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Sulphur ylide-mediated stereoselective synthesis of a stable ferrocenyl epoxide

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Abstract—The sulphur ylide-mediated synthesis of epoxides from aldehydes with in situ generation of diazocompounds has been used to prepare, for the first time, a stable epoxyferrocene, *trans*-2-phenyl-3-ferrocenyloxirane **3**. By means of a chiral sulphide, oxirane **3** has been obtained with high enantioselectivity. Nucleophilic opening of the epoxide ring in **3** by azide anion takes place regioselectively at the position adjacent to the ferrocene moiety and with retention of configuration.

Epoxides are very versatile compounds in organic chemistry, and their importance as synthetic intermediates cannot be overemphasised.[1] In accordance with that, the interest in the development of new methods for their preparation, especially in optically active form, continues unabated.[2] In the course of a research program devoted to the synthesis of new central chiral ferrocene derivatives,[3] we became aware of the fact that ferrocenyl-substituted oxiranes are practically unknown, extremely unstable compounds. While they have never been adequately characterised, their existence as reactive intermediates has been mainly inferred from the structures of the products obtained in their attempted formation.[4] On the other hand, β-ferrocenyl epoxides are perfectly stable.[4c,5] The instability of α-ferrocenyl epoxides has been attributed to the outstanding ability of the ferrocenyl group to stabilise an adjacent positive charge,[6] that renders the oxirane moiety very prone to a variety of ring-opening processes like nucleophilic opening or rearrangement to aldehydes (Chart 1).

Notwithstanding these precedents, we hypothesised that the use of mild reaction conditions and the introduction of appropriate substituents at the oxirane ring would give access to these hitherto elusive compounds. We report here on the successful implementation of these ideas, as exemplified by the synthesis of the first stable α-ferrocenyl epoxide, *trans*-2-ferrocenyl-3-phenyloxirane, both in racemic and in highly enantiopure form.

Among the available methods for the stereoselective preparation of epoxides, the sulphide-mediated epoxidation of aldehydes by diazo compounds, developed by some of us a few years ago,[7] seemed to be the most suitable one for our purposes as asymmetric oxidative processes were unlikely to be compatible with easily oxidised ferrocene moiety. This ylide process takes place under essentially neutral conditions, and has been successfully applied to a number of acid- and base-sensitive aldehydes.[8] Furthermore, by using a suitable chiral sulphide, highly enantiopure epoxides can be

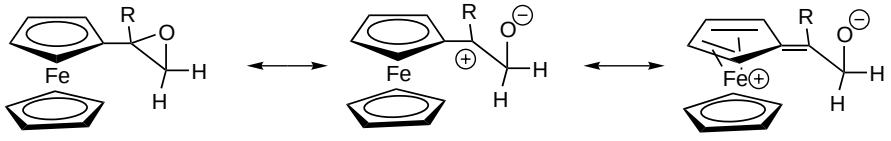

Chart 1. Resonance structures of an α-ferrocenyl epoxide.

Keywords: asymmetric synthesis; epoxides; ferrocenes; sulphur ylides.

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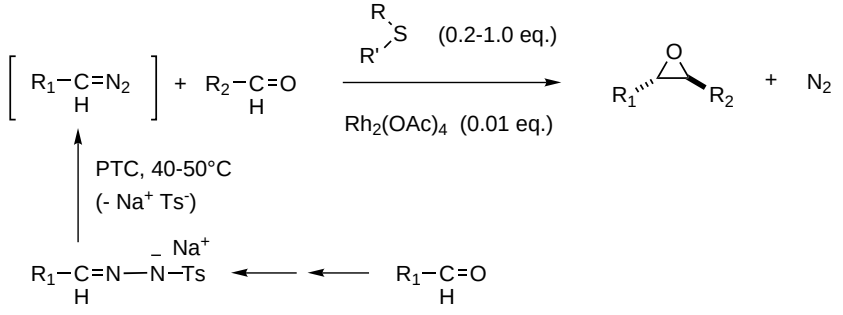
obtained.[9] From a practical point of view, the presently most convenient way to implement this methodology involves the in situ generation of the diazo compound by the thermal decomposition of a tosylhydrazone salt in a non-protic solvent with the aid of a phase-transfer catalyst (PTC)[10] (Scheme 1).

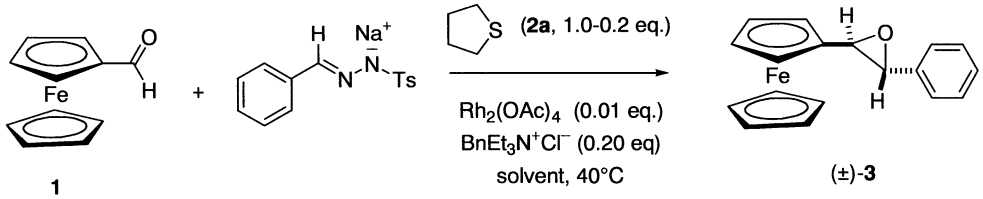
According to this methodology, when a mixture of ferrocenecarbaldehyde **1** (1 molar equiv.), tetrahydrothiophene **2a** (1.0–0.2 equiv.) and benzaldehyde tosylhydrazone sodium salt (1.5 equiv.) was heated at 40°C in the presence of benzyltriethylammonium chloride (0.2 equiv.) and of a catalytic amount of dirhodium(II) tetraacetate, the formation of the expected *trans*-2-ferrocenyl-3-phenyloxirane **3** was clearly observed by ^{1}H NMR analysis (Table 1). The rate of the process was highly dependent on the solvent used: when the reaction was run in acetonitrile, a substantial amount (ca. 30%) of ferrocenecarbaldehyde remained after 22 h (entry 1). Changing the solvent to 1,2-dimethoxyethane (entry 2), and in the absence of PTC, total conversion could only be achieved after 5 days; in 1,4-dioxane, the formation of the epoxide was complete in 8 h (entry 3). In this solvent, the use of substoichiometric amounts of **2a** resulted in longer reaction times (entry 4). After work-up, the crude reaction mixture contained essentially racemic epoxide **3**, identified on the basis of its spectral properties, together with small amounts of products arising from the tosylhydrazone sodium salt.

Although **3** appeared to be thermally stable (a sample stored for 7 months in the freezer showed no trace of ketonic rearrangement products), attempted chromatographic purification on silica gel resulted in extensive decomposition, and 1-ferrocenyl-2-phenylethane-1,2-diol could be isolated in 18% yield as the sole identifiable product. In order to get additional confirmation of the *trans*-stereochemistry of the epoxide,[11] crude **3** was reacted with a mixture of sodium azide and ammonium chloride in refluxing ethanol,[12] to give the azido alcohol **4** in 58% overall yield (from **1**) after chromatographic purification (Scheme 2). NOE experiments performed on this compound showed that the nucleophilic opening of the epoxide ring had taken place exclusively at the carbon vicinal to the ferrocene moiety. Catalytic hydrogenation of **4** afforded the corresponding amino alcohol **5**, that upon treatment with triphosgene in basic aqueous medium[13] was quantitatively converted into the 4-ferrocenyl-5-phenyl-1,3-oxazolidin-2-one **6**. The *trans* stereochemistry of **6** was established both by NOE experiments and by the 6.2 Hz value of the coupling constant between the heterocyclic ring protons.[3] This result is in complete accordance with the assumption of a *trans* relative configuration for **3**, and constitutes the first proof that nucleophilic substitution reactions at the ferrocene-substituted carbon of α-ferrocenylepoxides take place with total retention of configuration via a mechanism involving neighbouring group participation of the *d* electrons on iron, as observed with other ferrocene derivatives.[6c]



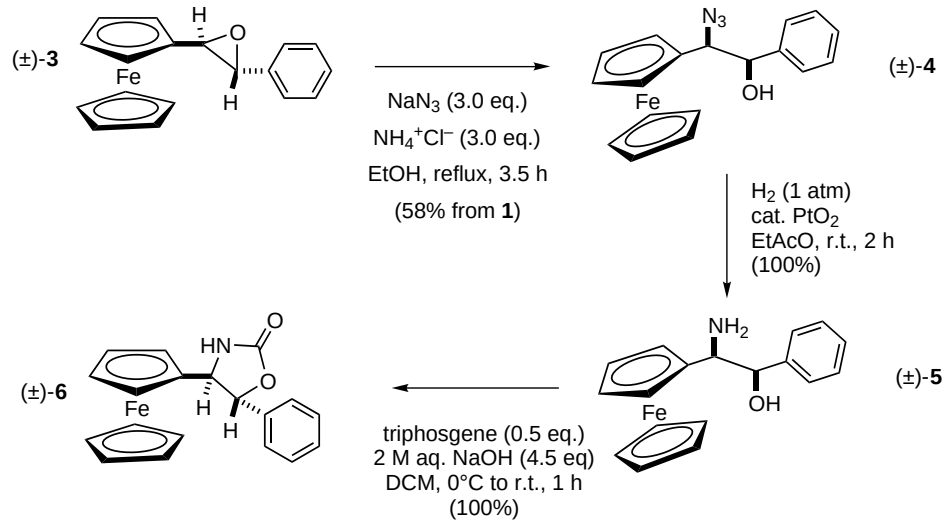
Scheme 1. Sulfide-mediated epoxidation of aldehydes by diazocompounds.

Table 1. Preparation of racemic *trans*-2-ferrocenyl-3-phenyloxirane **3**



Entry	**2a** (*x* mol%)	Solvent	Reaction time (h)	**3**:**1** ratio[a]
1	100	Acetonitrile	22	2:1
2	100	DME[b]	120	>98:2
3	100	1,4-Dioxane	8	>98:2
4	20	1,4-Dioxane	18	>98:2

[a] By ^{1}H NMR analysis of the crude product.
[b] (DME = 1,2-dimethoxyethane) No PTC was used in this case.

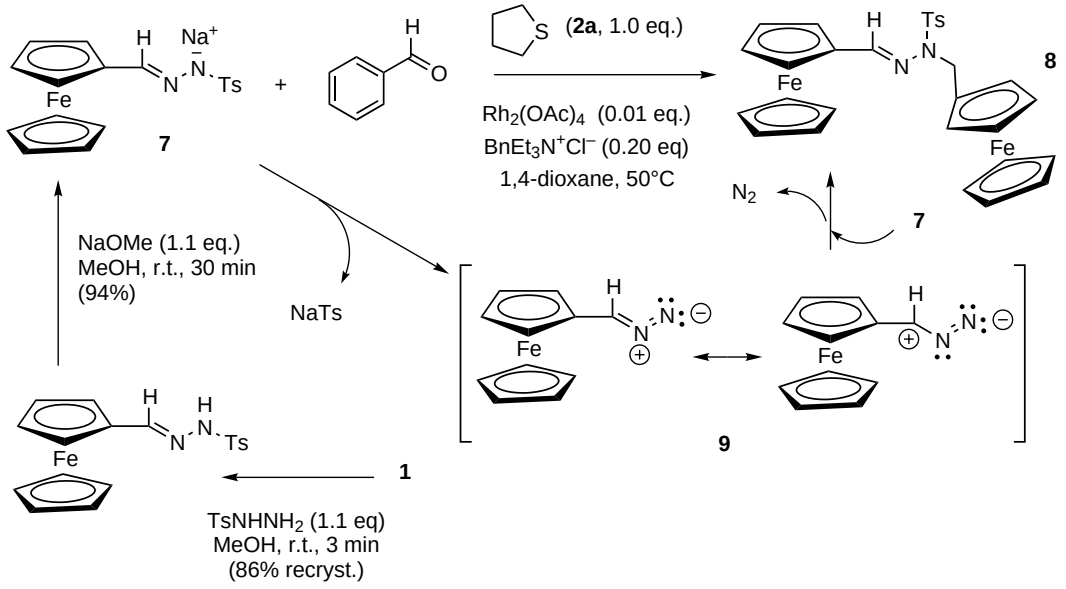


Scheme 2. Nucleophilic opening of ferrocenyloxirane **3**.

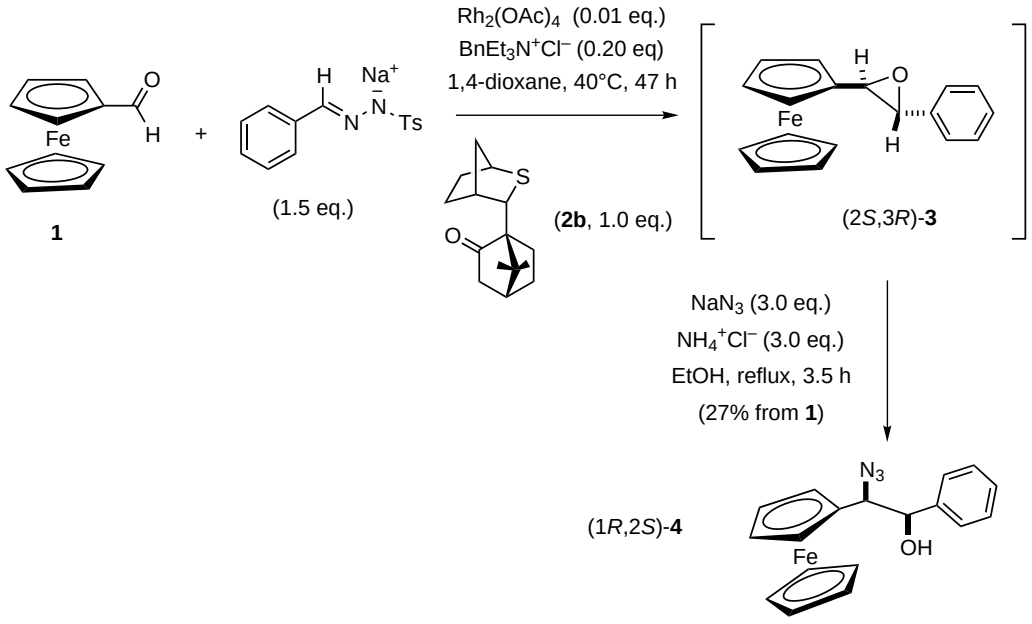
It is worth noting here that all attempts to generate **3** in an alternative way by reaction of benzaldehyde with the sodium salt of ferrocenecarbaldehyde tosylhydrazone (**7**) were unsuccessful, and led to complex mixtures in which the dimeric compound **8** could be identified (Scheme 3). The formation of this compound may be explained by assuming that, due to the ability of the ferrocene moiety to stabilise an adjacent positive charge, the initially produced ferrocenyldiazomethane (**9**) has a strong electrophilic character, and that it reacts with **7** faster than being converted to the rhodium carbene intermediate.

Finally, when 1 equiv. of the chiral sulphide **2b**[10] was used in the reaction of **1** with the benzaldehyde tosylhydrazone sodium salt, ^{1}H NMR of the product mixture showed that ferrocenyloxirane **3** was formed, approximately in 30% yield (Scheme 4). When the crude product of this reaction (containing starting aldehyde **1**, epoxide **3** and sulphide **2b**) was treated with sodium azide under the same conditions of Scheme 2, chromatographic purification led to the isolation of (1*R*,2*S*)-1-azido-1-ferrocenyl-2-phenylethanol **4**, in 27% yield (from **1**) of high enantiomeric purity (95% ee determined by HPLC on a Chiralcel-OD column). *trans*-2-Ferrocenyl-3-phenyloxirane **3** can thus be obtained with high enantioselectivity, although in low chemical yield, by means of sulphide **2b**; we assigned the (2*S*,3*R*) absolute configuration to **3** on the basis of the sense of asymmetric induction shown by **2b** in similar reactions.[10]

In summary, we have demonstrated that the sulphur ylide-mediated epoxidation of aldehydes with in situ generation of diazo compounds provides a unique tool for the synthesis of α-ferrocenyloxiranes, and that the



Scheme 3. Attempted reaction of tosylhydrazone sodium salt **7**.



Scheme 4. Enantioselective preparation of ferrocenyloxirane **3**.

presence of an aryl substituent in the 3-position renders these compounds stable enough for their complete characterisation. Moreover, we have also shown that by means of a suitable chiral sulphide these epoxides can be obtained with high enantioselectivity. These results pave the way for the preparation of new chiral auxiliaries or ligands[14] derived from this hitherto almost unknown class of ferrocene derivatives.[15]

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11. The low vicinal coupling constant of 2.5 Hz exhibited by **3** is typical of *trans* epoxides.
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15. All new compounds were completely characterised and gave satisfactory spectral and analytical data. Experimental procedures for **3** and **4**. *trans*-**2-Ferrocenyl-3-phenyloxirane 3**. Tetrahydrothiophene (30 mg, 0.34 mmol), anhydrous 1,4-dioxane (1 mL), rhodium(II) acetate dimer (1.5 mg, 0.0034 mmol), benzyl triethylammonium chloride (15 mg, 0.066 mmol), ferrocenecarbaldehyde (**1**, 71 mg, 0.33 mmol) and benzaldehyde tosylhydrazone sodium salt (148 mg, 0.50 mmol) were added sequentially to a 5 mL flask. The reaction mixture was stirred under a static nitrogen pressure at room temperature for 10 min and then at 40°C for 7 h. After cooling to room temperature, the reaction was quenched by the addition of water (0.5 mL) and ethyl acetate (0.5 mL), and the phases were separated. The aqueous layer was washed with ethyl acetate (2×1 mL) and the combined organic phases dried (Na_2SO_4), filtered, and concentrated in vacuo, to afford crude epoxide **3** (130 mg, quantitative yield) that was not further purified. When the reaction was performed in the conditions described above but using 6 mg (0.068 mmol, 0.2 mol equiv.) of tetrahydrothiophene, essentially the same results were obtained after stirring the mixture for 18 h at 40°C. IR (NaCl film): $\nu = 3091$, 2918, 1494, 1455, 1164, 1106 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 3.62$ (d, $J = 2.5$ Hz, 1H), 3.88 (d, $J = 2.5$ Hz, 1H), 4.20 (m, 2H), 4.24 (m, 5H), 4.27 (m, 1H), 4.35 (m, 1H), 7.35 (m, 5H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 61.3$ (CH), 62.3 (CH), 66.2 (CH), 67.7 (CH), 68.3 (CH), 68.5 (CH), 68.7 (CH), 83.3 (Cq), 125.3 (CH), 128.1 (CH), 128.5 (CH), 137.4 (Cq) ppm. MS (CI, NH_3): $m/e = 199$ (44%), 305 (MH^+, 100%), 322 (MNH_4^+, 9%). HRMS (CI) calcd for $C_{18}H_{16}FeO$: 304.0551; found: 304.0554. **(1*R**,2*S**)-2-Azido-2-ferrocenyl-1-phenylethanol 4**. To a solution of the crude epoxide **3** obtained above (0.33 mmol) in absolute ethanol (1 mL) sodium azide (65 mg, 1 mmol) and ammonium chloride (54 mg, 1 mmol) were added sequentially. The resulting mixture was heated to reflux and stirred under nitrogen for 3.5 h. After cooling at room temperature, the solids were filtered out and washed thoroughly with ethanol. After removal of the solvent in vacuo, the residue was dissolved in ethyl acetate (5 mL), the solution was washed with water (2×1 mL) and the phases were separated. The aqueous phase was washed with ethyl acetate (2×1 mL) and the combined organic phases dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by column chromatography (triethylamine-pretreated silica gel, 2.5% v/v) eluting with hexane/diethyl ether mixtures of increasing polarity, to afford 66 mg (58% overall yield from **1**) of the azido alcohol **4** as an orange-coloured oil. IR (NaCl film): $\nu = 3440$, 3089, 3031, 2921, 2105, 1453, 1262, 1169, 1106 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.59$ (d, $J = 5.0$ Hz, 1H, OH), 3.82 (m, 1H), 4.20 (m, 8H), 4.40 (d, $J = 7.5$ Hz, 1H), 4.69 (m, 1H), 7.20 (m, 5H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 66.6$ (CH), 68.0 (CH), 68.1 (CH), 68.8 (CH), 68.9 (CH), 77.9 (CH), 85.7 (Cq), 126.7 (CH), 128.1 (CH), 128.3 (CH), 140.3 (Cq) ppm. MS (CI, NH_3): $m/e = 305$ (25%), 347 (M^+, 20%), 365 (MNH_4^+, 9%). HRMS (CI) calcd for $C_{18}H_{17}FeN_3O$: 347.0721; found: 347.0712.