Iron-Catalyzed Oxidation in Metal Organic Frameworks

Thesis by

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DEDICATION

To my mother and father, Susan and Stephen Strobel, for their unconditional love and support

-- And --

To Dr. Doug Genna, for his invaluable mentorship, guidance, and friendship.

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ABSTRACT

The ability to directly activate C-H and C=C bonds for functionalization can be used to develop synthetic pathways which new yield products with high selectivity, minimal waste, and fewer steps than previously established procedures. Due to iron's high natural abundance, low cost, and negligible toxicity, Heme and non-heme iron complexes have long been utilized as catalysts in these transformations. However, these catalysts suffer from low reactivity due to their decomposition via the formation of bimolecular μ-oxo species. We propose that by sequestering the catalyst within a metal organic framework, bimolecular decomposition will be abated, leading to increased yields.

Herein are described research efforts towards realizing the efficient heterogeneous C-H and C=C activation with iron catalysts. Catalyst encapsulation, ion exchange and incorporation within a metal-metalloporphyrinic framework, respectively, are used as strategies to synthesize heterogeneous catalysts. The reactivity of these heterogeneous catalysts and their homogeneous counterparts are compared for carbene C-H insertion, C-H functionalization, and alkene oxidation reactions. Results from the alkene oxidation trials are most promising, suggesting that the metal-metalloporphyrinic framework PCN-222(Fe) is more reactive in catalyzing the epoxidation of styrene than its homogeneous counterpart, Fe(III)Cl-H$_4$TCPP.

CHAPTER 1

Introduction

1.1 Iron: An ideal transition metal catalyst

The unprecedented growth in global population[1] and energy consumption[2] over the late 20th and early 21st century has motivated efforts towards chemical processes that minimize waste formation, while maximizing yield and selectivity. Transition metals provide chemists previously inaccessible levels of reactivity when employed as catalysts; however, widespread implementation is limited due to decreasing availability and increasing monetary costs. For example, palladium, an attractive catalyst for hydrogenation and C-H functionalization, costs $0.58 per mole, and constitutes only 0.0063 parts per million of the Earth's crust by mass.

Iron is well-suited for the economic and regulatory pressures facing modern chemistry. The most abundant transition metal on Earth, iron is inexpensive ($0.001 per mole), abundant (63,000 parts per million of the Earth's crust by mass), and environmentally friendly.[3] Furthermore, iron has already proven an effective catalyst at the industrial level; for example, the Haber-Bosch process, which utilizes iron as its primary catalyst for the conversion of nitrogen gas into ammonia, produces over 450 million tons of nitrogen fertilizer annually.[4]

Heme and non-heme iron ligands (for examples, see figure 1.1.1) provide significant improvement to the catalytic properties of iron. In these complexes, an iron atom is partially or completely coordinated by the heme or non-heme ligand. The chelating ligand provides unique

reactivity to the catalyst via its steric bulk, and electronics. In the literature, these complexes are noted for their efficiency catalyzing carbene C-H insertion, C-H activation, and alkene oxidation chemistry.

Figure 1.1.1. Non-Heme (2*S*,2'*S*-(-)-[*N*,*N*'-Bis(2-pyridylmethyl)]-2,2'-bipyrrolidine) (**1**) and Heme (tetraphenylporphyrin) (**2**) Ligands

H$_2$-(*S*,*S*-PDP) (**1**)

H$_2$TPP (**2**)
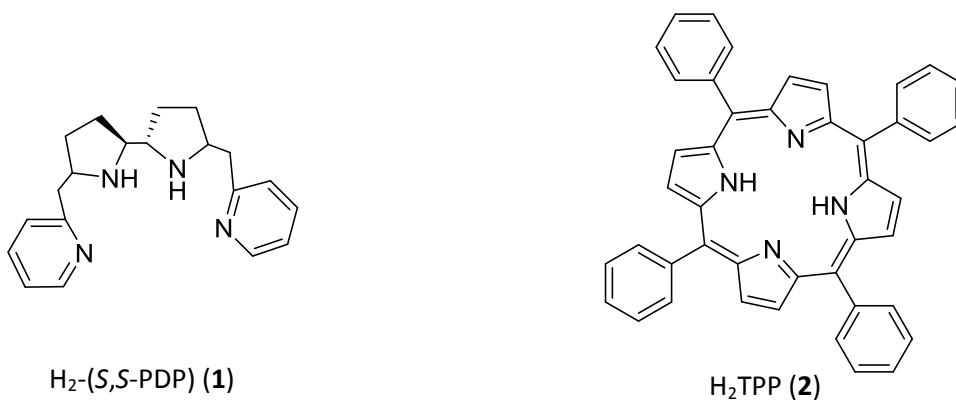
1.2 Iron Catalyzed Carbene C-H Insertions

C-H functionalization is one of the most important new methods in chemical synthesis. By achieving a desired transformation through the activation of a traditionally inert carbon-hydrogen bond, intermediary steps which consume time and generate waste might be avoided. Additionally, because these transformations occur at the chemically ubiquitous C-H bond, their potential for broad application across a diverse range of substrates is high.

One reaction type which is posed to realize these advantages is carbene C-H insertion. In 2008, Mbuvi and Woo published on C-H insertions utilizing Fe^{III}(TPP)Cl. Initial studies utilizing toluene as substrate, and dimethyl diazomalonate as the carbene source resulted in 68% yield in 54 hours, with a 2:1 ratio of products a:b (Scheme 1.2.3).

Scheme 1.2.1. Fe(TPP)Cl Catalyzed C-H Insertion with Ethyl Diazoacetate[5]

A   B
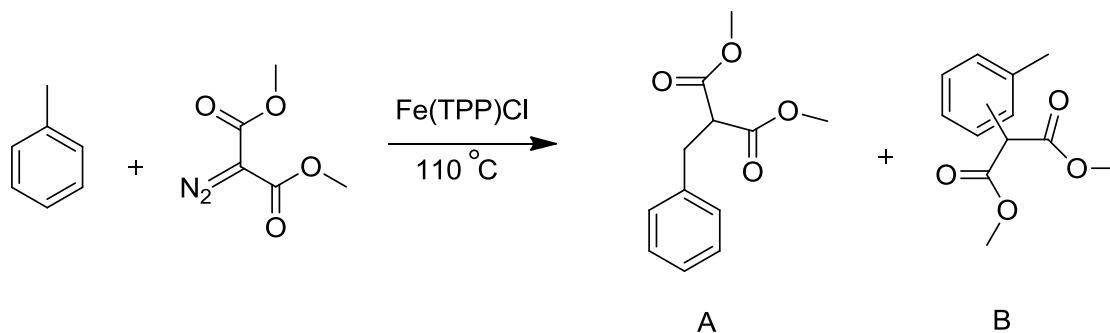
Shortened reaction times were achieved using *p*-methoxy methyl 2-phenyldiazoacetate (Scheme 1.2.2). Using this diazo reagent, the system successfully catalyzed C-H insertions with cyclohexane, THF, mesitylene and 2,2,4-TMP as substrates in moderate to high yield.

Scheme 1.2.2. Fe(TPP)Cl Catalyzed C-H Insertion with *p*-Methoxy Methyl 2-Phenyldiazoacetate[5]
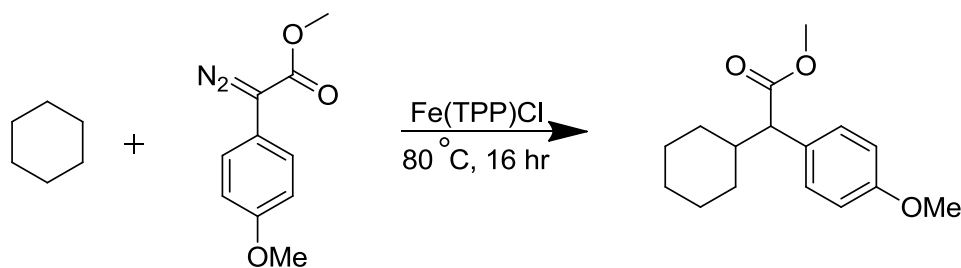
1.3 Iron Catalyzed C-H Functionalization

In C-H functionalization, inherently unreactive C-H bonds are activated for previously inaccessible chemistry. One of the challenges of this technique is the regioselective activation of C-H bonds. Broadly defined, regioselectivity is a reaction's ability to selectively favor a transformation at one C-H bond over another. This is difficult to achieve

due to the chemically indistinct and ubiquitous nature of the C-H bond in organic molecules. However, this selectivity is necessary if meaningful synthetic routes for C-H functionalization are to be achieved.

Cytochrome P450, a metalloenzyme found in nature, utilizes an iron heme center to perform C-H functionalization with high selectivity and throughput.[6] Seeking catalysts with which to model and further study cytochrome P450's reactivity, Groves and Nemo reported the first example of iron porphyrins being utilized as catalysts in C-H functionalization.[7]

Scheme 1.3.1. Oxidation of Aliphatic Bonds in Cyclohexane[7]. TTP = tetratolylporphyrin.

31 %   6 %
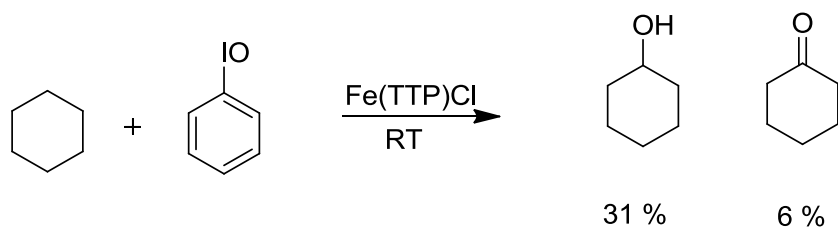
In addition to the trial illustrated in scheme 1.3.1, the catalyst's preference for tertiary C-H bonds to secondary C-H bonds was also noted; a 20:1 tertiary to secondary site selectivity ratio was observed for the oxidation of admantane with Fe(TTP)Cl . In order to achieve the yields in scheme 1.3.1, Groves and Nemo purified the catalyst on basic alumina, excluding a species observed as a red band. This species was hypothesized to be the catalytically poisoned μ-oxo dimer $(FeTTP)_2O$ (Figure 1.3.1). This astute observation would come to characterize one of the principle difficulties of working with iron porphyrins and non-heme compounds in oxidation reactions, the decomposition of reactive catalyst species via bimolecular decomposition.

Figure 1.3.1. Bimolecular µ-oxo Iron Porphyrin Decomposition Product.
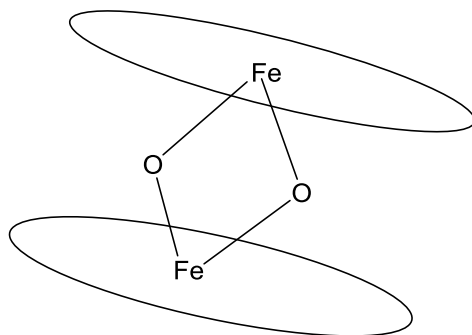
Building off of this work, Groves and Viski reported a chiral iron porphyrin (**3**) capable of asymmetric hydroxylation.[8] Porphyrin **3** (Scheme 1.3.2) was capable of oxidizing ethylbenzene to 1-phenylethanol with a 40 % yield, and a 71:29 ratio of *R* and *S* enantiomers.

Scheme 1.3.2. Asymmetric Hydroxylation of Ethylbenzene.
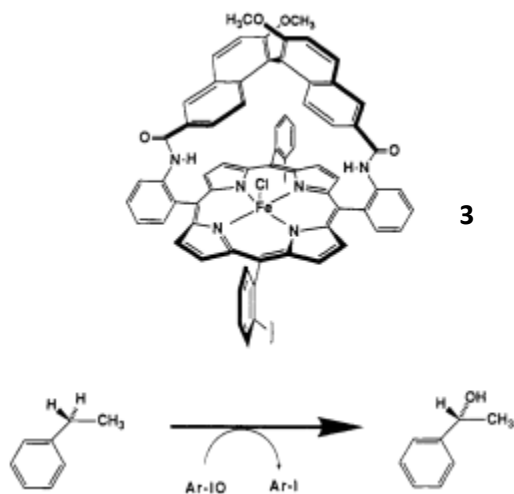
In 1997, Kim et al. described a non-heme iron complex that catalyzed the C-H oxidation of *cis*- and *trans*-1,2-dimethylcyclohexane to *cis*- and *trans*-1,2-dimethylcyclohexanol/cyclohexanone, respectively.[9] Utilizing [Fe(TPA)(CH$_3$CN)$_2$](ClO$_4$)$_2$ (TPA = tris(2-pyridylmethyl)amine) as its catalyst and H$_2$O$_2$ as oxidant, it was the first example of a non-heme iron catalyst utilizing H$_2$O$_2$ for stereospecific alkane hydroxylation. Additionally, the group claimed a benefit of non-heme iron compounds was a lower susceptibility to catalyst degradation via the formation of μ-oxo dimers. In 1999, the same group achieved a marked increase in yield (still moderate at 5.6 TON or 56 % yield) replacing Fe(TPA) with [Fe^{II}(bpmen)(CH$_3$CN)$_2$](ClO$_4$)$_2$.[10]

Most recently, [Fe(*S,S*-PDP)(CH$_3$CN)$_2$](SbF$_6$)$_2$ (**4**), (scheme 1.3.3) has been identified as a capable non-heme iron catalyst for the selective oxidation of C-H bonds. In their paper published in 2007, Chen and White detail Fe(*S,S*-PDP)'s competency across a wide range of substrates.[11] Order of substitution of carbon centers is reported to be the most significant factor in site selectivity for the catalyst. Improving over Fe(TTP)Cl, Fe(*S,S*-PDP) follows the order of substitution and does not generate a mixture of secondary and tertiary site products. Despite these gains in selectivity, the activity of these catalysts remains modest (6 TON), and relies on a high loading for synthetically useful yields. This is presumably done to compensate for the bimolecular decomposition of the catalyst to the inactive μ-oxo species.

Scheme 1.3.3. Selective Aliphatic C-H Oxidation using Fe(PDP) (**4**)
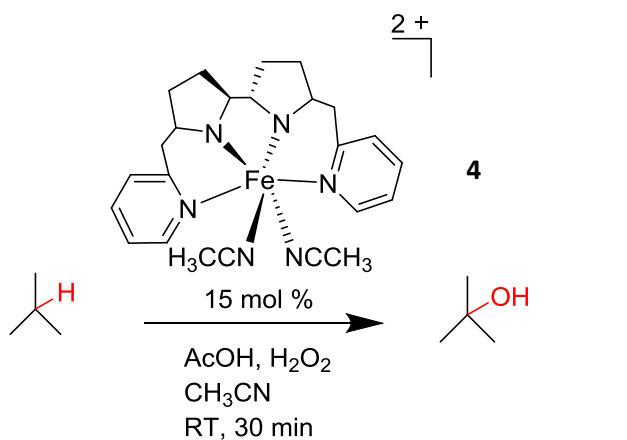
Selected Products   Isolated % Yield

      52

      52

      92

1.4 Iron Catalyzed Alkene Oxidation

Similar to C-H oxidation, alkene oxidation by an iron porphyrin was first reported by Groves and Nemo (Scheme 1.4.1). Fe(TPP)Cl in the presence of iodosylbenzene catalyzed the epoxidation of several different alkene substrates.[12]

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Scheme 1.4.1. Epoxidation Catalyzed by Fe(TPP)Cl and Iodosylbenzene

% Yield

55

74

82
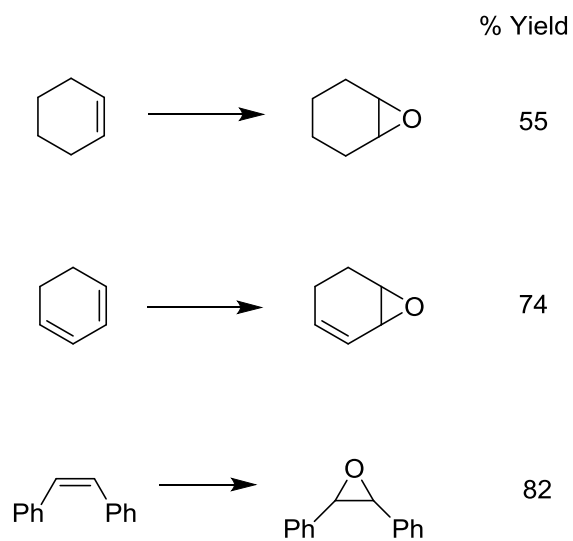
The current literature on alkene oxidation, namely epoxidation, catalyzed by iron heme and non-heme complexes details a variety of unique systems. One of the highest yielding systems was reported by Mas-Balleste et al. in 2007.[13] Utilizing Fe(TPA) as catalyst, H_2O_2 as oxidant, and acetic acid as a co-oxidant, a quantitative yield of cyclooctene oxide is observed.

Scheme 1.4.2 Oxidation of Cyclooctene with Fe(TPA)
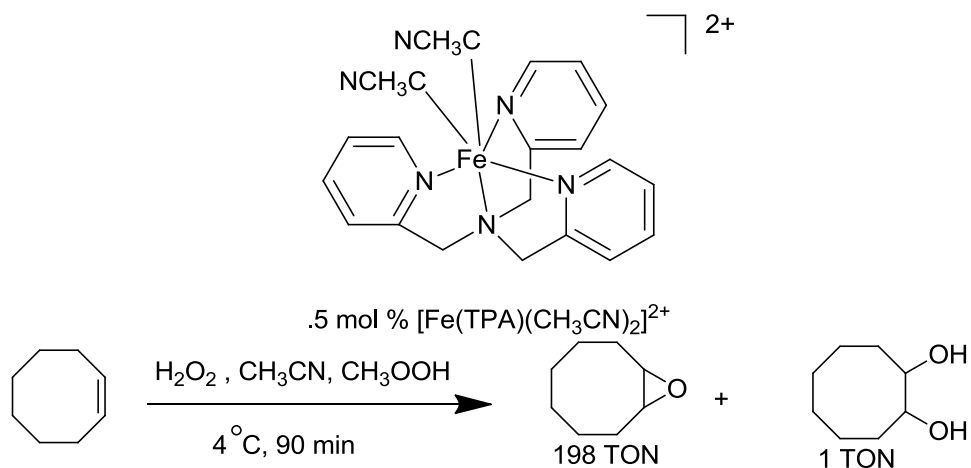
In 2013, Prat et al. reported alkene oxidation using $[Fe(CF_3SO_3)_2(^{Me,H}PyTACN)]$ (**5**) as catalyst (Scheme 1.4.3). With H_2O_2 as the limiting reagent, their system achieved quantitative yields, albeit with poor selectivity. This is reportedly solved by adding oxidant in excess, making the alkene the limiting reagent. When the amount of hydrogen peroxide is doubled, a 6:1 ratio of di-hydroxyl to epoxide product is observed. In addition to cyclooctene, 16 other substrates were screened.

Scheme 1.4.3 Oxidation of Cyclooctene with $[Fe(CF_3SO_3)_2(^{Me,H}PyTACN)]$

9
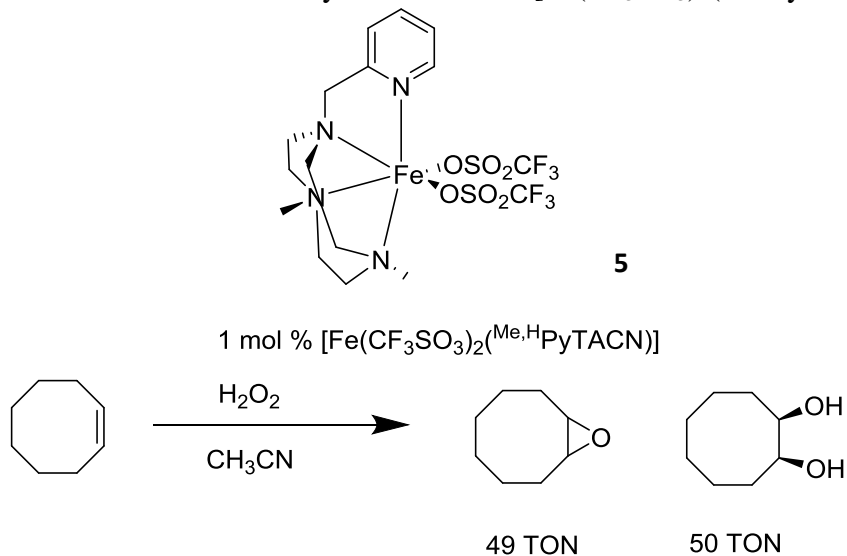
1.5 Shortcomings of Iron Heme and Non-Heme Catalysis

Iron heme and non-heme catalysts are capable of a wide range of reactivity. However, they are particularly susceptible to decomposition via the formation of bimolecular μ-oxo species.[14] Within the literature describing these transformations, a solution to this limitation has yet to be identified. Currently, time- and catalyst-consuming "multiple additions" of catalyst and oxidant, are utilized to obtain reasonable yields.[11] Additionally, while the variety of chemical transformations possible has significantly increased over the past 30 years, reactions still often afford complex mixtures of regioisomeric or over-oxidized products.

1.6 Catalytically Active Metal Organic Frameworks

This thesis details a proposed alternative solution to improving site selectivity and retarding bimolecular catalyst decomposition by sequestering the catalyst within a porous crystalline network, namely a metal organic framework (MOF). MOFs are 1-D, 2-D, or 3-D porous crystalline coordination polymers, consisting of metal nodes (ions or metal ion clusters) coordinated to organic linkers. An ideal MOF catalyst is able to catalyze a specific transformation after several recycles without loss of activity, does not leach catalytic material into the liquid phase of the reaction (i.e. is truly heterogeneous), and achieves reactivity that is comparable or improved over homogeneous conditions.

The concept of utilizing a catalytically active MOF to perform oxidation chemistry similar to the iron reactions discussed above is established in the literature. PIZA-3, reported in 2005 by Suslick et al., was the first porphyrin-MOF with the ability to catalyze C-H functionalization and epoxidation reactions.[15] Consisting of repeated units of $(Mn(TCPP)(Mn_{15})(C_3H_7NO)\cdot5C_3H_7$ connected by trinuclear, bent cobalt cluster, the MOF was

capable of moderate yields utilizing either iodosylbenzene or peracetic acid as oxidant (Scheme 1.6.1)

Scheme 1.6.1. C-H and Alkene Oxidation catalyzed by PIZA-3
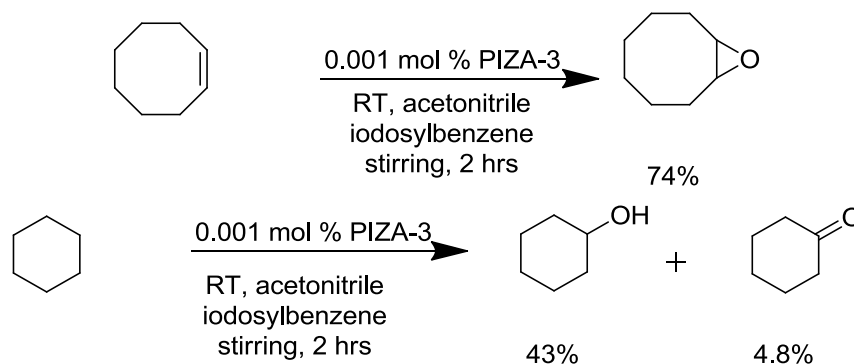
Recently, scientists at Zhejiang University (ZJU) have reported several highly catalytic MOFs for alkene oxidation.[16] ZJU-18, a metalloporhyrinic framework consisting of $[Mn_5Cl_2(MnCl-OCPP)(DMF)_4(H_2O)_4]\cdot 2DMF\cdot 8CH_3COOH\cdot 14H_2O$ (**6**) (Figure 1.6.1), produces over 8000 TON of 1-phenyl enthanone from ethylbenzene with ^tBuOOH oxidant (Scheme 1.6.2). Notably, the MOF recycles with no loss of reactivity.

Figure 1.6.1. $[Mn_5Cl_2(MnCl-OCPP)(DMF)_4(H_2O)_4]\cdot 2DMF\cdot 8CH_3COOH\cdot 14H_2O$
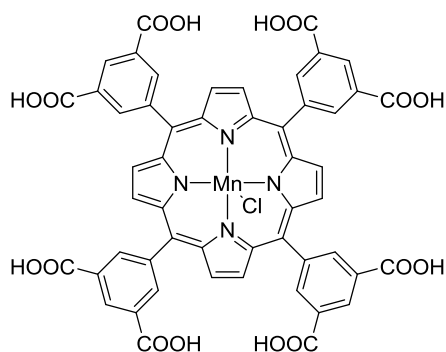
6

Scheme 1.6.2 C-H Oxidation Catalyzed by ZJU-18
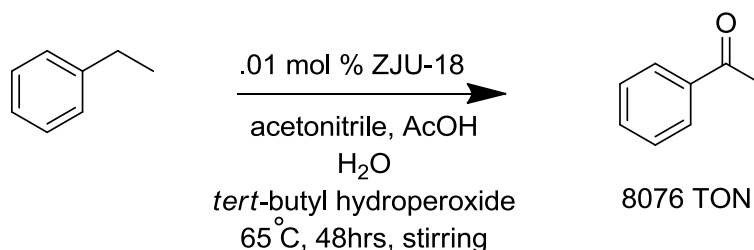
The group at ZJU has also reported metalloporphyrinic MOFs consisting of Fe- or Mn-TCPP and Zn or Cd nodes.[17] Of the materials reported, the material utilizing Zn nodes and the Mn porphyrin yielded the best catalytic activity (Scheme 1.6.3).

Scheme 1.6.3. Oxidation of ethylbenzene via ZJU Fe- and Mn-TCCP MOFs[17]
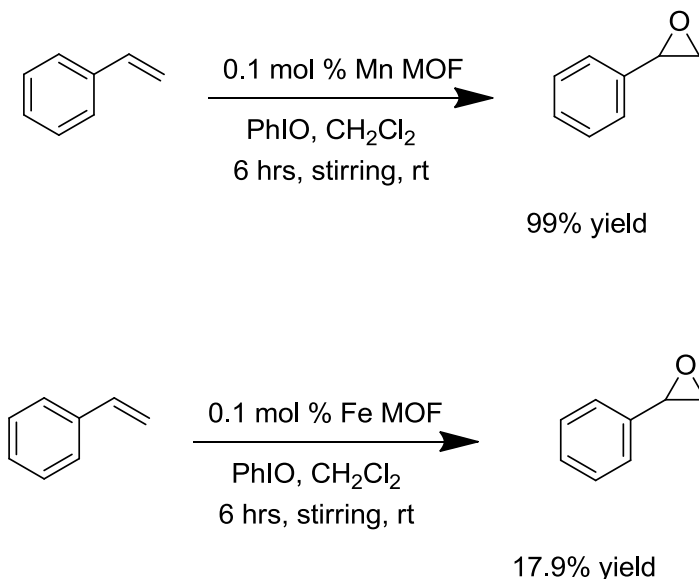
While these MOFs report impressive reactivity, there are still limitations. Metallo-porphyrinic MOFs rely on highly symmetric porphyrins with functional groups capable of forming bonds with metal linker nodes (often carboxylic acid functional groups, as in the case of ZJU-18's linker, **6**). This prevents the utilization of non-heme catalysts and metalloporhyrins

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lacking these functionalities. Methods which covalently link the catalyst to the MOF during or following MOF synthesis also suffer from this limitation. We propose that by rendering the MOF catalytically active by either catalyst encapsulation or ion exchange, a greater variety of catalysts will be accessible for experiment.

Catalyst encapsulation describes a technique by which a MOF is synthesized with the catalyst present. During the formation of the framework, catalyst molecules preferentially locate themselves in what become the pores of the MOF. The catalyst then becomes sterically trapped within the pore, much like building a ship-in-a-bottle, rendering the MOF catalytically active.

Catalyst encapsulation has been employed with success in the literature. Zhang et al. reported the synthesis of porph@MOM-10 via the encapsulation of cationic CdTMPyP within an anionic Cd(II) carboxylate framework. Unlike ion-exchange encapsulation, which dopes the MOF with catalyst post-synthesis, porph@MOM-10's framework grows around the CdTMPyP units, incorporating them in a "ship-in-a-bottle" fashion. Mnporph@MOM-10-Mn and Cuporph@MOM-11-CdCu, which contain MnTMPyP and CuTMPyP respectively, generated ~180 TON (80 % yield) of *trans*-stilbene oxide in the epoxidation of *trans*-stilbene.[18] Significant limitations to this technique include the requirements that the catalyst must exceed the pore size of the MOF, and that the catalyst must survive the harsh conditions of MOF crystal growth.

Scheme 1.6.4. Ion-exchange encapsulation of catalyst in MOF[19]
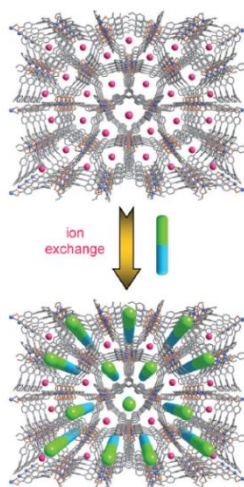
A second strategy, ion-exchange, renders a MOF catalytically active via ionic doping. In this approach, an anionic MOF which contains cationic guest molecules (typically $H_2NMe_2^+$) is placed in a doping solution containing a cationic catalyst. This catalyst will then exchange with the cationic guest molecules, yielding a catalytically active MOF. This technique was employed with success recently by Genna et al., providing a Rh-doped MOF capable of catalyzing the hydrogenation of 1-octene (~4300 TON after 5 recycles).[19] However, this method also has limitations: given that the MOF is doped post-synthesis, the cationic catalyst must be small enough to move through the dimensions of framework's pores. Additionally, reactions utilizing these ion-exchange MOFs cannot utilize or generate cationic species, or catalyst leaching will occur. Lastly, catalyst scope is limited by the stipulation that the catalyst must be cationically charged.

Herein, we describe efforts to perform heterogeneous iron-catalyzed C-H insertion, C-H functionalization and alkene oxidation, utilizing catalytically active MOFs synthesized via ion-exchange and catalyst encapsulation methodologies.

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CHAPTER 2

Iron Catalyzed Carbene C-H Insertion

2.1 Introduction

Carbon-hydrogen bonds are ubiquitous in organic chemistry. Alkanes, molecules comprised of only C-H sp^3 bonds, account for approximately 30 % of petroleum, making them a candidate for inclusion as a precursor for industrial and research processes due to their widespread availability.[1] The capability to selectively functionalize C-H bonds would eliminate the need for many multi-step syntheses, and reduce the waste associated with the elaborate protecting and de-protecting steps used to achieve them. However, until recently and despite their widespread availability, C-H bonds remained mostly inaccessible for functionalization, due to their high bond dissociation energies (90-100 kcal/mol), low acidity, and low basicity.

Over the past 30 years, significant progress has been made in developing catalytic systems which can functionalize C-H bonds. Utilizing diazo compounds as a carbene source, metalloporphyrins have been reported as capable catalysts for C-H insertion reactions.[2] Herein, we report studies towards the creation of a heterogeneous system capable of carbene C-H insertion. It is proposed that by encapsulating a metalloporphyrin within a MOF, a catalyst capable of being recycled and reused in multiple catalytic trials will be created. Additionally, by confining the catalyst inside pores of the MOF, unique regioselectivities may be accessed.

2.2 Results and Discussion

Our investigation into iron catalyzed carbene C-H insertion began with the selection of an appropriate MOF. Catalyst encapsulation (e.g. ship-in-a-bottle) was selected as our initial

strategy to create catalytically active MOFs, due to the competency of heme metalloporphyrins as catalysts in these transformations.[3]

The syntheses of several porphyrin-encapsulated MOFs were attempted, including porph@MOM-4 and FeZn-RPM. Porph@MOM-4, reported by Zhang et al., consists of the metalloporphyrin Fe[TMPyP] encapsulated inside a MOF with twisted boracite topology consisting of 3-connected benzene-1,3,5-tricarboxylate ligands and 4-connected [Fe(COO)$_4$] square paddlewheels. This geometry is isostructural to that of the well-studied MOF, HKUST-1.[4] In order to achieve fine crystal growth, the synthesis of porph@MOM-4 is carried out in an 80°C oven for twelve hours (Scheme 2.2.1).

Scheme 2.2.1. Synthesis of Porph@MOM-4[4]
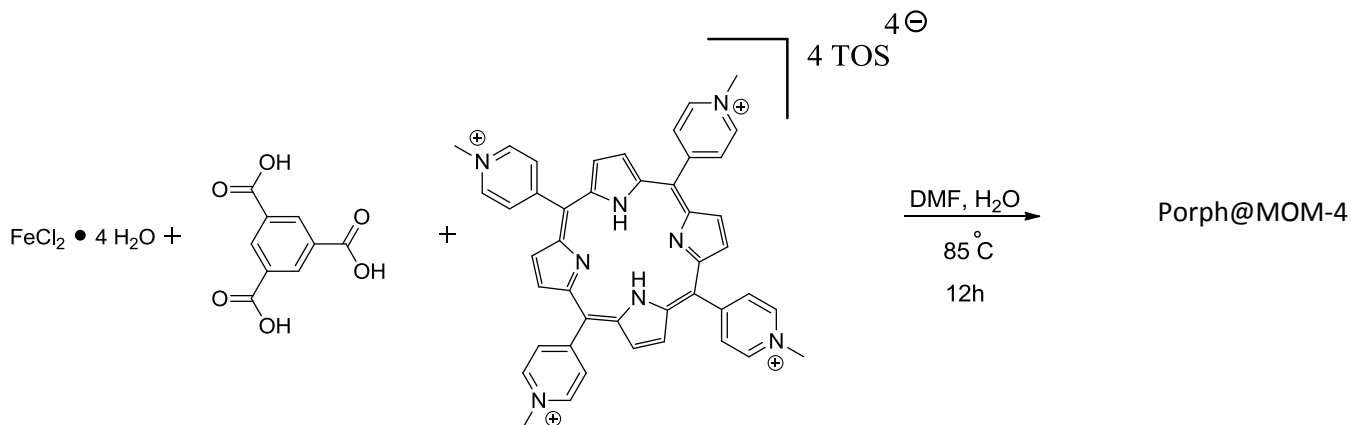
FeZn robust porphyrinic material (RPM) utilizes the carboxylic acid and pyridyl functionalities of two unique porphyrins, pictured in scheme 2.2.2, to bind to zinc nodes in a paddlewheel-coordinated fashion. Unlike previously reported pillared paddlewheel MOFs, FeZn-RPM avoided ligation at catalytically active Fe[TCP]Cl metal sites. Encouragingly, Farha et al. report that ZnMn-RPM catalyzes the epoxidation of styrene with up to 2150 TON, compared to the 780 TON attainable with homogeneous Mn[TPFPP]Cl. Given the presence of two unique

metalloporphyrins in one MOF, it is hypothesized that unique reactivity can be achieved in M^{1}M^2-RPMs through cooperative catalysis.[5]

Scheme 2.2.2. Synthesis of FeZn RPM[3]
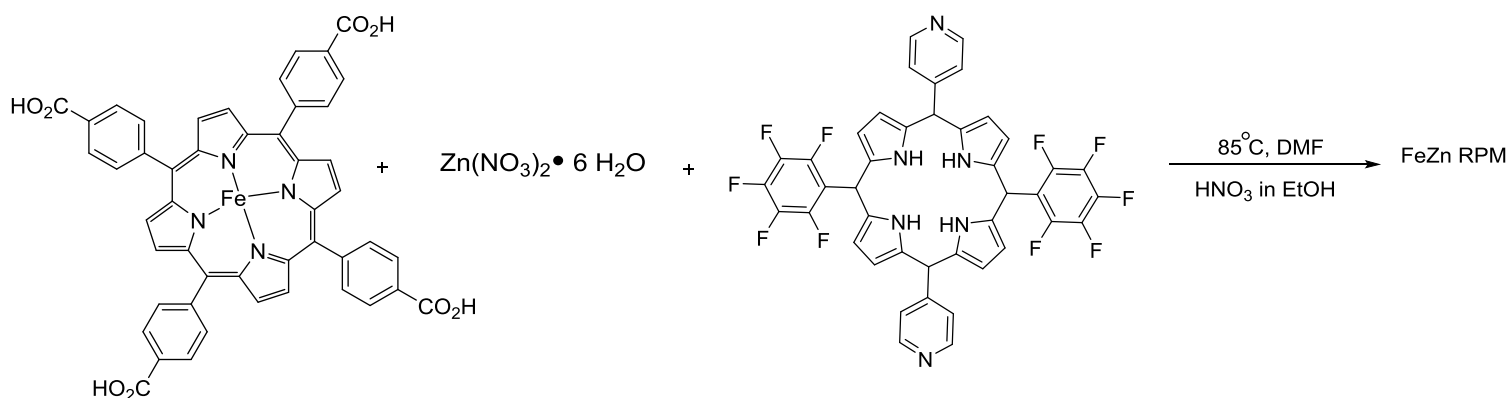
Unfortunately, we were unable to successfully reproduce the synthesis of either Porph@MOM-4 or FeZn RPM as reported in the literature. While the formation of crystalline material was often observed, these crystals were opaque, deformed, and unsuitable for further study.

We next attempted to synthesize MOF-5, a framework whose large pore size held potential for metalloporphyrin encapsulation. MOF-5 consists of tetrahedral Zn_4O clusters, utilizing 1,4-benzenedicarboxylate as linker molecules.[6] We first thought it prudent to make MOF-5 without any encapsulated porphyrin. Initial syntheses did not yield crystalline material of uniform phase. However, cubic crystal growth of MOF-5 was eventually attained by not subjecting the reaction mixture to sonication prior to oven synthesis.

Figure 2.2.1. Cubic MOF-5[7]
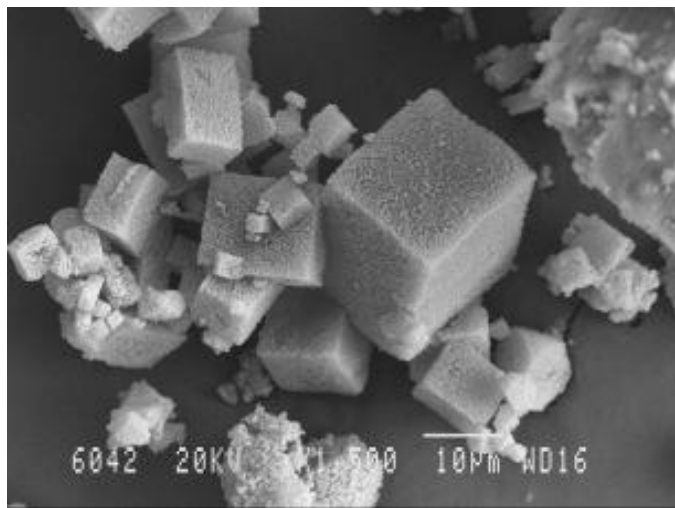
The ship-in-a-bottle encapsulation of iron metalloporphyrins Fe[TPP]Cl and Fe[OEP]Cl inside MOF-5 was next attempted using the general procedure outline in scheme 2.2.3. Porphyrin incorporation was observed for both TPP and OEP. However, whereas Fe[OEP]Cl @ MOF-5 (2% Fe by ICP) crystals grew as ordered, single phase cubes, Fe[TPP]Cl @ MOF-5 (1% Fe by ICP) was deformed, opaque and non-cubic. Thus catalytic studies were undertaken with Fe[OEP]Cl @ MOF-5.

Scheme 2.2.3. M-Porphyrin @ MOF-5 Synthesis

$Zn(NO_3)_2 \cdot 4\ H_2O$ + (terephthalic acid) + M-porphyrin $\xrightarrow[\text{DEF, ~15 hrs.}]{100^{\circ}C}$ M-porphyrin @ MOF-5
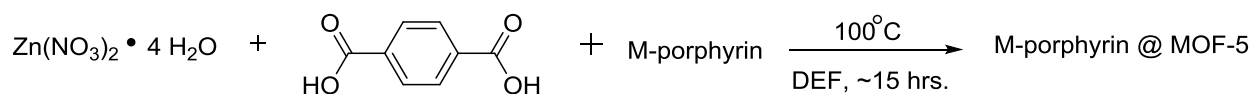
Fe[OEP]Cl's ability to catalyze carbene C-H insertion was probed. Treatment of tetrahydrofuran with *p*-methoxy methyl 2-phenyldiazoacetate in the presence of Fe[OEP]Cl catalyst led to 53% yield (determined by ^{1}H NMR) of the C-H insertion product (Scheme 2.2.4). A 1:1.6 ratio of constitutional isomers was observed (C-H insertion to ring opening product).

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Mbuvi reports 82% yield and a 3.6:1 ratio of regioisomers with Fe[TPP]Cl. This opposite

selectivity is likely due to our utilization of Fe[OEP]Cl rather than Fe[TPP]Cl as reported.

Scheme 2.2.4. Homogeneous Fe[OEP]Cl Carbene C-H Insertion[a]
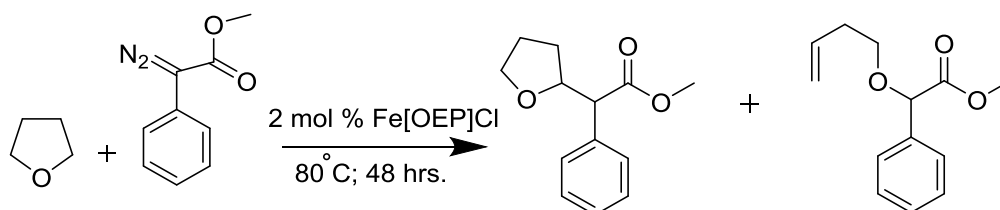
[a] Conditions: *p*-methoxy methyl 2-phenyldiazoacetate (0.0302 g, 172 mmol, 1 equiv), Fe[OEP]Cl (0.0019 g, 0.00313 mmol, 0.0182 equiv), THF (1 mL)

Using Fe[OEP]Cl @ MOF-5 as catalyst, a yield of 66% by NMR was observed, with an

identical 1:1.6 ratio of regioisomers. In an attempt to improve the selectivity of the

heterogeneous reaction for the C-H insertion product, trials were run at reduced temperatures. At

60 °C, a 1.25:1 ratio of regioisomers was attained with 57.5 % yield, as shown in table 2.2.1.

Table 2.2.1. Fe[OEP]Cl @ MOF-5 Temperature Trials[a]
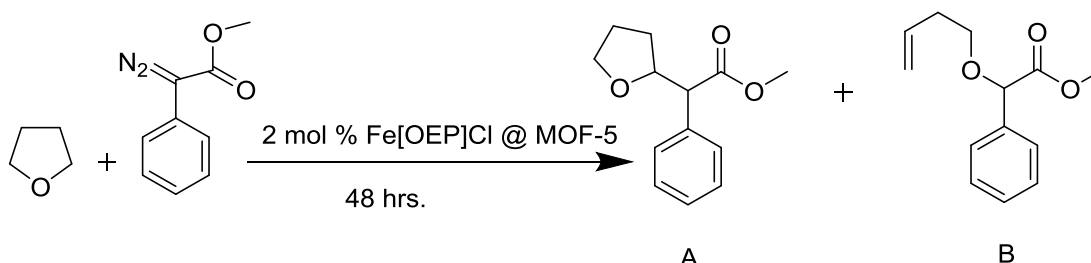
Temperature (°C)	% Yield[b]	Selectivity (A:B)
25 (room temperature)	0	N/A
40	0	N/A
60	57.5	1.25:1
80	66	1:1.6

[a] Conditions: *p*-methoxy methyl 2-phenyldiazoacetate (0.0302 g, 172 mmol, 1 equiv), Fe[OEP]Cl @ MOF-5 (0.0087 g, 0.00313 mmol Fe, 0.0182 equiv Fe), THF (1 mL) [b] Determined via NMR relative to acetophenone as a standard

Further gains in yield and selectivity were achieved by optimizing reaction time. An average 64% yield and a 5.2:1 ratio of constitutional isomers was attained over ten trials run for 24 hours at 60 °C. It is hypothesized that product A decomposed to product B over time, and that by shortening the reaction time we were able to avoid a significant amount of this decomposition. While slightly lower yielding, Fe[OEP]Cl @ MOF-5 attains significantly improved selectivity relative to that reported by Mbuvi for homogeneous Fe[TPP]Cl.[8]

This system's substrate scope was next investigated. As demonstrated in table 1.2.2, Fe[OEP]Cl @ MOF-5 is capable of catalyzing C-H insertion for a variety of substrates. For cyclohexane, the heterogeneous catalyst yielded 84 % yield (213 TON) of product, whereas the homogeneous catalyst produced a modest 47 % yield (100 TON). This heterogeneous system also catalyzed the transformation of cycloheptane in high yield (91 %).

Table 2.2.2. Fe[OEP]Cl Substrate Screen[a]

Catalyst	Substrate	% Yield[b]
Fe[OEP]Cl @ MOF-5	Cyclopentane	40
Fe[OEP]Cl @ MOF-5	Cycloheptane	91
Fe[OEP]Cl @ MOF-5	Cyclohexane	84
Fe[OEP]Cl[c]	Cyclohexane	47

[a] Conditions: *p*-methoxy methyl 2-phenyldiazoacetate (0.0302 g, 172 mmol, 1 equiv), Fe[OEP]Cl @ MOF-5 (0.0087 g, 0.00313 mmol Fe, 0.0182 equiv Fe), Substrate (1 mL), 24 hr, 85 °C [b] Determined via NMR relative to acetophenone as a standard [c] Fe[OEP]Cl (0.0019 g, 0.00313 mmol, 0.0182 equiv)

Three identical trials of the C-H activation of cyclohexane were undertaken to determine if Fe[OEP]Cl @ MOF-5 could be recycled without loss in reactivity, and without leaching catalyst into the liquid phase. The results of this experiment, shown in table 2.2.3, revealed a

fatal shortcoming of this transformation. While the MOF did recycle with only a moderate loss in yield (~ 10 %), the filtrate (obtained by filtering out MOF) of the pre-recycle trials demonstrate nearly equal reactivity to the recycled MOF. UV-Vis absorption studies of the filtrate did not detect any Fe[OEP]Cl in solution, ruling out catalyst leaching.

Table 2.2.3. Fe[OEP]Cl @ MOF-5 Recycle and Filtrate Tests[a]
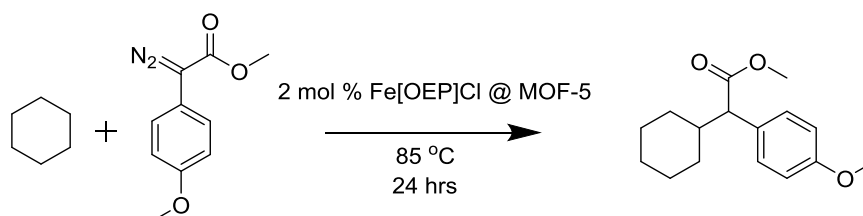
Trial	% Yield[b,c]	% Yield Recycle[b,c]	% Yield Filtrate[b,c]
A	43.3 ± 5.4	40.3 ± 0.5	40 ± 7.1

[a] Conditions: *p*-methoxy methyl 2-phenyldiazoacetate (0.0302 g, 172 mmol, 1 equiv), Fe[OEP]Cl @ MOF-5 (0.0087 g, 0.00313 mmol Fe, 0.0182 equiv Fe), Substrate (1 mL), 24 hr, 85°C [b] Determined via NMR relative to acetophenone as a standard [c] Reported as average of three trials with error

Further study indicated that most, if not all, of the yields reported using Fe[OEP]Cl were not due to that metalloporphyrin's catalytic activity. As seen in table 2.2.4, a control trial, containing only diazo and neat cyclohexane, produced a 48% yield by NMR. It is hypothesized that this reactivity observed throughout our experiments was a result of thermal activation of the carbene. This reaction's lack of reproducibility (note that yield fluctuates from 80 % to 40 %) is troublesome. It is possible that the catalyst contribute some reactivity to the system, but that the

background reactivity is significant. Alternatively, it is possible that thermal activation of the carbene inherently varies from trial to trial.

Table 2.2.4. Fe[OEP]Cl @ MOF-5 Recycle and Filtrate Tests[a]

Catalyst	% Yield[b]
Fe[OEP]Cl	51
None (Control)	48

[a] Conditions: *p*-methoxy methyl 2-phenyldiazoacetate (.0302 g, 172 mmol, 1 equiv), Fe[OEP]Cl (.0019 g, .00313 mmol, .0182 equiv), Substrate (1 mL), 24 hr, 85 °C [b] Determined via NMR relative to acetophenone as a standard

2.3 Conclusion

In conclusion, this chapter has described the results of catalytic studies utilizing Fe[OEP]Cl encapsulation in MOF-5. Initial results suggested that this heterogeneous system was capable of catalyzing carbene C-H insertion reactions for a variety of substrates with moderate to high yields. In the case of THF, Fe[OEP]Cl @ MOF-5 offered improved selectivity relative to homogeneous Fe[TPP]Cl.[8] Unfortunately, filtrate and control studies revealed that this transformation was not being accomplished through the use of our catalyst, but rather through the thermal activation of the carbene reagent. Further research could attempt to select less reactive diazo reagents, which may not be suspect to thermal activation. Meaningful catalytic studies could then be undertaken in a similar fashion to those reported here.

2.4 Experimental Procedures and Characterization Data

General Procedures. NMR spectra were obtained on a Varian MR400 (400.52 MHz for ^{1}H) spectrometer. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. NMR calibrated yields are reported relative to acetophenone as an internal standard.

Materials and Methods. porph@MOM-4[4], FeZn-RPM[5], undoped MOF-5[6], and *p*-methoxy methyl 2-phenyldiazoacetate[9] were all synthesized as reported in the literature. Fe[OEP]Cl and Fe[TPP]Cl were obtained from Aldrich. DEF was obtained from TCI and stored over powdered charcoal and was purified via silica plug filtration prior to use. All other commercial substrates, reagents, and solvents were used as received without further purification.

Synthesis of Fe[porphyrin]Cl @ MOF-5. DEF (15 mL), $Zn(NO_3)_2 \cdot 4 H_2O$ (0.54 g, 1.82 mmol, 165 equiv), and terephthalic acid (0.1 g, 0.6 mmol, 50 equiv) were sequentially added into a 20 mL scintillation vial. Fe[OEP]Cl (0.005 g, 0.008 mmol, 0.7 equiv) or Fe[TPP]Cl (0.008 g, 0.011 mmol, 1 equiv) was then added, and the solution vigorously shaken until a dark, homogeneous solution was obtained. The scintillation vial was tightly sealed with a Teflon cap, and placed in a $100\,^{\circ}C$ oven overnight (~15 hrs). The vial was then removed from the oven and allowed to cool. The dark purple cubic MOF-5 crystals were rinsed (3 x 3 mL) with DMF and then soaked in DMF (3 x 3 mL) for 30 min while being agitated on an orbital shaker. Solvent was decanted and crystals were dried under hi-vac (~0.1 torr) line overnight. The isolated crystals were stored in a desiccator charged with drierite.

General Procedure for C-H Insertion Reactions. Catalyst (0.00313 mmol, 0.0182 equiv) was dissolved in 1 mL of substrate in a 20 mL scintillation vial. To this solution, *p*-methoxy methyl 2-phenyldiazoacetate (0.037 g, 0.172 mmol, 1 equiv) was added. The vial was then capped and heated in an oven (for trials at $80\,^{\circ}C$ or greater) or on an aluminum block). Following the reaction's completion, the vial was removed from heat and allowed to cool to room temperature. The crude reaction mixture was then doped with acetophenone (20 μL, 0.18 mmol) and an NMR yield was obtained.

p-Methoxy methyl 2-phenyldiazoacetate Insertion with THF. The general procedure was used with *p*-methoxy methyl 2-phenyldiazoacetate (0.037 g, 0.172 mmol, 1 equiv), either Fe[OEP]Cl (0.0019 g, 0.00313 mmol, 0.0182 equiv) or Fe[OEP]Cl @ MOF-5 (0.0087 g, .00313 mmol Fe, 0.0182 equiv Fe), and 1 mL of THF. Product yield was determined via ^{1}H-NMR, and the spectra matched literature values.[8,10]

p-Methoxy methyl 2-phenyldiazoacetate Insertion with Cyclohexane. The general procedure was used with *p*-methoxy methyl 2-phenyldiazoacetate (0.037 g, 0.172 mmol, 1 equiv), either Fe[OEP]Cl (0.0019 g, 0.00313 mmol, .0182 equiv) or Fe[OEP]Cl @ MOF-5 (0.0087 g, 0.00313 mmol Fe, 0.0182 equiv Fe), and 1 mL of cyclohexane. Product yield was determined via ^{1}H-NMR; the spectra matched literature values.[10]

p-Methoxy methyl 2-phenyldiazoacetate Insertion with Cyclopentane. The general procedure was used with *p*-methoxy methyl 2-phenyldiazoacetate (0.037 g, 0.172 mmol, 1 equiv), either Fe[OEP]Cl (0.0019 g, 0.00313 mmol, 0.0182 equiv) or Fe[OEP]Cl @ MOF-5 (0.0087 g, 0.00313 mmol Fe, 0.0182 equiv Fe), and 1 mL of cyclopentane. Product yield was determined via ^{1}H-NMR; the spectra matched literature values.[11]

p-Methoxy methyl 2-phenyldiazoacetate Insertion with Cycloheptane. The general procedure was used with *p*-methoxy methyl 2-phenyldiazoacetate (0.037 g, 0.172 mmol, 1 equiv), either Fe[OEP]Cl (0.0019 g, 0.00313 mmol, 0.0182 equiv) or Fe[OEP]Cl @ MOF-5 (0.0087 g, 0.00313 mmol Fe, 0.0182 equiv Fe), and 1 mL of cycloheptane. Product yield was determined via ^{1}H-NMR; the spectra matched literature values.[11]

2.5 References

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CHAPTER 3

Iron Catalyzed C-H Functionalization

3.1 Introduction

Molecules containing carbon-oxygen bonds are of great significance in both industrial and academic settings. For example, cyclohexanone, formed via the oxidation of cyclohexane, is produced on the billion ton scale, much of which is used as a commodity feedstock in the synthesis of a precursor to Nylon 61.[1] Similarly, the widely produced polymer polyethylene glycol (PEG) is synthesized from ethylene oxide. An energy-efficient catalytic oxidation of gaseous methane, the primary component of natural gas, to liquid methanol would provide an impactful solution for energy transport and greenhouse gas reclamation.[2] Lastly, the biochemical reactivity of molecules such as progesterone, testosterone, and other hormones are governed by the nature of their oxygenated cores.[3]

Figure 3.1.1. Important Compounds Containing Hydroxyl and Carbonyl Units
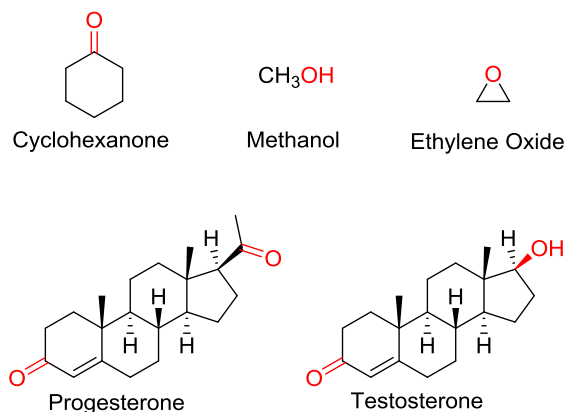
Given their widespread importance, the synthesis of these oxygen containing functionalities is of great interest. One prevalent synthetic route for installing these groups is C-

H oxidation. As described in section 1.3 of chapter 1, this synthetic method utilizes the carbon-hydrogen backbone of an organic substrate for oxidation chemistry.

Over the past 50 years, steady progress has been made towards realizing the potential of the C-H oxidation reaction. Recent efforts have greatly broadened the variety of chemical transformations possible at the C-H bond however regioselective reactivity had until recently remained elusive. In 2007, Chen and White reported a novel method for catalytic aliphatic C-H oxidation.[4] Utilizing the catalyst [Fe(*S,S*-PDP)(CH$_3$CN)$_2$] (SbF$_6$)$_2$ (**1**) (Figure 3.1.2), moderate yields are attained over a range of substrates. Significantly, the system is capable of truly selective C-H functionalization based on the order of substitution of carbon centers (Scheme 3.1.1).

Figure 3.1.2. [Fe(*S,S*-PDP)(CH$_3$CN)$_2$] (SbF$_6$)$_2$ (**1**)
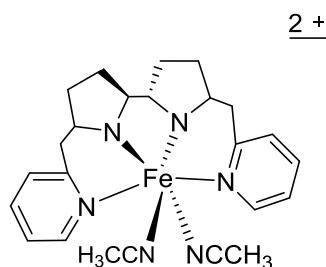
Scheme 3.1.1. Regioselective C-H Functionalization by **1**
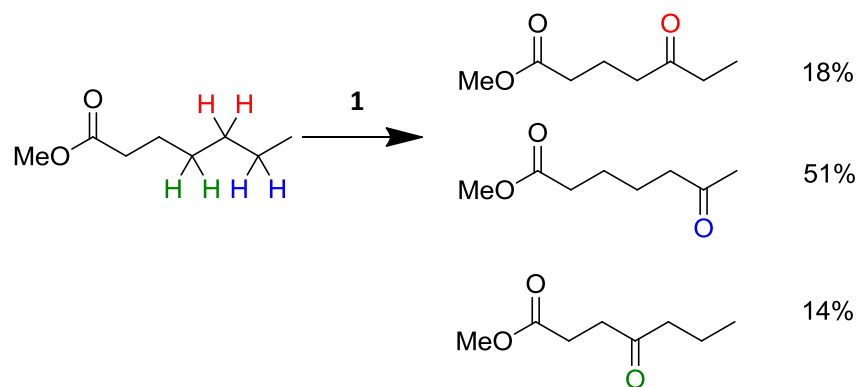
However, Chen and White's system suffers from several drawbacks. Principle among them is a laborious stepwise addition procedure, which calls for three separate loadings of catalyst, oxidant and co-oxidant. It is proposed by Chen and White that this, in addition to the high catalyst loadings utilized, is necessary due to the bimolecular decomposition of the catalyst.[5]

Herein, we detail investigations into heterogeneous C-H functionalization utilizing the Chen-White catalyst supported inside a metal organic framework. It is proposed that by encapsulating the catalyst within a MOF, bimolecular decomposition will be abated, eliminating the need for multiple additions of catalyst and increasing catalyst reactivity.

3.2 Results and Discussion

Our investigation to iron catalyzed C-H functionalization began with verification of homogeneous results as reported in the literature. Homogeneous trials were run using the reported stepwise addition procedure in comparison with a separate procedure using a single addition of all reactants at the onset of the reaction. As shown in table 3.2.1, we were able to successfully replicate Chen and White's published results. The greatly reduced TON of the single addition trial demonstrated the necessity of the stepwise addition procedure for the homogeneous reaction. A great deal of gas was evolved at the onset of the single addition trial, indicating that disproportionation of H_2O_2 into H_2O and O_2, along with catalyst decomposition, was likely affecting the yield.

Table 3.2.1. Replication of Literature Data for Fe(S,S-PDP)[4,a]

$$\text{(cyclohexane)} \xrightarrow[\text{RT, 30 min. CH}_3\text{CN}]{\substack{\text{15 mol \% (Fe(}S,S\text{-PDP)(CH}_3\text{CN)}_2\text{)(SbF}_6\text{)}_2 \\ \text{AcOH (1.2 equiv.) H}_2\text{O}_2 \text{ (3 equiv.)}}} \text{(cyclohexanone)}$$
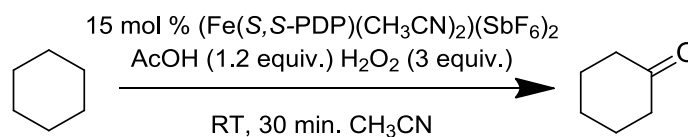
Addition Protocol	TON[b]
Stepwise Addition[c]	1.5
Single Addition	0.5
Literature Yield[4]	1.2

[a] Conditions: 50 wt % H_2O_2 (30.66 μL, 0.511 mmol, 3.04 equiv), Fe(S,S-PDP) (0.0194 g, 0.025 mmol, 0.148 equiv), AcOH (0.0125 g, 0.201 mmol , 1.19 equiv), cyclohexane (15 μL, 0.168 mmol, 1.00 equiv), acetonitrile (4.375 mL) [b] Determined via GC with ethylbenzene as a standard [c] Three equal portions of Fe(S,S-PDP), H_2O_2, and AcOH added over 30 minutes, with 10 minutes in between each addition, as reported by Chen and White[4]

Next, a metal organic framework was selected for catalyst incorporation. Due to the cationic charge of Fe(S,S-PDP), ion exchange was selected as our strategy for catalyst incorporation in the MOF.

Literature review and our lab's experience[6] led us to examine anionic MOF ZJU-28. This MOF is derived of single indium atom metal nodes coordinated to 4,4',4"-benzene-1,3,5-triyl-tribenzoic acid (H_3BTB) organic linkers; each indium atom is coordinated to four H_3BTB linkers. The structure of this framework is visible in figure 3.2.2. Importantly, ZJU-28 has anionic pores, which are populated by cationic $Me_2NH_2^+$ molecules. ZJU-28 synthesis was carried out according to the literature.[7]

Figure 3.2.1. Structure of ZJU-28[7]
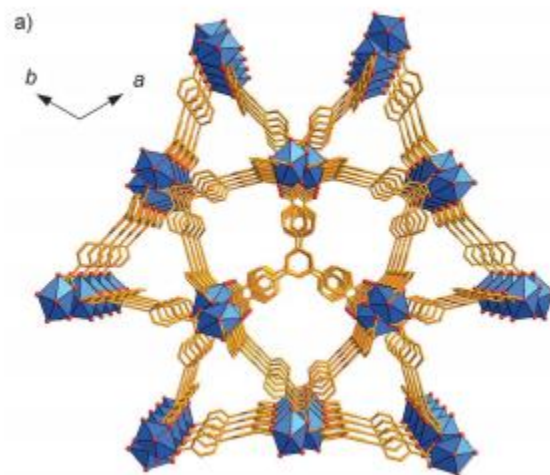
The stability of ZJU-28 under the reaction conditions of Chen and White's catalytic system was investigated. ZJU-28 (0.004 g) was placed in a scintillation vial containing H_2O_2 (30.66 µL, 50 wt %), AcOH (15 µL), and CH_3CN (5 mL). A separate vial was prepared without AcOH. Both vials were visually inspected every 10 minutes for evidence of decomposition (decomposition denoted by opaque and fragmented crystals), for a total of 30 minutes. The ZJU-28 did not appear to decompose in either trial.

The ion-exchange doping of ZJU-28 with Fe(*S,S*-PDP) was next attempted utilizing the procedure outlined in scheme 3.2.1. ICP-OES analysis determined that our doped ZJU-28 was 6.5 % iron catalyst (by weight) when DMF was used as the doping solvent. In contrast 5.6 % Fe loading was attained when CH_3CN was used as the doping solvent. Both batches (DMF and CH_3CN) were used throughout these experiments.

Scheme 3.2.1. Doping of ZJU-28 with Fe(*S,S*-PDP (**1**))
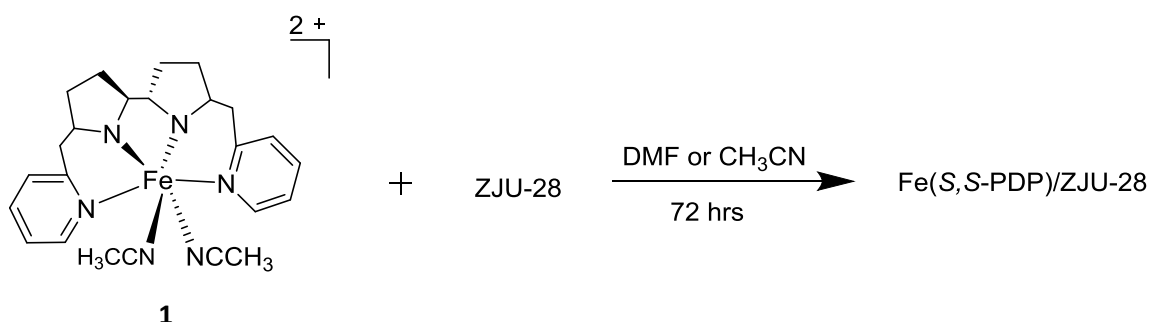
Figure 3.2.2. Initial Heterogeneous C-H Functionalization Trials[a,c]
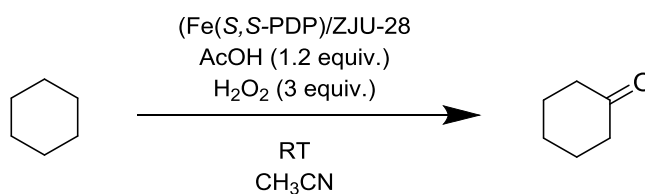
MOF Used (Identified by Doping Solvent)	Reaction Time (hrs)	Reaction Volume (mL)	TON[b]
DMF-Doped	0.5	4.375	0
DMF-Doped	27	4.375	0
DMF-Doped	0.5	1.0	0
DMF-Doped	27	1.0	0
CH₃CN-Doped	0.5	4.375	0
CH₃CN-Doped	27	4.375	0
CH₃CN-Doped	0.5	1.0	0
CH₃CN-Doped	27	1.0	0

[a] Conditions: 50 wt % H_2O_2 (30.66 μL, 0.511 mmol, 3.04 equiv), Fe(*S,S*-PDP)/ZJU-28 (0.004 g, 0.31 μmol Fe, 0.0006 equiv), AcOH (0.0125 g, 0.201 mmol , 1.19 equiv), cyclohexane (15 μL, 0.168 mmol, 1.00 equiv), acetonitrile (4.375 mL or 1mL) [b] Determined via GC with ethylbenzene as a standard [c] All reagents added at beginning of reaction

The catalytic activity of Fe(*S,S*-PDP)/ZJU-28 was probed. The conditions and results are found in table 3.2.2 above. None of the initial heterogeneous catalysis trials yielded product.

In order to be converted into product in the trials shown in figure 3.2.2, a cyclohexane molecule must traverse the pores of the MOF and reach an encapsulated catalyst molecule. We concluded that cyclohexane's inability to compete with acetonitrile for space within the pores of the MOF, in addition to the low catalyst loading utilized by our heterogeneous system, had resulted in our system's observed lack of reactivity. In an effort to compensate for this, experiments were run in neat cyclohexane. Two organic oxidants, peracetic acid and *meta-*chlororperoxybenzoic acid(mCPBA), were tested in an attempt to find a solution to our aqueous H_2O_2 solution's immiscibility in cyclohexane.

When run under neat conditions and with an organic oxidant, our heterogeneous system achieved modest catalytic activity (~3-8 TON). As seen in figure 3.2.3, both peracetic acid and mCPBA trials returned TONs equivalent to those reported by Chen and White. It is readily apparent however that these results are not internally consistent. Utilizing the CH_3CN doped MOF, neat cyclohexane and mCPBA, 7.8 TON is observed after 0.5 hours. However, after an identical 27 hour reaction, no product was detected by the GC. The inconsistency of these data was confirmed by select replicate trials. A possible explanation for our observation of no product after an extended reaction time is that the product is decomposing.

Figure 3.2.3. Heterogeneous reactions utilizing neat reaction conditions[a,c]
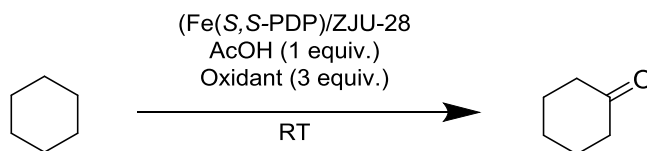
(Fe(*S*,*S*-PDP)/ZJU-28
AcOH (1 equiv.)
Oxidant (3 equiv.)
RT

MOF Used (Identified by Doping Solvent)	Oxidant	TON[b] after 0.5 hrs (replicate trial)	TON[b] after 27 hrs (replicate trial)
DMF-Doped	H_2O_2	0	0
DMF-Doped	Peracetic Acid	0 (1.25)	3.2 (1.72)
DMF-Doped	mCPBA	1.6 (1.32)	0 (0)
CH_3CN-Doped	H_2O_2	0	0
CH_3CN-Doped	Peracetic Acid	3.4	0 (0.67)
CH_3CN-Doped	mCPBA	7.8	0 (0)

[a] Conditions: 50 wt % H_2O_2 (30.66 μL, 0.511 mmol, 2.54 equiv), peracetic Acid (44 μL, 0.600 mmol, 2.98 equiv), mCPBA (0.100 g, 0.579 mmol, 2.90 equiv), Fe(*S*,*S*-PDP)/ZJU-28 (0.004 g, 0.31 μmol Fe, 0.0006 equiv), AcOH (0.0125 g, 0.201 mmol , 1.00 equiv), cyclohexane (1 mL) [b] Determined via GC with ethylbenzene as a standard [c] All reagents added at beginning of reaction

In an effort to determine the cause of this variability in yield, the role of AcOH as co-oxidant was further investigated. As demonstrated by the data shown in figure 3.2.4, acetic acid is required for catalysis by Fe(*S,S*-PDP). These trials were also repeated in neat cyclohexane, and similarly no product was detected by GC.

Figure 3.2.4. Determination of role of AcOH in C-H Functionalization[a,c]

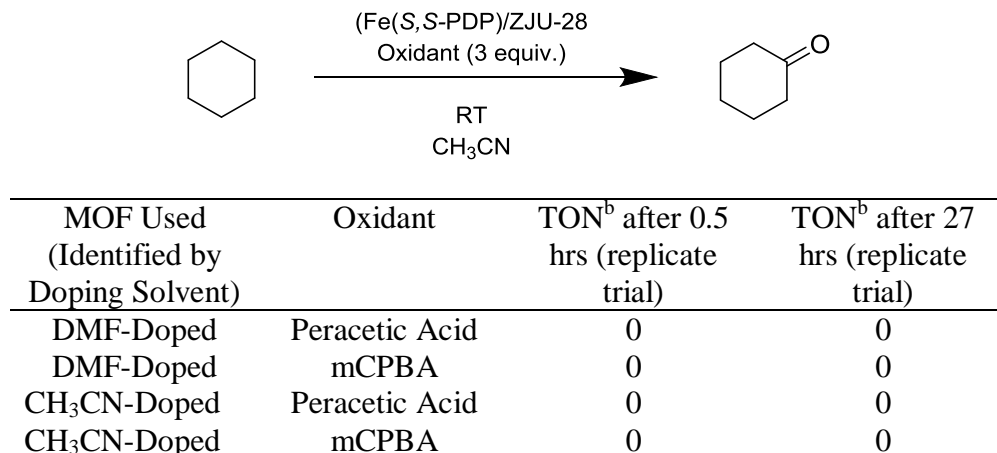| MOF Used (Identified by Doping Solvent)	Oxidant	TON[b] after 0.5 hrs (replicate trial)	TON[b] after 27 hrs (replicate trial)
DMF-Doped	Peracetic Acid	0	0
DMF-Doped	mCPBA	0	0
CH₃CN-Doped	Peracetic Acid	0	0
CH₃CN-Doped	mCPBA	0	0

[a] Conditions: 50 wt % H_2O_2 (30.66 μL, 0.511 mmol, 2.5 equiv), peracetic Acid (44 μL, 0.600 mmol, 3 equiv), mCPBA (0.100 g, 0.579 mmol, 2.9 equiv), Fe(*S,S*-PDP)/ZJU-28 (0.004 g, 0.31 μmol Fe, 0.0006 equiv), cyclohexane (1 mL) [b] Determined via GC with ethylbenzene as a standard [c] All reagents added at beginning of reaction

At this point, it was noted that the heterogeneous catalyst was changing color, from light purple to dark purple, during trials. The homogeneous catalyst was not observed to change color in this manner. This led us to repeat the ZJU-28 stability tests conducted at the onset of our studies, this time we would extend the duration of the study to 27 hours and include optical microscopy as an analytical tool.

The results of this stability study indicated that ZJU-28 was incompatible with AcOH, peracetic acid, and H_2O_2. Optical microscopy of the crystals exposed to these chemicals after 27 hours revealed opaque MOF that was no longer a single phase. Opaque crystals, usually implies collapse of the internal pore environment of the framework without leading to dissolution of the material. It is hypothesized that this degradation is present at the 30 minute time point used in our initial stability studies, but that the decomposition is too subtle to be observed with the naked eye. Additionally, the iron catalyst may significantly accelerate this decomposition.

In an effort to surmount ZJU-28's incompatibility with Chen and White's conditions, a brief literature review was conducted to determine if any alternative oxidants existed that could

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potentially catalyze this transformation in the absence of AcOH. Kim et. al's report on Fe(TPA)-catalyzed alkane hydroxylation detailed the use of ^{t}BuOOH as an oxidant for C-H functionalization, and achieved moderate TONs.[8] Unfortunately, Fe(*S,S*-PDP) only produced ~1 TON (~15 % yield) of product utilizing ^{t}BuOOH as its oxidant. This significant incompatibility of ZJU-28 with the Chen-White catalyst's reaction conditions, combined with a lack of viable alternatives to those conditions, led to a change of research direction towards alkene oxidation, which is the subject of chapter four.

3.3 Conclusion

In conclusion, this chapter has described the results of catalytic studies utilizing [Fe(*S,S*-PDP)(CH$_3$CN)$_2$] incorporated in ZJU-28. Initial results from stability studies utilizing undoped ZJU-28 suggested that the MOF was compatible with the reaction conditions utilized by Chen and White. However, inconsistent data and further stability studies using doped ZJU-28 indicated that the opposite was true, and that ZJU-28 was, in fact, being destroyed by AcOH, H$_2$O$_2$, and peracetic acid. This, combined with a lack of viable options to replace these reaction conditions, led us to move towards alkene oxidation.

3.4 Experimental Procedures and Characterization Data

General Procedures. Gas chromatography was carried out on a Shimadzu 17A using a Restek Rtx®-5 (Crossbond 5% diphenyl – 95% dimethyl polysiloxane; 15 m, 0.25 mm ID, 0.25 μm df) column. GC calibrated yields are reported relative to ethylbenzene as an internal standard.

Materials and Methods. ZJU-28 was synthesized as reported in the literature.[7] [Fe(*S,S*-PDP)(CH$_3$CN)$_2$] (SbF$_6$)$_2$, and ^{t}BuOOH were purchased from Strem chemicals. Cyclohexane, 50 wt % H$_2$O$_2$, peracetic acid, mCPBA, DMF, and CH$_3$CN were purchased from Aldrich. AcOH was purchased from Fisher. All commercial substrates, reagents, and solvents were used as received without further purification.

Doping of ZJU-28 with Fe(S,S-PDP). Fe(*S,S*-PDP) (0.068 g, 0.074 mmol, 1.0 equiv) and DMF (5 mL) were added to a 20 mL scintillation vial. This mixture was shaken until all catalyst is dissolved. ZJU-28 (0.100 g) was then added. The vial was placed on a shaker and agitated for 72 hours. The vial was then removed, and the doped ZJU-28 crystals rinsed (3 x 3 mL) with DMF and then soaked in DMF (3 x 3 mL) for 30 min on the shaker plate. Solvent was removed on the hi-vac line overnight, and the crystals were stored in a desiccator.

General Procedure for C-H Functionalization Reactions – Single Addition. Catalyst was combined with solvent in a 20 mL scintillation vial. To this mixture, cyclohexane was added, followed by AcOH (0.0125 g, 0.201 mmol , 1.00 equiv), and finally oxidant(see Figure 3.2.3). The vial was then capped and placed on a shaker plate. Following the reaction's completion, the vial was removed from the shaker plate, and the liquid phase was decanted and doped with ethylbenzene (12.2 µL). Yield was then determined via gas chromatography.

3.5 References

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CHAPTER 4

Iron Catalyzed Alkene Oxidation

4.1 Introduction

Building from the results of our C-H functionalization studies, more facile oxidation transformations were investigated in the form of alkene oxidation. Since Groves et al.'s 1979 paper describing the ability of Fe(TPP)Cl to epoxidize cyclohexene, a great deal of progress has been made in describing new iron alkene oxidation catalysts, and optimizing their reaction conditions. As mentioned in the introduction chapter, Prat et. al report a system utilizing [Fe(CF$_3$SO$_3$)$_2$(^{Me,H}PyTACN)] (**1**) as catalyst capable of quantitative yields.[1] However this homogeneous system and others like it yield a mix of products, often due to the alternative oxidation of the alkene.

Scheme 4.1.1. Oxidation of Cyclooctene with [Fe(CF$_3$SO$_3$)$_2$(^{Me,H}PyTACN)] (**1**)
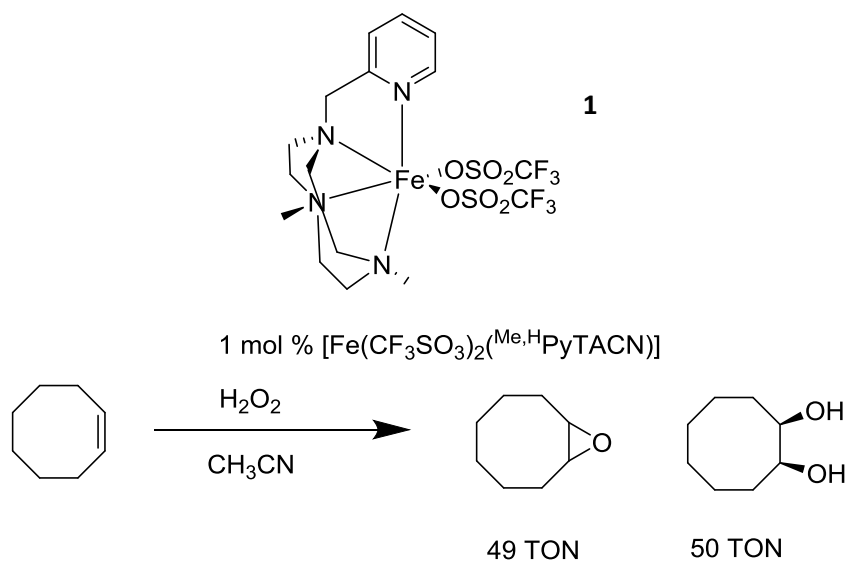
Incorporating the catalyst within a heterogeneous material is envisioned as a way to limit the over-oxidation. By placing the catalyst within the confines of a solid material, its reaction site may be sterically or electronically hindered in a manner which prevents further interaction of the epoxidized product with the catalyst. Studies by scientists at Zhejiang University confirm the legitimacy of this hypothesis: utilizing a Fe-TCCP MOF, a 17.9 % yield of solely styrene oxide is obtained from the oxidation of styrene, whereas the homogeneous reaction generates a mixture of products. However, this Fe MOF is poorly reactive, when compared to the analogous Mn-TCCP MOF which attains a quantitative yield of styrene oxide in the same transformation.[2]

Scheme 4.1.2. Proposed Over-Oxidation of Styrene Oxide to Benzaldehyde
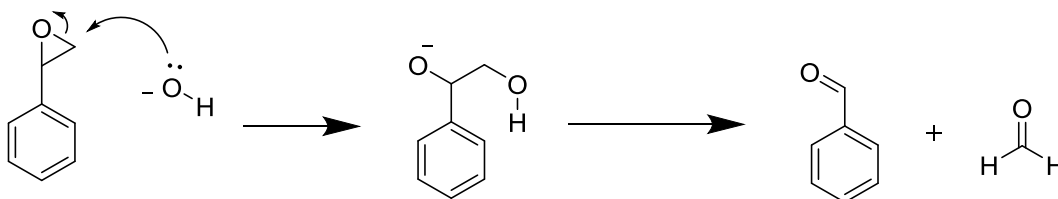
Herein, we report studies into the heterogeneous oxidation of styrene to styrene oxide and benzaldehyde, an over-oxidation product of styrene oxide. It is proposed that by incorporating these catalysts in porous frameworks, catalyst reactivity and selectivity will be increased.

4.2 Results and Discussion

Our investigation into iron catalyzed alkene oxidation began with the determination of the competency of [Fe(S,S-PDP)(CH$_3$CN)$_2$] (SbF$_6$)$_2$ and [Fe(TPA)(CH$_3$CN)$_2$](ClO$_4$)$_2$ as catalysts for the transformation of styrene to styrene oxide.[3,4] Due to their successful implementation in the literature, H$_2$O$_2$ and iodosylbenzene were used as oxidants in this transformation.

Figure 4.2.1. Fe(*S,S*-PDP) (**2**) and Fe(TPA) (**3**)

2 **3**
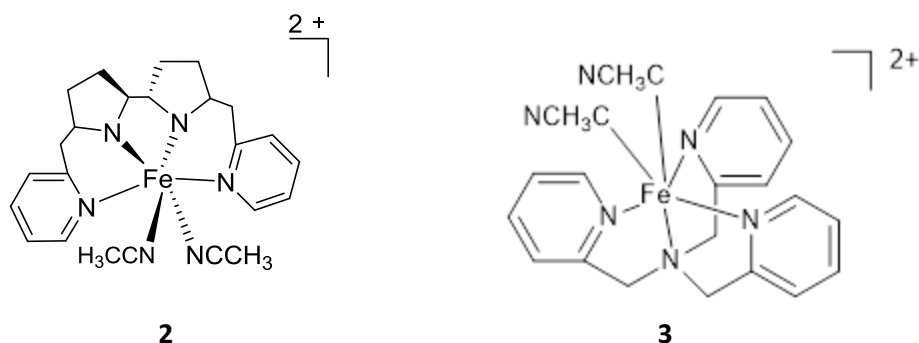
The results of these homogeneous styrene oxidation trials, found in table 1.2.1 were encouraging. Both Fe(*S,S*-PDP) and Fe(TPA) catalyzed the transformation of styrene to styrene oxide with moderate TONs. With Fe(*S,S*-PDP) as catalyst and iodosylbenzene as oxidant the highest TON (42) the four catalyst-oxidant pairings examined was achieved. These results led us to utilize Fe(*S,S*-PDP) as the catalyst for these transformations.

Table 4.2.1. Homogeneous Fe(*S,S*-PDP) and Fe(TPA) Styrene Oxidation Trials[a]

	Fe(*S,S*-PDP)		Fe(TPA)	
Oxidant	TON, Styrene Oxide[b]	TON, Benzaldehyde[b,c]	TON, Styrene Oxide[b]	TON, Benzaldehyde[b,c]
Iodosylbenzene	10	32	4	13
H_2O_2	14	17	5	2

[a] Conditions: 50 wt % H_2O_2 (11.90 μL, 0.21 mmol, 100 equiv), PhIO (0.046 g, 0.21 mmol, 100 equiv), Fe(*S,S*-PDP) (0.002 g, 0.0021 mmol, 1 equiv), Fe(TPA) (0.002 g, 0.0021 mmol , 1 equiv), styrene (245 μL, 2.1 mmol, 1000 equiv), acetonitrile (3 mL) [b] Determined via GC with ethylbenzene as a standard [c] Benzaldehyde only takes one TON of oxidant

The role of the oxidant in these transformations was next assayed. Interestingly, Fe(S,S-PDP) was observed to catalyze the transformation of styrene to benzaldehyde in the absence of exogenous oxidant. 29 TON of benzaldehyde, and 0 TON of styrene oxide, was observed after Fe(S,S-PDP) and styrene was stirred at room temperature for 24 hours. Note that with the addition of iodosylbenzene, only an additional 3 TON were observed (figure 4.2.1). Paradoxically, the addition of H_2O_2 seems to suppress Fe(S,S-PDP)'s ability catalyze the synthesis of benzaldehyde. Treating a solution of preformed styrene oxide under catalytic conditions yielded no benzaldehyde, implying that benzaldehyde is not formed as a result of the degradation of styrene oxide formed during the reaction.

With these preliminary results in hand, the synthesis of a heterogeneous Fe(S,S-PDP) catalyst was undertaken. Similar to those efforts reported in chapter three, ZJU-28 was selected as the solid support for catalyst incorporation via an ion-exchange strategy.[5] Ion-exchange doping of ZJU-28 with Fe(S,S-PDP) was accomplished in a manner identical to that reported in chapter 3.

Initial heterogeneous results indicated that the optimized homogenous conditions would not be sufficient for the heterogeneous system. TONs obtained with Fe(S,S-PDP)/ZJU-28, as seen in figure 4.2.2, were an order of magnitude smaller than those obtained under homogeneous conditions. In contrast to the homogeneous results shown in table 4.2.1, the heterogeneous reaction without oxidant yielded zero turnovers of benzaldehyde, and a trace amounts of styrene oxide. Control reactions, not shown in table 4.2.2, demonstrated that the reactivity of this system was dependent on the presence of the catalyst.

Table 4.2.2. Heterogeneous Fe(*S,S*-PDP)/ZJU-28 Replication of Homogeneous Styrene

Oxidation Trials[a]

Oxidant	TON, Styrene Oxide[b]	TON, Benzaldehyde[b]
Iodosylbenzene	0	0.7
H_2O_2	0.3	0.2
None	0.5	0
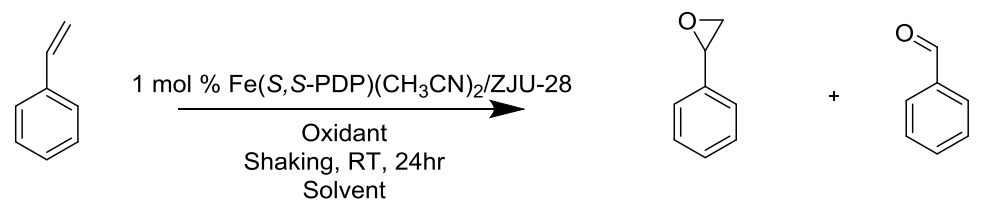
[a] Conditions: 50 wt % H_2O_2 (11.90 µL, 0.21 mmol, 100 equiv), PhIO (0.046 g, 0.21 mmol, 100 equiv), Fe(*S,S*-PDP)/ZJU-28 (0.002 g, 0.0031 mmol, 1 equiv), styrene (245 µL, 2.1 mmol, 1000 equiv), acetonitrile (3 mL) [b] Determined via GC with ethylbenzene as a standard

A solvent screen was investigated in order to identify optimized conditions for our system. Both homogeneous and heterogeneous trials were run. Significant improvement of TON was observed for the homogeneous trials utilizing DMF and acetone (Table 4.2.3). A combined 70 TON was achieved using DMF and H_2O_2 as oxidant. Unfortunately, these gains in reactivity in the homogeneous case were not realized in our heterogeneous trials. Low TONs were observed for trials utilizing Fe(*S,S*-PDP)/ZJU-28 as catalyst; for comparison, the heterogeneous

Table 4.2.3. Homogeneous Fe(*S,S*-PDP) Solvent Screen[a]

	Fe(*S,S*-PDP)(CH₃CN)₂ w/ H₂O₂		Fe(*S,S*-PDP)(CH₃CN)₂ w/o H₂O₂	
Solvent	TON, Styrene Oxide[b]	TON, Benzaldehyde[b]	TON, Styrene Oxide[b]	TON, Benzaldehyde[b]
CH₃CN	0	16	0	9.4
Nitromethane	0	11	0	0
DMF	39 (46)[c]	31 (31)[c]	4.6	9.5
THF	1.8	15	0	0
DCM	1.5	3	0	0
Acetone	2.6 (2.2)[c]	40 (51)[c]	0	0
Benzene	0	0	0	0
Styrene (Neat Rxn)	0	2.6	0	1.2

[a] Conditions: 50 wt % H_2O_2 (11.90 μL, 0.21 mmol, 100 equiv), Fe(*S,S*-PDP) (0.002 g, 0.0021 mmol, 1 equiv), styrene (245 μL, 2.1 mmol, 1000 equiv), solvent (3 mL) [b] Determined via GC with ethylbenzene as a standard [c] Yield reported for extended 48 hour reaction time

Table 4.2.4. Heterogeneous Fe(*S,S*-PDP)/ZJU-28 Solvent Screen[a]

| Solvent	Fe(*S,S*-PDP)(CH₃CN)₂-ZJU-28 w/ H₂O₂		Fe(*S,S*-PDP)(CH₃CN)₂–ZJU-28 w/o H₂O₂	
	TON, Styrene Oxide	TON, Benzaldehyde	TON, Styrene Oxide	TON, Benzaldehyde
CH₃CN	2.2	0.7	0	0
Nitromethane	0.7	1	0	0
DMF	2.2	0.3	0	0
THF	1.3	0.9	0	0
DCM	2.1	0.4	0	0
Acetone	3.0	1.5	0	0
Benzene	1.7	.2	0	0
Styrene (Neat Rxn)	1.2	.5	0	0

[a] Conditions: 50 wt % H_2O_2 (11.90 μL, 0.21 mmol, 100 equiv), Fe(*S,S*-PDP)/ZJU-28 ((0.002 g, 0.0031 mmol, 1 equiv), styrene (245 μL, 2.1 mmol, 1000 equiv), solvent (3 mL) [b] Determined via GC with ethylbenzene as a standard [c] Yield reported for extended 48 hour reaction time

trial utilizing DMF as solvent and H_2O_2 as oxidant yielded a combined 2.5 TON, a marked decrease compared to the homogeneous reaction. The reactivity of certain homogeneous trials (namely DMF), without the addition of oxidant, is hypothesized to be due to the catalyst's utilization of atmospheric O_2 as oxidant. As was observed previously, little to no reactivity is obtained for heterogeneous trials lacking H_2O_2 (this is readily observable in table 1.2.4's two rightmost columns). This is likely resultant from the fact that diffusion of O_2 into the MOF is rate-limiting, and results in negligible product accumulation over the timespan investigated.

Confronted by the meager reactivity attained using Fe(*S,S*-PDP)/ZJU-28, we moved to investigate other iron catalysts capable of alkene oxidation. Noting the success of Groves et al.'s

iron porphyrins in catalyzing these transformations, a metal-metalloporphyrinic framework called PCN-222(Fe) (**4**) was synthesized. This material is constructed of Fe(III)Cl-H$_4$TCPP (**5**) porphyrins as linkers, which are bound together by zirconium nodes. The advantage of this structure is that the framework itself consists of the catalyst. No encapsulation or incorporation must be accomplished, and the catalyst is not sensitive to ionic reaction conditions, like those incorporated via ion-exchange. Fe(III)Cl-H$_4$TCPP and PCN-222(Fe) were synthesized per the literature.[6]

Figure 4.2.2. PCN-222(Fe) (**4**) and Fe(III)Cl-H$_4$TCPP (**5**)
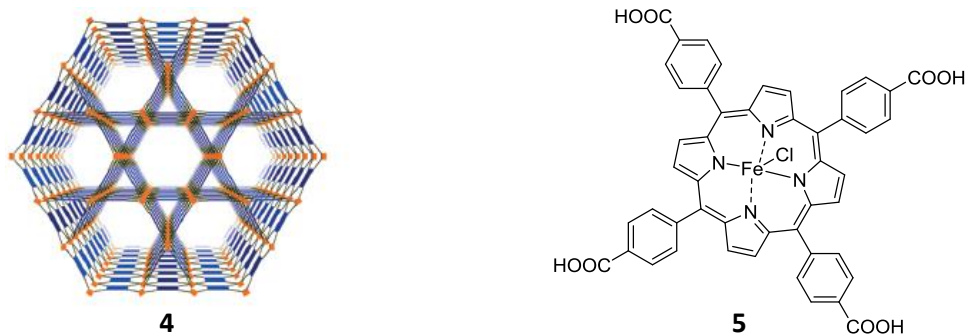

Preliminary results utilizing this system are promising. High TON of styrene oxide and benzaldehyde were observed at room temperature and at 60 ^{O}C. However, under both sets of conditions benzaldehyde formation is favored. Further solvent and oxidant optimization would enable the full exploitation of PCN-222(Fe)'s potential as a catalyst for alkene oxidation.

Table 4.2.5. Fe(III)Cl-H$_4$TCPP Homogeneous Trials[a]
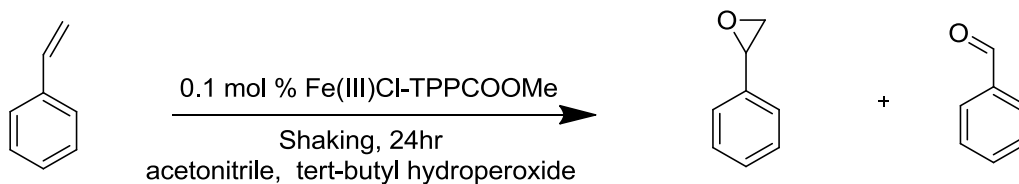
Temperature	TON, Styrene Oxide[b]	TON, Benzaldehyde[b]
Room Temperature	25	156
60 °C	34	237

[a] Conditions: 70 wt % ^{t}BuOOH (0.021 mL, 0.156 mmol, 100 equiv), Fe(III)Cl-H$_4$TCPP (0.0015 g, 0.0016 mmol, 1 equiv), styrene (178 µL, 1.56 mmol, 1000 equiv), CH$_3$CN (1 mL) [b] Determined via GC with ethylbenzene as a standard

Table 4.2.6. PCN-222(Fe) Heterogeneous Trials[a]
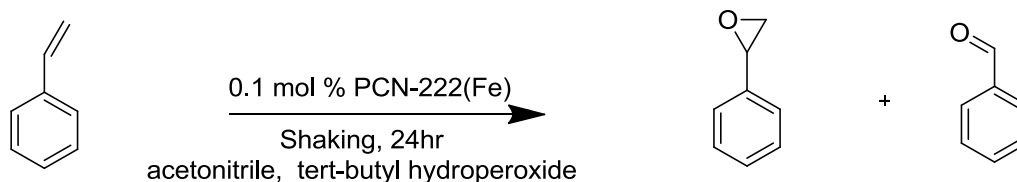
Temperature	TON, Styrene Oxide[b]	TON, Benzaldehyde[b]
Room Temperature	9	81
60 °C	54	100

[a] Conditions: 70 wt % ^{t}BuOOH (0.021 mL, 0.156 mmol, 100 equiv), PCN-222(Fe) (0.002 g, 0.0016 mmol, 1 equiv), styrene (178 µL, 1.56 mmol, 1000 equiv), CH$_3$CN (1 mL) [b] Determined via GC with ethylbenzene as a standard

4.3 Conclusion

In conclusion, this chapter has described the result of catalytic studies utilizing iron heme and non-heme compounds to achieve alkene oxidation. Fe(*S,S*-PDP), Fe(TPA), and Fe(III)Cl-H$_4$TCCP were utilized as catalysts in the transformation of styrene to styrene oxide and benzaldehyde. Fe(*S,S*-PDP) was incorporated into ZJU-28 via ion-exchange, and Fe(III)Cl-H$_4$TCCP was employed as linker in the metal-metalloporphyrinic material PCN-222(Fe). Fe(*S,S*-PDP) demonstrated moderate activity in homogeneous trials, but provided anemic TONs when incorporated into ZJU-28. The heterogeneous catalyst PCN-222(Fe) was found to be more reactive than its homogeneous counterpart Fe(III)Cl-H$_4$TCCP for the transformation of styrene to styrene oxide. Future studies should focus on optimizing the yields achieved with PCN-222(Fe), and exploring the recyclability of the catalyst.

4.4 Experimental Procedures and Characterization Data

General Procedures. Gas chromatography was carried out on a Shimadzu 17A using a Restek Rtx®-5 (Crossbond 5% diphenyl – 95% dimethyl polysiloxane; 15 m, 0.25 mm ID, 0.25 µm df) column. GC calibrated yields are reported relative to ethylbenzene as an internal standard.

Materials and Methods. ZJU-28[3], Fe(III)Cl-H$_4$TCPP[4], and PCN-222(Fe)[4] were synthesized as reported in the literature. [Fe(*S,S*-PDP)(CH$_3$CN)$_2$] (SbF$_6$)$_2$, and 70 wt % ^{t}BuOOH were purchased from Strem chemicals. Styrene, 50 wt % H$_2$O$_2$, iodosylbenzene, and all solvents were purchased from Aldrich. All commercial substrates, reagents, and solvents were used as received without further purification.

Doping of ZJU-28 with Fe(S,S-PDP). Fe(*S,S*-PDP) (0.068 g, 0.074 mmol, 1.00 equiv) and DMF (5 mL) were added to a 20 mL scintillation vial. This mixture was shaken until all catalyst is dissolved. ZJU-28 (0.100 g) was then added. The vial was placed on a shaker and agitated for 72 hours. The vial was then removed, and the doped ZJU-28 crystals rinsed (3 x 3 mL) with DMF and then soaked in DMF (3 x 3 mL) for 30 min on the shaker plate. Solvent was removed on the hi-vac line overnight, and the crystals were stored in a desiccator.

General Procedure for Alkene Oxidation Reactions – Homogeneous Catalyst. Catalyst (see table 4.2.1. and 4.2.5 for stoichiometry) was combined with solvent in a 20 mL scintillation vial. To this mixture, styrene was added, followed by oxidant (100 equiv., see table 1.2.1 for H_2O_2 and table 1.2.5 for ^tBuOOH). The vial was then capped and placed on a shaker plate. Following the reaction's completion, the vial was removed from the shaker plate. The reaction crude was doped with ethylbenzene (12.2 μL). Yield was then determined via gas chromatography.

General Procedure for Alkene Oxidation Reactions –Heterogeneous Catalyst. Catalyst (see table 4.2.2. and 4.2.6. for stoichiometry) was combined with solvent in a 20 mL scintillation vial. To this mixture, styrene was added, followed by oxidant (100 equiv., see table 1.2.1 for H_2O_2 and table 1.2.5 for ^tBuOOH). The vial was then capped and placed on a shaker plate. Following the reaction's completion, the vial was removed from the shaker plate. The crude reaction mixture was then decanted into a separate vial. This reaction crude was doped with ethylbenzene (12.2 μL). Yield was then determined via gas chromatography.

4.5 References

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