First Epoxidation Reaction of Carbonyl Compounds via Ferrocenyl Sulfur Ylides

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Abstract: Epoxidation reactions of carbonyl compounds (aldehydes and a ketone) mediated by sulfanyl ferrocenes have been successfully achieved in a one-pot reaction, under mild conditions. This reaction implies intermediary formation of a sulfonium salt (a ferrocenyl one was observed for the first time by 1H NMR) and then an ylide. The diastereoselectivity of the formation of stilbene oxide was unusual: the effect of steric hindrance and aromatic nature of the sulfide substituents have been evidenced. A catalytic asymmetric example with a planar chiral ferrocene is described.

Key words: sulfur , ylides, epoxidations, aldehydes, ferrocene, stereoselectivity

Ferrocene derivatives have received much attention in the two last decades. A number of ferrocenylphosphines were shown to be efficient bidentate ligands for transition-metal-catalysed asymmetric reactions.1–3 However, only a few examples of reactions using non-phosphino ferrocenes as catalysts were described in the literature. Sulfur derivatives of metallocenes may find useful applications in chemistry in connection with a variety of sulfur functional groups: sulfides, sulfoxides, sulfimines, thiocarbonyl compounds, etc. Togni reported the synthesis of a variety of ferrocenyl sulfides and some of their uses.4,5 Daï described Tsuji–Trost alkylations with ferrocenyl oxazoline ligands, 6 whereas Bolm used similar ligands for dialkylzinc additions to aldehydes.7 Bäckvall and co-workers developed ferrocenyl thiolates as ligands in the copper-catalyzed substitution of allylic acetates with Grignard reagents.8 More recently, 2-amino-substituted 1-sulfinylferrocenes were used as efficient ligands for the asymmetric addition of diethylzinc to aromatic aldehydes.9

Connecting an ylide moiety to a ferrocene may provide original structures and reactivity. Indeed, ferrocenyl phosphoros ylides are known and used in Wittig reactions.10 Surprisingly, their sulfanylated analogues have not yet been described in the literature (Scheme 1) and consequently, have never been applied for the epoxidation of carbonyl compounds. We anticipated sulfonium salt formation adjacent to the ferrocenyl group would be favored in analogy to the stabilization of ferrocenyl carboca-

Scheme 1

First of all, we have worked with achiral sulfides. The introduction of sulfur on the ferrocene molecule may be efficiently achieved by several methods. The most common way involves the formation of a ferrocenyllithium (substituted or not), followed by the introduction of the appropriate electrophile, i.e. a disulfide6,12–14 or a sulfinate. 9 An alternative involves nucleophilic substitution on a carbon adjacent to a Cp ring, by reacting a thioacetate with an acetate4 or an ammonium.3

Using the first method, Kagan and co-workers described the formation of methyl and phenyl sulfanyl derivatives from the reaction of ferrocenyllithium and the corresponding disulfides in moderate to good yields.12,15 We reproduced these syntheses with Kagan optimized conditions15 and extended them to others R1 groups (Scheme 2, Table 1).

Scheme 2

Art Id.1437-210X,E:2003,0,14,2249,2254,txt,en;C03903SS.pdf.
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Monosubstitution of ferrocene has been achieved in good yields. In the case of the phenyl compound (entry 2), the yield was improved from 40% to 54%. The problem of bis-lithiation was encountered, as previously reported. This was followed by the formation of the undesired disubstituted products (entries 1–5, Table 1). These compounds were isolated by slow elution through column chromatography. Compound (R = t-Bu) decomposed during these purification conditions (entry 3).

Table 1 Synthesis of Ferrocenyl Sulfides

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>Product</th>
<th>2 (%)</th>
<th>3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>a</td>
<td>67</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>b</td>
<td>54</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu</td>
<td>c</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Cy</td>
<td>d</td>
<td>67</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>Bn</td>
<td>e</td>
<td>61</td>
<td>23</td>
</tr>
</tbody>
</table>

* Decomposed on silica gel.

As ferrocenyl sulfonium salts had not been described in the literature, so we desired to monitor their formation by ¹H NMR. Methylsulfanylferrocene (2a) and 2 equiv of benzyl bromide were mixed together in a 9:1 mixture of CD₃CN–D₂O. The conversion of sulfide into sulfonium bromide was measured over 14 h (Scheme 3, Figure 1). After 5 min, a signal appeared at δ = 3.19, corresponding to the methyl group (δ = 2.27 in 2a). The reaction mixture composition seemed stable after 5 hours and the equilibrium ratio sulfide–sulfonium salt was about 7:93.

![Scheme 3](image)

Figure 1 Formation of ferrocenyl sulfonium salt

Deprotonation of the sulfonium salt was then monitored by adding 2 equiv of KOD. After 10 min, the ¹H NMR spectrum showed that the two benzylic hydrogens were exchanged. So, the deprotonation was fast and reversible, as expected from a previous study.

Since the sulfonium salt formation was effective, we investigated the potential of our derivatives in epoxidation reactions under the conditions recently reported with a C₂ symmetrical sulfide. They involve a practical one-pot procedure under mild conditions: at room temperature using a 9:1 mixture of t-BuOH–H₂O as solvent and a mineral base. In situ formation of the sulfonium salt and the ylide are requisite for a version that is designed to be catalytic in sulfide. The carbonyl compounds tested were aromatic and aliphatic aldehydes and a ketone (Scheme 4, Table 2).

![Scheme 4](image)

In all cases the expected oxiranes were formed as judged by ¹H NMR. Attempted isolation by column chromatography of the crude product revealed that they have a polarity very similar to that of ferrocenyl sulfides, requiring tedious separations. Then, we chose to oxidize the sulfide into the corresponding sulfoxide with 1 equiv of MCPBA. This reaction was fast and the new derivatives were more polar. This allowed easy purification by silica gel column chromatography.

In most cases, oxiranes were obtained in good to excellent yields (entries 1–7). For 2a, reaction times were comparable to those of a standard thiolane (entries 1 and 7). A catalytic amount (0.2 equiv) of sulfide 2a could be successfully used (entry 5) but needed 7 days for completion. This time could be significantly reduced (to 1.5 d) by using 1 equiv of iodide salt (entry 6) to perform halogen exchange and in situ formation of the more reactive benzyl iodide. Conversion of an aliphatic aldehyde, CyCHO, led mainly to cis-oxiranes (entries 7 and 15). This is unusual for sulfur ylides but similar trends were noted with the aromatic aldehyde series to the aliphatic one. With 2c and 2e (R = t-Bu and Bn, entries 13 and 17, respectively), no epoxidation reaction took place and degradation of aldehyde and auxiliary was observed. A ketone was converted into a trisubstituted oxirane but required prolonged reaction time (entry 8).

No epoxidation reaction occurred with the phenylsulfanyl ferrocene (2b) (entry 10). The reaction was conducted in the solvent mixture MeCN–H₂O (9:1) to improve the solubility of 2b. However, after 14 days, only tribenzylamine was formed from acetonitrile and benzyl bromide in the presence of NaOH. The use of the benzylsulfanyl derivative 2e (entry 16) showed moderate conversion, even after 14 days. Consequently, sulfides 2a, 2c and 2d (R = Me, t-Bu and Cy) are efficient for epoxidation reaction.
We have also compared the epoxidation reaction with monosulfanyl \textit{2a} and disulfanyl \textit{3a} derivatives (entries 1 and 9). No change was observed from \textit{2a} to \textit{3a}. Thus, disubstitution was not kinetically significant.

Diastereoselectivity is a synthetic key issue. It is not yet fully controlled for the epoxidation reaction, and deserves further studies. In our case, when the size of the R group increases, we observed a higher trans diastereoselectivity. For benzaldehyde, the diastereomeric ratio was about 60:40 with \textit{2a} (R = Me, entry 1) but rose to 80:20 with \textit{2c} and \textit{2d} (R = t-Bu and Cy, entries 11 and 14, respectively). Influence of the solvents was also studied, with the example of methylsulfanyl ferrocene (\textit{2a}).

Three different solvents of increasing polarity as mixture with H$_2$O were used (CH$_2$Cl$_2$ < MeCN < DMSO, entries 2–4). Results showed that the reactions were faster in more polar solvents (entries 2 and 4), probably due to a better stabilization of the charged intermediates (sulfonium salts, ylides and betaines). Diastereomeric ratios were higher in MeCN and DMSO (entries 3–4) than in t-BuOH (entry 1), in accordance to previous observations. 19 Somewhat surprisingly, the best dr was obtained in a biphasic CH$_2$Cl$_2$–H$_2$O system (entry 2).

How can we rationalize the effect of steric hindrance and nature of the solvent on diastereoselectivity? What do we know of kinetic versus thermodynamic control?

The reversibility of the formation of the \textit{syn} and \textit{anti} betaines has been investigated by equilibration and cross-over reactions.19,20 We wished to carry out such experiments with our ferrocenyl epoxidation system. We have thus synthesized independently the corresponding diastereomerically pure sulfonium salts by reaction of a ferrocene thiolate separately with trans- and cis-stilbene oxides,21 and S-alkylation of the resulting hydroxysulfides with methyl triflate.22 Treatment with sodium hydroxide provided stilbene oxides. To discount a possible base-catalyzed epimerization, a second set of experiments was performed by adding 3 equiv of a more reactive aldehyde, $p$-nitrobenzaldehyde (Scheme 5).

With both solvents (t-BuOH and CH$_2$Cl$_2$) the \textit{anti} betaine \textit{7} selectively gave the \textit{trans} epoxide, whereas the \textit{syn} one \textit{8} gave \textit{cis} (major) epoxide accompanied by the \textit{trans} isomer [15% in CH$_2$Cl$_2$–H$_2$O (9:1), 11% in t-BuOH–H$_2$O (9:1)]. In CH$_2$Cl$_2$–H$_2$O, cross-over product with $p$-ni-
trobenzaldehyde was observed (trans isomer, 25%), with a 1:3 ratio over the cis-stilbene oxide. In t-BuOH, 4% of cross-over product (trans only) was observed.

These experiments showed that formation of the anti betaine is irreversible whereas formation of the syn one was reversible to some extent, in both dichloromethane and protic solvent, t-BuOH. Our observations are somewhat different of those of Aggarwal and his group with dimethyl sulfide. They noticed that equilibration was more significant in CH₂Cl₂–H₂O, with 42:58 (trans/cis) ratio from the syn betaine. In DMSO, equilibration was complete.

We propose a tentative mechanism to explain the observed diastereomeric preferences, using a cisoid approach (Scheme 6). Indeed, recent calculations have led to the proposal that, in the case of dimethyl sulfide and benzaldehyde, the first intermediates were formed through a ‘cisoid’ approach, imposed by coulombic interactions between the sulfonium and the oxy group. Subsequent torsional rotation around the C–C bond gave the rotamer betaine where the charged groups were syn. Finally, trans elimination led to the oxiranes.

The higher trans selectivity noticed with ferrocenyl sulfur ylides of increasing steric hindrance may be due to steric interactions between R¹ and Ph in the syn betaine. Consequently, the torsional rotation in this betaine was disfavored, leaving starting material (ylide and aldehyde). As a result, more trans oxirane was formed.

Now, when comparing to standard sulfides, the stereoselectivities are puzzling. This led us to some complementar- y experiments with model sulfides, in our standard epoxidation conditions (Table 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfide</th>
<th>Time (d)</th>
<th>Stilbene Oxide Yield (%)</th>
<th>dr (trans–cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>thiolane</td>
<td>1</td>
<td>95</td>
<td>85:15</td>
</tr>
<tr>
<td>2</td>
<td>MeSMe</td>
<td>0.3</td>
<td>86</td>
<td>83:17</td>
</tr>
<tr>
<td>3</td>
<td>PhSMe</td>
<td>4</td>
<td>83</td>
<td>64:36</td>
</tr>
<tr>
<td>4</td>
<td>MeSt-Bu</td>
<td>2.15</td>
<td>98</td>
<td>94:6</td>
</tr>
</tbody>
</table>

Unhindered sulfides, thiolane and dimethyl sulfide, led to stilbene oxide with 85:15 and 83:17 (trans–cis) ratios (entries 1 and 2). With a more hindered compound, t-butyl methyl sulfide, the ratio rises to 94:6 (entry 4), confirming again that steric hindrance enhances the trans selectivity. These data are far from the ratios observed with ferrocenyl sulfides. For example, compound 2a (FeSMe) exhibits a ratio of 62:38 (trans–cis). An effect, other than steric, is thus operative here. Anticipating an electronic effect, we examined a sulfide with an aromatic group. Interestingly, thioanisole gave a 64:36 ratio (entry 3), very similar to that of ferrocenyl methyl sulfide 2a. The aromaticity of this structure, and consequently its ability to stabilize charged intermediates by delocalization seems to be a key point. This stabilization would reduce the difference in the syn and anti betaine transition state energies and induce less stereochemical discrimination than in the case of non-aromatic auxiliaries. In summary, for ferrocene sulfides, we have almost no kinetic stereoselectivity, and this is only slightly counterbalanced (in favor of the trans isomer) by a minor equilibration of the syn betaine. This stands in contrast with Aggarwal’s observations of a largely predominant trans selectivity and significant thermodynamic contribution.

Having shown that ferrocenyl sulfides efficiently mediate the epoxidation reaction, we wished to demonstrate that asymmetric induction was feasible, using an enantiopure sulfide bearing only planar chirality. We have tested the behavior of ferrocene 9, bearing a sulfanyl group with a sterically hindered tert-butyl, and an ortho-substituent, an amino group, whose nucleophilicity was reduced by an electro-withdrawing substituent. The sulfoxide, corresponding to 9, was an efficient catalyst for the asymmetric addition of diethylzinc to aldehydes. Under our standard conditions, a reaction has been performed with 0.2 equiv of sulfide 9 to lead to stilbene oxide in reasonable yield (Scheme 7). Again, an unexpected diastereomeric ratio (trans–cis, 56:44) was observed. The trans isomer was produced in a promising 67% enantiomeric excess, in favor of the S,S enantiomer.

Our strategy is thus feasible. This is the first example of an asymmetric conversion of aldehyde into oxirane mediated by sulfur ylides with planar chirality. Current studies are underway to explore the scope of this new type of
chiral catalysts and its design towards a higher stereoselectivity.

In summary, we have achieved the first epoxidation reaction of carbonyl compounds via ferrocenyl sulfur ylides. It involved formation of ferrocenyl sulfonium salts, observed for the first time and monitored by $^1$H NMR. Deprotonation and reaction with aldehydes led to oxiranes in good yields. The stereocchemical course kinetically favors more cis isomer than usual with other sulfides, probably related to an earlier transition state. Steric hindrance of the sulfide provided enhanced percentage of the trans isomer, with some reversibility of the cis precursor formation. An enantioselective version has been successfully achieved for the first time with planar chirality, and other structures are under investigation.

THF was freshly distilled from sodium-benzophenone before use. Hexane was distilled from P$_2$O$_5$. All non-aqueous reactions were carried out in oven-dried septum capped flasks, and under atmospheric pressure of N$_2$. Commercial reagents were used directly as received. All liquid reagents were transferred via oven–dried syringes. Lithium bases were purchased from Aldrich and concentrations were checked before experiments by titration with diphenylacetic acid. All reactions were monitored by TLC carried out on analytical silica gel TLC plates purchased from Merck silica gel and visualized with UV light and phosphomolybdic acid (1g in 100 mL –PrOH). Preparative flash liquid chromatography was performed with Merck 60 silica gel (40–63 microns) in the eluting solvents indicating below. Petroleum ether refers to the fraction of bp 35–60 °C. $^1$H NMR spectra were recorded on Bruker DPX 250 spectrometer. $^13$C NMR spectra were determined with the same spectrometer. $^13$C NMR spectra were run on Perkin–Elmer 684 and 16 PC FT–IR. Mass spectra were obtained with a Varian 3800 (GC) and Saturn 200 MS (c100) spectrometers. Elemental analyses were performed on elemental analyser, model Carloergo Erba 1108. Treatments are detailed below.

### Methyl Sulfanyl Ferrocene (2a)

#### General Procedure

A mixture of ferrocene (1.000 g, 5.37 mmol) in an anhyd mixture of THF–hexane (1:1, 2.50 mL) was stirred at r.t. for 30 min and then cooled to 0 °C. t-BuLi (10.00 mL, 10.70 mmol, 1.07 M in pentane) was then added at a rate of approximately 1 mmol/min. After 30 min, methyl disulfide (1.00 mL, 11.25 mmol) was added, the mixture was allowed to warm to r.t. and stirred until the reaction was complete as judged by TLC (petroleum ether–Et$_2$O, 95:5). Hydrolysis was performed withaq NaOH (2 M; 10 mL), theaq layer was extracted with Et$_2$O (3 × 10 mL). The organic layer was washed with brine (25 mL) and H$_2$O (25 mL), dried (MgSO$_4$), filtered then concentrated. Column chromatography (petroleum ether–Et$_2$O, 100:0 to 99:1) gave sulfide 2a [yield: 839 mg (3.61 mmol, 67%); orange oil] and disulfide 3a$^b$ [yield: 402 mg (1.44 mmol, 27%); dark orange oil].

### Phenyl Sulfanyl Ferrocene (2b)

Prepared from 1 (1.030 g; 5.54 mmol) in 54% yield as detailed for 2a. Flash chromatography (petroleum ether–EtOAc, 100:0 to 0:100) gave 2b [yield: 887 mg (3.01 mmol); orange crystalline solid] and 3b$^b$ [yield: 900 mg (2.24 mmol, 40%); dark orange crystalline solid]. Compound 3c was not isolated. Compound 1 (38 mg, 0.20 mmol, 8%) was recovered.

### t-Butyl Sulfanyl Ferrocene (2c)

Prepared from 1 (501 mg, 2.69 mmol) in 44% yield as detailed for 2a. Flash chromatography (petroleum ether–EtOAc, 100:0 to 250:2) gave 2c [yield: 326 mg (1.19 mmol); orange powder]. Compound 3c was not isolated. Compound 1 (23 mg, 0.12 mmol, 2%) was recovered.

### Cyclohexyl Sulfanyl Ferrocene (2d)

#### Methyl Sulfanyl Ferrocene (2e)

Prepared from 1 (1.000 g, 5.37 mmol) in 67% yield as detailed for 2a. Flash chromatography (petroleum ether–EtOAc, 100:0 to 99:1) gave 2d [yield: 1.075 g (3.58 mmol); orange powder] and 3d [yield: 497 mg (1.20 mmol, 22%); pale orange powder]. Compound 1 (23 mg, 0.12 mmol, 2%) was recovered.

### Cyclohexyl Sulfanyl Ferrocene (2d)

Prepared from 1 (1.000 g, 5.37 mmol) in 67% yield as detailed for 2a. Flash chromatography (petroleum ether–EtOAc, 100:0 to 99:1) gave 2d [yield: 1.075 g (3.58 mmol); orange powder] and 3d [yield: 497 mg (1.20 mmol, 22%); pale orange powder]. Compound 1 (23 mg, 0.12 mmol, 2%) was recovered.

### 1,1’-Bis(Cyclohexyl Sulfanyl)Ferrocene (3d)

Prepared from 1 (1.004 g, 5.40 mmol) in 61% yield as detailed for 2a. Flash chromatography (petroleum ether–EtOAc, 100:0 to 98:2) gave 2e [yield: 1.020 g (3.31 mmol); orange crystalline solid] and 3e$^{b,b}$ [yield: 534 mg (1.24 mmol, 23%); pale orange powder]. Compound 1 (54 mg, 0.29 mmol, 5%) was recovered.

### Benzyl Sulfanyl Ferrocene (2e)

Prepared from 1 (1.004 g, 5.40 mmol) in 61% yield as detailed for 2a. Flash chromatography (petroleum ether–EtOAc, 100:0 to 98:2) gave 2e [yield: 1.020 g (3.31 mmol); orange crystalline solid] and 3e$^{b,b}$ [yield: 534 mg (1.24 mmol, 23%); pale orange powder]. Compound 1 (54 mg, 0.29 mmol, 5%) was recovered.

### Benzyl Sulfanyl Ferrocene (2e)

Prepared from 1 (1.004 g, 5.40 mmol) in 61% yield as detailed for 2a. Flash chromatography (petroleum ether–EtOAc, 100:0 to 98:2) gave 2e [yield: 1.020 g (3.31 mmol); orange crystalline solid] and 3e$^{b,b}$ [yield: 534 mg (1.24 mmol, 23%); pale orange powder]. Compound 1 (54 mg, 0.29 mmol, 5%) was recovered.
2-Methyl-2,3-diphenyloxirane 6, 24
Yield: 87 mg (0.43 mmol); colourless oil.

Yield: 58 mg (0.28 mmol) pale yellow oil.

Ether–EtOAc, 95:5) gave ether–Et₂O, 98:2). H₂O (2 mL) was then added and the aq phase was dried (MgSO₄) and concentrated to dryness.

To a cooled solution of the crude oxiranes in CH₂Cl₂ (2 mL) was slowly added MCPBA (135 mg, 0.55 mmol) in CH₂Cl₂ (3 mL). The mixture was stirred at 0 °C for 45 min and then allowed to warm to r.t. The reaction was monitored by TLC (petroleum ether–EtOAc, 99:1 to 95:5). The mixture was washed with sat. aq NaHCO₃ (2 mL) and brine (4 mL). Column chromatography (petroleum ether–EtOAc, 99:1 to 95:5) afforded stilbene oxiranes 2-Cyclohexyl-3-phenyloxirane 5, 24
Yield: 99 mg (0.50 mmol, 99%); white oily solid.

Prepared from cyclohexanecarboxaldehyde (61/L, 0.50 mmol) in 56% yield as detailed for 4. Flash chromatography (petroleum ether–EtOAc, 95:5) gave 5.

Yield: 87 mg (0.43 mmol); colourless oil.

2-Methyl-2,3-diphenyloxirane 6, 24
Prepared from aceophenone (60 µL, 0.50 mmol) in 56% yield as detailed for 4. Flash chromatography (petroleum ether–EtOAc, 95:5) gave 6.

Yield: 58 mg (0.28 mmol); pale yellow oil.

Acknowledgments

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