Chapter 4

Highly Enantioselective sulfide oxidation with chiral iron complex using aqueous hydrogen peroxide as terminal oxidant
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4.1. Introduction

Chiral sulfoxides are valuable compounds for their application as chiral auxiliaries [1], ligands [2], organo-catalysts [3, 4] and in pharmaceutical industries [5-7]. The direct and most efficient synthetic route to synthesize chiral sulfoxides was simultaneously developed by Kagan et al. [8] and Modena et al. [9] by using modified Sharpless epoxidation catalytic system. Since then there was spurt of activity in this area of research and the last two decades have seen important piece of works [10, 11]. Some of the frequently used metal ions in asymmetric sulfoxidation include titanium [12-16], vanadium [17-20], manganese [21, 22] and iron [23-42] with various oxidant such as aqueous hydrogen peroxide (H$_2$O$_2$), tertiary butyl hydrogen peroxide (TBHP) and Cumene hydroperoxide (CHP). Besides these, aluminum [43, 44], copper [45] polyoxometalate [46, 47] based metal complexes were also explored. Alternatively organo catalysts [48, 49] have also shown their worth, however, their tedious multistep synthesis and expense of production restricts them in large scale synthesis. Though metal based catalysts are efficiently promoted the asymmetric sulfoxidation reaction, but the contamination of toxic metal in the product is a serious issue especially for the synthesis of biologically active intermediates and products. In this context iron based catalysts seek utmost attention [50, 51] as it is less toxic, inexpensive, most abundant and environment friendly. Recently, Benjamin List et al. reported asymmetric counter-anion directed catalysis (ACDC) [42] in asymmetric sulfoxidation using iron complex containing a chiral phosphate counter ion. This catalytic protocol provided excellent enantioselectivity for few substrates using PhIO as an oxidant. Among the asymmetric sulfoxidation protocol utilizing iron based catalysts, use of hydrogen peroxide as terminal oxidant looks more attractive due to environmental and economic reasons, although this combination has inherent problem, as most of the first row transition metals have high activity for the decomposition of H$_2$O$_2$, thereby cause catalyst destruction via hydroxyl radical generation [40]. Nevertheless, dinuclear iron-(−)-4,5-pinene-2,2’-bipyridine complex by Fontecave and co-workers [31-33] and iron-amino alcohol derived Schiff base complexes by Blom et al. [34] set the stage for the iron-H$_2$O$_2$ combination. Unfortunately the product yield and enantioselectivity remained in low to moderate domain. However, this complex showed a quantum improvement in its catalytic performance when a catalytic amount Li/Na salt of 4-methoxy benzoic acid was used as an additive [35, 36], but still show moderate enantioselectivity for the ortho substituted aryl methyl sulfides. Later on Katsuki et al. reported iron-salan complex catalyzed asymmetric
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sulfoxidation with H₂O₂ [38] in water medium giving the desired product in high yield and enantioselectivity. Still Fe-H₂O₂ combination is under represented for this reaction, except for couple of reports by Simonneaux et al. in 2011 [40] where iron-porphyrin catalyst was used giving moderate to high enantioselectivity of sulfoxide (highest ee being 87%) and by Tsogoeva et al. [41] in 2012 using in situ generated iron complex of primary amine-derived non-symmetrical Schiff base (with FeCl₃ as iron source) but with lower enantioselectivity (highest ee being 36%). Our conviction for Fe-H₂O₂ based catalytic system is that it may provide excellent results if we hit upon right combination of ligand design and iron source.

This chapter of the thesis demonstrates the synthesis of a series ONONO type ligands 8'-11’ and their in situ generated iron complexes as catalysts in enantioselective sulfoxidation of prochiral sulfides. Among these ligand 8’ with Fe(acac)₃ as iron source provided high enantioselectivity (highest ee being 98%), selectivity and good yield of the desired product under very mild reaction condition.

4.2. Experimental Section

4.2.1. General methods and materials

As mentioned earlier, all the substrates (sulfides) were purchased from TCI chemicals (Japan), Acros organics and Sigma Aldrich (USA) and were used without further purification. Starting materials for the synthesis of ligands viz. (S)-(+)-tert-leucinol, (S)-(+)‐valinol, (S)-(−)-phenylalaninol, (1R,2S)-(+)‐cis-1-amino-2-indanol, 4-tert-butyl-2,6-diformylphenol and iron salts such as iron(III) 2,4-pentanedionate, Iron(III) 1,3-diphenyl-1,3-propanedionate and iron(III) chloride for the synthesis of chiral complexes were purchase from Sigma Aldrich (USA). Urea hydrogen peroxide (UHP) and tert-butyl hydrogen peroxide (TBHP) were purchased from Merck, 30% aqueous H₂O₂ was from Rankem (India) and all required solvents were from Spectrochem (India). All reagents were used as received but the solvents were dried and stored over activated molecular sieve under nitrogen atmosphere. ¹H NMR and ¹³C NMR spectra of ligands were obtained from Bruker-Avance-DPX-200 (200 MHz) or 500 MHz spectrometer at ambient temperature using TMS as internal standard. Electronic spectra were recorded in chloroform on a Varian Cary 500 Scan UV–vis.–NIR spectrophotometer and TOFF mass of the catalysts and intermediates were determined on a Micromass Q-TOF-micro instrument. The enantiomeric excess of sulfoxides were determined by chiral Shimadzu-HPLC with SPD-M10A-VP and SPD-M20A UV detector and PDR-Chiral Lnc. advanced Laser Polarimeter (PDR-CLALP), using chiral Daicel Chiralcel columns with 2-propanol/hexane mixture as
eluent of the crude products. Absolute configurations of chiral sulfoxides were determined by comparing the sign of optical rotation (obtained from PDR-CLALP) and elution order with the literature. The conversion and selectivity were determined by integrating the methyl proton signal of sulfide, sulfoxide and sulfone in $^1$H NMR spectra of the crude reaction mixture, but for phenyl ethyl sulfoxide and phenyl benzyl sulfoxide products were isolated.

4.2.2. *Synthesis of amino alcohol derived Schiff base ligands 8*-11’

Chiral ligands were synthesized by the condensation reaction of readily available 4-tert-butyl-2,6-diformylphenol with chiral 2-aminoethanol derivatives by the modified procedure. The solvent for the condensation was taken depending on the solubility of the product.

4.2.2.1. **Procedure for the synthesis of ligand 8’**

To a stirring solution of 4-tert-butyl-2,6-diformylphenol (E) (1 mmol) in dry toluene (10 ml) under nitrogen atmosphere, was added (S)-(+-)tert-leucinol (2.2 mmol) solution in 2 ml dry toluene at room temperature under N$_2$ atm. (Scheme 4.1). After the addition of (S)-(+-)tert-leucinol, yellow precipitate of the ligand started to form. The reaction mixture was then heated to 70 °C and allowed to stir for 36 h. After the complete consumption of the bis-aldehyde (checked on TLC), yellow precipitate was filtered and washed three times with cold toluene to remove the excess L-tert-leucinol and dried under vacuum. The final compound was isolated as yellow solid; yield: 88 %; m.p.: 247-249 °C; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta = 14.65$ (s, 1H), 8.53 (s, 2H), 7.80 (s, 2H), 4.49 (s, 2H), 3.78 (d, 2H, $J = 10.5$ Hz), 2.86, (d, 2H, $J = 8.5$ Hz), 1.29 (s, 9H), 0.92 (s, 18H) ppm; $^{13}$C NMR (50 MHz, DMSO-d$_6$): $\delta = 159.15$, 139.73, 128.11, 120.64, 80.51, 60.45, 33.65, 32.76, 31.07 ppm; Anal. Calcd. for C$_{24}$H$_{40}$N$_2$O$_3$ C, 71.25; H, 9.97; N, 6.92; Found C, 71.31; H, 9.89; N, 6.97; TOF-MS (ESI+): m/z Calcd. for [C$_{24}$H$_{40}$N$_2$O$_3$] 404.30, Found 405.27 [M+H]$^+$. 

**Scheme 4.1** Synthesis of chiral ligand 8’
4.2.2.2.  **Procedure for the synthesis of ligand 9’**

To a stirring solution of 4-tert-butyl-2,6-diformylphenol (E) (1 mmol) in dry methanol (5 ml), was added (S)-(+)−valinol (2.2 mmol) in methanol (1 ml) (Scheme 4.2). After the addition of amino alcohol the color of the reaction mixture changes to from light yellow to deep yellow. The reaction mixture was then allowed to stir for 24 h. After the complete consumption of 4-tert-butyl-2,6-diformylphenol (checked in TLC), reaction mixture was concentrated and kept at RT for crystallization. Yellow crystals were filtered off and washed with little amount of cold methanol. Yield: 85 %; m.p.: 197-199 °C; 

$^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 14.57$ (s, 1H), 8.56 (s, 2H), 7.77 (s, 2H), 4.66 (s, 2H), 3.65 (d, 2H, $J = 10$ Hz), 3.00 (s, 2H), 1.90 (m, 2H), 1.27, (s, 9H), 0.86, (d, 12H, $J = 7$ Hz) ppm; 

$^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 159.48$, 139.64, 128.42, 120.67, 76.96, 62.74, 33.67, 31.09, 29.21, 19.89, 18.00 ppm; Anal. Calcd. for C$_{22}$H$_{36}$N$_2$O$_3$C, 70.18; H, 9.64; N, 7.44; Found C, 70.24; H, 9.59; N, 7.48; TOF-MS (ESI+): m/z Calcd. for [C$_{22}$H$_{36}$N$_2$O$_3$] 376.27, Found 377.44 [M+H]$^+$ and 378.49 [M+2H]$^+$. 

![Scheme 4.2 Synthesis of chiral ligand 9’](image)

4.2.2.3.  **Procedure for the synthesis of ligand 10’**

To a stirring solution of 4-tert-butyl-2,6-diformylphenol (E) (1 mmol) in dry methanol (4 ml), was added solid (S)−(−)−phenylalaninol (2.2 mmol) (Scheme 4.3). After 15 min, yellow precipitate of the product started to form. The reaction mixture was then allowed to stir for 24 h. at RT. After the complete consumption of the bis-aldehyde (checked in TLC), yellow precipitate was filtered and washed two times with little amount of ice-cold methanol to remove the excess amino alcohol and dried under vacuum. The final compound obtained as yellow solid; yield: 75 %; m.p.: 136-138 °C; 

$^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 14.25$ (s, 1H), 8.38 (s, 2H), 7.68 (s, 2H), 7.26-7.23 (m, 4H), 7.19-7.14 (m, 6H), 4.83 (s, 2H), 3.61 (m, 2H), 3.48 (d, 2H, $J = 3.5$ Hz), 2.97 (dd, 2H, $J = 13.5$ Hz).
Hz, $J = 3.5$ Hz), 2.79 (dd, 2H, $J = 13.5$ Hz, $J = 8$ Hz), 1.25 (s, 9H) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 159.19, 139.84, 138.90, 129.35, 128.13, 125.96, 120.45, 73.01, 64.24, 38.47, 33.74, 31.13$ ppm; Anal. Calcd. for C$_{30}$H$_{36}$N$_2$O$_3$: C, 76.24; H, 7.68; N, 5.93; Found C, 76.19; H, 7.74; N, 5.87; TOF-MS (ESI+): m/z Calcd. for [C$_{30}$H$_{36}$N$_2$O$_3$] 472.27, Found 473.48 [M+H]$^+$ and 474.54 [M+2H]$^+$.

Scheme 4.3 Synthesis of chiral ligand 10'

4.2.2.4. Procedure for the synthesis of ligand 11'

To a stirring solution of 4-tert-butyl-2,6-diformylphenol (E) (1 mmol) in dry methanol (4 ml), was added solid (1R,2S)-(+)-cis-1-amino-2-indanol (2.2 mmol). After 15 min. yellow precipitate of the product started to form (Scheme 4.4). The reaction mixture was then allowed to stir for 24 h. at RT. After the complete consumption of the bis-aldehyde (checked in TLC), yellow precipitate was filtered and washed two times with little amount of ice-cold methanol to remove the excess amino alcohol and dried under vacuum. The final compound obtained as yellow solid; yield: 78 %; m.p.: 195-197 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 14.18$ (br, 1H), 8.81 (s, 1H), 8.68 (s, 1H), 7.82 (s, 1H), 7.53 (d, 1H, $J = 2.5$ Hz), 7.43 (d, 1H, $J = 2.5$ Hz), 7.35-7.34 (m, 1H), 7.31-7.27 (m, 2H), 7.23-7.21 (m, 3H), 7.14-7.12 (m, 1H), 5.04 (br, 2H), 4.77-4.70 (m, 2H), 4.53 (q, 2H, $J = 5$ Hz), 3.17-3.07 (m, 2H), 2.99-2.89 (m, 2H), 1.27 (s, 9H) ppm; $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 166.43, 161.38, 158.84, 142.39, 142.07, 141.81, 141.63, 141.17, 140.98, 139.17, 139.06, 128.52, 128.48, 127.99, 127.78, 126.69, 126.57, 126.46, 125.58, 124.99, 124.62, 124.62, 124.55, 124.43, 117.35, 87.28, 78.48, 74.05, 73.77, 73.20, 68.35, 33.72, 31.12 ppm; Anal. Calcd. for C$_{30}$H$_{32}$N$_2$O$_3$: C, 76.90; H, 6.88; N, 5.98; Found C, 76.84; H, 6.93; N, 6.07; TOF-MS (ESI+): m/z Calcd. for [C$_{30}$H$_{32}$N$_2$O$_3$] 468.24, Found 469.51 [M+H]$^+$.
4.2.3. General procedure for asymmetric sulfoxidation

The mixture of \(8'-11'\) (0.0075 mmol) and Fe(acac)\(_3\) (0.005 mmol) in dry DCM (1 ml), was stirred for 3 h at room temperature. After the formation of complex \(p\)-OMeC\(_6\)H\(_4\)COOH (0.005 mmol) was added to the reaction mixture and continued stirring for 20 min. Thereafter the addition of appropriate sulfide (0.25 mmol), the reaction mixture was allowed to stir for another 20 min. Finally 1.2 equiv. of aqueous hydrogen peroxide (30%; 34 μl, 0.3 mmol) was added in 6 fraction over 40 min. and the reaction mixture was allowed to stir for 12 h. Then the reaction was quenched by washing the organic layer was washed three times with water (1 ml \(\times\) 3), sample of the crude reaction mixture was taken for the HPLC to check the enantioselectivity of the product and \(^1\)H NMR analysis to determined, conversion and selectivity.

4.3. Results and Discussion

In the beginning of study we have synthesized a series of ONONO donor ligands (8’-11’) by the simple condensation of commercially available 4-tert-butyl-2,6-diformylphenol with different chiral amino alcohols (Scheme 4.5). Thereafter these ligands were stirred with iron salt to generate the corresponding iron complexes in situ in DCM for sulfoxidation reaction.

To evaluate the catalytic efficiency towards the sulfide oxidation using aqueous H\(_2\)O\(_2\) as a stoichiometric oxidant, these complexes were used as catalyst for the asymmetric oxidation of methyl phenyl sulfide in DCM at RT.

Since free metal itself can catalyze the oxidation of sulfide in non-chiral pathway, to insure the complete complexation of iron, 1.5 equiv. of ligand with respect to iron salt was taken for the ligand screening experiments (Table 4.1). The selectivity for the desired product is excellent for all the ligands and the yield is moderate to high, but in terms of...
enantioselectivity the ligand 8', derived from *tert*-leucinol provided quite high ee (73%) for the initial experiment. Rest of the ligands except 9' (40% ee) showed very poor enantioselectivity (Table 4.1, entries 3-5).

**Scheme 4.5** Synthesis and structure of the synthesized ligands

**Table 4.1** Screening of ligands for asymmetric sulfoxidation of methyl phenyl sulfide.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion (%)(^b)</th>
<th>Selectivity (%)(^b)</th>
<th>ee (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8'</td>
<td>82</td>
<td>95</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>9'</td>
<td>75</td>
<td>90</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>10'</td>
<td>67</td>
<td>98</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>11'</td>
<td>55</td>
<td>98</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^a\) Reaction condition: methyl phenyl sulfide (0.25 mmol), Fe(acac)\(_3\) (2 mol%), Ligand (3 mol%), aqueous H\(_2\)O\(_2\) (30%, 1.2 equiv.), in DCM (1 ml) at RT for 12 h.

\(^b\) Conversion and selectivity were calculated by \(^1\)H NMR analysis.

\(^c\) Enantiomeric excess were determined by HPLC analysis on a chiral phase Daicel Chiralcel OD column.
After the optimization of the ligands, next we tested Fe(1,3-di-Ph acac)$_3$ and FeCl$_3$ as alternative sources of iron for the *in situ* generation of catalyst, considering the effect of counter ion on the catalytic activity (Figure 4.1). The selectivity of these metal sources were comparable but both provided very poor enantioselectivity and conversion.

![Figure 4.1 Screening of iron source for the enantioselective oxidation of methyl phenyl sulfide using 8' as ligand and aqueous H$_2$O$_2$ as oxidant at RT.](image)

So based on these experiments 8' was selected as ligand and Fe(acac)$_3$ as metal source for the optimization of catalyst loading and metal to ligand ratio (Table 4.2). We observed a considerable decrease in the enantioselectivity when the catalyst loading was decreased to 1 mol% (conversion 70%, ee 59%) from 2 mol% (conversion 82%, ee 73%) with minor decrease in the conversion and on increasing the catalyst loading to 4 mol% (conversion 93%, ee 72%) the yield increased slightly without any improvement in the ee value, but a significant drop in selectivity (95% to 85%) was noted at higher catalyst loading (Table 4.2, entries 1-3). Considering the structure and the number of the donor centre in the catalyst we could not denied the binding of two iron atom with one ligand, so next the metal to ligand (8') ratio was optimized by keeping the amount of metal source fixed. With the metal to ligand ratio 1:0.5, a significant drop in both conversion and enantioselectivity (conversion 67%, ee 55%) was observed, with 1:1 ratio conversion was almost comparable (conversion 73%, ee 64%) but the ee value still little less than obtained with 1:1.5 ratio. Further increase in the metal to ligand ratio 1:2 (conversion 76%, ee 68%) caused only marginal decrease in the enantioselectivity. The obtained results (Table 4.2,
entries 4-6) suggest the binding of one iron atom with one ligand to generate the active catalyst *in situ*. Furthermore we found that at once addition of the oxidant caused a substantial drop in enantioselectivity (Table 4.2, entry 7).

**Table 4.2** Optimization of catalyst loading and metal to ligand ratio with 8′/Fe(acac)₃.¹

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading (mol%)</th>
<th>Metal:Ligand</th>
<th>Conversion (%)ᵇ</th>
<th>Selectivity (%)ᵇ</th>
<th>ee (%)ᶜ</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1:1.5</td>
<td>70</td>
<td>94</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1:1.5</td>
<td>82</td>
<td>95</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>1:1.5</td>
<td>93</td>
<td>85</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1:0.5</td>
<td>67</td>
<td>94</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>1:1</td>
<td>73</td>
<td>96</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1:2</td>
<td>76</td>
<td>96</td>
<td>68</td>
</tr>
<tr>
<td>7ᵈ</td>
<td>2</td>
<td>1:1.5</td>
<td>81</td>
<td>95</td>
<td>65</td>
</tr>
</tbody>
</table>

¹ Reaction condition: methyl phenyl sulfide (0.25 mmol), Fe(acac)₃, 8′, aqueous H₂O₂ (30%, 1.2 equiv.), in DCM (1 ml) at RT for 12 h.

ᵇ Conversion and selectivity were calculated by ¹H NMR analysis.

ᶜ Enantiomeric excess were determined by HPLC analysis on a chiral phase Daicel Chiralcel OD column.

ᵈ H₂O₂ was added at once.

Considering the structure and the number of the donor atoms in the ligand, the formation of bimetallic complex cannot be ruled out (**Scheme 4.6**). To examine this we have analyzed the UV-vis. (**Figure 4.2**) and ESI-MS (**Figure 4.3 and 4.4**) spectroscopy of the *in situ* generated complexes obtained from the 1:1 and 1:0.5 ratio of iron source and ligand. The characteristic peaks in UV-vis. spectra for metal to ligand ratio of 1:1 were observed at 332, 340 and 430 nm, while for 1:0.5 ratio these peaks lie at 359, 388 and 432 nm, which clearly indicate the formation of different predominant complexes at different ratio of Fe and 8′. ESI-MS spectra for 1:1 ratio indicate the formation of monometallic (8′-Fe, 558 [8′-Fe+H]+) complex as predominant species (**Figure 4.3**) with some trace of bimetallic (8′-Fe₂, 711 [(8′-Fe₂)-acac]+) whereas, in 1:0.5 ratio significant amount of bimetallic complex was observed along with monometallic complex (**Figure 4.4**). Interestingly, the saturated solution of the complex (formed with 8′ and Fe(acac)₃ in 1:1 ratio) in CH₂Cl₂ or CHCl₃ on aging (>2 days) partially crystallize out 8′, and what remains in solution correspond to mixture of bimetallic 8′-Fe₂ and monometallic complexes as
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evidenced by UV-viz and ESI-MS. Due to this behavior it was prudent to optimize the ligand (8') to metal ratio. With the metal to ligand ratio 1:0.5, a significant drop in both conversion and enantioselectivity (conversion 67%, ee 55%) was observed, with 1:1 ratio conversion was almost comparable (conversion 73%, ee 64%) but the ee value still little less than what was obtained with 1:1.5 ratio. An increase in the metal to ligand ratio beyond 1:1.5 like in the case of 1:2 (conversion 76%, ee 68%) provided be counterproductive. These experimental results (Table 2, entries 4-6) and spectral studies as discussed above clearly indicate that the monomeric complex (8'-Fe) is more reactive and enantioselective then the dimeric complex (8'-Fe$_2$). Notwithstanding these observations, it is worth noting that a drop-wise addition of oxidant required for getting best results, as addition of the oxidant, all at once caused a substantial drop in enantioselectivity (Table 2, entry 7).

Continuing along the process of optimization of reaction parameter, urea hydrogen peroxide (UHP) and tert-butyl hydrogen peroxide (TBHP) were also tested as stoichiometric oxidant (Figure 4.5). The conversion and enantioselectivity obtained for UHP were moderate, where as those were very poor for TBHP as oxidant. However, the catalyst retained the high selectivity for the desired product with both UHP and TBHP.

**Scheme 4.6** Plausible structures of the *in situ* generated monomeric (8'-Fe) and dimeric (8'-Fe$_2$) complex.
Figure 4.2 UV-vis. spectra of *in situ* generated complex with metal to ligand ratio of 1:1 and 1:0.5.

Figure 4.3 ESI-MS spectra of the *in situ* generated complex with 1:1 metal to ligand ratio.
Thereafter we found that the strength of $\text{H}_2\text{O}_2$ is having prominent effect on the activity, chemo and enantioselectivity of the reaction (Figure 4.6). The use of 15% aqueous $\text{H}_2\text{O}_2$ caused little decrease in both conversion (70%) and enantioselectivity (67% ee) and when the strength was increased to 50%, we observed a sharp decrease in the enantioselectivity (55% ee) with more or less similar level of conversion (78%). Concerning the selectivity, a gradual decrease was noted with the increasing strength of $\text{H}_2\text{O}_2$.

![Figure 4.4 ESI-MS spectra of the in situ generated complex with 1:0.5 metal to ligand ratio.](image)

**Figure 4.4** ESI-MS spectra of the *in situ* generated complex with 1:0.5 metal to ligand ratio.

![Figure 4.5 Effect of oxidant on the enantioselective oxidation of methyl phenyl sulfide catalyzed by *in situ* generated Fe-8’ complex at RT.](image)

**Figure 4.5** Effect of oxidant on the enantioselective oxidation of methyl phenyl sulfide catalyzed by *in situ* generated Fe-8’ complex at RT.
**Figure 4.6** Effect of the concentration of H₂O₂ on the enantioselective oxidation of methyl phenyl sulfide, catalyzed by *in situ* generated 8'-Fe complex at RT.

Next the catalytic activity in various solvents was screened to find the best catalytic system in terms of conversion and enantioselectivity. Here we found the similar level of activity and enantioselectivity for both CH₂Cl₂ and CHCl₃ (Table 4.3, entries 1 and 2). In rest of the solvents used, low to moderate ee were obtained (Table 4.3, entries 3-5). A trial to replace the chlorinated solvent with green solvent DMC and DEC (Table 4.3, entries 6-7) was failed as in these solvents the catalyst gave very poor conversion and ee compare to the CH₂Cl₂ and CHCl₃. Furthermore, we observed a little increase in the enantioselectivity with decreasing reaction temperature to 15 °C, but further decrease did not improve ee, rather it caused lowering of conversion (Table 4.3, entries 8 and 9).

**Table 4.3** Variation of solvents for the asymmetric oxidation of methyl phenyl sulfide with 8'/Fe(acac)_3 system.³

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conversion (%)b</th>
<th>Selectivity (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCM</td>
<td>82</td>
<td>95</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>75</td>
<td>96</td>
<td>70</td>
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<tr>
<td>3</td>
<td>MeOH</td>
<td>67</td>
<td>98</td>
<td>14</td>
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<td>4</td>
<td>THF</td>
<td>60</td>
<td>98</td>
<td>55</td>
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<td>5</td>
<td>PhCH₃</td>
<td>85</td>
<td>96</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>DMC</td>
<td>20</td>
<td>97</td>
<td>10</td>
</tr>
</tbody>
</table>
Reaction condition: methyl phenyl sulfide (0.25 mmol), Fe(acac)$_3$ (2 mol%), 8’ (3 mol%), aqueous H$_2$O$_2$ (30%, 1.2 equiv.), in organic solvent (1 ml) at RT for 12 h.

Conversion and selectivity were calculated by $^1$H NMR analysis.

Enantiomeric excess were determined by HPLC analysis on a chiral phase Daicel Chiralcel columns.

The reaction was carried out at 15 °C.

The reaction was carried out at 5 °C.

Taking the example of Blom et al.’s report [35, 36], we further tried to increase the enantioselectivity using sub stoichiometric amount of electron rich benzoic acid derivatives as an additive. Initial study with $p$-OMeC$_6$H$_4$COOH (Figure 4.7) as an additive revealed that 2 mol% of additive is beneficial in terms of yield and enantioselectivity (conversion 91%, ee 88%). Further increase in additive amount caused to decrease the enantioselectivity significantly. Thereafter the aid of several electron rich benzoic acid derivatives and sodium salt of $p$-OMeC$_6$H$_4$COOH were checked in the final optimization experiment (Table 4.4). Here we observed same output for $p$-NH$_2$C$_6$H$_4$COOH and $p$-OMeC$_6$H$_4$COONa as obtained with $p$-OMeC$_6$H$_4$COOH as additive. But with $p$-OHC$_6$H$_4$COOH and $o$-OMeC$_6$H$_4$COOH no improvement and with $p$-MeC$_6$H$_4$COOH, we observed slight negative effect on the enantioselectivity.

Figure 4.7 Effect of the concentration of $p$-OMeC$_6$H$_4$COOH on enantioselective oxidation of methyl phenyl sulfide catalyzed by in situ generated 8’-Fe complex at 15 °C.
Table 4.4 Screening of benzoic acid derivatives as additive for the enantioselective oxidation of methyl phenyl sulfide with 8’/Fe(acac)$_3$ system.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversion (%)$^b$</th>
<th>Selectivity (%)$^b$</th>
<th>ee (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$p$-OHC$_6$H$_4$COOH</td>
<td>89</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>$p$-OMeC$_6$H$_4$COOH</td>
<td>91</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>$p$-MeC$_6$H$_4$COOH</td>
<td>87</td>
<td>96</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>$o$-OMeC$_6$H$_4$COOH</td>
<td>87</td>
<td>95</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>$p$-NH$_2$C$_6$H$_4$COOH</td>
<td>90</td>
<td>94</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>$p$-OMeC$_6$H$_4$COONa</td>
<td>90</td>
<td>94</td>
<td>88</td>
</tr>
</tbody>
</table>

$^a$ Reaction condition: methyl phenyl sulfide (0.25 mmol), Fe(acac)$_3$ (2 mol%), 8’ (3 mol%), additive (2 mol%), aqueous H$_2$O$_2$ (30%, 1.2 equiv.), in organic solvent (1 ml) at 15 $^\circ$C for 12 h.

$^b$ Conversion and selectivity were calculated by $^1$H NMR analysis.

$^c$ Enantiomeric excess were determined by HPLC analysis on a chiral phase Daicel Chiralcel OD column.

Finally taking 2 mol% of Fe(acac)$_3$, 3 mol% 8’, 2 mol% $p$-OMeC$_6$H$_4$COOH as additive and 1.2 equiv. of aqueous H$_2$O$_2$ as terminal oxidant in DCM at 15 $^\circ$C as optimum reaction conditions, we applied this catalytic protocol for the asymmetric oxidation of various prochiral aryl alkyl sulfides (Table 4.5). For the electron withdrawing $para$ substituted phenyl methyl sulfides (Table 4.5, entries 2-5) such as F (conversion 78%, ee 95%), Cl (conversion 82%, ee 95%), Br (conversion 81%, ee 94%) and NO$_2$ (conversion 72%, ee 96%) we obtained high enantioselectivity, excellent selectivity for the desired product but with low conversion compare to the phenyl methyl sulfides. The same trend was followed by the electron withdrawing Cl (conversion 80%, ee 91%) and Br (conversion 78%, ee 90%) substituent at $ortho$ position as well as Cl (conversion 79%, ee 96%) and Br (conversion 80%, ee 94%) substituent at the $meta$ position of the phenyl ring (Table 4.5, entries 8-11). Replacement of electron withdrawing substituent at the $para$ position with donating Me and OMe group (Table 4.5, entries 6 and 7) almost retained both conversion and ee as obtained for representative substrate, but we noticed a little lowering of selectivity for the most electron rich substituent $p$-OMe Phenyl methyl sulfide (93%). Finally we have used phenyl ethyl sulfide (Table 4.5, entries 12) and phenyl benzyl sulfide (Table 4.5, entries 13) as variant for the methyl group and obtained good result in terms of conversion...
and enantioselectivity for phenyl benzyl sulfide (conversion 89%, ee 85%) having bulkier ethyl group compare to methyl group. In case of phenyl benzyl sulfide (conversion 88%, ee 75%) a significant drop in enantioselectivity was observed probably due to the steric effect of the benzyl group.

Table 4.5 Enantioselective oxidation of various prochiral sulfides with \textit{in situ} generated $8'$-Fe(acac)$_3$ complex.$^a$

\[
\text{Fe(acac)$_3$ (2 mol\%) } \quad 8' \quad (3 \text{ mol\%}) \quad \text{H}_2\text{O}_2 \text{ (1.2 equiv.) \quad DCM (1 ml), RT.}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfide</th>
<th>Conversion (%)$^b$</th>
<th>Selectivity (%)$^b$</th>
<th>ee$^c$</th>
</tr>
</thead>
<tbody>
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<td>95</td>
<td>88</td>
</tr>
<tr>
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<tr>
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<tr>
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<td><img src="image4" alt="Sulfide" /></td>
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<td>97</td>
<td>94</td>
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</tr>
<tr>
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<td>93</td>
<td>85</td>
</tr>
<tr>
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<td>79</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Sulfide" /></td>
<td>80</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td><img src="image10" alt="Sulfide" /></td>
<td>80</td>
<td>95</td>
<td>91</td>
</tr>
</tbody>
</table>
Reaction condition: Sulfide (0.25 mmol), Fe(acac)$_3$ (2 mol%), $8^*$ (3 mol%), \( p \)-OMeC$_6$H$_4$COOH (2 mol%), additive (1 mol%), aqueous H$_2$O$_2$ (30%, 1.2 equiv.), in DCM (1 ml) at 15 °C for 12 h.

Conversion and selectivity were calculated by $^1$H NMR analysis.

Enantiomeric excess were determined by HPLC analysis on a chiral phase Daicel Chiralcel OD column.

### 4.4. Probable catalytic route of the reaction

The sulfoxidation reaction mechanism with biomimetic non-heme iron (II)/(III) complexes has been studied over the last two decades and the involvement of Fe (IV)-oxo species has been established as an active oxidant \[52\]. In parallel, a debate is going on in favor \[53, 54\] and against \[55, 56\] the involvement of iron(III)-hydroperoxo species as active oxidant. Compare to these other iron based catalytic systems involving salen and aminoalcohols derived Schiff base ligands were not studied adequately to find out the actual oxidant. Based on spectroscopic techniques, kinetic measurement and electrochemical properties analysis Sivasubramanian et al. \[57\] and Rajagopal et al. \[58\] identified Fe(IV)-oxo salen species as active oxidant, but Fujii et al. \[59, 60\] demonstrated Fe(III)-monophenoxyl radical as the active oxidizing species for sterically hindered Fe-salen complex at very low temperature (193 K). Possibility of Fe(III)-monophenoxyl radical as the active oxidizing species can be cancelled as our reaction temperature is very close to RT. The UV-vis. and ESI-MS spectroscopic analysis suggest the formation of unstable [Fe(III)-OH]$^{+\cdot}$ after the addition of H$_2$O$_2$, which is then converted to the [Fe(IV)=O]$^{+\cdot}$ species. Our assumption supported by the study of Costas et al. \[61\], which has shown that the formation Fe(V)=O of species passes through the Fe(IV)-OH intermediate.

The present ligand shows two characteristic peaks at 343 nm and 445 nm. After the addition of Fe(acac)$_3$ the color of the reaction mixture changes from deep red to brown and
we observed red shift of the peak at 445 nm to 430 nm with hyperchroism due to ligand to metal charge transfer (LMCT) transition (Figure 4.7) confirms the formation of complex 8'-Fe (Scheme 4.8).

Figure 4.7 The UV-vis. spectra obtained on the sequential addition of Fe(acac)_3 (1 equiv.), oxidant (5 equiv.) and substrate (1 equiv.) to the solution of 8' in CHCl_3.

Scheme 4.8 Preparation of 8'-Fe complex in situ.

The absorbance of LMCT initially increased [57] then decreased with red shift of 6 nm (424 nm) at 523 nm on the addition of H_2O_2 [57, 58] and we observed an increase in absorbance in the region 520-650 nm [58] with an isobestic point at 523 nm due to the formation of a new species, most probably the active oxidizing species. The pattern of spectral changes is very similar to the observation of Sivasubramanian et al. [57] and Rajagopal et al. [58] for Fe(III) salen system. Thus the Fe(V)=O species is likely to be the active oxidant in our catalytic system as well. To further probe into this matter, we performed ESI-MS spectroscopic analysis of the reaction mixture after 3 min of the addition of H_2O_2 at RT which showed molecular mass peaks equivalent to [Fe(III)-OH] (X1) and [Fe(III)-OOH] (X2) species (Figure 4.9) in the reaction mixture after 3 min. of the addition of H_2O_2 at RT.
Figure 4.9 ESI-MS spectra after (3 min.) the addition of 50 equiv. of H$_2$O$_2$ to the solution of 8'-Fe complex in methanol.

After 10 min. peaks corresponding to [8'-Fe(III)-OH] (X1) and X2 species disappeared and a new peak equivalent to mass [8'-Fe(IV)=O] (Y) appeared (Figure 4.10). Based on the above study we proposed a catalytic cycle (Scheme 4.8) including Y species as an active oxidant generated from 8'-Fe complex in the presence of H$_2$O$_2$ as an oxidant. UV-vis study too corroborates our proposed mechanism where a decrease in the LMCT peak after the addition of substrate to the in situ generated [8'-Fe(IV)=O] intermediate (Y) was observed, suggesting thereby the binding of the substrate to form intermediate Z. Finally intramolecular oxygen transfer takes place to form sulfoxide and regenerate the 8'-Fe complex.
**Figure 4.10** ESI-MS spectra at 10 min. after the addition of 50 equiv. of H$_2$O$_2$ to the solution of 8'-Fe complex in methanol.

**Scheme 4.8** Plausible catalytic route for catalytic sulfide oxidation with 8'-Fe/H$_2$O$_2$ system.

**4.5. Conclusion**

In conclusion, a new iron based catalytic protocol was developed for asymmetric sulfoxidation using environment benign oxidant H$_2$O$_2$ as terminal oxidant. The simplicity of the procedure and reaction condition makes it attractive over other metal catalyzed catalytic systems. Catalyst not only showed high enantioselectivity (up to 96%) for sterically and electronically diverse type of sulfides, it provided excellent chemo selectivity (up to 98%) and good conversion (up to 92%). Substrates containing electron withdrawing substituent are seems to be less reactive as those gave comparatively low conversion, but provided slightly higher enantioselectivity and chemo selectivity even for ortho substituted sulfides as well. Besides this based on the UV-vis and ESI-MS analysis we have detected the probable active oxidizing agent and proposed a plausible path for the catalytic oxidation of prochiral sulfides.
4.6. References


