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Planar Chiral Pseudo-Isocoumarins by Copper Catalysed Desymmetrisation

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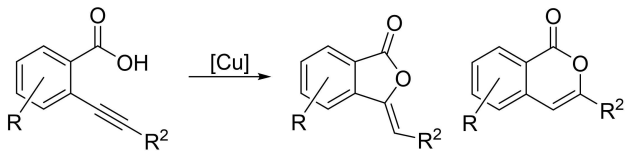
A new copper catalysed desymmetrisation reaction of bisalkynyl ferrocenecarboxylic acids using (*R,R*)-Ph-Pybox results in the first asymmetric synthesis of planar chiral pseudo-isocoumarins in up to 64% enantiomeric excess and up to 99% yield with complete regioselectivity. Tri-functionalised planar chiral ferrocenes are synthesised in five steps from commercially available materials, without the need for traditional directing group chemistry via an easily diversified route exploiting the double Sonogashira coupling reaction. The absolute configuration of the chiral heterocycles is proven by chemical correlation and circular dichroism spectroscopy giving the asymmetric reaction synthetic utility and opening the way for the rational extension of this method to produce bioactive isocoumarin-fused ferrocene derivatives.

Introduction

Isocoumarins have shown potential to be used for a wide range of medicinal applications[1–3] and asymmetric variants have been reported with a chiral substituent in the 3-position, from a chiral pool.[4] Isocoumarin structures are commonly synthesised by acid catalysed carboxylic acid-alkyne cyclisation,[5] but the copper catalysed cyclisation of analogous structures had been previously reported in the literature (Scheme 1).[6–9]

These cyclisations usually suffer from regioselectivity issues and can occur unavoidably as side-reactions due to copper(I) present in Sonogashira coupling.[10]

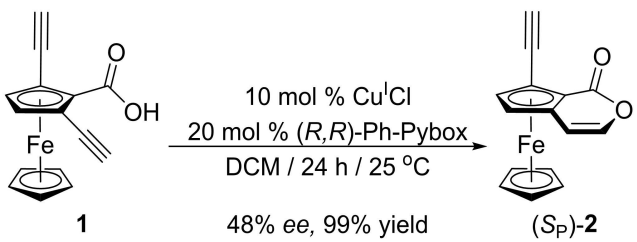
Substituted ferrocenes, and other organometallic moieties are finding increasing acceptance as part of novel, pharmaceutically valuable, bioactive compounds, including antibiotics.[11–13] Similarly, there are many naturally occurring and synthetic isocoumarins that have antibiotic properties,[14,15] so combining both pharmacophores in the same structure offers a unique approach to the design and development of novel antibiotics, currently a priority target because of increasing concern about the spread of resistant strains of many clinically significant microorganisms.[16,17] Unsymmetrically substituted ferrocenes have planar chirality, so when an isocoumarin ring is fused to a cyclopentadienyl ligand of ferrocene, issues about enantioselective synthesis are unavoidable, especially since for development of a new drug candidate, enantiopure compounds are much preferred to racemates when assessing bioactivity. The synthesis of planar chiral ferrocenes, usually by directed lithiation mediated by a chiral directing group,[18–23] is of ongoing interest while metal catalysed enantioselective cyclisations on activated alkynyl ferrocenes and desymmetrisation strategies for the installation of planar chirality are becoming more frequently used.[24–29] We report here a new method of asymmetric synthesis of isocoumarin-fused ferrocenes, based on our interest in the desymmetrisation of prochiral ferrocene diynes[30] by asymmetric click chemistry.[31]



Scheme 1. Representative, previously reported copper catalysed acid-alkyne cyclisations.

Results and Discussion

The availability of structure **1** (Scheme 2) gave us the opportunity to examine the unexplored potential of a desymmetrisa-



1 (SP)-**2**

Scheme 2. The asymmetric desymmetrisation of bisalkyne **1** generating planar chirality.

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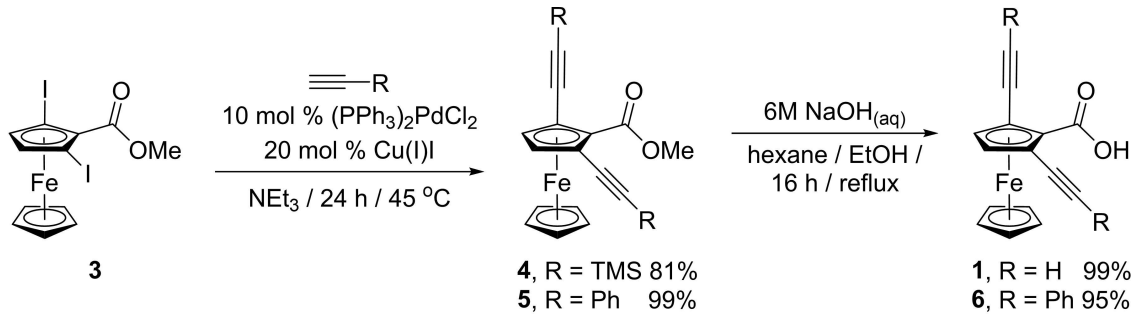


Scheme 3. The two-step procedure for the generation of bisalkynyl acids for desymmetrisation from diiodo compound **3**.

tion approach to synthesise planar chiral substituted isocoumarin-type structures based on ferrocene, so a test reaction was carried out using (*R,R*)-Ph-Pybox and copper(I) to see if cyclisation could occur and generate non-racemic planar chirality. We were pleased to find complete regioselectivity, generating only the 6 membered ring via a 6-endo-dig cyclisation, and an acceptable 48% enantiomeric excess in near quantitative yield.

The regioselectivity was determined by examining the Heteronuclear Single Quantum Correlation (HSQC) spectrum. The two protons on the double bond (6.92 and 6.25 ppm) were shown to be bonded to different carbons (signals corresponding to ^{13}C signals at 143.3 and 105.3 ppm respectively), supporting the presence of a six-membered ring, rather than a five-, which would have the two protons on the same external carbon.

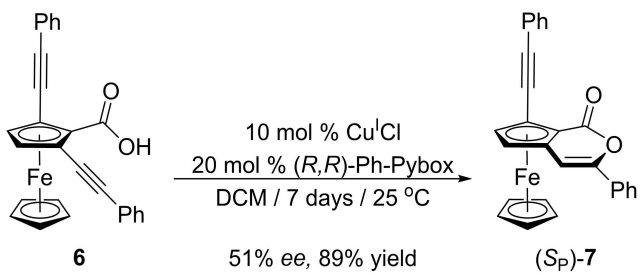
A selection of chiral ligands were then assessed, but our best results remain with (*R,R*)-Ph-Pybox. Surprisingly, the simpler (*S,S*)-Ph-box proved completely ineffective although the product **2** was still obtained in a $>90\%$ yield. Indeed, all four examples presented in Table 1 consistently provided excellent yields in the range 95–99%. Because of the modest but promising enantioselectivity obtained with the (*R,R*)-Ph-Pybox ligand, more structurally diverse oxazoline based ligands were explored, Spirobox[32,33] and InTOX.[34,35] Although both of these ligands successfully generated an *ee*, we were disappointed that neither could improve on the original result. We found it particularly surprising that no *ee* was generated when using bisoxazoline ligand (*S,S*)-Ph-box, although this could indicate that kinetic resolution played a major role in the *ee* generated in an analogous asymmetric copper catalysed azide-alkyne cycloaddition reaction.[30] This copper-ligand catalyst system cannot discriminate between the two enantiotopic alkynes in this process, so it is unlikely that *ee* is generated in an asymmetric induction process with an analogous compound in an asymmetric click reaction. If the monoalkyne formed by the desymmetrisation is of low *ee*, the *ee* observed in the sample of monoalkyne isolated when the reaction is worked up must arise from kinetic resolution in the step that forms the bisalkyne, depleting the minor enantiomer of the monoalkyne.

Li *et al.* have cyclised methyl 2-(phenylethynyl)benzoate using copper(II) chloride in 1,2-dichloroethane,[36] so we decided to examine the analogous ferrocene-based structure with phenyl groups in the terminal alkyne positions. This was synthesised by a double Sonogashira approach (Scheme 3),[37,38] to investigate the hypothesis that the asymmetric copper reaction conditions could also cyclise this structure. This simple two-step sequence allows a wide variety of structures to be generated from the 2,5-diiodomethyl ester **3** and the extension of our previous preparation of **1** afforded **6** in excellent yield. Ferrocene derivatives with substituted alkynes either side of an acid group could allow for isocoumarin synthesis with different groups in the 3-position.

The asymmetric cyclisation of **6** was first attempted using non-chiral reaction conditions, copper(I) chloride in dichloromethane, but this gave no reaction. After adding the (*R,R*)-Ph-Pybox ligand, however, and heating to reflux overnight, cyclisation of bisalkyne **6** had occurred. This reaction gave a 51% yield but a disappointing 4% *ee*, probably due to the more forceful reaction conditions. This reaction was repeated at 25 °C for 7 days and gave an improved 89% yield and 51% *ee* of the desired cycle **7** as shown in Scheme 4. Encouraged by

Table 1. The results of the ligand screening based on Scheme 2 for the desymmetrisation of ferrocenyl acid **1**.

Entry	Ligand	Product yield [%]	*ee* [%]	Major enantiomer
1	(*R,R*)-Ph-Pybox	99	48	S_P
2	(*S,S*)-Ph-box	97	*rac*	
3	(*S,S,S*)-Spirobox	95	37	R_P
4	(*S,R*)-InTOX	99	34	S_P



Scheme 4. The asymmetric desymmetrisation of bisalkyne **6** generating planar chirality.

this improved 51% *ee* with the phenyl substituted example, a wider range of chiral ligands was now surveyed (Table 2).

We are pleased to report an improved *ee*, albeit at the cost of conversion, of 64% when using the SpiroBOX ligand. In view of the longer time required for the preliminary test reaction shown in Scheme 4, the ligand screen reactions were allowed to run for 30 days in an attempt to ensure complete conversion. Despite this extended reaction time, to our surprise, Table 2 shows a wide range of yields, from 13 to 90%.

As with the desymmetrisation of bisalkyne **3**, PhPyBox and Spirobox were effective for the desymmetrisation of bisalkyne **6**. The best *ee* of 64% was obtained when using spiro ligand (*S*,*S*,*S*)-Spirobox, which gave the R_P enantiomer for desymmetrisation with both the terminal alkyne and phenyl alkynyl substrates. Phosphorus ligands (*R*,*R*)-^{i}Pr-DUPHOS and (R_P)-Xyl-PHANEPhos were not effective in this reaction. (*R*,*R*)-^{i}Pr-DUPHOS, for example, gave excellent conversion, but could not introduce a significant level of asymmetry. Oxazoline ligands proved to be most effective, with ligands (*S*,*S*,*S*)-Spirobox, (*S*,*R*)-InTOX, (*S*,*R*)-(Indenyl)-Pybox all generating noteworthy *ee*s. We hypothesised that these good results could in part be due to an acid-base interaction between the nitrogen atoms of the pendant oxazoline rings on the ligands and the acid group of the ferrocene substrates, and so isoquinoline based ligands (S_P,R_C)-^{n}Bu-QuinaPhos and (R_P)-QUINAP that had previously been shown effective in rhodium and ruthenium chemistry were tested,[39,40] but, to our disappointment, generated unimpressive *ee*s. Ligands (*R*,*R*)-Ph-Pybox and (*S*,*S*)-Ph-box gave the same enantiomer of ferrocene based isocoumarin [(S_P)-**7**, *vide infra*]. The structure of **7** was determined from the chemical shifts (^{1}H and ^{13}C) of the of the alkene CH by comparison with the corresponding position in compound **1** where this hydrogen is observed as a doublet. With the adjacent phenyl group, this coupling is absent in **7**, and this CH is assigned as 6.73 ppm and 100.3 ppm in the proton and carbon NMR spectra, respectively.

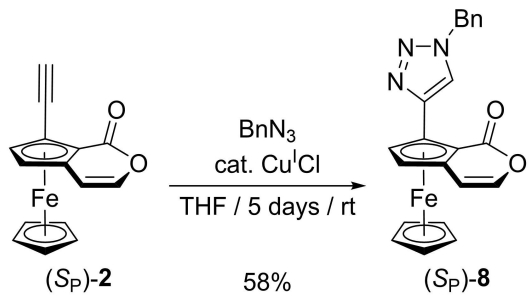
A similar stereoselectivity effect is observed between the results of indenyl ligands (*S*,*R*)-InTOX and (*S*,*R*)-(Indenyl)-Pybox; the chirality of the oxazoline groups is the same, but by introducing the central pyridine ring into ligand (*S*,*R*)-(Indenyl)-Pybox, the major enantiomer of the product formed is changed.

The configuration of the major enantiomer obtained from the desymmetrisation reactions was established by chemical correlation by synthesis of triazole **8** by two methods. One, the post-desymmetrisation modification of the unreacted alkyne of **2** to form a triazole (Scheme 5), and the other by the ester hydrolysis and cyclisation of mono-triazole **9** of known configuration obtained from our asymmetric copper catalysed azide-alkyne cycloaddition reaction (Scheme 6). It is not surprising that the (*R*,*R*)-Ph-Pybox copper-ligand system activates the same alkyne for both the cyclisation to generate (S_P)-**2** and the click reaction to generate (R_P)-**9**.[30]

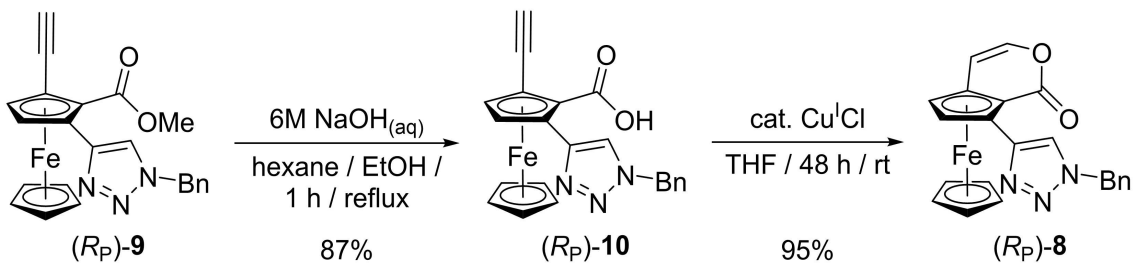
Comparison of the circular dichroism spectra of compound (S_P)-**2** generated in Table 1, entry 1 and (R_P)-**7** generated in Table 2, entry 6 allow the assignment of the absolute configuration of the phenyl-substituted example in Scheme 4. These two compounds, with opposite signs of optical rotation, are shown to be pseudo-enantiomeric by comparison of the diagnostic peak at approximately 500 nm in the circular dichroism spectra, Figure 1.[41] In our best examples, oxazoline ligands (*R*,*R*)-Ph-Pybox, (*S*,*S*,*S*)-Spirobox and (*S*,*R*)-InTOX favoured the formation of the same enantiomer when using both substrates, and the (*S*,*S*)-Ph-box ligand, which was extremely

Table 2. The results of the extended ligand screening based on Scheme 4 for the desymmetrisation of ferrocenyl acid **6**.

Entry	Ligand	Product yield [%]	*ee* [%]	Major enantiomer
1	(*R*,*R*)-Ph-Pybox	89	51	S_P
2	(*S*,*S*)-Ph-box	49	15	S_P
3	(*R*,*R*)-^{i}Pr-DUPHOS	90	4	R_P
4	(R_P)-Xyl-PHANEPhos	13	9	S_P
5	(*S*,*S*,*S*)-Spirobox	61	64	R_P
6	(*S*,*R*)-InTOX	25	42	S_P
7	(S_P,R_C)-^{n}Bu-QuinaPhos	82	23	R_P
8	(*S*,*R*)-(Indenyl)-Pybox	80	27	R_P
9	(R_P)-QUINAP	89	6	S_P



Scheme 5. Derivatisation of the unreacted alkyne of (S_P)-**2** to form a triazole.



Scheme 6. Generation of compound (R_P)-**8** in known absolute configuration, for comparison to the product of Scheme 5.

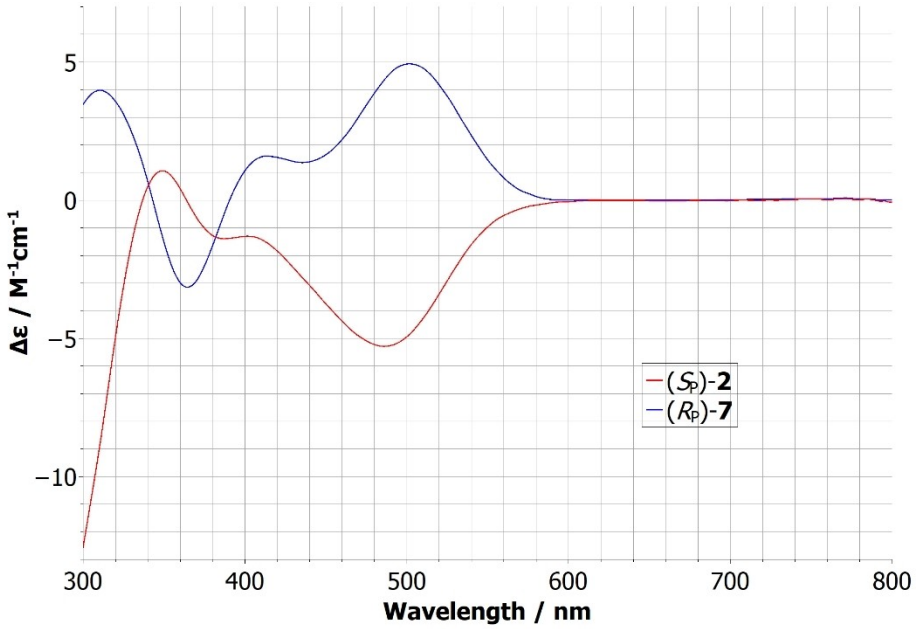


Figure 1. The circular dichroism curves of pseudo-enantiomers (S_P)-**2** and (R_P)-**7** used to determine the absolute configuration of **7**.

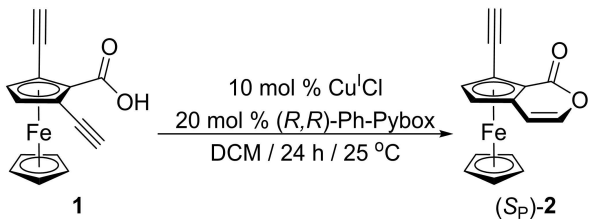
effective in our asymmetric click work,[30] was surprisingly ineffective in this system.

Conclusion

This work demonstrates the synthesis and desymmetrisation of 2,5-diethynylferrocenecarboxylic acids to generate enantiomerically enriched isocoumarin-fused planar chiral ferrocenes. While only moderate enantiomeric excesses are obtained, this work provides an inroad to the application of this cyclisation methodology to the synthesis of analogous structures, and because the absolute configuration has been proven, the compounds generated have synthetic utility. In just five synthetic steps, complex trisubstituted ferrocenes are generated in up to 64% *ee*. The method shows promise for further development for efficient enantioselective synthesis of bioactive planar chiral pseudo-isocoumarins including examples of diastereoselectivity where the pseudo-isocoumarin itself includes planar stereogenicity.

Experimental Section

A representative experimental procedure for the desymmetrisation of 2,5-diethynylferrocenecarboxylic acid 1.



1 (S_P)-**2**

Copper(I) chloride (1 mg, 7 μmol) and (*R*,*R*)-Ph-Pybox (5 mg, 14 μmol) were stirred in anhydrous dichloromethane (0.7 mL) for 10 minutes. Bisalkyne **1** (20 mg, 72 μmol) was added, and the solution was stirred at 25 °C for 24 hours. Distilled water was added (10 mL) and the reaction mixture was extracted with dichloromethane (3× 10 mL). Combined organics were dried over sodium sulfate. Solids were removed by filtration and the solvent removed *in vacuo*. Column chromatography (a gradient of hexane and dichloromethane from 50% to 75%) gave the cyclised product (S_P)-**2** in the second fraction (20 mg, 99%, 48% *ee*) as an orange oil; $[\alpha]_D^{22} = -162$ ($c = 1.79$, $CHCl_3$), δH (500 MHz, $CDCl_3$) 6.92 (d, $J = 5.7$ Hz, 1H), 6.25 (d, $J = 5.7$ Hz, 1H), 4.78 (d, $J = 2.6$ Hz, 1H), 4.75 (d, $J = 2.6$ Hz, 1H), 4.22 (s, 5H), 3.10 (s, 1H) ppm, δC (125 MHz, $CDCl_3$) 167.2, 143.3, 105.3, 85.4, 79.5, 78.1, 76.4, 73.0, 66.6, 66.1, 64.4 ppm, ATR-IR (νmax/cm^{-1}) 3281, 3109, 2923, 2850, 2131, 1736, 1373, 1223, 962, CD λmax (DCM) / nm 349 (Δε/$M^{-1}cm^{-1}$ 1.06), 387 (−1.39), 486 (−5.29), MS (ES+, TOF) *m/z*: $[M+H]^+$ calculated for $C_{15}H_{11}O_2{}^{56}Fe$ 279.0108, found 279.0118. The enantiomeric excess was determined using a Daicel Chiralcel AY-3 HPLC column (4.6 mm x 250 mm) at 25 °C, eluted with hexane/IPA = 70/30 at 0.8 mL/min, λ = 258 nm, t-(major) = 17.71 mins, t(minor) = 27.07 mins.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Asymmetric catalysis · Asymmetric synthesis · Circular dichroism · Chirality · Metallocenes

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