Planar Chirality

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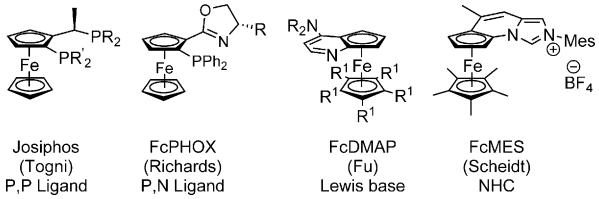
A Family of Chiral Ferrocenyl Diols: Modular Synthesis, Solid-State Characterization, and Application in Asymmetric Organocatalysis

*Chris Nottingham, Helge Müller-Bunz, and Patrick J. Guiry**

Dedicated to Dr. James B. Thomson[1]

Abstract: *Readily available chiral diol scaffolds are useful as sources of chirality for asymmetric synthesis, however, few such scaffolds are readily available in enantiopure form. Reported herein is a cheap and modular synthesis of a novel family of chiral ferrocenyl diols in excellent yields with excellent enantio- and diastereoselectivity (> 99 % ee and 99 % de). These diols possess not only planar and central chirality, but also axial chirality around the central iron atom. Characterization of these diols by X-ray crystallography revealed intra- and intermolecular hydrogen-bond networks depending on substitution at the carbinol positions. The potential of these diols as catalysts was subsequently demonstrated in an asymmetric hetero-Diels–Alder reaction which provided cycloadducts in up to 84 % yield with ee values ranging from −92 to +72 %.*

With applications as chiral auxiliaries, ligands, and catalysts, C_2-symmetrical diols represent one of the most important structural motifs in asymmetric synthesis.[2] Such diols often serve as valuable synthons for chiral diamine ligands, diphosphine ligands, phosphoramidites, and phosphoric acids, further highlighting their potential and making them among the most sought after motifs in asymmetric catalysis.[3] Indeed, out of the eight privileged chiral ligands and catalysts originally identified by Yoon and Jacobsen,[4] three were either derived from, or were chiral diols (TADDOL, BINOL, and BINAP). In line with this finding, 1,2-disubstituted ferrocenes which possess planar chirality have proven to be excellent ligand/catalyst backbones for asymmetric catalysis (Scheme 1).[5]



Scheme 1. Planar-chiral ferrocenyl ligands and catalysts.

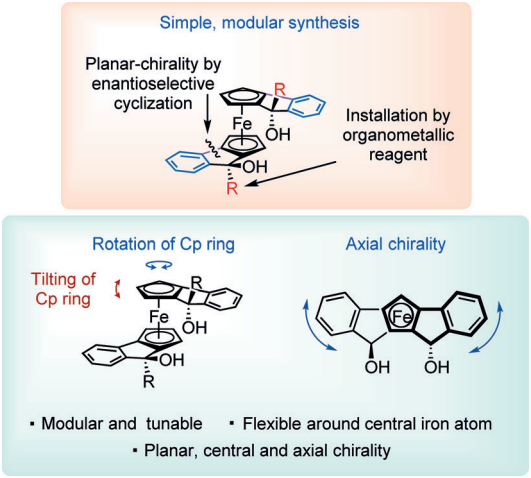


Figure 1. Novel ferrocenyl-based diol scaffold. Cp = cyclopentadienyl.

Encouraged by the potential offered by a new diol scaffold and the success of ferrocenyl planar chirality as a control element in asymmetric transformations, we set out to design a novel family of planar-chiral ferrocenyl diols which could take advantage of the flexible nature of the ferrocenyl backbone (Figure 1). These diols would possess planar chirality on both ferrocenyl Cp rings, central chirality at both carbinol carbon atoms, and axially chirality around the iron center. Such enantiopure, C_2-symmetrical diols would have potential not only in asymmetric synthesis, but also in materials chemistry.[2c,6]

Key to our synthetic strategy was the elegant catalytic asymmetric C–H activation/cyclization methodology reported independently by the groups of You and Gu.[7] Indeed, the synthesis of the key intermediate diketone (R_p)-**1** was reported by both You and Gu as part of their substrate scope, although the preparation of the required starting materials **2** and **3** was unfortunately not described in detail and the ligand and precatalyst loadings reported for the asymmetric cyclization step were quite high (for structures see Table 1). Furthermore, (R_p)-**1** was reported to decompose at room temperature.[7b] However, we found this to be a robust, bench-stable compound over the course of our studies (18 months). Aware that a simple and cost-effective synthesis enhances the application opportunities of any new chiral scaffold we began to optimize a synthetic route towards

[*] C. Nottingham, H. Müller-Bunz, P. J. Guiry
Centre for Synthesis and Chemical Biology
School of Chemistry, University College Dublin
Belfield, Dublin 4 (Ireland)
E-mail: p.guiry@ucd.ie

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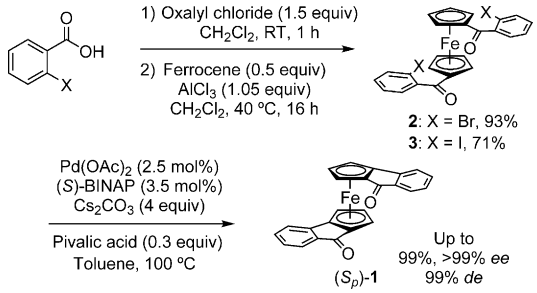
Additional X-ray crystal structures for **5**, **11**, **12**, and **17** are included in the Supporting Information. CCDC 1480208–1480215 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(S_p)-**1**. This culminated in a high-yielding, chromatography-free synthesis of the requisite starting materials **2** and **3** and an optimized, chromatography-free synthesis of (S_p)-**1** utilizing low palladium and ligand loadings to provide the desired products in excellent yields with complete enantiocontrol (Table 1). These optimized reaction conditions facilitated the preparation of multigram quantities of our key intermediate, (S_p)-**1**, in just two steps from cheap and readily available starting materials.[8]

Table 1: Optimized synthesis of (S_p)-**1**.

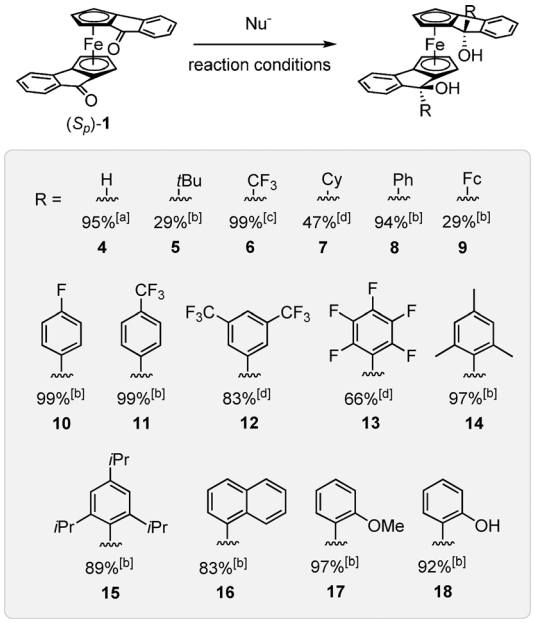


Entry	X	BINAP (mol%)	$Pd(OAc)_2$ (mol%)	*t* [h]	Yield [%]	*ee* [%]	*de* [%]
Gu[7a]	I	13.0	10.0	5	61	98[a]	92
1	I	3.5	2.5	20	99	>99	99
You[7b]	Br	5.0	2.5	53	97	99[b]	–
2	Br	3.5	2.5	1	96	>99	98

[a] (*R*)-BINAP was used to provide (R_p)-**1** without pivalic acid. [b] (*R*)-BINAP was used to provide (R_p)-**1** in *p*-xylene at 80 °C with 1.5 equiv of Cs_2CO_3. See the Supporting Information for additional screening results. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

With access to large quantities of (S_p)-**1**, we prepared a range of 15 diols, with varying electronics and sterics at the carbinol position, in generally good to excellent yields and all with complete enantiocontrol provided by stereoselective *Re* attack on the diketone (Scheme 2). An X-ray crystal structure of **4** confirmed the absolute configuration at the carbinol position and revealed an intricate hydrogen-bonding network between five individual molecules in the unit cell (Figure 2; left). This type of hydrogen bonding is similar to that observed with the privileged ligand TADDOL.[2c] Furthermore, because of axial rotation around the metal center of ferrocene, the diol can adopt a number of orientations, thus showcasing the flexible nature of the scaffold (Figure 2; right). Conversely, the tertiary diols generally crystallized with a "folded" conformation as illustrated with the CF_3-substituted diol **6** (Figure 3). In this case the two Cp rings of ferrocene have rotated to direct the two hydroxy groups away from each other, thus eliminating the possibility of intramolecular hydrogen bonding. As the aryl–aryl distance between the two benzene rings is roughly 3.7 Å in each case, it is possible that π–π stacking interactions are stabilizing the diols in this folded conformation.

An exception to this general trend with tertiary diols was the C_6F_5-substituted diol **13**, which crystallized with the same "open" conformation as the secondary diol **4**, thus resulting in the formation of both inter- and intramolecular hydrogen bonds to provide the dimer shown (Figure 4).



Scheme 2. Synthesis of substituted diols. [a] $NaBH_4$. [b] Organolithium reagent. [c] $TMSCF_3$/TBAF. [d] Grignard reagent; see the Supporting Information for details. Cy = cyclohexyl, Fc = ferrocenyl, TBAF = tetra-*n*-butylammonium fluoride, TMS = trimethylsilyl.

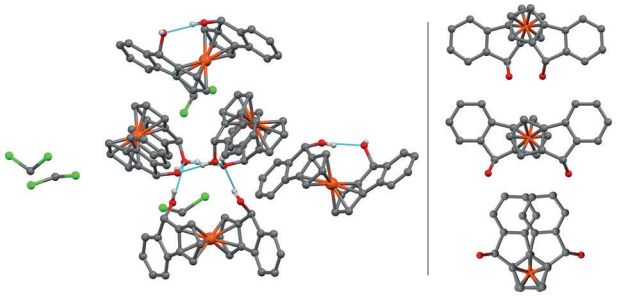


Figure 2. Left: Unit cell of secondary diol **4** showing an intra- and intermolecular hydrogen-bonding network. Right: Individual molecules of **4** taken from two separate crystal structures illustrate the flexibility of the diol scaffold. O red, Fe orange, Cl green.

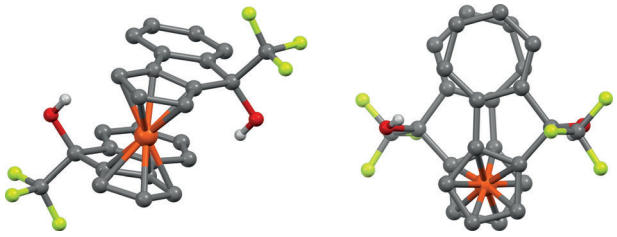


Figure 3. Front view (left) and top view (right) of the CF_3-substituted diol **6** in the solid state showing possible π–π stacking. O red, Fe orange, F yellow.

With members of our novel diol family demonstrating their propensity to form hydrogen bonds in the solid state we sought to apply these diols in asymmetric catalysis as a proof of concept.[2d] To this end we drew inspiration from the

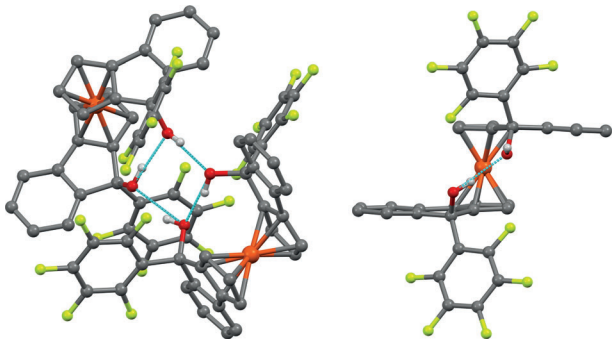
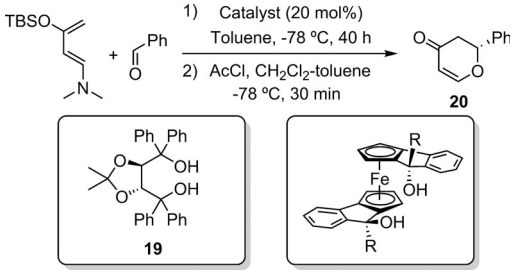


Figure 4. Dimer (left) and cross-section (right) of the C_6F_5-substituted diol **13** in the solid state. O red, Fe orange, F yellow.

elegant work of Rawal and co-workers, who demonstrated that diols such as TADDOL and BAMOL catalyze the hetero-Diels–Alder reaction between activated amino siloxy dienes and aldehydes.[9] As an initial test we employed the privileged catalyst TADDOL **19** as a control in the reaction of Rawal's diene with benzaldehyde before screening our range of novel diols, which allowed us to identify two of our diols as suitable chiral catalysts (Table 2). Interestingly, while all

Table 2: Catalyst screen for hetero-Diels–Alder reaction.



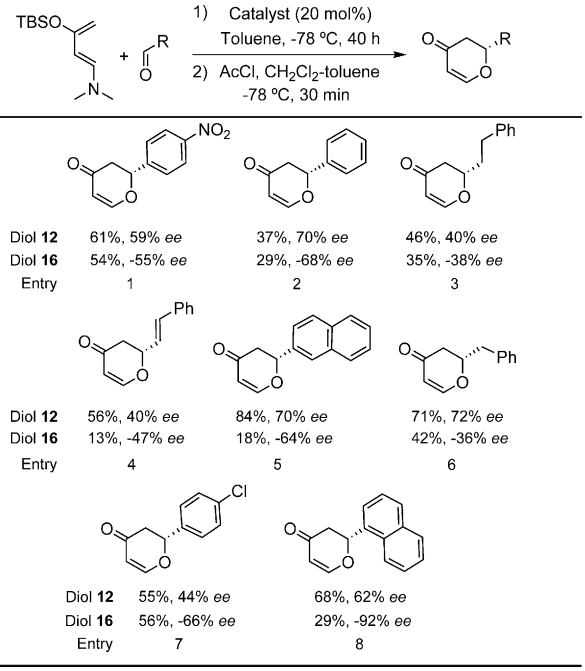
Entry	Catalyst	R	Yield [%]	*ee* [%]	Config.
1	**19**	n.a.	46	47	*S*
2	**12**	3,5-$(CF_3)_2C_6H_3$	37	70	*R*
3	**16**	1-Naphthyl	29	68	*S*

Yield is that of the isolated product. The *ee* value was determined by chiral SFC, see the Supporting Information for details and additional screening results. n.a. = not applicable, TBS = *tert*-butyldimethylsilyl.

aspects of chirality for the two diols **12** and **16** are identical, they provide cycloadducts of opposite absolute configuration (entries 2 and 3).

To probe if this sense of asymmetric induction was general we carried out a substrate scope with both catalysts (Table 3). A variety of different aldehydes were examined, including 5-aryl aldehydes with varying substitution at the *ortho*-, *meta*-, and *para*-positions (entries 1, 2, 5, 7, and 8) along with 2-alkyl aldehydes (entries 3 and 6) and one vinyl aldehyde (entry 4). With all eight substrates, **12** provided the same sense of stereoinduction with moderate to high yields (37–84%) and moderate to good *ee* values (40–72%). Conversely, the diol **16** consistently provided the other enantiomer in excess, with low to moderate yields (13–56%) and moderate to excellent

Table 3: Substrate scope for hetero-Diels–Alder.



Yield is that of the isolated product. The *ee* value was determined by chiral SFC, see the Supporting Information for details.

ee values (36–92%). In many cases the two diol catalysts **12** and **16** provided complementary results with similar *ee* values being obtained for the *R*- and *S*-enantiomers of the same product (entries 1–5). Although the yields and *ee* values obtained are modest in most cases, the fact that both enantiomers of the same product can be made simply by varying the aryl hydroxymethyl group on the catalyst is quite intriguing. This variation allowed us to obtain *ee* values of 72% for the *R*-configured product to 92% of the *S*-configured product with the same hand of catalyst and highlights the potential of this ligand/catalyst scaffold.

With regards to the mode of activation, we propose that the active catalyst contains both one intramolecular and one intermolecular hydrogen bond.[10] In this case the intramolecular hydrogen bond would further activate the remaining hydrogen by charge stabilization. Indeed, when the monoalcohol analogue of **12** (bottom Cp ring unsubstituted) was employed as a catalyst, no product was formed, even after 48 hours, thus indicating that the intramolecular hydrogen bond is essential for activation of the aldehyde. On the basis of our crystallographic studies and the observed absolute configuration of the cycloadducts obtained, we propose the following possible transition states to account for the observed stereodivergence (Figure 5 and Figure 6). With **12**, *Re-cis* would be the major source of the *R*-configured product with competition with the *Si-trans* transition state accounting for the moderate *ee* values obtained. With **16**, *Re-cis* is blocked by steric interactions between the aldehyde R group and the catalyst's upper naphthyl group, thus, accounting for the moderate to high *ee* values of the *S*-configured product obtained.

In summary, we have presented an optimized, chromatography-free synthesis of the chiral diketone (*Sp*)-**1**. The

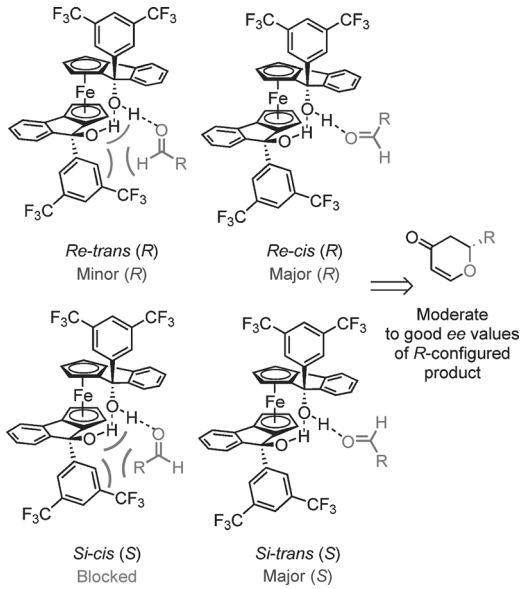


Figure 5. Possible transition states for catalyst **12**. The terms *Si* and *Re* define the face of aldehyde primed for attack by the diene while *cis* and *trans* define which aldehyde lone pair coordinates to the hydroxy proton.

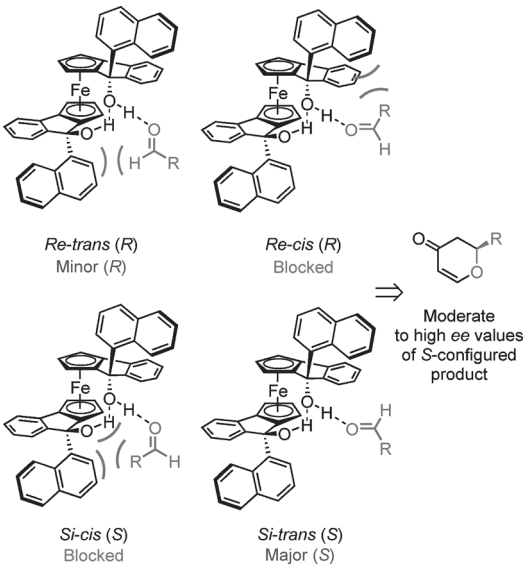


Figure 6. Possible transition states for catalyst **16**. The terms *Si* and *Re* define the face of aldehyde primed for attack by the diene while *cis* and *trans* define which aldehyde lone-pair coordinates to the hydroxy proton.

utility of this compound as a readily modifiable chiral scaffold has been effectively demonstrated with the preparation of 14 chiral diols and 1 chiral tetraol, all with complete enantiocontrol. Crystallographic studies of these diols revealed the formation of either intricate hydrogen-bond networks or π–π stacking interactions in the solid state. As a proof of concept, these diols were investigated as hydrogen-bond donor catalysts in an asymmetric hetero-Diels–Alder reaction, thus providing cycloadducts in up to 84% yield with *ee* values ranging from −92 to +72%. Further applications of these diols in both materials chemistry and asymmetric catalysis, along with the synthesis of new ligands and catalysts from this enantiopure scaffold are currently ongoing in our laboratory and will be reported in due course.

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Keywords: chirality · cycloaddition · diols · organocatalysis · planar chirality

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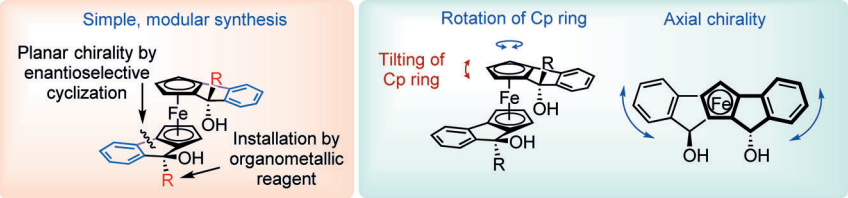
Communications

Planar Chirality

C. Nottingham, H. Müller-Bunz, P. J. Guiry* ——— ■■■■–■■■■

A Family of Chiral Ferrocenyl Diols: Modular Synthesis, Solid-State Characterization, and Application in Asymmetric Organocatalysis



Triple crown of chirality: Reported is the synthesis of a novel family of chiral ferrocenyl diols possessing planar, central, and axial chirality. X-ray crystallography reveals dense intra- and intermolecular hydrogen-bond networks. The potential of these diols as organocatalysts was demonstrated in an asymmetric hetero-Diels–Alder reaction, thus providing cycloadducts in up to 84% yield with *ee* values ranging from −92 to +72%.