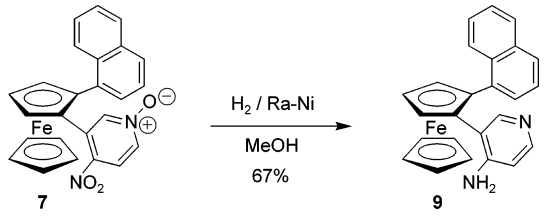


The chiral sulfoxide auxiliary could then be cleaved off using *t*-BuLi to yield an optically pure planar chiral anion, which may be subjected to aromatic cross coupling conditions. However, despite considerable efforts we were not able to couple 2- or 3-bromo-DMAP onto the ferrocene using either Suzuki-, Stille-, or Negishi-type cross coupling methodology. It became clear that the electron-rich nature of both DMAP and the ferrocene did not allow coupling and we thus turned toward coupling of electron-deficient pyridine derivatives in order to subsequently convert these to the desired DMAP derivatives. As is evident, the strategy involved the synthesis of two novel planar chiral *N*-oxides **7** and **8**, which were obtained in decent yields (Scheme 2).

Preparation of the tin intermediate **4** was performed under standard conditions with removal of the chiral auxiliary by treatment with *t*-BuLi followed by electrophilic quench with *n*-Bu_3SnCl. We found that **4** hydrolyzed when worked up by normal flash column chromatography, and the crude mixture was therefore flushed through a plug of silica gel with hexane as the only purification. The mixture thus obtained consists primarily of the desired planar chiral tin compound **4** and some protonated material and the ratio of these two components could be determined from the ^1H NMR spectrum. The use of CuI was crucial for the success of the subsequent Stille coupling which gave a purified yield of 57% (**7**) and 26% (**8**) overall from **3**. The low yield in the formation of **8** is partly due to a demanding column purification.

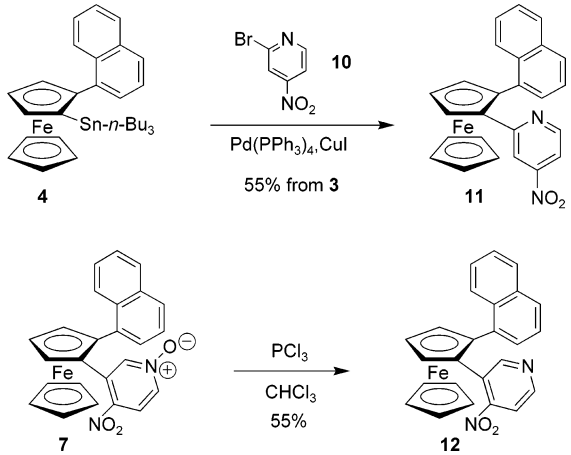
Reduction of **7** using H_2/Ra−Ni proved quite trivial, resulting in aminopyridine **9** (Scheme 3). Disappointingly, reductive methylation proved impossible using standard conditions of $NaCNBH_3$/AcOH in the presence of paraformaldehyde, in which case only the starting amine **9** could be isolated. Literature has shown that it is possible to acylate the amino functionality with Boc_2O and subsequently reduce this to the methyl.[26] However, only the monomethylated derivative is available this way and the procedure would have to be applied twice. Because of the length of the synthetic sequence, we abandoned this method in order to find a better solution.

SCHEME 3. Reduction of 7



We then turned to another strategy, by preparing the two nitro derivatives **11** and **12** in order to try a direct conversion of these into the target compounds. The 2-coupled nitropyridine **11** was prepared by reacting 2-bromo-4-nitropyridine **10** under the optimized Stille conditions. Gratifyingly, none of the purification problems that characterized the preparation of the *N*-oxide **8** were encountered and the product could be isolated with an overall yield of 55%. 3-Bromo-4-nitropyridine is not easily accessible and the 3-coupled derivative **12** could, therefore, not be prepared in a similar way. Instead, we tried deoxygenation of the oxo functionality in **7** by treatment with PCl_3 and it was possible to isolate 55% of the desired product **12** (Scheme 4).

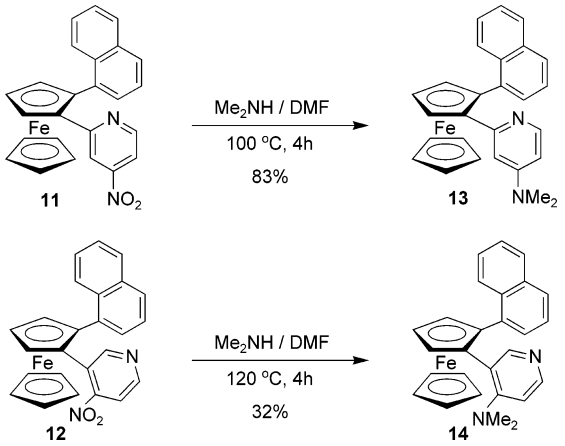
SCHEME 4. Synthesis of 11 and 12



To our great pleasure, the nitro compounds **11** and **12** reacted with dimethylamine in DMF to give the desired

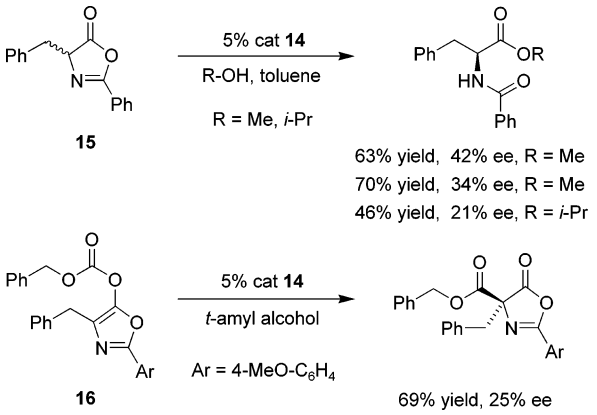
compounds. The reaction toward **13** proceeded quite smoothly to give an impressive yield of 83% after 4 h at 100 °C. The reaction to prepare **14** proved more troublesome and gave, under optimized conditions, a low yield of 32% however, with a 30% recovery of starting material (Scheme 5). As far as we know these are the first examples of direct ipso-aminations of aromatic nitrogroups.

SCHEME 5. Synthesis of Catalysts 13 and 14



Testing the Catalysts. Catalysts **13** and **14** were initially tested for activity and selectivity in the kinetic resolution of 2-phenyl ethanol. Disappointingly, no selectivity was observed for either catalyst and only catalyst **14** displayed high catalytic activity. We then tried other test reactions, known to be catalyzed by nucleophiles (Scheme 6).

SCHEME 6. Dynamic Kinetic Resolution and Rearrangement Reaction of Azlactones

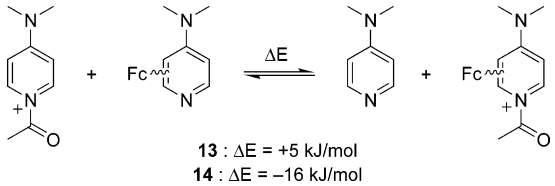


Following the lead of Fu et al.[34] we performed a dynamic kinetic resolution of azlactone **15** with the catalyst **14** and we obtained 63% yield with 42% ee and in a duplicate run, 70% yield with 34% ee. Not surprisingly, catalyst **13** was still unreactive. When the steric bulk was increased by using *i*-PrOH, a decrease in selectivity was observed, which is contrary to what was expected and to the findings of Fu who observed an increase in selectivity. Furthermore, the reaction was extremely slow and, therefore, not practically useful. The rearrangement of O-acylated azlactones has also been shown to be susceptible to asymmetric nucleophilic catalysis.[16] In the rearrangement reaction of O-acylated azlactone **16** we obtained 69% yield with 25% ee. The above examples show that we certainly have possibilities with this catalyst system, which is stable and allows efficient catalyst recovery. Importantly, this constitutes only a first-generation catalyst and with design development it may be possible to obtain the main goal set forth, namely a highly reactive and selective catalyst.

Catalyst Structure and Activity. The crystal structures of catalysts **13** and **14** are shown in Figure 2. As anticipated, the two aryl substituents are aligned in a coplanar fashion with the ortho substituents situated above the upper ferrocenyl structure as observed in other pseudo-biarylic complexes prepared by our group.[33,35] Visual inspection of the two structures allows a qualitative rationalization of the observed activities. In **13**, the catalytically active pyridine nitrogen is situated in a strongly asymmetric but also very crowded environment. The former is a prerequisite for asymmetric induction, whereas the latter will serve to reduce the activity. On the other hand, the active nitrogen of **14** is pointing away from the bulk of the catalyst, and thus would be expected to behave similarly to unsubstituted DMAP.

To enable a quantification of the catalytic activity, we performed a computational study of DMAP, **13**, and **14**, together with their *N*-acetylated forms. The conformational space of each species was first screened using PM3(tm) in Spartan.[36] Low-energy conformations were then fully optimized at the B3LYP level[37,38] with the LACVP* basis set[39] in Jaguar 4.2.[40] The computational method was validated by comparison of the structures of **13** and **14** to the crystal structures. Assuming that the formation of the acetylated intermediate is the rate-determining step in the catalytic cycle, the catalytic activity relative to DMAP can be expected to correlate with the energy of the isodesmic acetylation equilibrium shown in Scheme 7.

SCHEME 7. Isodesmic Equilibrium for 13 and 14 with Ac-DMAP$^+$



Looking first at the highly active catalyst **14**, we can see that it is preferentially acetylated relative to DMAP

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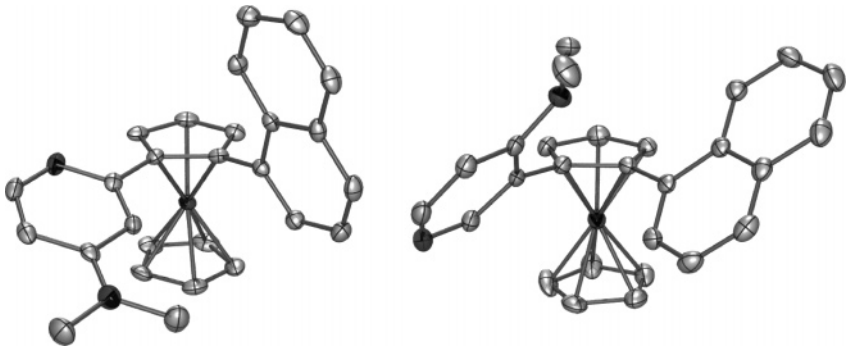

FIGURE 2. X-ray crystal structures of catalysts **13** (left) and **14** (right). Thermal ellipsoids are displayed at the 50% probability level.

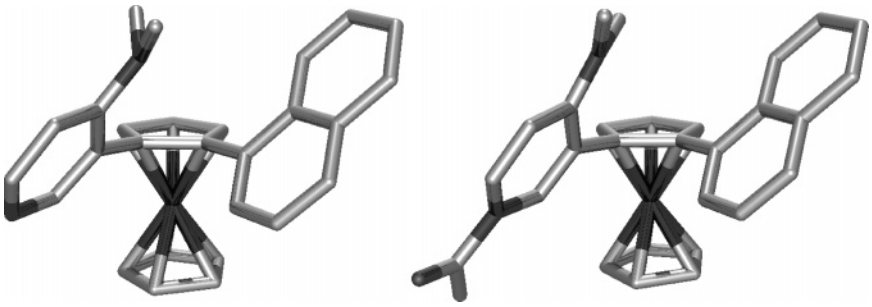

FIGURE 3. Calculated structures of catalyst **14** and acetylated derivative Ac-**14**.

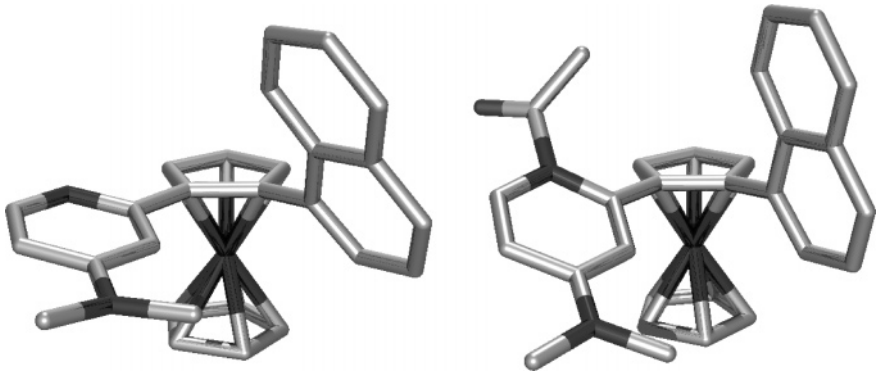

FIGURE 4. Calculated structures of catalyst **13** and acetylated derivative Ac-**13**.

by approximately 16 kJ/mol, corresponding to a difference in reactivity of almost 3 orders of magnitude. The calculated structures are shown in Figure 3.

It is interesting to note that there are no direct interactions between the acetyl group and the ferrocenyl moiety in Ac-**14**. The strong increase in activity must therefore be electronic in nature, partly due to an inductive effect from the electron-rich ferrocene core, and partly from a stabilizing interaction between the naphthalene core and the $-NMe_2$ moiety, which has a partial positive charge due to strong conjugation with the reaction center. It is also immediately clear that attack on the acetyl group of Ac-**14** in a Bürgi−Dunitz trajectory can be achieved without encountering steric hindrance, in good accordance with both the high activity and low selectivity in the model system (vide supra).

The structure of Ac-**14** can be used for design of improved catalysts. A first step toward achieving better selectivity could be to block one face of the acetyl group to approaching nucleophiles. One way to accomplish this asymmetric shielding of the reaction center would be to extend the ortho substituent on the ferrocene by replacing the naphthyl moiety by a 9-anthracyl or 9-phenanthryl moiety.

The calculated structures of the nonactive catalyst **13** and acetylated derivative Ac-**13** are shown in Figure 4. The steric strain in Ac-**13** is immediately obvious from the twisting of the acetyl group, by approximately 47°. The strain is also evident from the isodesmic comparison in Scheme 7. Despite the electronic influence of the ferrocene core, Ac-**13** is disfavored by 5 kJ/mol relative to Ac-DMAP. At this point, we also want to note that the gas-phase calculations performed here selectively favor the larger, more delocalized cations derived from **13** and **14** relative to DMAP. Thus, the loss of activity is probably more severe than the mere 1 order of magnitude implied by the calculated energy difference. On the other hand, the difference of 3−4 orders of magnitude (21 kJ/mol) between **13** and **14** should not suffer from this systematic error.

Looking in more detail at the structures of **13** and Ac-**13**, it is clear that the loss of activity is mainly due to the coplanarity of the DMAP moiety and the upper ferrocene ring, leading to a collision between the ferrocene ring and the nitrogen substituent in the acylated form. Thus, a less planar form would be expected to display some activity while still keeping the pyridine nitrogen in a strongly asymmetric environment. Several methods could be suggested for reducing the planarity. The synthetically most feasible would be to replace the naphthalene moiety with a substituent that provides more steric bulk in the plane of the ferrocene ring. A more daunting proposal would be to link the $-NMe_2$ moiety covalently to the lower ferrocene ring.

Conclusion

In conclusion, we have developed a first-generation catalyst system for asymmetric nucleophilic catalysis based on a planar chiral ferrocene skeleton with either a DMAP or pyridine *N*-oxide moiety attached. It is a modular synthesis that allows for the incorporation of various arylic substituents next to the DMAP or pyridine moiety and, thus, potentially fine-tuning catalyst reactivity and selectivity to a given test reaction. The synthesis is enantioselective and hence no separation of enantiomers by chiral HPLC or other means is necessary and the methodology used should allow for the preparation of both enantiomers simply by changing the order of attachment of the DMAP and aryl group onto the ferrocene. Although the performance of the present catalysts **13** and **14** is, at best, moderate, the modularity of the methodology allows for easy catalyst development in order to increase catalyst performance.

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Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra for compounds **3**, **7**−**9**, **11**−**14** and ^1H NMR of **4**. Molecular modeling data and crystallographic information files (CIF) for compounds **13** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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