DESIGN AND SYNTHESIS OF FLAVIN-BASED ORGANOCATALYSTS FOR

BIOMIMETIC AEROBIC OXIDATION REACTIONS

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November 7, 2013

Abstract

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SHUAI CHEN, PhD

The University of Texas at Arlington, 2013

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Oxidation reactions are among the most costly and least selective transformations in synthetic chemistry. Catalytic methods that utilize O_2 as a terminal oxidant strive to reduce the inefficiency in this large area of synthesis. Recent efforts have been aimed primarily at metal-/organometallic- or enzyme-catalyzed transformations. The goal of the research described in this dissertation was to develop organocatalytic systems based on natural biosynthetic catalysts in order to develop selective metal-free aerobic oxidations that function at room temperature. Prior to our work, riboflavin mimics were previously investigated to understand flavoenzyme function and to perform catalytic oxidations of primarily heteroatom systems. We set out to extend this relatively limited area of organocatalysis to the oxidation of more valuable carbon centers in a mild, chemoselective and stereoselective manner.

In Chapter 1, a description of the development and application of biomimetic flavin organocatalysts thus far reported in the literature are summarized.

In Chapter 2, the flavin-catalyzed Dakin oxidation is discussed. A range of riboflavin derivatives is used as catalysts to accelerate the transformation of *o*- or *p*-hydroxyl benzaldehydes into dihydroxybenzenes using H_2O_2 as the terminal oxidant. An

aerobic version of this transformation is developed using the flavin catalysts and NAD(P)H mimics.

In Chapter 3, an aerobic asymmetric Weitz-Scheffer epoxidation of enals using flavin and chiral, non-racemic pyrrolidines in a dual catalysis strategy is discussed. High enantioselectivity and diastereoselectivity are observed in the epoxides obtained using this method. A mechanistic study is conducted to elucidate the characteristics of the reaction pathway.

In Chapter 4, the flavin catalyzed aerobic aromatization of heterocycles is discussed. Riboflavin derivatives are used to convert substituted dihydropyridines and benzothiazolines to pyridines and benzothiazoles with molecular oxygen as terminal oxidant under mild reaction conditions.

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Chapter 1

Introduction to Biomimetic Flavin Catalysis

1.1 Flavoproteins and the mechanisms of their function

The first report of riboflavin isolation dates back to 1879. A. Wynter Blyth, an

English chemist, isolated a bright-yellow pigment in his study on the composition of cow's

milk. He termed the matter lactochrome at that time which is known now as riboflavin.[1]

The same pigment was later isolated from a variety of sources and the structure was

determined by Richard Kuhn in Heidelberg and Paul Karrer in Zurich in 1934 and 1935.[2,3]

The compound was recognized as a component of vitamin B complex and the name was

finalized to be riboflavin, derived from the N^{10}-ribityl substitution and bright yellow color of

the conjugated ring system, 'flavus' meaning yellow in latin and vitamins end in 'in'.
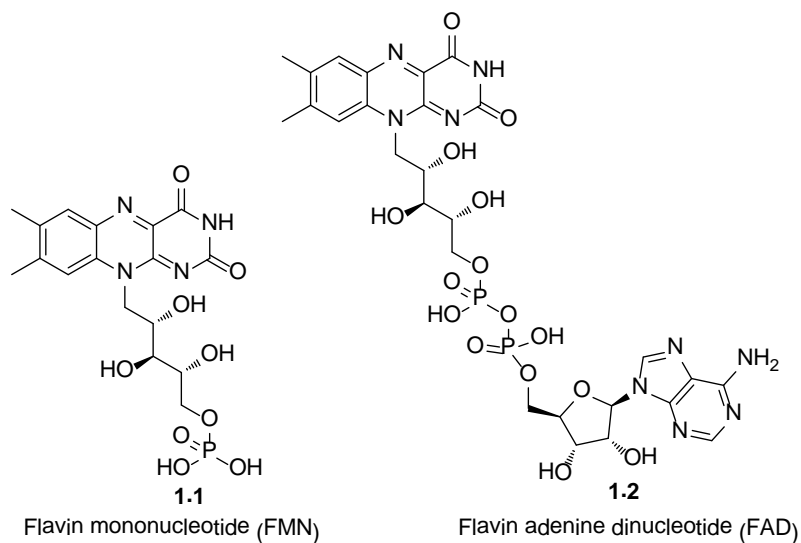
Figure 1.1 Riboflavin cofactors: FMN and FAD

Riboflavin derivatives were determined to be enzyme cofactors based on studies

by Hugo Therell in 1935.[4] Apoprotein and the flavin-related pigent were separated from a

bright-yellow-colored yeast protein which was essential for cellular respiration. Therell

found that neither apoprotein nor the pigment alone could catalyze the oxidation of

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NADH, but combination of the two restored the enzyme activity. The catalytic pigment was later identified as flavin mononucleotide 1.1 (FMN), which along with flavin adenine dinucleotide 1.2 (FAD), are the two of the most common flavin cofactors (Figure 1.1).

In flavoproteins, flavins exist either as a covalently-bonded components or non-covalently bonded as coenzymes or prosthetic group. Depending on the nature of the substrate, the type of the chemical reaction they catalyze, the physicochemical properties of the enzyme, flavoproteins are classified into distinctive categories.[5]

1. biological agents which are responsible for oxidation of substrates via activation of triplet molecular oxygen;

2. biological dehydrogenating agents; and

3. flavodoxins which are responsible for electron transfer by alternating between the flavin semiquinone radical and reduced state.

Examples of such enzymes are monooxygenases, hydroxylases; dehydrogenases; and DNA photolyase, respectively. Here, the detailed mechanism and structure of flavin monooxygenase and dehydrogenase will be discussed. The following scheme is the general flavin catalytic mechansim in biologic system (Figure 1.2). It served as a guide for the development of flavin-related chemistry throughout this dissertation.
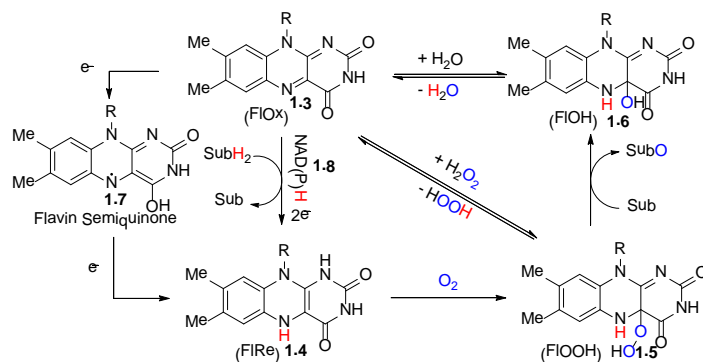
Figure 1.2 Overall flavin catalytic mechanism (single electron transfer process not shown)

As is shown in Figure 1.2, the oxidized flavin (FlOx 1.3) can be reduced to the reduced flavin (FlRe 1.4) by via two single electron transfer or one two electron transfer process. The one electron reduced flavin radical is defined as flavin semiquinone (1.7). The reduced flavin 1.4 reacts with triplet oxygen by donating one electron to oxygen followed by spin inversion to form 4a-hydroperoxyflavin (FlOOH 1.5). The FlOOH can oxidize substrates by transfer one oxygen atom to substrates to form products and the resulting 4a-hydroxyflavin (FlOH 1.6). FlOH regenerate FlOx by eliminating one molecule of water. The direct process of adding H_2O_2 to FlOx to generate 4a-FlOOH is known as the peroxide shunt process. It is worth noting that the peroxide shunt process is reversible, the FlOOH can eliminate H_2O_2 to regenerate the oxidized flavin FlOx.

1.1.1 Flavoprotein monooxygenase

Flavoprotein monooxygenases incorporate a single atom of oxygen from molecular oxygen into an organic substrate. The process starts with the generation of reduced flavin 1.4 from the reduction of oxidized flavin 1.3 with external electron donors such as NAD(P)H 1.8.(Figure 1.3) Then, the reduced flavin 1.4, which contains a polarized and electron-rich alkene, reacts with triplet molecular oxygen to form hydroperoxyflavin 1.5.The direct reaction between triplet and singlet molecules to yield a singlet product is a spin-forbidden process because chemical combination reaction rates are much faster than spin inversion rates. However, easily oxidizable singlet organic molecules, such as reduced flavin 1.4, are able to react with triplet oxygen by forming a resonance-stabilized (one-electron oxidized) radical 1.7, which pair with superoxide to form a triplet complex 1.10. The singlet 4a-hydroperoxyflavin 1.5 is generated by spin inversion sequentially.[6-7]
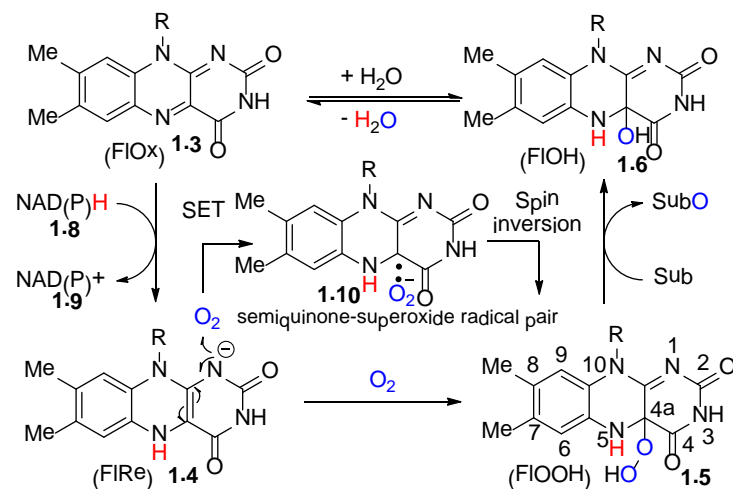
Figure 1.3 Mechanism of flavin containing monooxygenase

The O-O bond of 4a-FlOOH 1.5 is inductively polarized by the electronegativity of the N^1, N^5, N^{10} and C^4=O of the ring. The electronegativity of the C^{4a} position is responsible for the low pKa value of the FlOOH terminal proton and the electrophilicity of the peroxide terminal oxygen. 4a-FlOOHs are powerful reagents for the electrophilic *N*-oxidation of tertiary, secondary and hydroxyl amines as well as *S*-oxidation of sulfides. These oxidations are first order in both 4a-FlOOH and substrate to generate *N*-oxide or *S*-oxide and the 4a-FlOH pseudobase 1.6. The second-order rate constant of flavin catalyzed reaction exceeds those obtained with H_2O_2 and *t*-BuOOH by 10^4 to 10^5 times.[5]

In addition to the electrophilic oxidations mentioned above, the nucleophilic Baeyer-Villiger oxidation of ketones to lactone or esters are known to be achieved by flavin containing monooxygenase.[8] These flavoproteins were found in various bacteria and fungi. The most extensively studied and utilized Baeyer-Villiger monooxygenase (BVMO) is cyclohexanone monooxygenase(CHMO) from Acinetobacter sp. NCIB 9871, which has been shown activities of oxidizing a range of acyclic, cyclic, bicyclic, tricyclic and heterocyclic ketones with variety of substituents and substitution patterns, to chiral lactones and esters with high chemo-, regio- and enantioselectivity.[8] The crystal

structures of several types of BVMO have been obtained.[9] These structures revealed that

the monooxygenase (phenylacetone monooxygenase and cyclohexanone

monooxygenase) is constructed with a FAD-binding and a NADPH-binding domain,

where the active site can be found in a cleft at the interfaces of the two domains. The

enzyme active site contains a strictly conserved arginine (R337 in PAMO) which was

suggested to play an important role in the stabilization of the 4a-hydroperoxyflavin and

Criegee intermediate. However, recent detailed kinetic study showed that 4a-

hydroperoxyflavin is still formed and stabilized upon replacing Arg337 by an alanine in

these enzymes, questioning the need for cationic activation and stabilization of this

transfermation.[10]

1.1.2 Dehydrogenases

Dehydrogenase and reductase enzymes transfer electrons from one substrate to

another. Dehydrogenases oxidize an organic substrate with the use of a specific acceptor

such as $NADP^+$ 1.9, while reductases transfer electrons from a specific electron donor

such as NADH to their organic substrate.(Figure 1.4)
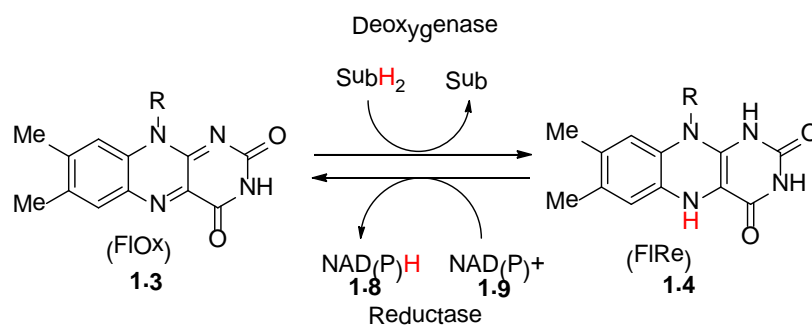
Figure 1.4 Mechanism of flavin containing dehydrogenase and reductase

For example, the introduction of unsaturation α, β to a carboxyl group is

performed by an important group of flavoenzymes. Acyl-CoA dehydrogenases involved in

the oxidation of fatty acids 1.11 and 1.14. (Figure 1.5) The mechanism has been

proposed that the initial step is the ionization of the proton α to the carboxyl group

followed by flavin oxidation of the resultant carbanion 1.12 and 1.15 to form products 1.13

and 1.16. The mechanistic details of how the flavin oxidizes the carbanion (radical

process or two-electron transfer) are still unknown.[5]
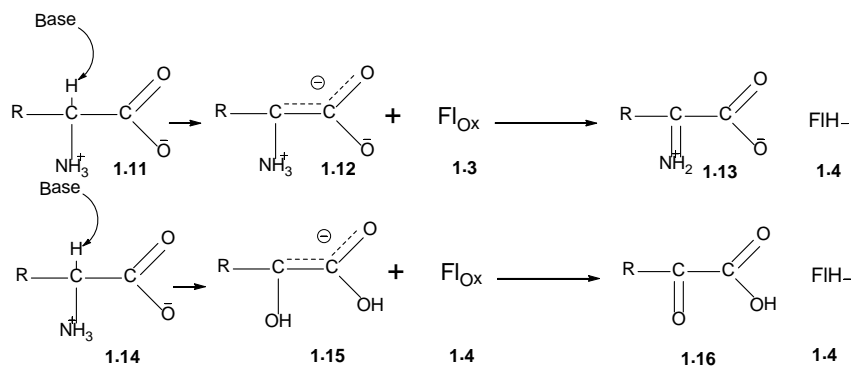
Figure 1.5 Proposed mechanism of flavin containing dehydrogenase

1.2 Biomimetic Flavin Organocatalysts

The catalysis with small organic molecules, where an inorganic element is not

part of the active mechanism, has become a highly dynamic area in chemical research.

The catalyst utilized is defined as organocatalyst.[11] Organocatalysis has superior

advantages over biocatalysis and metal catalysis in many aspects. Compared to

biocatalysis, which requires sensitive and specific enzymatic system and expensive

stoichiometric bio-reagnt such as NAD(P)H, organocatalysts have broader substrate

scope, more tolerance of large concentration changes in substrates and products, heat,

air and moisture, as well as considerable lower cost. Compared to metal catalysis,

organocatalysis has the advantages of lower toxicity and cost. Therefore, organocatalysis

is very attractive in the development of selective, mild, sustainable, and cost effective

reaction processes.[11]

Flavin organocatalysis thrived over the last two decades because of its high

reactivity toward a range of electrophilic and nucleophilic oxidation reactions. In general,

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two categories of flavin organocatalysts were designed and synthesized in the literature: alloxazine 1.17 and isoalloxazine 1.18. (Figure 1.6) Depend on the role of flavin organocatalyst in specific reactions, they can be utilized for catalyzing both electrophilic oxidations and nucleophilic oxidations. Besides electrophilic and nucleophilic oxidations, flavin's application on photooxidation, reduction reaction, drug delivery and bio-imagine will also be discussed.

1.17
N1,N3,N5-substituted flavin:
Alloxazine

1.18
N3,N5,N10-substituted flavin:
Isoalloxazine
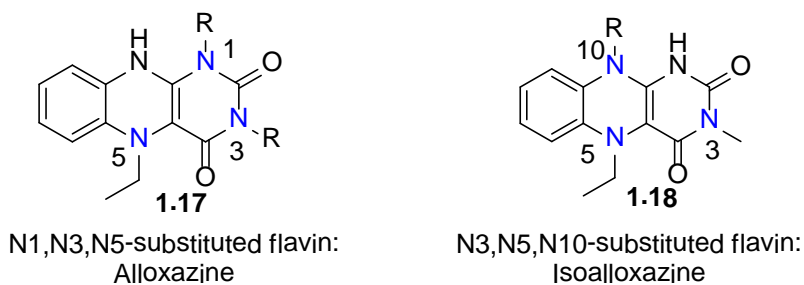
Figure 1.6 Artificial flavin organocatalysts: Alloxazine and isoalloxazine

1.2.1 Flavin Catalyzed Electrophilic Oxidations

1.2.1.1 Sulfur Oxidation

Murahashi and coworkers utilized lumiflavin derived catalyst 1.21a to oxidize aromatic and aliphatic sulfide 1.19 to sulfoxide 1.20. (Figure 1.7) Sulfoxide can be further oxidized to sulfone with one additional equivalent of H_2O_2. The mechanism can be summarized in the catalytic cycle shown below.[12]

7
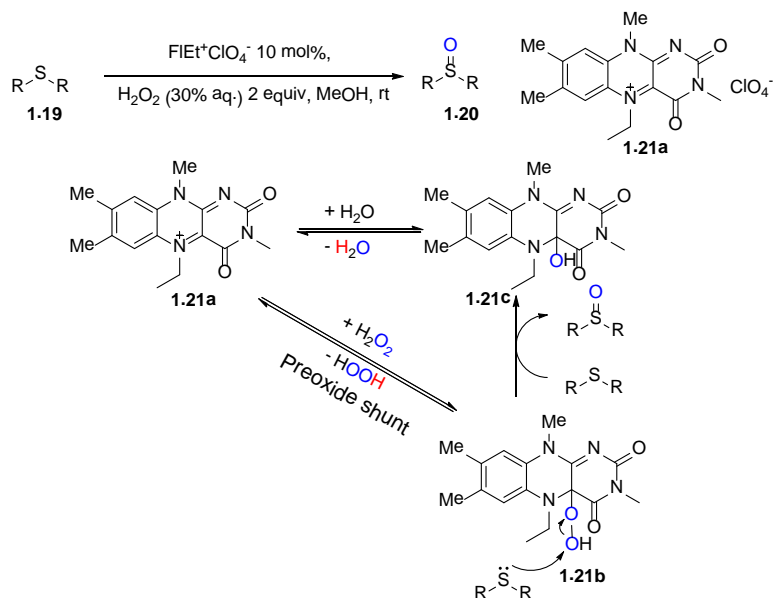
Figure 1.7 H_2O_2 sulfur oxidation with isoalloxazine

The same group published the aerobic version of sulfur oxidation of sulfide to sulfoxide using the same lumiflavinium catalyst 1.21a.[13] (Figure 1.8) Instead of using H_2O_2 as terminal oxidant, the authors take advantage of oxygen and a reducing agent, hydrazine monohydrate 1.22, to turn over the flavin catalyst. The only byproducts are nitrogen gas and water. These oxidations were carried out in trifluoroethanol (CF_3CH_2OH), a solvent known for good oxygen solubility and a relatively *p*Ka. Great atom economy was achieved with this biomimetic transformation. The mechanism is as shown below.
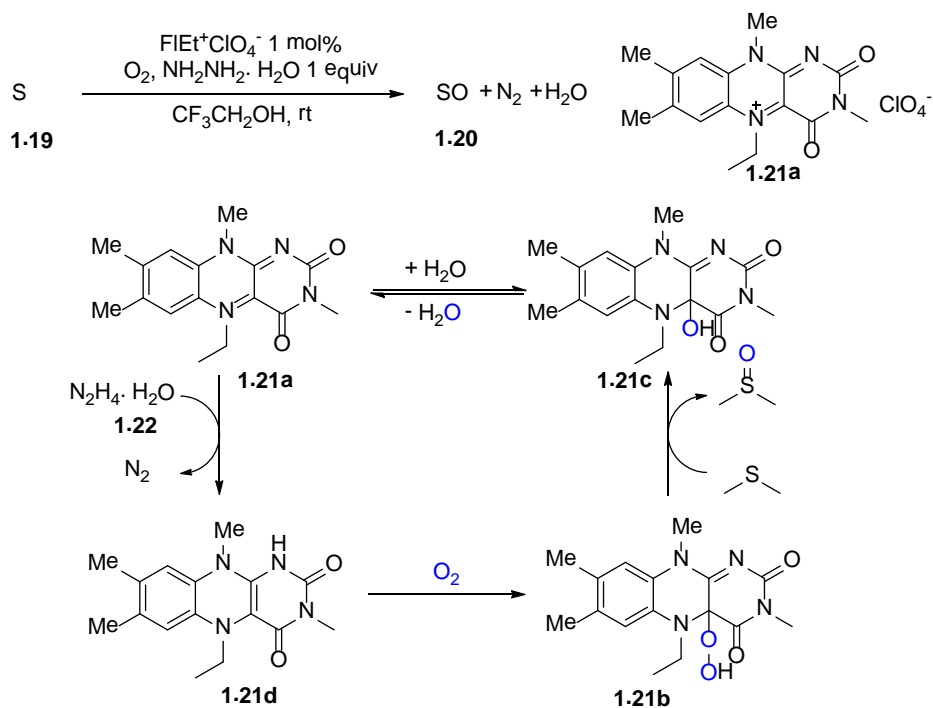
Figure 1.8 O_2 sulfur oxidation with isoalloxazine

Bäckvall and coworkers used *N,N,N*-1,3,5-trialkylated flavin organocatalyst 1.23a

to accelerate the H_2O_2 *S*-oxidation of a range of vinyl sulfides with great

chemoselectivity.[14] (Figure 1.9) No sulfones were isolated in this case. These reactions

were performed in methanol. The advantage of using this alloxazine catalyst over

isoalloxazine catalysts 1.21a (Scheme 1.5) which were utilized by the Murahashi group

is that the elimination of OH⁻ from 4a-hydroxyflavin 1.23c to form oxidized flavin 1.23d is

favored due to aromatization. Since reduced flavin FlEtH$_2$ 1.23a was used as a

precatalyst, the activation of the catalyst using oxygen gas was necessary.
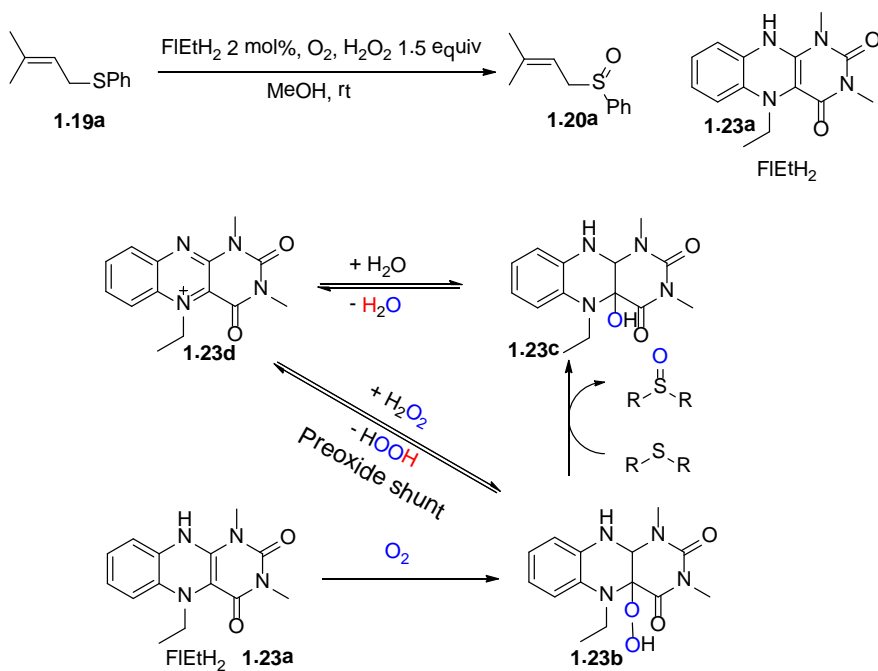
Figure 1.9 H_2O_2 sulfur oxidation with alloxazine

A range of alloxazine flavin catalysts with different substituents on the C^7, C^8 positions of the ring was synthesized by Bàckvall and coworkers. (Figure 1.10) The catalytic efficiencies of these alloxazine and isoalloxazine were compared using *N*-oxidation and *S*-oxidation as model reactions. They showed that alloxazine catalysts 1.23a, 1.24 and 1.27 are better catalysts than isoalloxazine on both *S*-oxidation and *N*-oxidation under the conditions given. They believed that electronegative substituents such as fluorines on the alloxazine could increase the electrophilicity of 4a-hydroperoxyflavin through inductive effects. The main reason why isoalloxazines 1.25, 1.26 and 1.21d had poorer catalytic effect is that they likely had difficulty eliminating the hydroxyl group from 4a-hydroxyflavin 1.21c to oxidized flavin 1.21a (Figure 1.8). In fact in the presence of a tertiary amine, the deprotonation of the 4a-hydroxyl group further prevents the elimination process.
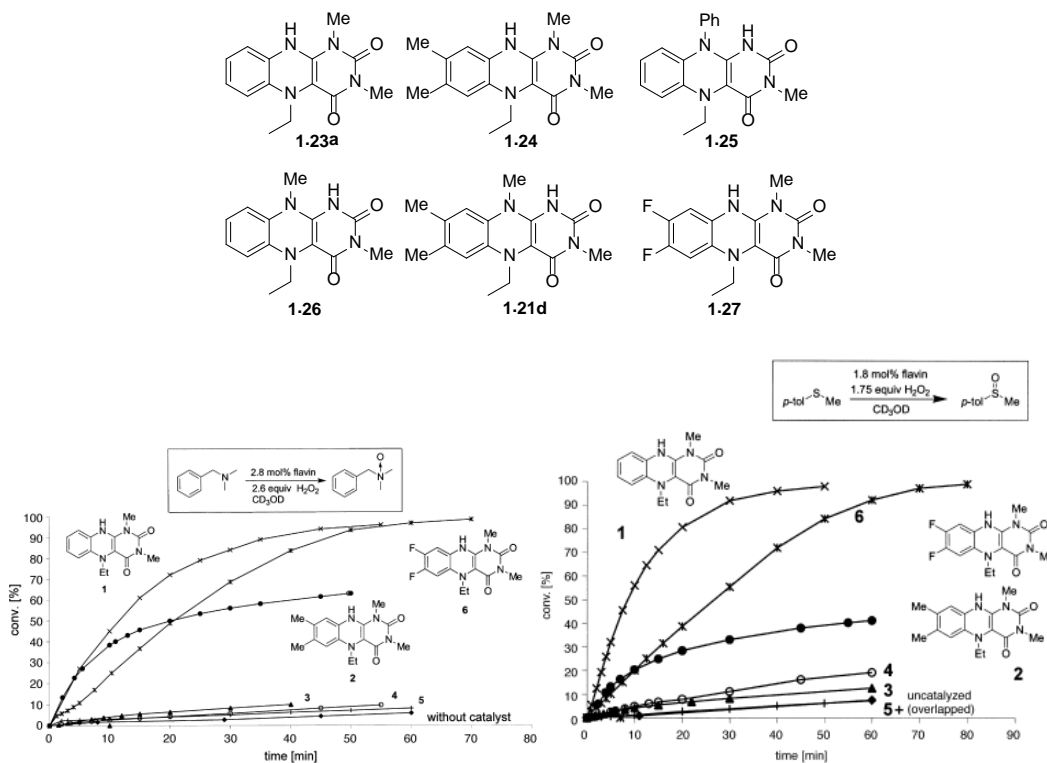
Figure 1.10 Comparison of a range of alloxazine and isoalloxazine catalysts' ability to accelerating amine and sulfur oxidation[14]

Based on established catalyst core structure, the flavin could be functionalized further to achieve specific applications. Carboxylated flavin 1.28 immobilized in an ionic liquid ([BMIm]PF$_6$) was used for the highly selective oxidation of sulfides to sulfoxides by hydrogen peroxide.[15] (Figure 1.11) The sulfoxides were obtained in good to high yields and high selectivity without any detectable overoxidation to sulfone. The catalyst in the ionic liquid was recycled up to seven times without loss of activity or selectivity. A long alkyl chain substituted on N^{10} of isoalloxazine organocatalyst 1.29 was designed and synthesized by Cibulka and coworkers.[16] This catalyst was solubilized in micelles of sodium dodecylsulfate (SDS), hexadecyltrimethylammonium chloride (CTAC), hexadecyltrimethylammonium nitrate (CTANO$_3$) or Brij 35. Reaction rates were strongly

dependent on the type of micellar matrix and on the pH value. The highest acceleration rate was found in SDS micelles at pH 4.4 (TOF = 3×10^3 h^{-1}). The reaction rate was higher compared to the reaction in homogeneous solution. The factor of acceleration ranged from approximately 1.5 (non-ionic micelles) to 3 (anionic micelles).
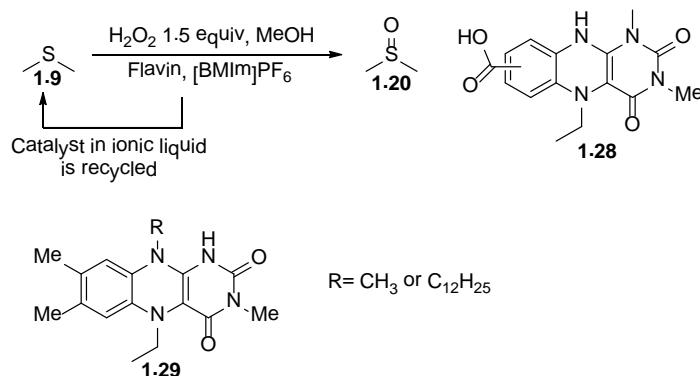
Figure 1.11 Functionalized flavins to meet special application

Carbery's group focused on applying bridged flavinium catalysts on different oxidation reactions.[17] (Figure 1.12) 1.31c showed good catalytic activity on *S*-oxidation. No over oxidation product was observed in the H$_2$O$_2$ based oxidation.
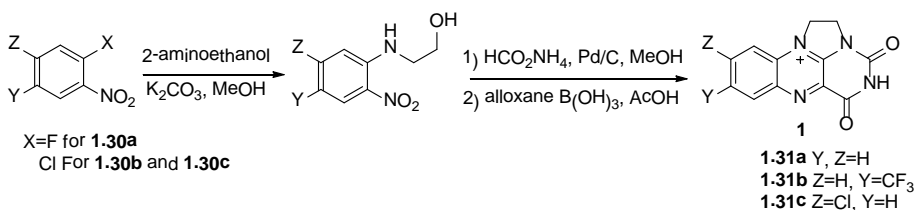
Figure 1.12 Synthesis of bridged flavinium catalysts

Cibulka's group utilized non-racemic N^1,N^{10}-ethylene-bridged flavinium salts with a stereogenic center derived from L-valinol to catalyze oxidation of sulfides to sulfoxides and the oxidation of 3-phenylcyclobutanone to the corresponding lactone at room temperature.[18] The flavinium salts react with hydrogen peroxide to form flavin-10a-hydroperoxides 1.32a and 1.32b, which were the agents responsible for oxidation of the

substrate. (Figure 1.13) Although the flavin-10a-hydroperoxides existed with a diastereomeric ratio of 3:1, the attempts to utilize the flavin for asymmetric *S*-oxidation failed.

1.32a **1.32b**
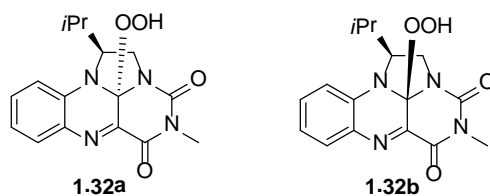
Figure 1.13 L-valinol derived bridged flavinium catalysts

Asymmetric sulfur oxidation to enantioenriched sulfuroxide is a targeted research area for flavin chemists for a long time. The oxidation of sulfides with H_2O_2 using basket-shaped, optically active flavin 1.33 affords the corresponding sulfoxides with high enatioselectivity.[19](Figure 1.14)
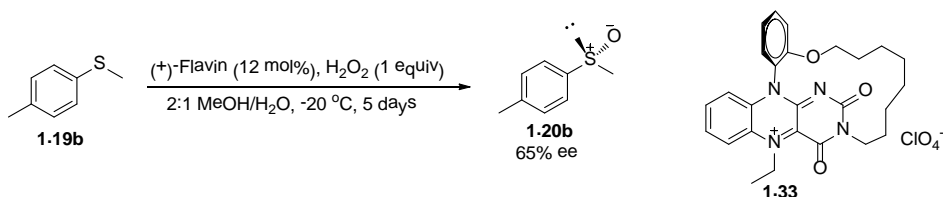
Figure 1.14 Basket-shaped flavinium salt catalyst catalyzed sulfur oxidation

Cibulka's group designed a novel planar chiral flavinium salt, 3-benzyl-5-ethyl-10-(8 phenylnaphthalen-1-yl)isoalloxazinium perchlorate 1.34, which bears a phenyl cap that covers one side of the isoalloxazinium skeleton plane. (Figure 1.15) Chiral HPLC was used to separate the racemic precatalyst followed by N^5 reductive alkylation to activate the catalyst. Sulfoxides with 34-54% e.e. was obtained using enantiopure catalyst at -20 °C.[20]
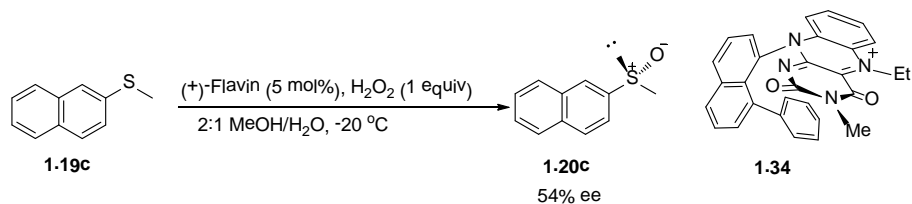
Figure 1.15 Planar chiral flavinium salt catalyst catalyzed sulfur oxidation

A beta-cyclodextrin flavin conjugate 1.35 was demonstrated by Cibulka and coworkers as highly efficient catalyst for the oxidation of electron-rich methyl phenyl sulfides to sulfoxides by hydrogen peroxide.[21] (Figure 1.16) The catalyst showed fast near quantitative conversions and high enantioselectivities, reaching up to 80% e.e.. It is also remarkable that the reactions can proceed in neat aqueous media with only 0.2 mol% loading of the catalyst.
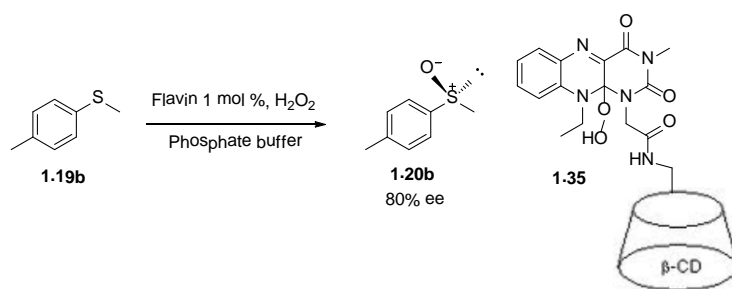
Figure 1.16 Beta-cyclodextrin flavin conjugates catalyzed sulfur oxidation

Main-chain optically active riboflavin polymer 1.36 was synthesized and used for chiral sulfur oxidation.[22] Sulfur oxidation was achieved with up to 60% e.e. in THF at -40 °C.(Figure 1.17)
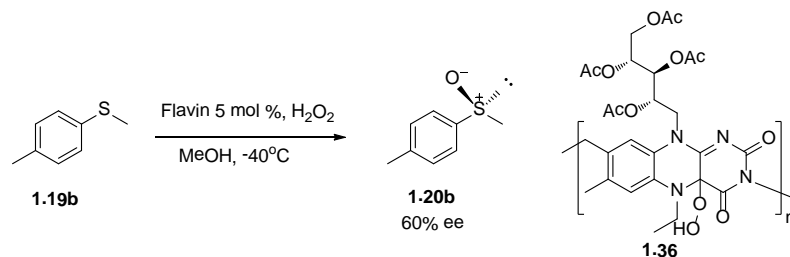
Figure 1.17 Riboflavin polymer catalyzed sulfur oxidation

1.2.1.2 Amine Oxidation

Murahashi and coworkers utilized lumiflavin derived isoalloxanium catalyst 1.21a to oxidize secondary amines 1.37a to nitrones 1.38a, hydroxyl amine 1.37b to nitrone 1.38b with excess H_2O_2 as terminal oxidant in methanol.[12](Figure 1.18)
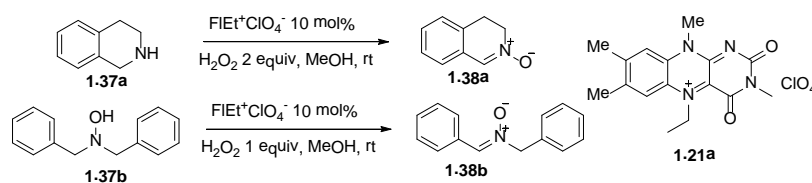
Figure 1.18 Isoalloxazinium catalyzed *N*-oxidation of secondary amine

The same group published the aerobic version of *N*-oxidation of a series of secondary amine, hydroxyl amine and tertiary amines using the same lumiflavinium catalyst 1.21a.[13] (Figure 1.19) The oxidations were carried out in CF_3CH_2OH. The mechanism of aerobic *N* oxidation is similar as that of the aerobic sulfur oxidation.
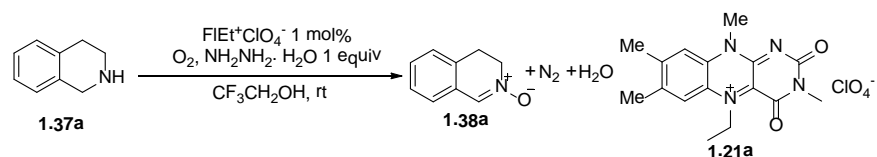
Figure 1.19 O_2 *N*-oxidation of secondary amine with isoalloxazinium

Băckvall and coworkers used their alloxazine catalyst 1.23a to oxidize the tertiary amine to *N*-oxide in methanol efficiently.(Figure 1.20) The reduced alloxazine 1.23a was used, so oxygen activation of the precatalyst was necessary.[23]

Figure 1.20 H_2O_2 *N*-oxidation of tertiary amines with alloxazine

Cibulka's group performed a systematic study of the comparison of the catalytic abilities of various alloxazine and isoalloxazine sources on sulfur oxidation and tertiary amine oxidation.[24] They concluded that in the case of sulfur oxidation, for alloxazine catalysts, both alloxazine 4a-methoxy adduct and alloxazinium salt can be used as catalyst. But the latter needs a base as a cocatalyst to generate HOO^- because the neutral H_2O_2 is not nucleophilic enough to attack alloxazinium to form 4a-hydroperoxyflavin. In the isoalloxazine series, the C^{4a}-hydroxy adduct FlOH or dihydroform FlH_2 can also be utilized but only in the presence of the catalytic amount of an acid. The acid is needed to help elimination of the hydroxyl group to generate the oxidized isoalloxazinium anion, which is the rate determining step for this series of catalysts. In the case of amine oxidation, only alloxazine derivatives, i.e. dihydroalloxazines FlH_2 and their methoxy adducts $FlOCH_3$ or alloxazinium salts can be used as catalysts for the oxidation, as the catalytic activity of isoalloxazinium salts and their derivatives is inhibited under basic conditions.

In the flavin catalysis, it is very important to understand the property of different types of catalysts and the pH of system as well as solvent effect, as each factor could dramatically alter the reactivity of the catalysts.

1.2.2 Flavin Catalyzed Nucleophilic Oxidation

In flavin catalyzed nucleophilic oxidations, 4a-hydroperoxyflavin or 4a-hydroperoxyflavin anion attack the electrophilic site of the substrate followed by the dissociation of the hydroxyl flavin anion. Hydroxyl flavin eliminates one molecule of water

to complete the catalytic cycle by regenerating the oxidized flavin. The following examples showed the applications of flavin on Baeyer-Villiger oxidation.

1.2.2.1 Baeyer-Villiger Oxidation

Furstoss and coworkers first demonstrated the use of isoalloxazinium catalyst 1.25 in the Baeyer-Villiger oxidation of cyclobutanones 1.41a into γ-lactone 1.42a in t-BuOH with two equivalents of H_2O_2.[25] (Figure 1.21) However, this catalyst only performed the oxidation on cyclobutanones. Five membered and six membered cycloketones were not effective substrates under the published condition.
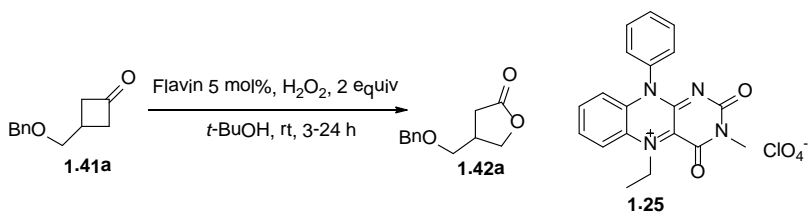
Figure 1.21 H_2O_2 Baeyer-Villiger oxidation of cyclobutanones catalyzed by isoalloxazinium

Murahashi's group synthesized a C_2-symmetric bis-isoalloxazinium perchlorate salt 1.43 for the asymmetric Baeyer-Villiger oxidation of cyclobutanones.[26] (Figure 1.22) Substrates needed to have an aromatic substituent to interact with the catalyst through pi-pi stacking. Good facial selectivity was achieved and up to 74 % e.e. was obtained when the reaction was carried out at -50 ^{o}C in a solvent mixture of $CF_3CH_2OH/MeOH/H_2O$. Similarly to the previous example, no cyclopentanone or cyclohexanone was reported.
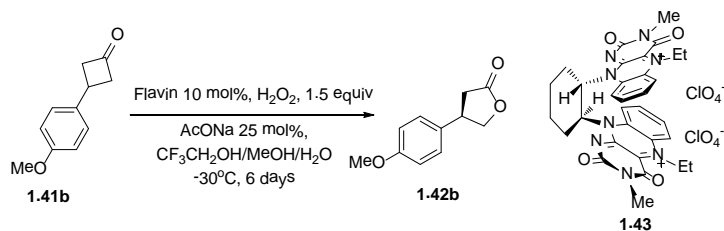
Figure 1.22 Asymmetric Baeyer-Villiger oxidation of cyclobutanones catalyzed by bis-

isoalloxazinium

The same group developed an aerobic Baeyer-Villiger oxidation methodology

using a riboflavin derived isoalloxazinium 1.44 as catalyst and zinc metal as

stoichiometric reducing agent to oxidize cyclobutanone with oxygen as terminal oxidant.[27]

(Figure 1.23) This catalyst also showed excellent chemoselectivity of nucleophilic BV

oxidation over electrophilic sulfur oxidation. Unfortunately, no cyclopentanone or

cyclohexanone was reported with this catalyst.
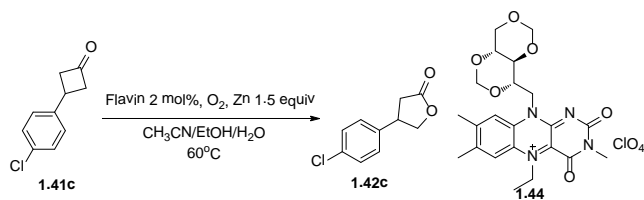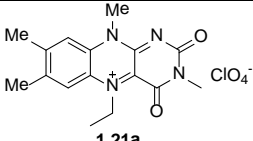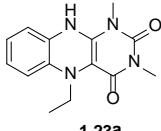
Figure 1.23 Aerobic Baeyer-Villiger oxidation of cyclobutanones catalyzed by riboflavin

derived isoalloxazinium

In most case, isoalloxazine 1.21a or alloxazine 1.23a can be used to conduct

sulfur, amine or Baeyer-Villiger oxidation.This following Table 1.1 summarizes the types

of oxidation reactions versus kinds of catalysts that have been utilized and the conditions

(additive, solvent) needed in each case.

Table 1.1 The choice of conditions for different oxidations

Oxidation	Sulfur oxidation		Amine oxidation			BV oxidation	
Oxidation Mode	H_2O_2	Aerobic	Secondary		Tertiary	H_2O_2	Aerobic
			H_2O_2	Aerobic			
Catalyst	1.21a or 1.23a	1.21a or 1.23a	1.21a	1.21a	1.23a	1.21a	1.21a
Solvent	MeOH	CF_3CH_2OH	MeOH	CF_3CH_2OH	MeOH	t-BuOH	Mix-solvents
Reductant	N/A	NH_2NH_2	N/A	NH_2NH_2	N/A	N/A	Znic

1.2.3 Applications of Flavin Other Than as Organocatalyst

Not only used as organocatalysts in synthetic organic chemistry, but flavins also find their applications in many other areas such as medical and pharmaceutically devices.

1.2.3.1 Flavin Biomarker

One example is that riboflavin was utilized to target tumor cells. Riboflavin is an essential component for cellular metabolism and is highly upregulated in metabolically active cells. Tumor cells are highly energy-demanding; therefore they require a relative large amount of flavin cofactor to activate the necessary catabolic enzymes. Target-specific and fluorescent flavin mononucleotide (FMN) coated Ultra Small Super Paramagnetic Iron Oxide nanoparticles (USPIO) 1.45 was designed by Fraaije's group to

mark the riboflavin carrier protein. (Figure 1.24) High efficiency of labeling cancer cells (PC-3, DU-145, LnCap) and activated endothelial cells was demonstrated with this novel biomarker.

1.45
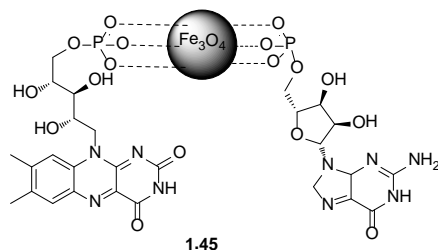
Figure 1.24 Riboflavin derived biomarker for detecting tumor cell

1.2.3.2 Flavin drug carrier

Riboflavin binding protein dodecin from *Halobacterium salinarum* was used by Nöll's groups to deliver riboflavin bonded drugs to the targeted position.[29] Dodecin binds oxidized flavin with high affinity 1.46 but releases the flavin when the flavin is reduced 1.47. (Figure 1.25) Upon blue-light triggered reduction of riboflavin, drugs can be transported at desired time and to desired location with high accuracy.
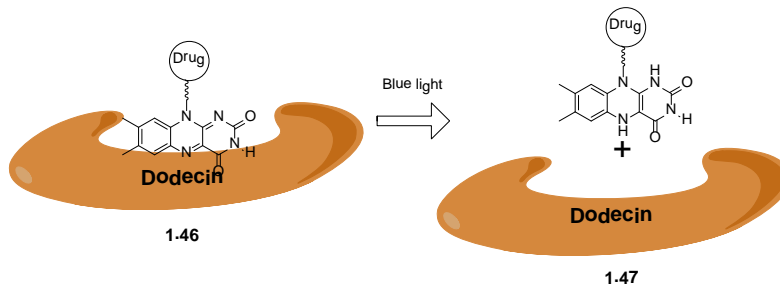
Figure 1.25 Blue light induced dissociation of flavin from dodecin

1.3 Outline of Dissertation

In this dissertation, I will focus on the discussion on the recent development of flavin organocatalysts as nucleophilic oxidizing agents for oxidizing carbon centers, i.e. Dakin oxidation and Weitz-Scheffer oxidation. A dual catalytic system will be described to

conveniently impose stereoselectivity to flavin catalyzed reactions in a cost effective

manner Also, the flavin's application on the oxidation of pre-aromatic heterocyclic

compounds will also be described.

Chapter 2

Flavin Catalyzed Dakin Oxidation

2.1 Baeyer-Villiger Oxidation

The Baeyer-Villiger oxidation (BVO), reported by Adolf Baeyer and Victor Villiger in 1899, is one of the most well-known and widely applied reactions in organic synthesis.[30] A variety of carbonyl compounds such as acyclic or cyclic ketones, benzaldehydes could be oxidized into esters, lactones, phenols or benzoic acids.

One advantage of this reaction is that the chemoselectivity can be precisely predicted with migratory aptitude as following: alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > CH_3.[31] Various oxidants could perform Baeyer-Villiger oxidation, with their reactivity decreasing in the order CF_3CO_3H > monopermaleic acid > monoperphthalic acid > 3,5-dinitroperbenzoic acid > p-nitroperbenzoic acid > m-CPBA ≈ HCO_3H > $C_6H_5CO_3H$ > CH_3CO_3H » H_2O_2 > t-BuOOH.

The most active oxidants are expensive and hazardous peracids, which significantly limit the usage of BVO in industrial setting. BVO conducted by H_2O_2 with the activation of a catalyst in non-halogenated solvents is attractive because it avoids many issues such as high cost of oxidant, environmental, healthand safety issues.[32-33]

Although H_2O_2 is a preferred green oxidant in chemistry industry for BVO, there are several problems associated with it. Commercially available hydrogen peroxide is in aqueous solution (30% or 60%). Water labile compounds may hydrolyze or decompose under reaction condition using aqueous H_2O_2. Also, H_2O_2 could be decomposed by metal impurities to generate O_2 therefore build up pressure and create a potentially unsafe combination with flammable organic solvents.[31]

Precautions to avoid such problems include: 1) avoid any contamination of reaction vessel. 2) avoid build-up O_2 pressure by purging with N_2. 3) keep the

concentration of peroxo compounds below 20% mol/mol by slow addition of H_2O_2. 4) Destroy excess H_2O_2 before work up. 5) avoid using acetone or any other low boiling ketone as the solvent for cleaning or workup. [31]

Molecular oxygen has been used as a terminal oxidant for BVO. Free radical autoxidation of an aldehyde is facile and affords the corresponding peracid, which oxidizes ketones 2.1 into esters 2.2.[35] (Figure 2.1) Ishii group reported the "aerobic" BVO of a cyclohexanol/cyclohexanone mixture to yield lactones.[36] However, in this reaction hydrogen peroxide generated by autooxidation of cyclohexanol 2.3 instead of peracid is the true oxidant in the BV reaction. Using O_2 for the in situ formation of hydrogen peroxide as the actual oxidants has been receiving much attention over the past years because it is cheaper than hydrogen peroxide itself.
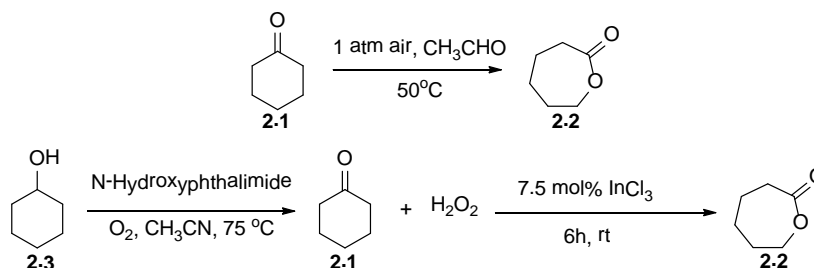
Figure 2.1 Aerobic Baeyer-Villiger oxidations

The mechanism of BV oxidation is a two-step reaction that involves the so-called Criegee intermediate. (Figure 2.2) In the first step, a peroxide 2.5 attacks the polarized C=O bond of 2.4 to form Criegee intermediate 2.6. The second step follows a concerted migration pathway. In the Criegee intermediate 2.6, a proper alignment is required for the rearrangement step: The migrating group R^M needs to be antiperiplanar to the O-O bond of the leaving group (primary stereoelectronic effect) and antiperiplanar to a lone pair of the hydroxyl group (secondary stereoelectronic effect). The elimination of an acid 2.7 affords the product ester 2.8.
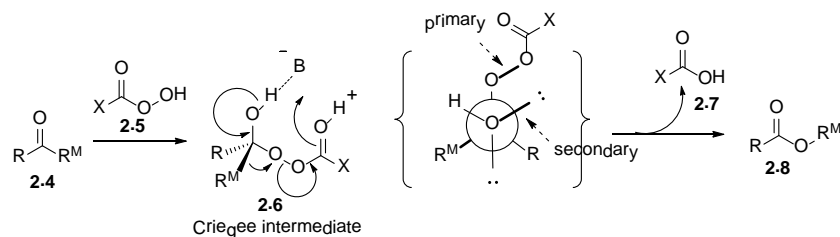
Figure 2.2 Stereoelectronic requirement of 1, 2 migration of Criegee intermediate

There are several activation modes that one can use the achieve catalysis of BVO using hydrogen peroxide as terminal oxidant (Figure 2.3). 1. Electrophilic activation of the substrate, 2. electrophilic activation of the intermediate, 3. nucleophilic activation of the intermediate, 4. nucleophilic activation of hydrogen peroxide, and 5. electrophilic activation of hydrogen peroxide.[31]
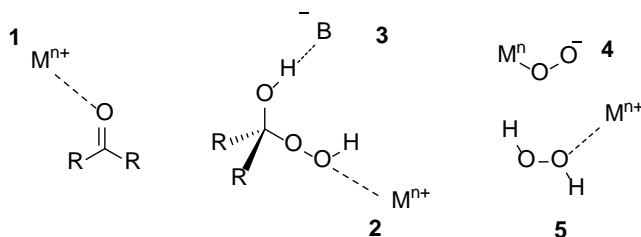
Figure 2.3 Activation mode of Baeyer-Villiger oxidation

The attempts to extend the currant flavin catalyzed BVO of cyclobutanones to cycloketones with larger ring size, i.e. cyclopentanones and cyclohexanones, was conducted regarding the importance of this transformation.

Five alloxazine catalysts and one isoalloxazine catalyst were synthesized to be used as the BVO catalysts.

The synthesis of the five alloxazine was adopted from Bӓckvall's publication.[14] Condensation of *o*-phenylenediamine 2.9 with alloxan monohydrate 2.14 in acidic condition affords the tricyclic core structure 2.10. (Figure 2.4) Methylation of N^1 and N^3 position happens smoothly with iodomethane in the presence of K_2CO_3 to form 2.11. The

reductive alkylation of N^δ position of 2.11 was conducted under strictly anaerobic

condition by Pd/C-catalyzed hydrogenation using excess freshly distilled acetaldehyde in

the presence of acid. Instead of keeping the product 2.12 at reduced state by working up

the reaction under strictly inert atmosphere, the reaction is exposed to air to generate the

active hydroperoxyflavin 2.13. This strategy not only simplifies the work up procedure

greatly but also provides stable and useful flavin catalysts that are ready to enter the

catalytic cycle without the additional oxygen activation step. Catalysts 2.13a and 2.13e

were not previously reported. The reductive amination of dichloroalloxazine 2.11a gave

exclusive dechlorinated product 2.13c in EtOH/H_2O under standard condition. To obtain

the desired dichlorocatalyst 2.13a, extensive optimization of the reductive amination step

was conducted. Changing the types of metal catalysts (Pd/C, Pt or Lindlar catalyst),

amount of acid (0-10 equivalents) or H_2 pressure (15 psi or 80 psi) did not affect the

dehalogenation process. However, when EtOH/H_2O solvent mixture was replaced with

1:1 EtOH/DCM, 1:1 of dichloro catalyst 2.13a/dehalogenated product 2.13c was isolated.

1.7:1 2.13a:2.13c was observed with in 1:4 EtOH/DCM. By omitting the protic solvent

ethanol and using pure dichloromethane, 2.13a can be obtained in 80% isolated yield.

Luckily, difluoro alloxazine 2.11b underwent Pd/C catalyzed reductive amination without

the formation of dehalogenated products. However, higher H_2 pressure (80 psi) was

needed in order to obtain good yield of the 2.13b.
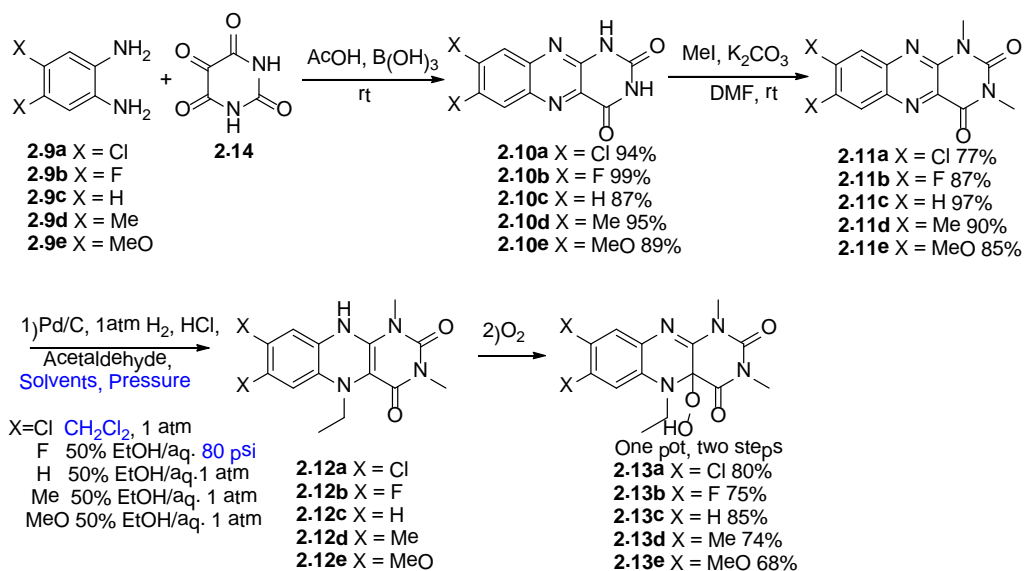
Figure 2.4 Synthesis of five alloxazine catalysts

Synthesis of isoalloxazine catalysts starts with nucleophilic substitution of chloride in 6- chlorouracil 2.16 by aniline 2.15 in neat condition. (Figure 2.5) Cyclization of 2.17 with nitrosobenzene 2.18 gives compound 2.19. A similar reductive amination step affords N^5 ethylated isoalloxazine. The reduced isoalloxazine is then oxidized and converted to stable isoalloxazinium perchlorate catalyst 2.20, which is ready for catalysis.[37]
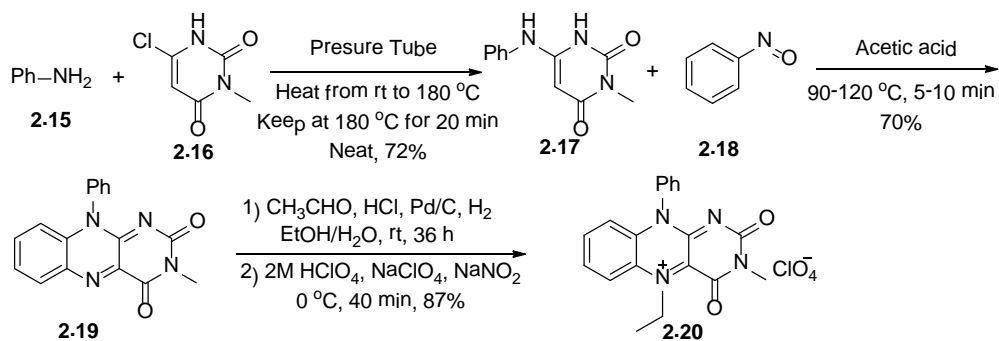
Figure 2.5 Synthesis of isoalloxazine catalyst

26

Three factors were considered in the condition screening: 1. Lewis acids; 2. solvents; 3. temperatures.

Lewis acid are known to facilitate the BVO in two aspects.[36] (Figure 2.6) One, they activate the carbonyl functionality toward nucleophilic attack of peroxide or peracid via increasing the polarization of the C=O double bond. Lewis acid increases H_2O_2's acidity and therefore increases hydrogen bonding to the carbonyl functionality TS1. Two, the Lewis acid also facilitates the rearrangement step by migrating to the outer peroxygen, creating a BF2OH leaving group rather than a hydroxide leaving group TS2.
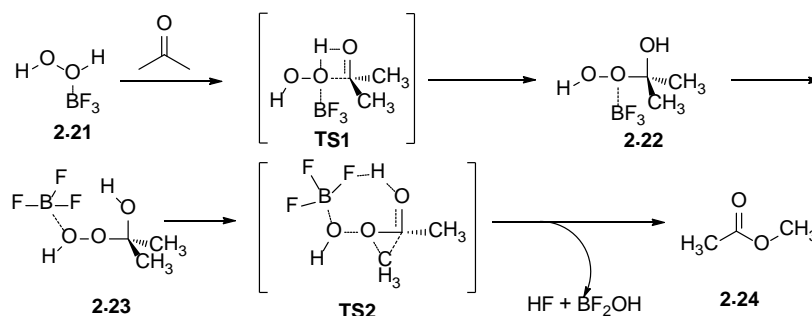
Figure 2.6 Lewis acid BF_3 assisted BV oxidation of acetone

However, with flavin catalysts and H_2O_2, neither cyclopentanones 2.25 and 2.26 nor cyclohexanones 2.27 and 2.28 were converted to desired lactones in the presence of $CaCl_2$, $BF_3.OEt_2$, LiCl, $Zn(OAc)_2$, $AlCl_3$ or $MgCl_2$. (Table 2.1) The reactions were conducted at room temperature and 50 ^{o}C, only starting materials were recovered in these reactions. This initial failure led us to question the mechanistic barriers to flavin activation of H_2O_2, flavoperoxide BVO, and catalytic cycle turnover.

Table 2.1 Conditions examined with flavin catalyzed BV oxidation of 5-and 6-membered

cycloketones

	Cyclopentanone 2.25	2-methylcyclopentanone 2.26	Cyclohexanone 2.27	Cyclohexenone 2.28
Lewis acid	$AlCl_3, BF_3·OEt_2,$	$AlCl_3, BF_3·OEt_2$	$CaCl_2, BF_3·OEt_2, LiCl, AlCl_3,$ $Zn(OAc)_2, MgCl_2$	$AlCl_3, BF_3·OEt_2,$
Catalyst	2.13c, 2.13d, 2.20	2.13c, 2.13d, 2.20	2.13c, 2.13d, 2.20	2.13c, 2.13d, 2.20
Solvent	MeOH	MeOH	MeOH	MeOH
Temperature (℃)	25℃/ 50℃	25℃/ 50℃	25℃/ 50℃	25℃/ 50℃

The difficulty of conducting BVO with acyclic ketones, cyclopentanone as well as cyclohenxanone was described in Ding and coworker's study by performing theoretical calculations on phosphoric acid catalyzed BVO using H_2O_2 as oxidant. [38]

In the phosphoric acid catalyzed BVO, the rate determining step was believed to be the acid mediated 1, 2 -rearrangement of alkyl group starting from the Criegee intermediate. The activation barriers of the migration for cyclobutanone, acetone, cyclopentanone and cyclohexanone were calculated to be 20.2, 31.2, 27.0 and 25.5 kcal/mol respectively. These results are interpreted in terms of the larger ring strain in cyclobutanone weakens the C-C bond and makes the migration of methylene group more

favorable. Similarly, they failed to apply phosphoric acid catalyzed BVO to more challenging larger ring ketones. [38]

2.2 Dakin Oxidation

2.2.1 Current Methods for Dakin Oxidation

The Dakin oxidation is a variant of Baeyer-Villiger oxidation, bearing a broadly similar mechanism. Instead of an aliphatic ketone substrate, the Dakin oxidations convert *o*- or *p*-hydroxyl substituted benzaldehydes and acetophenones into phenols or hydroquinones and a carboxylate byproducts with H_2O_2 in the presence of sodium hydroxide. Overall, the sp^2-sp^2 aryl bond is oxidized and H_2O_2 is reduced.

The mechanism of Dakin oxidation differs with different reaction conditions. In general, it can be categorized into acid-catalyzed or base-catalyzed mechanisms. Both conditions involve a 1, 2-aryl shift associated with the collapse of tetrahedral Criegee intermediate 2.31. The proposed mechanism for base-catalyzed Dakin oxidation of 2-hydroxybenzaldehyde or acetophenone generates catechol 2.33 via an aryl formate 2.32, followed by hydrolysis. (Figure 2.7)
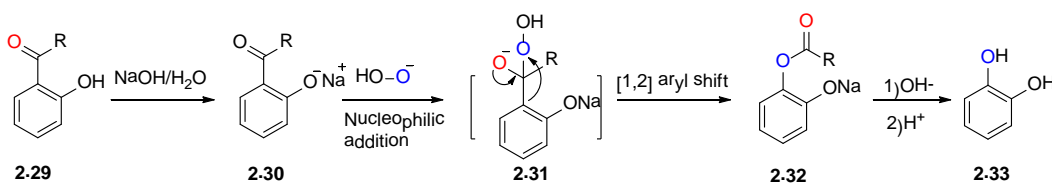
Figure 2.7 Mechanism of Dakin oxidation under basic condition

Many methodologies were developed to facilitate this transformation.

Methyltrioxorhenium (MTO) 2.34 can be used as a catalyst to achieve Dakin oxidation of *meta* or *para* methyoxy or hydroxyl substituted benzaldehydes to give

corresponding phenols with H_2O_2 in good yield.[39] (Figure 2.8) The reactive intermediate

is a bis-peroxo metal $[CH_3ReO(O_2)_2]$ complexes dpRe 2.36. In this system, 2 mol% of

MTO was generally applied and excess H_2O_2 was needed. EtOH was proving the best

solvent. The reaction typically was stirred at 50 ^oC for 24 hours. No base or acid is

required. 57-86% phenol products were isolated. However, noticeable amount of benzoic

acid byproduct and unhydrolyzed ester were isolated in some cases.
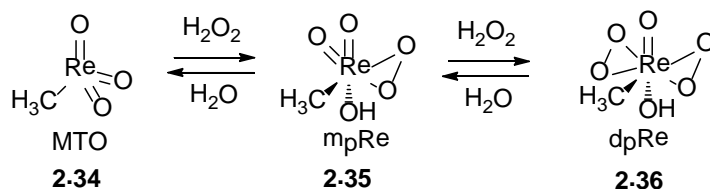
Figure 2.8 Methyltrioxorhenium(MTO), mono-peroxo complexes (mpRe) and active

intermediate bis-peroxo complexes (dpRe)

The same catalyst 2.34 has been used with the help of ionic liquid [bmim]PF_6

2.37 as a solvent.[40] (Figure 2.9) Good yield was achieved in 2-24 hours, which was

relatively faster than the reactions conducted in traditional organic solvents.
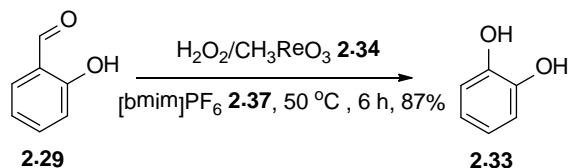
Figure 2.9 MTO catalyzed Dakin oxidation in ionic liquid

Solvent free Dakin oxidation was achieved by mixing starting benzaldehydes and

solid mCPBA using pestle and mortar.[41] A range of non-hydroxylated benzaldehydes was

converted to phenols in the absence of a base.

Sodium percarbonate 2.38 ($Na_2CO_3 \cdot 1.5\ H_2O_2$) was used as a stoichiometric

oxidant for Dakin oxidation of a range of hydroxyl benzaldehydes and acetophenones.[42]

(Figure 2.10) The oxidant acts as its own base and a typical reaction was conducted in

2:5 water:THF dual solvent system under ultrasonication in argon atmosphere. A THF-DMF-H_2O solvent system was used for Dakin oxidations for acetophenone.
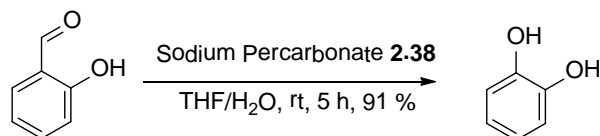
Figure 2.10 Dakin oxidation using sodium percarbonate as oxidant

Strong acid condition were shown to be suitable for oxidizing benzaldehydes and acetophenones to phenols. Boric acid has been used to conduct Dakin oxidation in presence of H_2O_2 and concentrated H_2SO_4. [43] Typical reactions use 5 equivalents of boric acid, 2 equivalents of H_2O_2 and excess of H_2SO_4. Although phenol was the main product, benzoic acid was detected for most of the substrates.

Urea-hydrogen peroxide 2.39 (UHP) can be used as stoichiometric oxidation for the Dakin oxidation in neat condition.[44] (Figure 2.11) Benzaldehydes and acetophenones are active substrates. These reactions were conducted at 85 ^{o}C.
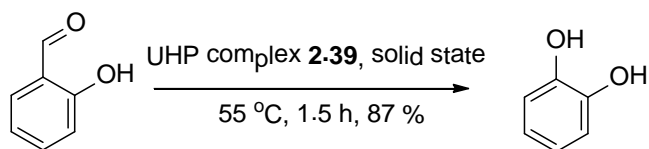
Figure 2.11 Dakin oxidation using urea-hydrogen peroxide complex as oxidant

2.2.2 Flavin Catalyzed Dakin Oxidation Using H_2O_2 as Terminal Oxidant

Although a handful of reagents and conditions are available for Dakin oxidation, many of them require heat, metal catalysts, harsh pH conditions as well as stoichiometric strong oxidants. We thought that flavin analogs could be used as an organocatalyst to accelerate this transformation in ambient temperature and milder pH condition, which could be attractive for the application of Dakin oxidation on structural complex molecules or large scale reactions. Inspired by the H_2O_2 shunt process in the flavin biomimetic cycle

(Figure 2.12 highlighted in red), we planned to develop a flavin catalyzed Dakin oxidation using H_2O_2 as a terminal oxidant to turn over the reaction catalytic cycle.
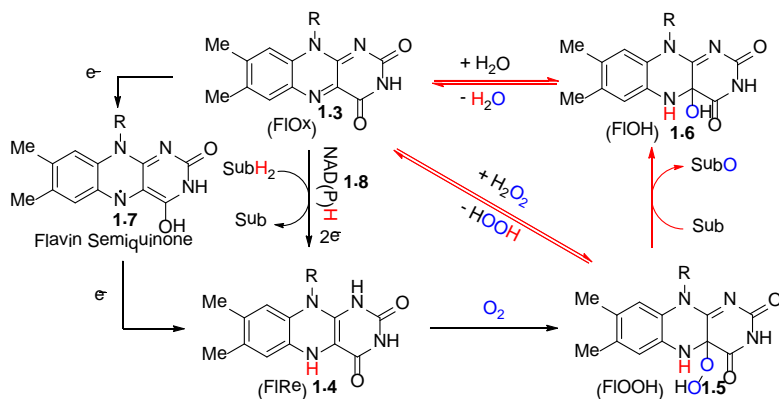
Figure 2.12 Dakin oxidation inspired by flavin H_2O_2 shunt process

Due to the lower pKa and O-O heterolytic bond lability of 4a-hydroperoxy alloxazine in comparison to H_2O_2 and other alkyl peroxides, we envisioned that alloxazine catalyzed reactions should be more effective under mild conditions compared to hydrogen peroxide and other alkyl peroxide reactions.

To understand how electronic effect alters the reactivity of alloxazine catalysts, previously synthesized five alloxazines 2.13a-e were used as Dakin oxidation catalysts.

We initially used 7, 8-diH alloxazine catalyst 2.13c for the catalysis of Dakin oxidation of salicylaldehyde under strong basic condition (with 1 equiv NaOH). In this case, both catalyzed reaction and non-catalyzed reaction were very fast. Within 10 minutes, all of the starting material was converted to catechol. We envisioned that the fast background HOO- oxidation dominated the reaction pathway. Also, under strong basic condition, we have observed hydrolysis degradation of alloxazine catalyst 2.11c. Byproduct such as 2.40 could be formed, which may cause the loss of catalytic activity of the alloxazine. (Figure 2.13)

NaOH, H₂O

2·11c   2·40
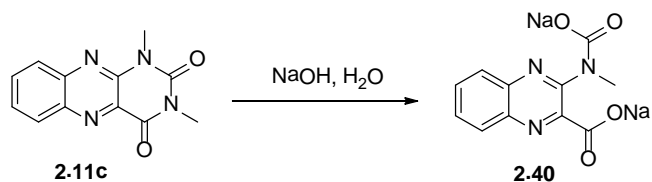
Figure 2.13 Possible alloxazine degradation pathway under strong basic condition

In order to create a condition that does not need a strong base like NaOH, which may cause problems of chemoselectivity when there are base labile functional groups in more complex molecules, we performed a base study to find the mildest base that was needed for the flavin catalyzed Dakin oxidation. The following Figure 2.14 showed relative rate of difluoroalloxazine catalyzed Dakin oxidation of salicylaldehyde compared to non-catalyzed reaction using different types of bases. The data was obtained using HPLC by calculating the concentration of salicyladehyde after 30 minutes and 60 minutes (Figure 2.14. The first bar of the same color represent the non-catalyzed reaction, the second bar represent the catalyzed reaction).
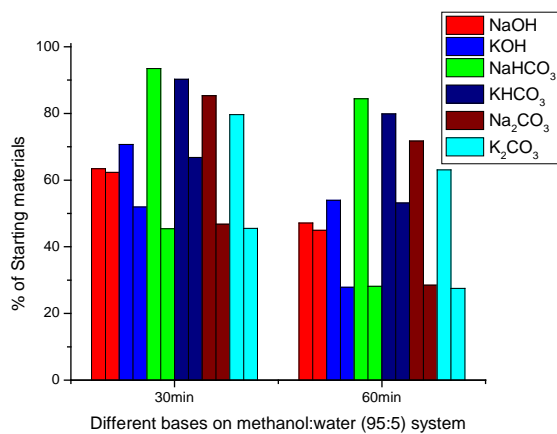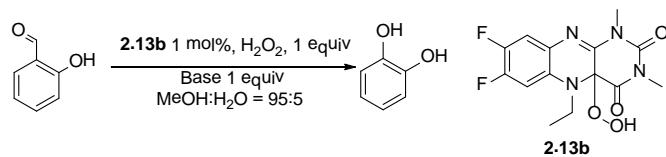
Figure 2.14 Base effect of flavin catalyzed Dakin oxidation

The reactions with hydroxide bases (NaOH and KOH) showed almost no flavin catalytic effects. Both the catalyzed reaction and the control had similar amount of starting material left after 30 minutes and one hour. However, for weaker bases ($NaHCO_3$, $KHCO_3$ and Na_2CO_3), the catalyzed reactions were faster in all cases, leaving less starting material after 30 minutes and 60 minutes. Control reactions with weaker bases were a lot slower compared to controls with strong bases, while catalyzed reactions with weaker bases were generally faster or equivalent to catalyzed reactions with strong bases. We were pleased to find out weaker bicarbonate bases perform Dakin oxidation with flavin catalyst very efficiently.
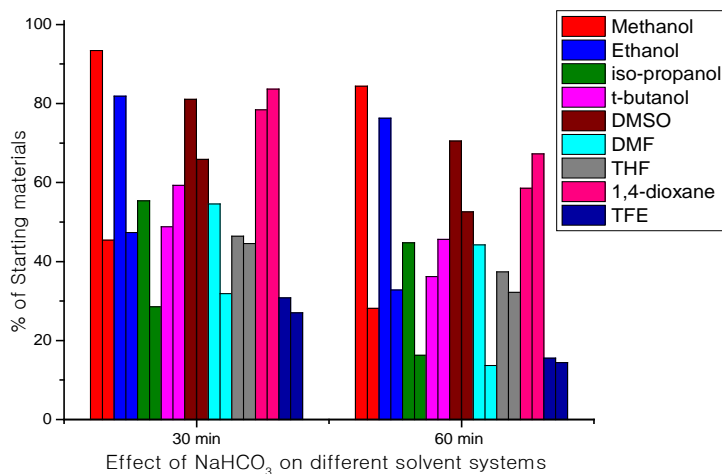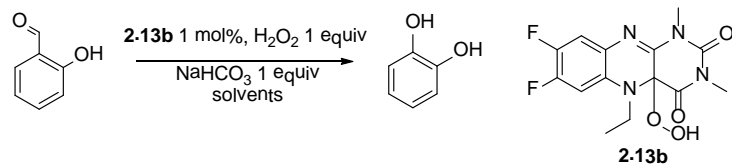
Figure 2.15 Solvent effect of flavin catalyzed Dakin oxidation

Solvent plays an important role in the progress of the flavin catalyzed reaction (Figure 2.15). A similar HPLC study was conducted with different solvents for catalyzed reaction as well as controls. Most alcoholic solvents showed rate acceleration for catalyzed reactions except for *t*-BuOH. DMSO is a poor solvent for Dakin oxidation, even with the help of flavin catalyst. DMF showed good reaction rate, but due to work-up difficulties associated with the solvent, we did not use it for further substrate study. TFE (2, 2, 2-trifluoro ethanol) showed good result for both catalyzed and non-catalyzed reactions. However, due to environmental safety and cost concerns, we did not use it as a solvent in our further study. As a result, we finalized methanol as the solvent for the substrate studies.
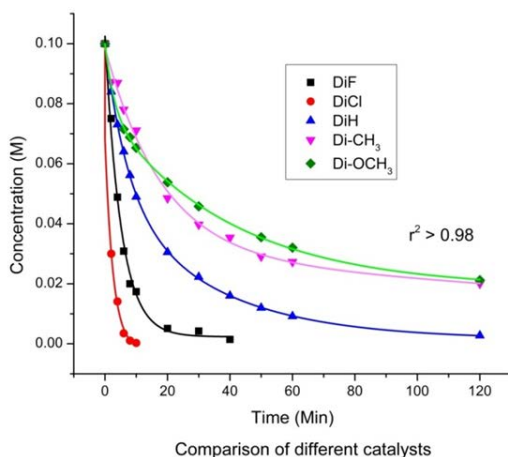
Figure 2.16 Comparison of the catalytic abilities of alloxazines on Dakin oxidation of

salicylaldehyde

The catalytic efficiency of Dakin oxidation was evaluated by comparing the rate of Dakin oxidation of salicylaldehydes using five different alloxazine catalysts (Figure 2.16). The reaction progresses were monitored by HPLC and the concentrations of starting material salicylaldehyde were calculated with the reference of anisole as an internal standard. As shown in Figure 2.4, dichloro-alloxazine 2.13a resulted in the fastest consumption of starting material, followed by difluoro 2.13b, dihydrogen 2.13c, dimethyl 2.13d and dimethoxy-alloxazine 2.13e.

Comparing blank and catalysed reactions
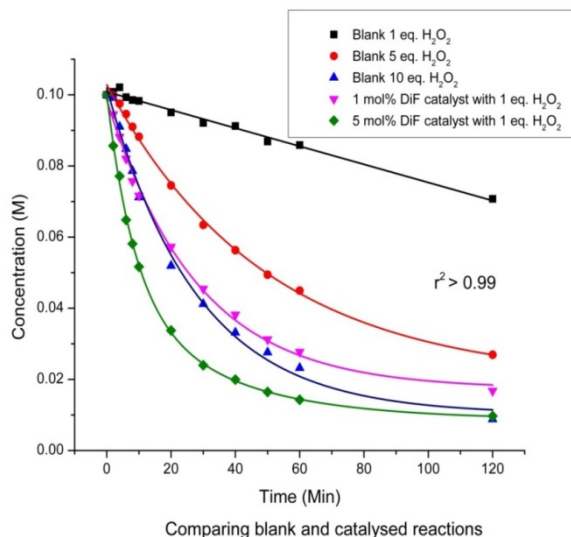
Figure 2.17 Rate acceleration effect of alloxazine catalyst

To illustrate the rate acceleration effect of flavin catalyzed Dakin oxidation, un-catalyzed reactions with different amount of H_2O_2 were set up along with the catalyzed reactions. (Figure 2.17) Similar to last chart, starting material concentrations versus time was shown in Figure 2.17. 1 mol% difluoro-alloxazine 2.13b catalyzed reaction with 1 equivalent of H_2O_2 (magenta) had similar initial reaction rate as that of the un-catalyzed reaction with 10 equivalents of H_2O_2 (Blue), which was faster than uncatalyzed reaction with 5 equivalents H_2O_2 (red). By increasing the catalytic loading to 5 mol% (green), the reaction rate was much faster than the control reaction (black).

These results showed that alloxazine accelerated the Dakin reaction under mild basic condition (NaHCO$_3$ as base). Presumably, alloxazine could facilitate Dakin oxidation in two aspects. (Figure 2.18) First, because of the electron deficient nature of the alloxazine ring, the terminal proton of the 4a-hydropreoxy alloxazine 2.13 is more acidic than that of the hydrogen peroxide, so that it can undergo deprotonation very well in the presence of sodium bicarbonate to generate the active nucleophilic oxidative

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species, hydroperoxy alloxazine anion. Second, in the 1, 2 aryl migration step of Dakin oxidation mechanism, hydroxyl anion leaving group is generated. Alloxazine 2.41 can stabilize the negative charge by inductive effect of either the electron-withdrawing groups on the aromatic ring or the nearby N^5-nitrogen and C^4-carbonyl group.
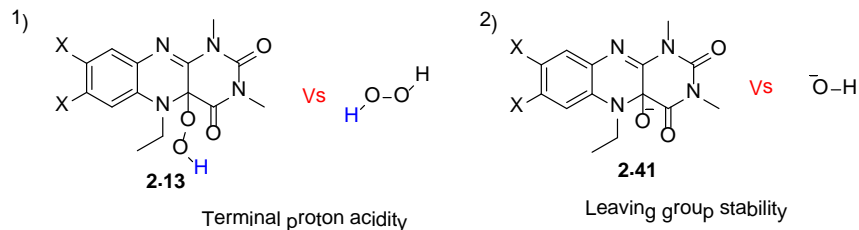
Figure 2.18 Rational of the rate acceleration by alloxazine catalyst

With the optimized condition, we established the standard reaction condition for the substrate scope study: 10 mol% dichloro-alloxazine 2.13a, 5 equivalents H_2O_2, 1 equivalent $NaHCO_3$ with 95% aqueous methanol as solvent at room temperature. (Figure 2.19) 0.2 mmol scale reactions were set up for different substrates and monitored by TLC. To our delight, most of *ortho* or *para* hydroxyl benzaldehyde we tested underwent Dakin oxidation very efficiently under standard reaction condition. Typically, reactions finished within 30 minutes and more than 75% yields were isolated. Catechols or hydroquinones were the only products observed and isolated for these substrates. No hydride migration products, benzoic acids, were detected in these reactions. For 2.42f, quinone was generated through phenol intermediate, likely due to their electron rich nature.
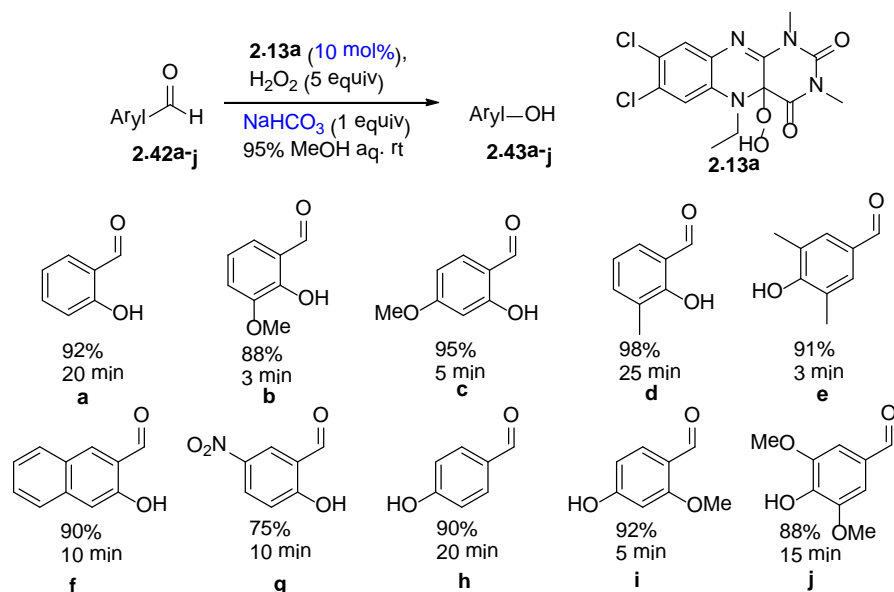
Figure 2.19 Alloxazine catalyzed Dakin oxidation of hydroxyl benzaldehyde

Benzaldehyde substituents and their substitution pattern are important to the results of the flavin catalyzed Dakin oxidation. Benzaldehydes without hydroxyl substitution mostly did not generate phenol product. With one exception, 2.42k was converted to phenol product 2.43k by difluoro-alloxazine 2.13b catalyzed condition with extended reaction time. Presumably, the 1, 2-aryl migration of the Criegee intermediate is facilitated through the resonance electron donating effect of the *ortho* or *para* hydroxyl substitution, which is even better if hydroxyl is deprotonated to form more electron-rich hydroxyl anion. (Figure 2.20)
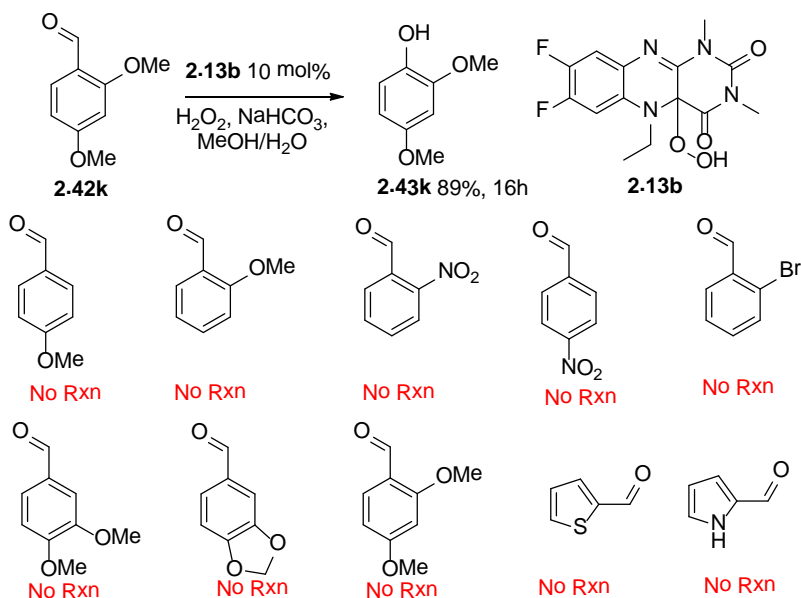
Figure 2.20 Non-hydroxylated substrates failed to undergo Dakin oxidation

In fact, a recent relevant finding by Carbery's group showcased the bridged flavin 2.44 catalyzed Dakin oxidation of electron-withdrawing group substituted benzaldehyde 2.42l. (Figure 2.21) In this case, 1, 2-hydride migration was favored over aryl shift because the aryl group was too electron-poor. So, benzoic acids 2.43l were obtained instead of phenols.[45]
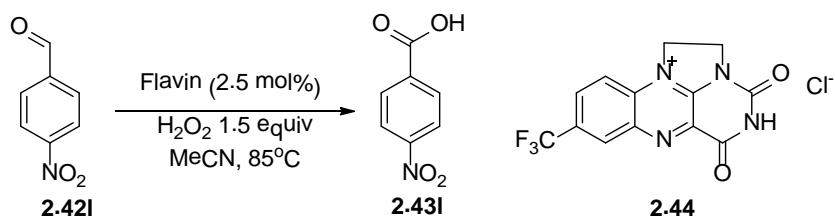
Figure 2.21 Benzoic acid formation from electron poor benzaldehyde

Dakin oxidation of less reactive acetonphenones is more challenging because ketone carbonyl is less reactive towards nucleophilic attack. A range of Lewis acids additives was tested but resulted in no product. (Figure 2.22) Serendipitous finding allowed the Dakin oxidation of 2-hydroxyl acetophenone to catechol by using 10% DMSO

as a co-solvent in aqueous MeOH solution. However, 4-hydroxyacetophenone failed the

Dakin oxidation even with enhanced solvent system.
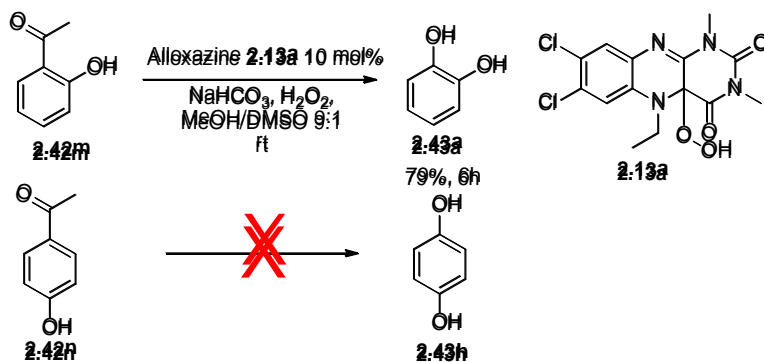
Figure 2.22 Dakin Oxidation of hydroxylated acetophenones

To identify the rate-determining step within the oxidation experimentally, a

Hammett linear free-energy relationship was constructed between the initial rates of

Dakin oxidations by different catalysts with various inductive effects. Linear agreements

occurred between the individual or summed σ_i values and $\log(k_R/k_H)$ yielding a positive

slope ($\rho > 0$). (Figure 2.23) This indicates an increase of charge on the catalyst during the

rate-determining step. This is consistent with formation of a 4a-alkoxyflavin anion (FlO-

2.13-3) during collapse of Criegee intermediate 2.13-2 (Figure 2.24).
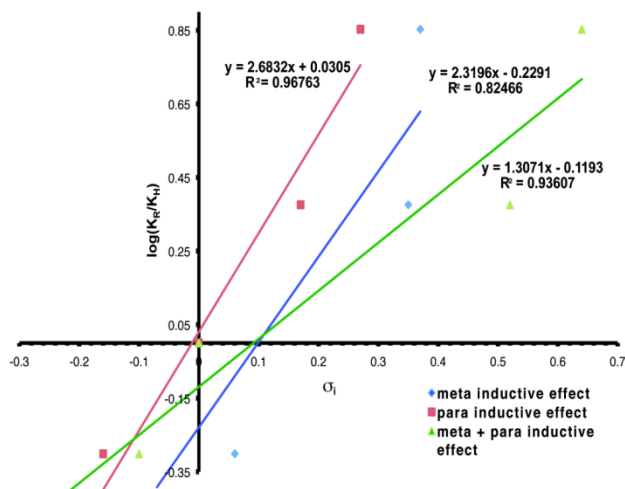
Figure 2.23 Hammett Plot for meta (7-substituent), para (8-substitution), and meta+para

inductive effects vs. relative initial rates.

Therefore, we propose the mechanism of alloxazine catalyzed Dakin oxidation as following. (Figure 2.24) FlOOH 2.13 enters the catalytic cycle by base deprotonation to form nucleophilic oxidant FlOO- 2.13-1, which attacks substrates to generate Criegee intermediate 2.13-2. The rate determining collapse of the CI- affords a leaving group FlO- 2.13-3 and the product. FlO- is protonated by solvent to form FlOH 2.13-4. Then it ionized to form an ion pair 2.13-5, which undergoes nucleophilic attack by a H_2O_2 molecule in the presence of a base to regenerate 2.13-1.
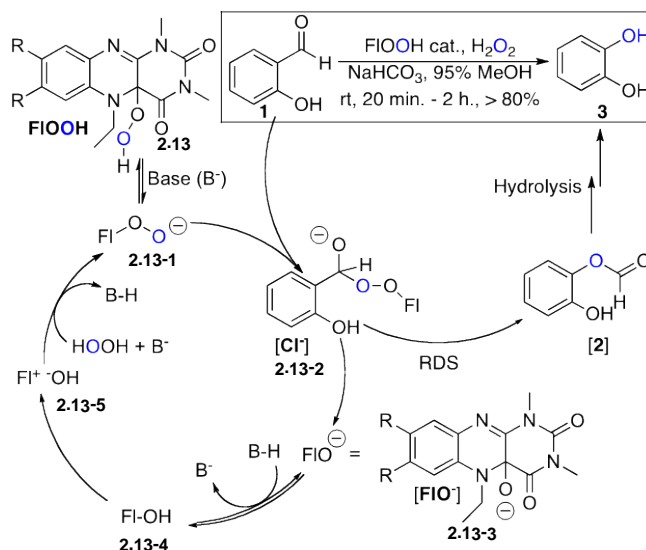
Figure 2.24 Proposed mechanism of alloxazine catalyzed Dakin oxidation

In conclusion for the alloxazine catalyzed Dakin oxidation using H_2O_2 as terminal oxidant, the biomimetic H_2O_2 shunt process was used as a guideline. Electron-withdrawing groups on the C^7 and C^8 positions of the alloxazine facilitate catalysis. Mild reaction conditions including a weak base and room temperature were achieved with the help of alloxazine catalyst. Electron rich o-hydroxybenzaldehydes generally were good substrates. Additional optimization is needed to extend this methodology to more challenging substrates such as non-hydroxylated benzaldehydes or acetophenones. The mechanistic study indicated that the rate determining step was the collapse of the Criegee intermediate.

2.2.3 Flavin Catalyzed Dakin Oxidation Using O_2 as Terminal Oxidant

Conducting the Dakin oxidation using molecular oxygen as a terminal oxidant is a logical development inspired by the flavin biomimetic cycle. Nature utilizes NAD(P)H to reduce oxidized flavin cofactor via hydride transfer to form the reduced flavin that takes molecular oxygen to generate 4a-hydroperoxy flavin. (Figure 2.25 Highlighted by red

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color) Excess H_2O_2 is not needed in this process, which could be dangerous to organisms. With limited concentration of active peroxide, substrates could be converted to products very high efficiency and selectivity.
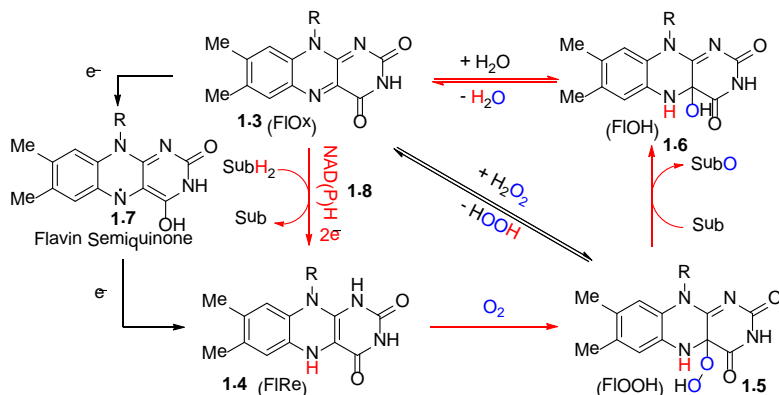
Figure 2.25 Dakin oxidation inspired by flavin biomimetic cycle using O_2 as oxidant

Previously, flavin catalyzed aerobic oxidations were conducted mimicking the cycle showed above. In aerobic amine and sulfur oxidation reactions, hydrazine monohydrate was used to reduce isoalloxazine catalyst to turn over the catalyst.[13] The same group developed aerobic Baeyer-Villiger oxidation with metallic zinc as a two-electron reductant to reduce oxidized isoalloxazine to complete reaction cycle.[27] Although not mentioned, the switch of the reductant from hydrazine to zinc in BVO was presumably due to undesired hydrazone formation between cyclobutanones and hydrazine. Nonetheless, both of the aerobic oxidations were very successful in terms of atom economy and chemoselectivity.

Similarly, in Dakin oxidation system, reducing agent selection was the key to the success. Hydrazine predictably formed hydrazones with benzaldehyde substrates, yielding no desired product. Activated zinc showed good reactivity in the oxidation of salicylaldehyde to produce catechol. However, when applying the Zn/O2 protocol to substituted salicylaldehydes, products were isolated in very low yields. Either robust

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bisphenolate zinc complexes, such as 2.44 or polyphenols are believed to form, sequestering the desired product.[46] (Figure 2.26) Various methods (acid, base, EDTA treatment and extraction) to liberate product from the possible organometallic structures were unsuccessful.
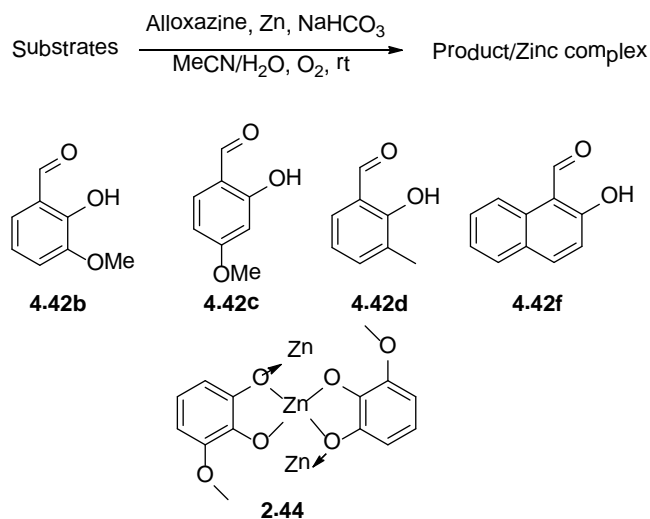
Figure 2.26 Zinc complexes were formed for the various 2-hydroxyl benzaldehydes

Other reducing agents, such as Na2S2O4, NaBH3CN, NaBH(OAc)3 and trialkylsilanes yielded no desired products. Other d-block species (Mg, Cu, and Fe) were expected to result in decomposition of the reactive hydroperoxyflavins by Fenton or Fenton-like chemistry. No catechol was detected by these metal reducing agents.

Knowing that the mechanism of flavin reduction is actually C=N double bond reductions, mild reducing agents that selectively reduce C=N were investigate to accomplish flavin reduction. Hantzsch ester, the hydrogen transfer reagent closely related to NAD(P)H's 2.45 nicotinamide reactive core,[47] selectively reduces imines in the presence of aldehydes.[48-49] (Figure 2.27) Access to Hantzsch ester is fairly easy. Multi-component condensation between an aldehyde such as formaldehyde 2.46, 2 equivalents of a β-keto ester such as ethyl acetoacetate 2.47 and a nitrogen donor such

as ammonium acetate 2.48 or ammonia in polar protic solvents gives rise to Hantzsch

dihydropyridine 2.49.
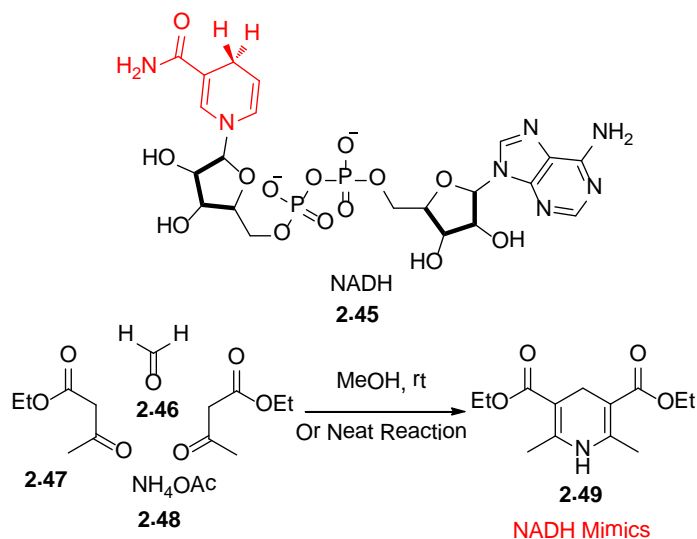
Figure 2.27 Hantzsch ester as a NAD(P)H mimics

When zinc powder was replaced with one equivalent of 2.49, aerobic Dakin

oxidations proceeded smoothly to form corresponding phenol products. (Figure 2.28) The

production of undesired benzyl alcohols or benzoic acids were not detected. Diethyl 2,6-

dimethylpyridine-3,5-dicarboxylate 2.50, could be isolated from reactions as the oxidized

byproduct. Control reactions without flavin catalysts ensured that no peroxyacid formation

resulted by autooxidation of benzaldehydes occurred.[50-52] Reactions were also performed

in the dark to eliminate possible photooxidation pathways.
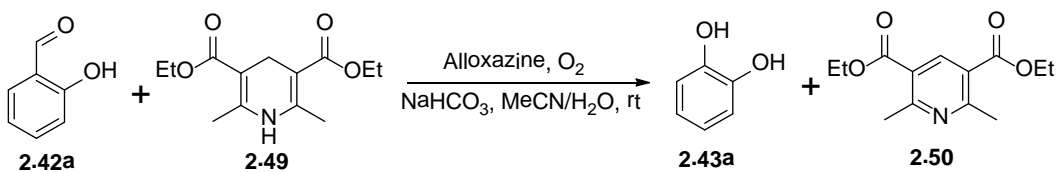
Figure 2.28 Dakin oxidation using dihydropyridine as reducing agent

The aerobic Dakin oxidation condition was then optimized by changing three variables: catalyst substitution, solvent, and base.

Using the five alloxazine catalysts 2.13a-e available from the H_2O_2 based Dakin oxidation study, we set up aerobic Dakin oxidation of salicylaldehyde with 5 mol% of each alloxazine and Hantzsch ester (HEH) as a stoichiometric reducing agent. The conversion of salicylaldehyde to catechol was calculated by NMR, utilizing DMSO as an internal standard. Flavin 2.13c showed the greatest reactivity, followed by 7,8-dimethyl 2.13d and 7,8-dimethoxy 2.13e substituted alloxazines. Electron-poor 7,8-difluoro 2.13b and 7,8-dichloro 2.13a alloxazines, which provided the fastest reaction rates in H2O2-fueled Dakin oxidations, performed the aerobic oxidation poorly.(Figure 2.29)
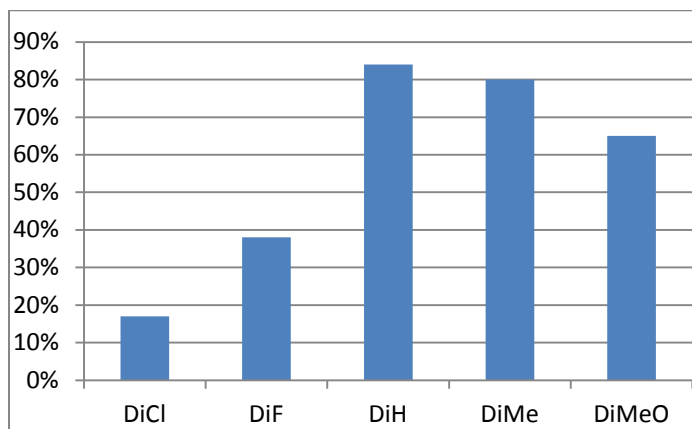
Figure 2.29 Alloxazine screening on aerobic Dakin oxidation

The catalyst reactivty results suggest that competing rate determining steps influence the observable reaction rate: (1) collapse of the Criegee intermediate via 1,2-aryl shift (the putative rate-determining step of the Dakin oxidation indicated from our previous study) and (2) molecular oxygen activation by reduced flavins.[5,53] While we previously showed that electronwithdrawing groups facilitate the Dakin oxidation by stabilizing the 4a-oxaflavin anion (FlO- 2.13-3 Figure 2.24) leaving group, the same substituents attenuate the single electron transfer process from flavin to triplet oxygen by

altering the oxidation potentials of the reduced flavins.[54-55] The hypothesis, in correlation with previous data, is that: electron-poor hydroperoxyflavin 2.13a and 2.13b, in comparison to more electron-rich catalysts, are more efficient Dakin oxidation catalysts, but their respective reduced structures FlH_2 react with O2 more slowly.

Solvents were investigated. Water miscible solvents were investigated to solvate sodium bicarbonate by 5% water addition, which also promotes hydrolysis of the Dakin oxidation intermediate. Acetonitrile, 95% in water, achieved the fastest reaction rate and highest yields. In general, alcohols suppressed reaction rates. Anhydrous acetonitrile failed as an aerobic Dakin oxidation solvent.

Base is essential in the flavin catalyzed Dakin oxidation system. However, only mild bases (sodium bicarbonate or carbonate) were necessary. Hydroxides were not as effective in this system, presumably due to hydrolysis of the flavin catalyst. (Figure 2.30)
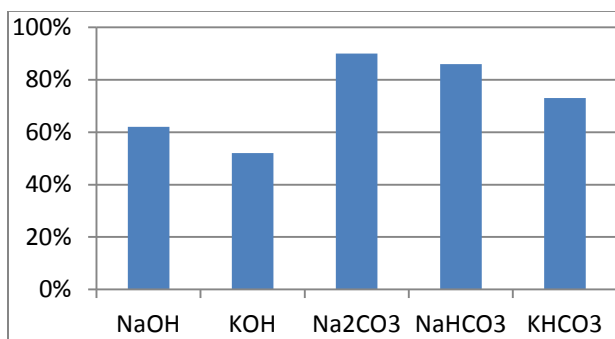
Figure 2.30 Base screening on aerobic Dakin oxidation

In the aerobic Dakin oxidation system, another function of the base is to depress 2.13-6 formation and H_2O_2 shunt elimination from 4a-hydroperoxy alloxazine 2.13 by deprotonating the hydroperoxyl proton to form 4a- hydroperoxyanion 2.13-1. (Figure 2.31) An aerobic reaction was set up without adding salicylaldehyde. No pyridine was detected by flavin catalyzed HEH oxidation. However, when acetonitrile was changed into trifluoroethanol, even without the presence of substrate, HEH was fully converted into

pyridine. Trifluoroethanol facilitates elimination of H_2O_2 and regeneration of oxidized

flavin, presumably because of the acidic nature of the solvent.
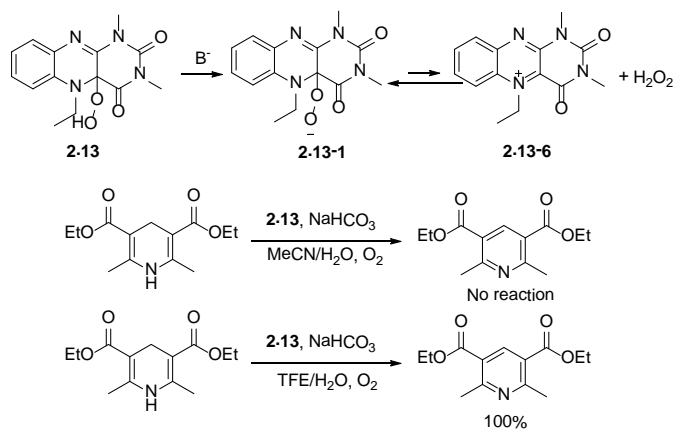
Figure 2.31 The effect of base on flavin catalyst

The substrates scope of the aerobic Dakin oxidation is similar to that of the H_2O_2

based Dakin oxidation. (Figure 2.32) Electron rich benzaldehydes underwent aerobic

oxidation efficiently. Nitro-containing substrates were converted to catechols but with

longer reaction time. No benzoic acid byproduct was observed in any of the substrates

evaluated. However, similarly to the H_2O_2 based Dakin oxidation, non-hydroxylated

benzaldehydes or acetophenones were generally not successful, even at elevated

temperature.
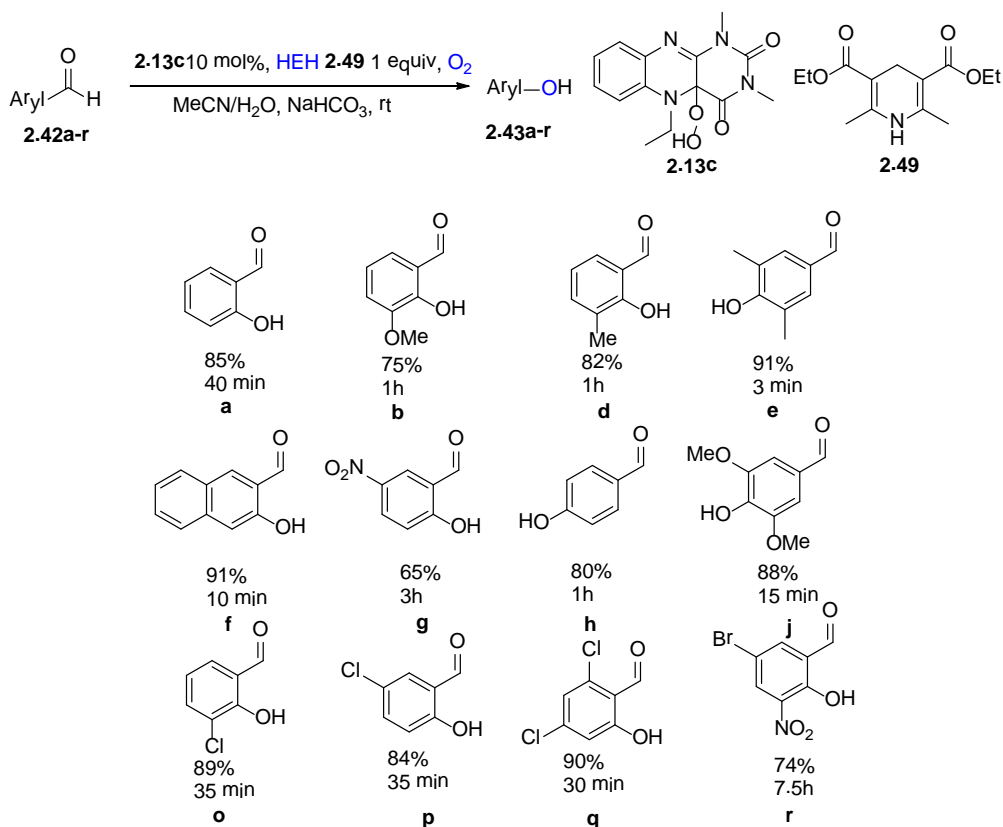
Figure 2.32 The substrate scope of aerobic Dakin oxidation

The aerobic Dakin reaction worked with low catalytic loading and air as the oxygen source. A 10 mmol scale Dakin oxidation of 2.42a, with 0.1 mol % of catalyst 2.13c and air as oxygen source, was performed to challenge our catalytic system; 91% yield of the product was achieved after three days at room temperature.

In conclusion, we have developed an aerobic and mild catalytic system for the Dakin oxidation. A range of electron rich benzaldehydes react in the presence of two biomimetic redox partners: alloxazine catalysts and Hantzsch ester. The selection of Hantzsch ester was crucial to the success of this reaction and provides an alternative reductant for flavin-catalyzed aerobic oxidations, especially those with ketones and

aldehydes. Catalyst loading was effective at 0.1 mol %. Again, extensive condition

optimization is needed to broaden substrate scope to more challenging starting materials.

Chapter 3

Flavin Catalyzed Weitz-Scheffer Oxidation

3.1 Dual Catalysis Strategy for Flavin Catalyzed Asymmetric Oxidations

The excellent rate accelerating performance of flavin in various oxidation reaction draws people's attention on developing asymmetric methodologies to generate more valuable enantio rich oxidation product using this biomimetic organocatalyst.

The strategy that was used to conduct asymmetric oxidation with flavin organocatalyst had been designing and synthesizing enantiopure chiral flavin organocatalysts which covalently bonded to chiral substituents. The following examples 3.1-3.6 have been shown in the literature and mentioned earlier in this dissertation.[19-22, 26] (Figure 3.1)
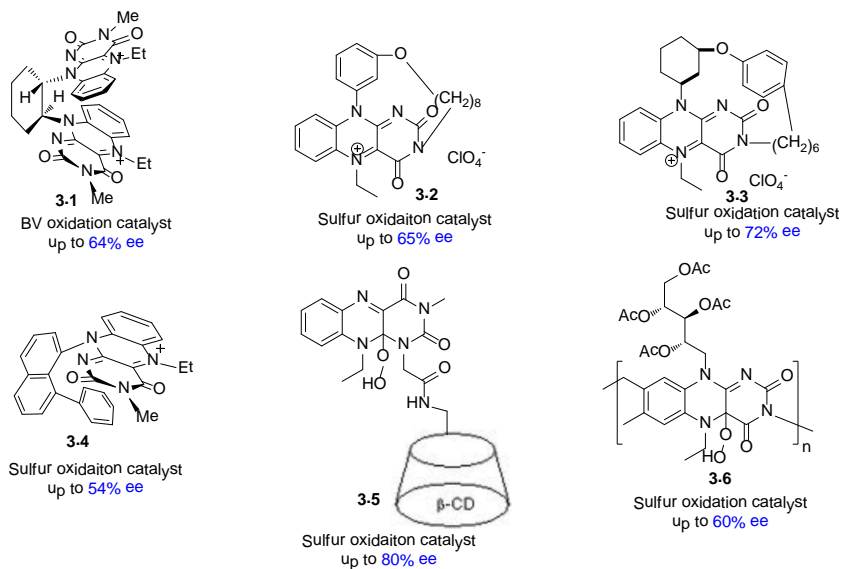
Figure 3.1 Asymmetric sulfur and Baeyer-Villiger oxidation flavin catalysts

However, the non-racemic flavins have many drawbacks. First, chiral flavins are more difficult to prepare compared to simple alloxazines and isoalloxazines. Five to nine steps were generally required to synthesize these compounds [20, 22, 26] and sometimes

chiral separation was required to obtain the organocatalyst.[20] Second, the

enantioselectivity of the oxygen transfer of these chiral flavin catalyzed reaction was not

optimal. The enantiometric excess of the products obtained from these reactions rarely

exceeded 80%. Lastly, the substrate scope was quite limited. Effective substrates usually

contained an aromatic substituent, which was believed to interact the aromatic moiety of

flavin tricyclic structure via π-π stacking.[20, 22] These shortcomings of these known chiral

flavin derivatives strategy limit the development of flavin catalyzed asymmetric reactions

using these catalysts and an alternate way of methodology designing is needed.

We proposed to use a dual catalysis strategy in which one catalyst is a simply

prepared flavin 3.7 or 3.8 which is responsible for oxygen transfer; the other is a chiral

ligand 3.9-3.13 that controls the facial selectivity of oxygen transfer by interacting with the

substrate through a covalent bond or a hydrogen bond. (Figure 3.2) A range of chiral

cocatalyst is ready available in the literature that is able to induce an asymmetric

environment of substrates efficiently. [56-59]
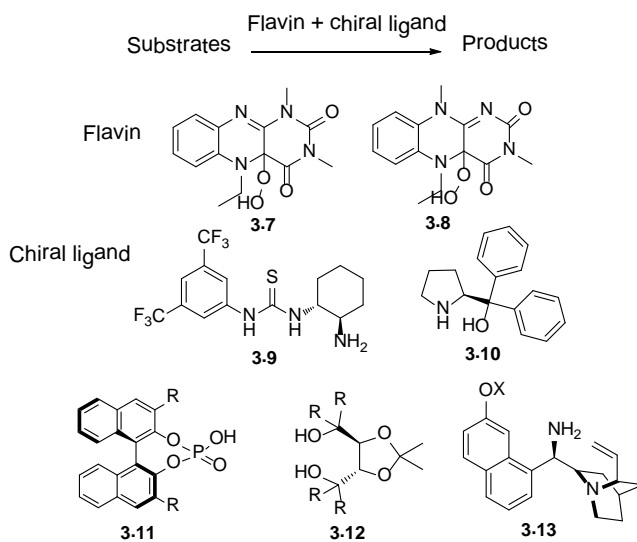
Figure 3.2 Dual catalysis strategy of asymmetric oxidation

3.2 Aerobic Asymmetric Weitz-Scheffer Epoxidation

The Weitz-Scheffer oxidation is a type of nucleophilic epoxidation of electron-deficient double bonds through the attack of alkaline hydroperoxides.[60] Nucleophilic epoxidation methods represent an alternative to electrophilic methods such as Sharpless epoxidation,[61] Jacobsen epoxidation[62] and Shi epoxidation,[63] which often do not preform epoxidation on electron-deficient double bonds efficiently.

The mechanism of Weitz-Scheffer oxidation is described by Bunton and Minkoff to be a two-step process.[64] (Figure 3.3) First, conjugate addition of a peroxy anion 3.15 which is generated by H_2O_2 or alkyl peroxide under basic condition at the β position of α, β-unsaturated ketone 3.14 affords β-peroxyenolate 3.16. Then, intramolecular nucleophilic displacement at the proximal oxygen atom breaks the weak O-O single bond generating a leaving group, hydroxide or alkoxide 3.17, to furnish epoxide 3.18.
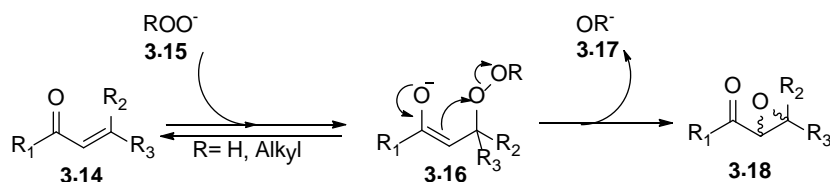
Figure 3.3 Proposed mechanism of Weitz-Scheffer oxidation

The non-stereospecificity of these reactions is a strong indication for the formation of an intermediate 3.16 in the course of the reaction. The epoxidation of both *trans*- and *cis*-configured α, β-unsaturated ketone with alkaline hydrogen resulted in *trans*-epoxide as the main product. The convergent result further implies that hydroperoxide addition is reversible and causes isomerization by rotation about the vinylic bond in the peroxyenolate.

Numerous catalysts were developed to furnish asymmetric epoxidation of enones or enals. Representative work in this area including: 1) Asymmetric epoxidation using

alkylated Cinchona alkaloids as phase transfer catalysts.[65-68] 2) Polyamino acid mediated epoxidation (Juliá-Colonna epoxidation).[69-70] 3) Epoxidation using chiral ligands and metal peroxides.[71-72] 4) Epoxidation using LUMO lowering organocatalysts.[73-74] In most of these methods, 35% aqueous H_2O_2 or other strong oxidants were used as stoichiometric oxidant. No example used oxygen as the terminal oxidant to perform epoxidation of enals or enones.

The topic of aerobic alkene epoxidation has attracted significant attention within the last decade. Predominately, aerobic epoxidation of isolated and unactivated alkenes can be achieved via radical-mediated autooxidation pathways or via monooxygenase like oxidation with a coreductant.[75] Both approaches can be catalyzed by a range of transition metal bearing catalysts, such as Schiff's base complexes, metalloporphyrin complexes and metal cyclam complexes.[76-78] In addition, the asymmetric aerobic epoxidation of unfunctionlized alkenes was also achieved by metal salen catalysts.[79-87]

Aerobic Weitz-Scheffer oxidation is surprisingly rarely reported. Until recently, Shibata's group disclosed a groundbreaking one pot aerobic asymmetric epoxidation of trifluoromethyl substituted β, β-disubstituted enones 3.19 using cinchona derived catalyst 3.20 and H_2O_2, which was generated in situ by methylhydrazine, a base and molecular oxygen. (Figure 3.4) However, only β CF_3 substituted enones participated in this aerobic epoxidation with high enantioselectivity.[88] Itoh's group published a two-step process where H_2O_2 was first generated in situ using the known anthraquinone 3.23 oxidation (AO) process with excess isopropanol as a sacrificial reductant, followed by adding enone 3.19 and a strong base to achieve epoxidation.[89] While the initial foundation of aerobic Weitz-Scheffer oxidation is established, diversified methods are urgently demanded to broaden of utility of this interesting transformation.
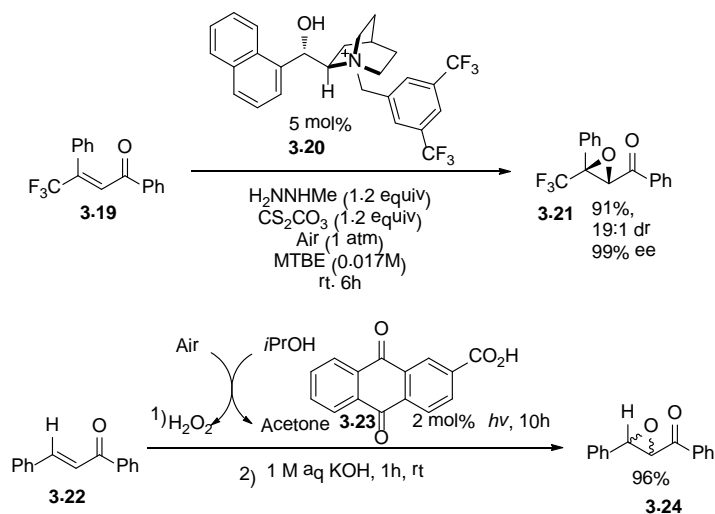
Figure 3.4 Recent development of aerobic epoxidation of enones

Many literature reports showed flavin containing monooxygenases' role in the epoxidation of unactivated alkenes, enones and enals, there is no direct application of this phenomenon as a bio-inspired epoxidation methodology.[90-92] (Figure 3.5)
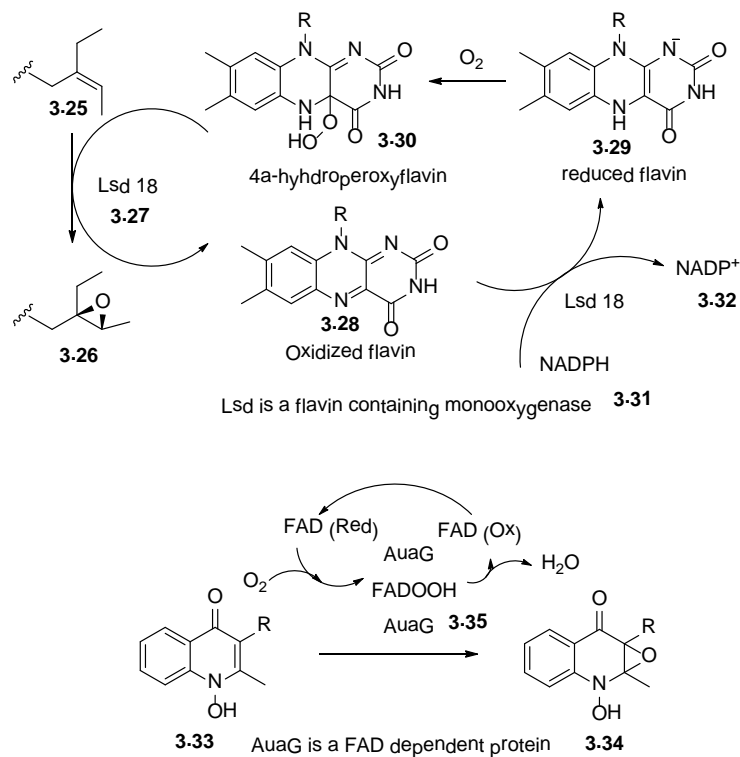
Figure 3.5 Examples of flavin protein catalyzed epoxidation

To our knowledge, there is no method that achieves the asymmetric epoxidation of enals aerobically in an organocatalyst catalyzed system. Herein, we describe the first asymmetric aerobic epoxidation of α,β-unsaturated aldehydes catalyzed by flavin/pyrrolidine duel catalytic systems using benzothiazoline as a stoichiometric coreductant, achieving good yield, excellent diastereoselectivity and enantioselectivity.

We know that flavin catalyzed aerobic Dakin Oxidation of aryl aldehydes can be turned over with Hantzsch esters 3.38 as the stoichiometric reductant. Starting from established method, we initially attempted to transplant the aerobic Dakin oxidation system directly to the epoxidation of enal, using cinnamaldehyde 3.35a as a model compound. (Figure 3.6) Unfortunately, no epoxide was detected from the reaction. We envisioned two possible problems of the system: 1, the active oxidant, either 4a-

hydroperoxy flavin 3.37 or H_2O_2 (eliminated from 4a-hydroperoxy flavin), is not

nucleophilic enough to attack the β position of enal. 2, the β-carbon of enal is not

electrophilic enough to attract the peroxide lone pair electrons.

3·37 a R=Cl **b** R=F **c** R=H
d R=Me **e** R=OMe
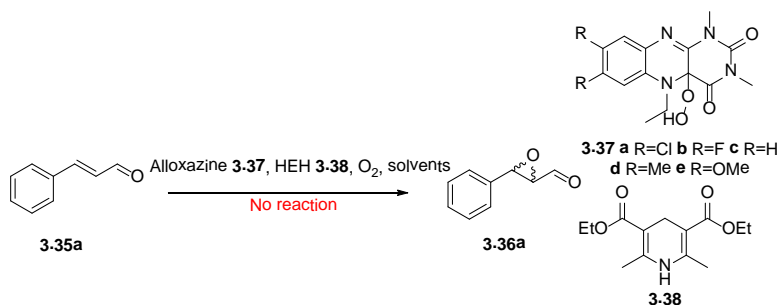
Figure 3.6 Aerobic Dakin oxidation condition failed on epoxidation of enal

Luckily, there is a ready answer to solve the second problem. A range of L-

proline derived organocatalysts was available in the literature, first recognized by

Jørgensen's group as a LUMO lowering catalyst to achieve asymmetric epoxidation of

enal with H_2O_2.[73] (3.39a-d Figure 3.7) Inspired by this research, we tried to add different

prolinols or prolinol silyl ethers as a LUMO lowering co-catalyst into our aerobic oxidation

system.
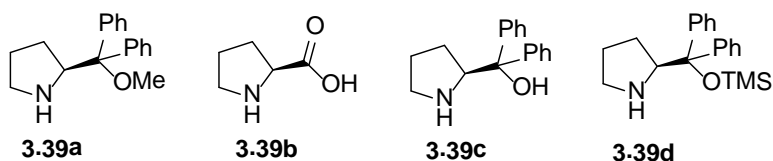
Figure 3.7 L-proline derived organocatalysts

Not surprisingly, with the help of further activation of the iminium, epoxidation of

cinnamaldehyde was achieved. (Figure 3.8) Trimethylsilyl protected diphenyl prolinol

3.39d resulted in higher chemical yield and diastereomeric ratio of epoxide than the non-

protected prolinol 3.39c and methyl protected prolinol 3.39a, for its excellent steric

blocking effect.[93] In our system, 20 mol% of prolinol catalyst 3.39d was needed to obtain

good yield of product within a few hours.
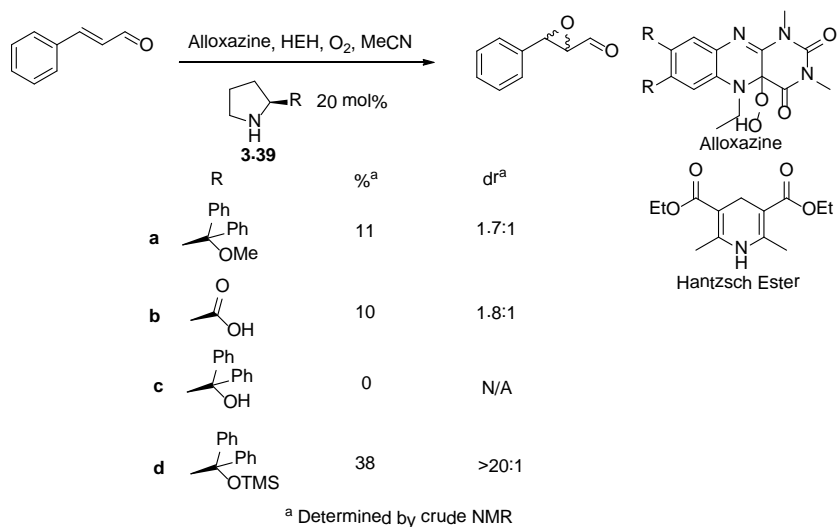
Figure 3.8 Comparison of pyrrolidine cocatalyst

However, before we moved on to the optimization process, an unexpected

conjugate reduction product, hydrocinnamaldehyde 3.40, was detected. (Figure 3.9)

Indeed, prolinol catalyzed conjugate reduction of enals with Hantzsch esters as hydride

transfer reagent was well-known in the literature.[94] In our epoxidation system, the

Hantzsch ester 3.38 not only reduced the flavin but also the activated double bond of the

enal. To avoid this chemoselectivity issue,the Hantzsch ester must be substituted by

another reductant, which can differentiate the C=N double bond in flavin and the double

bond in enal selectively. Therefore, a range of reductants that can potentially reduce

flavin were tested. (Table 3.1 Entry 4-8) Metal reductant, such as Zn, led to no epoxide

formation. Hydrazine, known to be able to reduce flavin, formed hydrazone with enal

immediately and precipitated out of solution, and performed no epoxidation. Thus,

attention was turned to benzothiazoline 3.41, a prearomatic heterocycle readily obtained

by the condensation of benzaldehyde and 2-aminothiophenol. Benzothiazolines were

known as very mild hydride transfer reagents which selectively reduce C=N double bond under neutral conditions. [95-96] Fortunately, with 1.2 equivalent benzothiazoline 3.41b as reductant, aerobic epoxidation of cinnamaldehyde 3.35a proceeded as expected without the formation of hydrocinnamaldehyde.
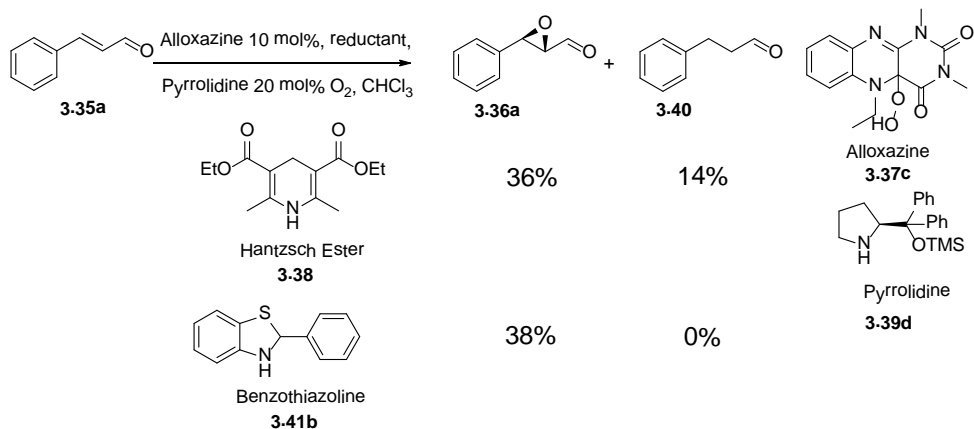
Figure 3.9 Comparison of reductant in aerobic epoxidation

Among benzothiazolines (Table 3.1, entry 4-8), some, such as 3.41b, tended to undergo hydrolysis to form benzaldehyde 3.43 and 2-aminothiophenol 3.42, especially when the substrate or the chloroform was contaminated by acid impurities. (Figure 3.10) To prevent this from happening, the chloroform and substrates used in the reaction were freshly purified. The nitro containing benzothiazoline (3.41a Table 3.1 Entry 2), proved to be less liable to hydrolysis under acid catalysis, was chosen as the stoichiometric reductant in our system.
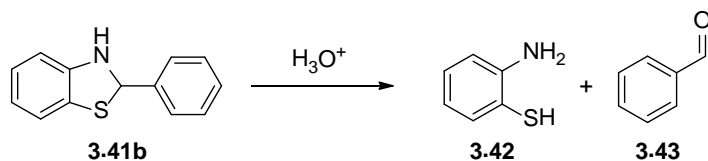
Figure 3.10 Hydrolysis of benzothiazoline

Next, flavin catalyst was optimized. (Table 3.1 Entry 10-14) In aerobic Dakin oxidation system, 7,8-dihydrogen substituted alloxazine (3.37c) was proven to be the best flavin compared to catalysts with other substitutions. In the aerobic epoxidation system, the same trend was observed. Also, the flavin catalytic loading was very important to the success of aerobic epoxidation. Lower catalyst loading (0.1 - 5 mol%) led to longer reaction times, but the chemical yield was not affected. However, when 10-20 mol % flavin catalyst was added, the chemical yield was reduced substantially. This can be explained by flavin catalyzed N-oxidation of prolinol nitrogen. It is known that flavins accelerates the oxidation of secondary amine to nitrone with hydrogen peroxide.[12-13] Nitrone formation was confirmed by taking HRMS of crude reaction mixture. Once oxidized, the prolinol catalyst was poisoned and therefore lost its ability to form an iminium ion with enal. Therefore, we chose to use 5 mol% flavin catalyst 3.37c to perform the aerobic epoxidation. Good rate and maximized chemical yield was obtained.

Chlorinated solvents such as dichloromethane or chloroform were chosen to perform asymmetric epoxidation of enals. We have screened several other solvents and finalized chloroform as the solvent considering yield and enantioselectivity. (Table 3.1 Entry 15-19) Chloroform proved to be a great solvent in our system because it solubilizes everything at the beginning of the reaction. As the reaction proceeds, the benzothiazole byproduct generated in situ precipitates out of chloroform.

The summarized condition screening and results are presented in the following Table 3.1

Table 3.1 Asymmetric aerobic epoxidation of 4a: condition optimization

3-37a: R=Cl
3-37b: R=F
3-37c: R=H
3-37d: R=Me
3-37e: R=OMe

3-39a: R=OMe
3-39c: R=OH
3-39d: R=OTMS

3-41a: R=4-nitrophenyl
3-41b: R=phenyl
3-41c: R=2,6-dimethylphenyl
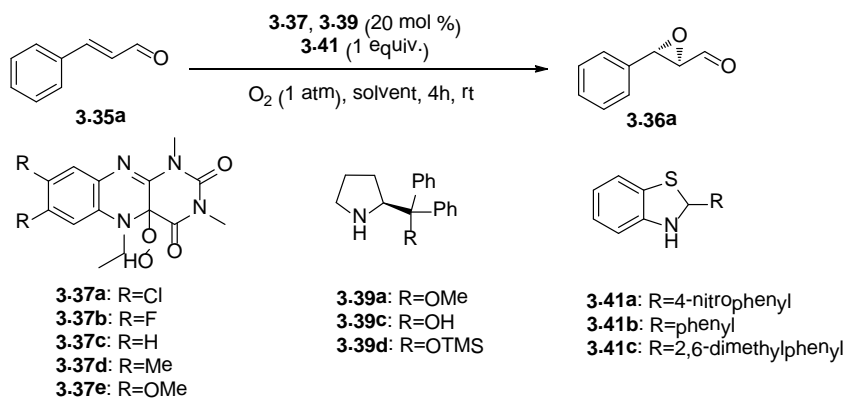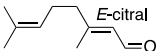
Entry	Polinol	Red	Flavin	Solvent	d.r.	Yield [e](%)
1	-	HEH[a]	10 mol % **3.37c**	CHCl$_3$	n.d.	n.d.
2	**3.39d**	**3.41a**	10 mol % **3.37c**	CHCl$_3$	10:1	38
3	**3.39a**	**3.41a**	10 mol % **3.37c**	CHCl$_3$	2:1	44
4	**3.39c**	**3.41a**	10 mol % **3.37c**	CHCl$_3$	n.d.	7
5	**3.39d**	Zn	10 mol % **3.37c**	CHCl$_3$	n.d.	n.d.
6	**3.39d**	HEH	10 mol %**3.37c**	CHCl$_3$	10:1	36[b]
7	**3.39d**	**3.41b**	10 mol % **3.37c**	CHCl$_3$	10:1	38[c]
8	**3.39d**	**3.41c**	10 mol % **3.37c**	CHCl$_3$	10:1	56[d]
9	**3.39d**	**3.41a**	5 mol % **3.37c**	CHCl$_3$	10:1	74
10	**3.39d**	**3.41a**	20 mol % **3.37c**	CHCl$_3$	10:1	32
11	**3.39d**	**3.41a**	10 mol % **3.37b**	CHCl$_3$	10:1	16
12	**3.39d**	**3.41a**	10 mol % **3.37a**	CHCl$_3$	10:1	14
13	**3.39d**	**3.41a**	10 mol % **3.37 d**	CHCl$_3$	10:1	6
14	**3.39d**	**3.41a**	10 mol % **3.37e**	CHCl$_3$	10:1	7
15	**3.39d**	**3.41a**	5 mol % **3.37c**	DCM	10:1	54
16	**3.39d**	**3.41a**	5 mol % **3.37c**	MeCN	10:1	34
17	**3.39d**	**3.41a**	5 mol % **3.37c**	C$_6$H$_6$	10:1	16
18	**3.39d**	**3.41a**	5 mol % **3.37c**	THF	10:1	n.d
19	**3.39d**	**3.41a**	5 mol % **3.37c**	Hexane	10:1	n.d.

[a] HEH stands for Hantzsch ester. [b] 14% hydrocinnamaldehyde was detected. [c] 30% benzaldehyde from hydrolysis was detected. [d] 13% 2,6-dimethylbenzaldehyde from hydrolysis was detected. [e] NMR yield was determined using DMSO as an internal standard. d.r. was determined by NMR

With the optimized condition, 5 mol% flavin 3.37c and 20 mol% prolinol 3.39d, 1.2 equivalent of benzothiazole 3.41a, 1 atm of oxygen gas in chloroform, we started to exploit the scope of this aerobic epoxidation. First of all, a range of enals with aryl substitutions on beta position was epoxidized under standard condition. (Table 3.2. Entry 1-4) Good yield was achieved with all of them (74–85%) after 4-6 hours. Good diastereoselectivity (7:1 to 17:1) of trans versus cis product was detected. To our delight, the enantioselectivity of epoxide was excellent. The e.e. values ranged from 94% to 96% for the favored 2S,3R-oxirane with the (S)-prolinol as the LUMO lowering catalyst. Beta mono alkyl -substituted enals generally obtain epoxide with higher d.r.(13:1 to >20:1) but slightly lower e.e.(87-92%). For low molecular weight short chain enals, the oxirane 2-carbaldehydes obtained were directly reduced to corresponding alcohols with sodium borohydride before isolation. (Table 3.2. Entry 6-12) Beta disubstituted enals oxidized efficiently under aerobic condition, however, with a reduced ratio in diastereoselectivity and enantioselectivity. (Table 3.2. Entry 6, 13)

Table 3.2 Flavin/pyrrolidine catalyzed epoxidation substrate study
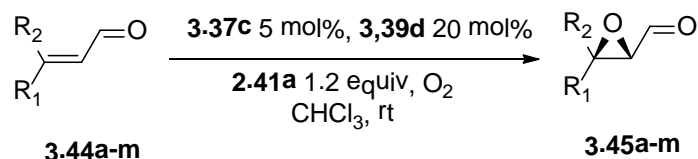
Entry	3.45	R_1	R_2	Yield[a] (%)	Time (h)	d.r.[b]	% ee[c]
1	a	Ph-	H	78	4	13:1	94
2	b	o-NO$_2$-Ph-	H	85	5	7:1	95
3	c	p-NO$_2$-Ph-	H	84	6	17:1	96
4	d	p-Cl-Ph-	H	74	6	14:1	96
5	e	Me-	Me	55[d]	2	N/A	73
6	f	Et-	H	48[d]	2	13:1	87
7	g	isopropyl-	H	53[d]	2	>20:1	93
8	h	n-propyl-	H	63[d]	2	>20:1	92
9	i	n-butyl-	H	69	3	14:1	90
10	j	n-hexyl-	H	71	5	15:1	91
11	k	n-heptyl-	H	74	5	>20:1	92
12	l	-CO$_2$Et	H	61	4	10:1	93
13	m	E-citral		62	6	2:1	53

[a] Isolated yields. [b] d.r. were determined by NMR and GC. [c] % e.e. were determined by chiral GC or HPLC (see SI). [d] Isolated yields refer to the corresponding alcohols after NaBH$_4$ reduction.

When compared our results with the values (reaction time, yield, d.r. and e.e.) achieved by existing enal epoxidation methods using prolinol catalyst and hydrogen peroxide as oxidant, we found that they were coincidently very similar.[73,93] This led us to think about the mechanism of the epoxidation: What is the real oxidant in the reaction,

4a-hydroperoxy flavin or H_2O_2 (eliminated from 4a-hydroperoxy flavin)? What is the role

of flavin in changing the course of the reaction? Considering that increased steric effect

of alkylperoxide led to a loss of stereoselectivity in their work, we hypothesized that the

true oxidant was not the hindered 4a-hydroperoxyflavin but H_2O_2, a dissociation product

in equilibrium with hydroperoxyflavins.

To answer these questions, three reactions were set up with different loadings of

flavin catalyst. One of the advantages of choosing benzothiazolines as the reductant was

the ease with which its consumption may be tracked by integration of ^{1}H NMR signals of

benzothiazoline and its oxidized product, benzothiazole. Therefore, the courses of these

reactions were monitored with ^{1}H NMR. The consumption of benzothiazoline (Table 3.4)

and the generation of epoxide (Table 3.3) were calculated over 4.5 hours. Each

experiment was carried out three times and the results were the average of repeated

reactions.

Table 3.3 Epoxide concentration Vs Time

Time(Min)	5mol% average	10mol% average	20mol% average
10	12.2	14.13	14.73
20	18.13	22.16	20.93
30	26	28	25
40	35	34.1	27
60	45.33	39.1	29.56
90	56.66	42.66	32.33
180	67.9	44.66	32.33
270	73.2	46.33	32.83

Table 3.4 Benzothiazoline concentration Vs Time

Time(Min)	5mol% average	10mol% average	20mol% average
10	71.83	51.13	27.4
20	57.96	35.33	13.33
30	46.6	20.7	0
40	37.66	15.83	0
60	23	4.333	0
90	13.33	0	0
180	0	0	0
270	0	0	0

With 5 mol % loading, benzothiazoline was consumed in a moderate rate. After 3 hours, no benzothiazoline was left. While epoxide concentration increased gradually with the consumption of the reducing agent and stopped at 74 % by 4.5 hours. (Figure 3.11)
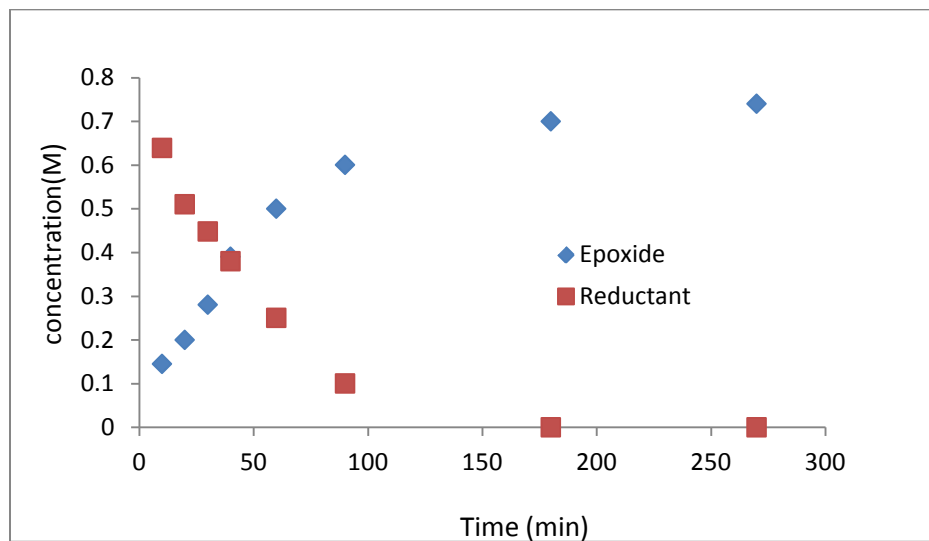
Figure 3.11 5 mol % flavin: Product/Reductant Vs Time

With 10 mole % loading, benzothiazoline consumption was significantly faster. Within 50 minutes, all of reducing agent was oxidized. However, the epoxide formation

was not as fast as 5 mol % reaction and after 4.5 hours, only yielded 39% product.

(Figure 3.12)
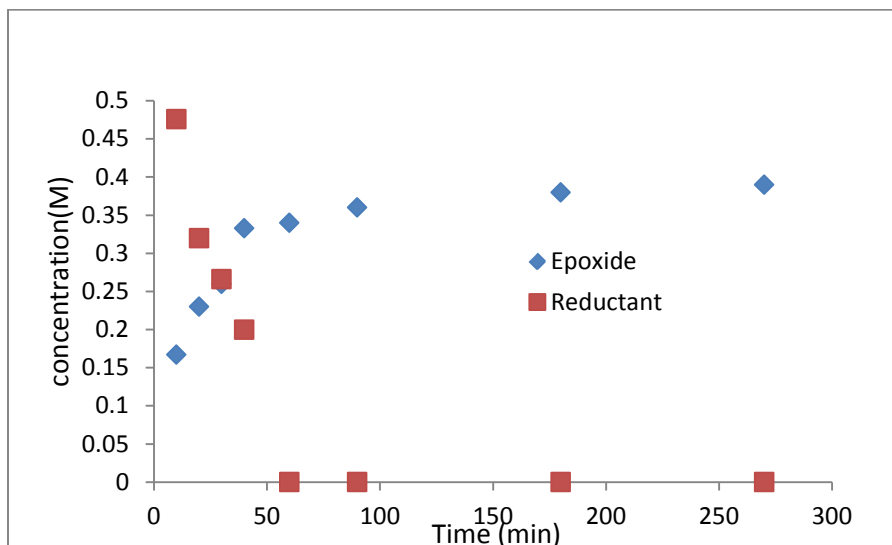
Figure 3.12 10 mol % flavin: Product/Reductant Vs Time

When the flavin loading was increased to 20 mol %, the consumption of

reductant required only 30 min. Surprisingly, the product formation was even slower,

yielding only 32% epoxide after 4.5 hours. (Figure 3.13)
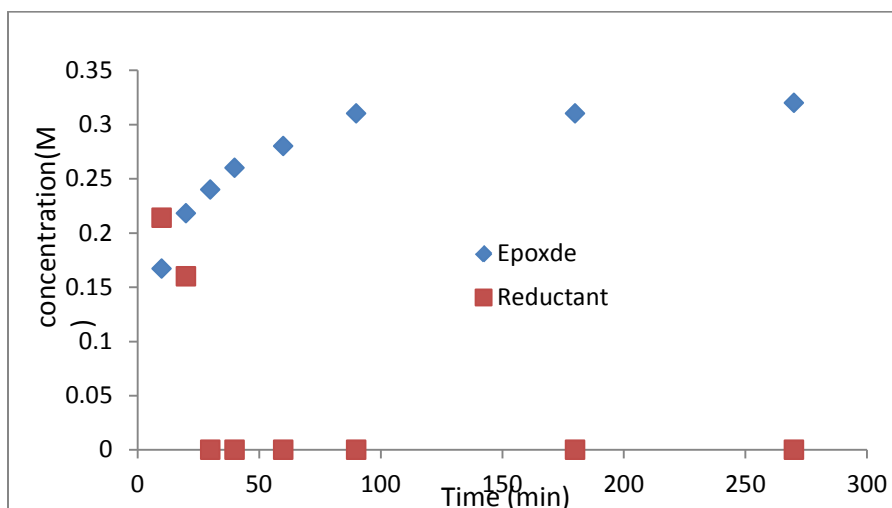
Figure 3.13 20 mol % flavin: Product/Reductant Vs Time

The information of peroxide formation versus time was plotted as following Figure 3.14. And the initial rate of three reactions was calculated and summarized below. (Table 3.5)
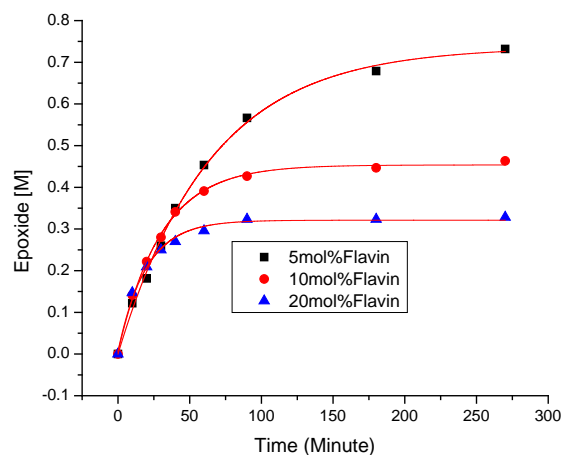
Figure 3.14 Epoxide formation progress for reactions with different flavin loadings

Table 3.5 Peroxide formation reaction initial rates

Flavin loading	Initial rate(M/min)
5mol%	0.011
10mol%	0.0148
20mo%	0.015

The information of benzothiazoline concentration versus time was plotted as following figure. (Figure 3.14) And the initial rate of three reactions was calculated and summarized below. (Table 3.6)
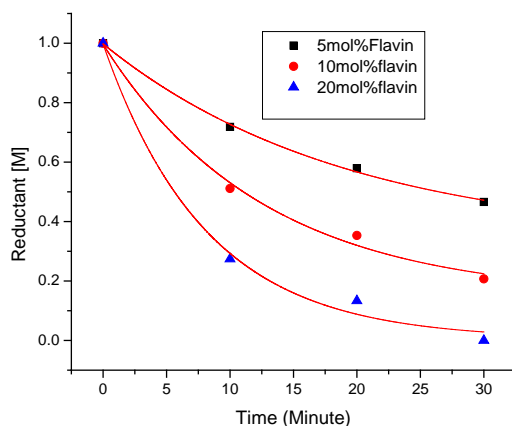
Figure 3.15 Benzothiazoline concentration progress for reactions with different flavin loadings

Table 3.6 Reductant consumption reaction initial rates

Flavin loading	Initial rate(M/min)
5mol%	0.035
10mol%	0.0675
20mo%	0.1225

The initial rates of both peroxide formation and reductant consumption were plotted as a function of flavin catalytic loading to reveal how flavin concentration affected the reaction progress. (Figure 3.16)
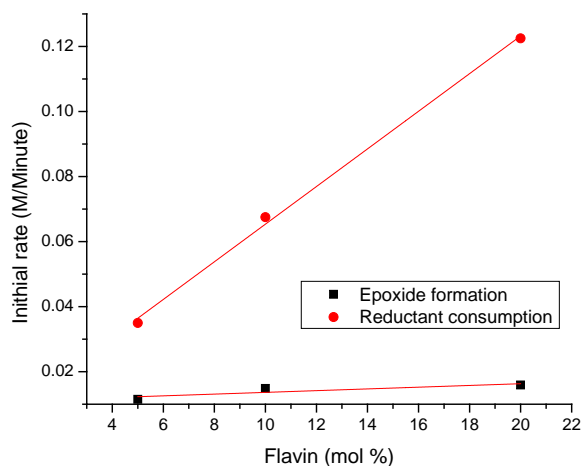
Figure 3.16 Initial rate of epoxide formation and reductant consumption as a function of

flavin loading

As is shown in the plot, the initial rate of product formation was almost independent of flavin loading. In contrast, reductant consumption rate was proportional to flavin loading. The dramatically different initial rates for epoxide formation and reductant consumption support an uncoupled redox process.

We believe that oxidized flavininium 3.47b are reduced by benzothiazoline 3.41a to form the reduced dihydroalloxazine FlH_2 3.47c, which reacts with oxygen to form 4a-hydroperoxyflavin FlOOH 3.47a. (Figure 3.17) In polar solvents, 4a-hydroperoxyflavin can dissociate to give the oxidized alloxazinium 3.47b and H_2O_2, which directly oxidizes enal. The rate of this process is proportional to the concentration of flavin. However, the rate of product 3.36a formation is determined by the concentration of iminium ion 3.48. Therefore flavin concentration does not affect the initial rate of epoxide formation. This hypothesis is reinforced by the oxidative poisoning of pyrrolidine 3.39d to nitrone 3.47 in the presence of additional flavin.
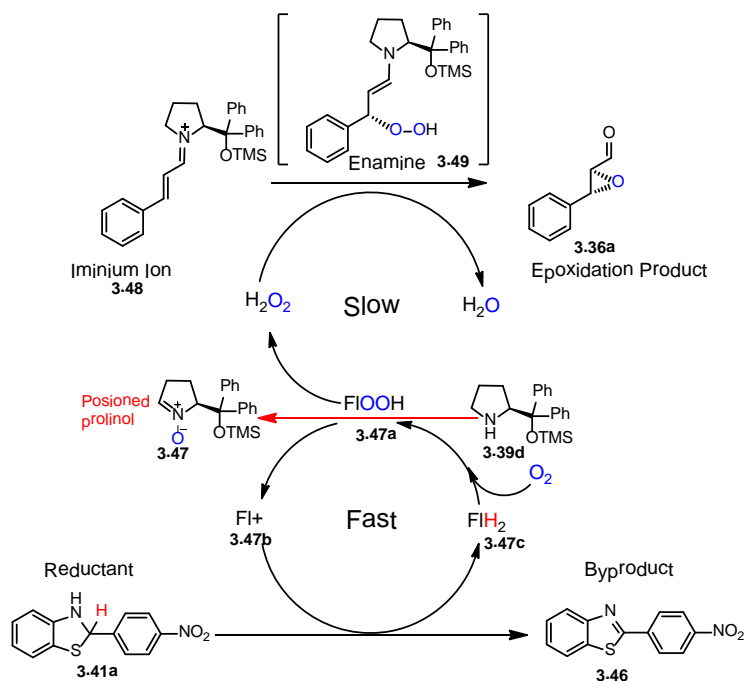
Figure 3.17 Proposed mechanism for alloxazine/pyrrolidine catalyzed aerobic epoxidation

Realizing H_2O_2 was the direct oxidant of the system, one should be able to detect its generation with only flavin catalyst, reducing agent, and oxygen. Indeed, in the reaction of 0.2 mmol of Hantzsch esters or benzothiazoline, 10 mol % flavin catalyst, and O_2 (1 atm) in chloroform yielded 0.11-0.13 mmol (55-65%) hydrogen peroxide, as detected after 30 minutes by titration of Fe^{3+} with UV-Vis detection or oxygen electrode.[97] (Figure 3.18)
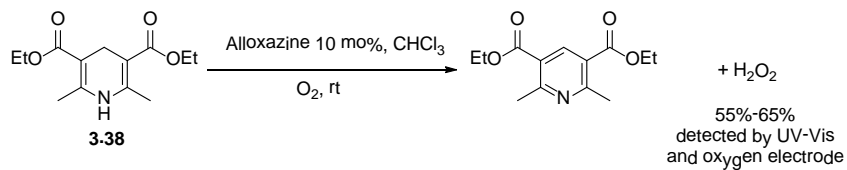
Figure 3.18 Aerobic H_2O_2 formation by alloxazine catalyzed dehydrogenation of benzothiazoline

Some flavoenzymes generate superoxide in the presence of oxygen.[98] While the direct role of superoxide species in the epoxidation is unlikely and not detected by KO_2 control reactions, the disproportionation of superoxide produces O_2 and H_2O_2.

In conclusion, we have developed a flavin/pyrrolidine dual catalytic approach to aerobic organocatalytic oxidation and shown its application in the asymmetric epoxidation of enals. This metal-free organocatalytic system uses oxygen as the terminal oxidant to achieve epoxidation of enals. This dual catalysis system, different from previous chiral flavin strategy, utilized easily synthesized flavin catalyst and a commercially available chiral cocatalyst to achieve oxidation of substrates with high yield, diastereoselectivity, and enantioselectivity.

Stoichiometric reductant benzothiazoline chemoselectively reduced flavin in the presence of enals/eniminiums. Benzothiazolines, together with Zn, hydrazine and dihydropyridines, provided another alternative category of reductant for aerobic flavin chemistry.

This method provides also opportunities to introduce isotopically labeled oxygen atoms to substrates with $^{18}O_2$ as the terminal oxidant in anhydrous systems. While sustainable and cost effective reducing agents and solvents would enhance the system, this dual catalysis synergistic effect may enable transformations that flavin or chiral catalyst alone cannot perform, such as Baeyer-Villiger oxidation of cyclopentanones and cyclohexanones.

Chapter 4

Flavin Catalyzed Heterocycle Aromatization

4.1 Heterocycle Aromatization Reactions

Heterocyclic compounds, such as dihydropyridine, benzothiazole, benzimidazole and benzoxazoles, are important building core in numerous natural products and biologically active reagents which are of great interests to synthetic community and pharmaceutical industry.

4.1.1 Dihydropyridine

The first synthesis of a dihydropyridine is attributed to Arthur Hantzsch for the work done more than a century ago.[99] The reaction produced 1,4-dihydropyridines (DHPs), or "Hantzsch esters", as isolable intermediates, he found that these could then be oxidized to pyridines. The synthesis had not drawn much attention until 1970s and 1980s, when it was known to be able to treat hypertension. Amlodipine 4.1, Felodipine 4.2, Isradipine 4.3 and Nifedipine 4.4 are among the best selling drugs.[100] (Figure 4.1)
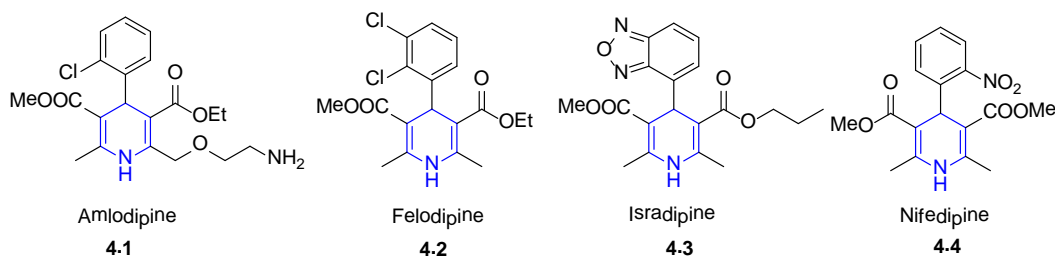
Figure 4.1 Dihydropyridine containing drugs for hypertension treatment

The way these drug effects is to bind to calcium channels and consequently to decrease the passage of the transmembrane calcium current, associated in smooth muscle with a long lasting relaxation and in cardiac muscle with a reduction of contractility throughout the heart.[101-102]

Metabolic studies of 1,4-DHP drugs in the human body have shown that these compounds are oxidized to pyridine derivatives by the action of cytochrome P450 in the liver.[103] The results indicate that the enzyme P-450 IIIA4 is probably the major human catalyst involved in the formal dehydrogenation of most but not all 1,4-dihydropyridine drugs. Although it is well know that these 1, 4-DHP drugs are closely related to NAD(P)H structurally and NAD(P)H can be oxidized by flavin cofactors, there is no direct evidence that the metabolism of these drugs is a function of flavin containing proteins in human body.

The pyridines as the oxidation product of ready available 1, 4- dihydropyridine showed anti-hypoxic and anti-ischemic activities. The main representative of oxidized 1,4-DHPs is cerivastatin 4.5, which has activity in the treatment of atherosclerosis and other coronary deseases.[104] (Figure 4.2) Therefore, oxidative aromatization of 1,4-DHPs has attracted continuing interests of organic and medicinal chemists.

4.5
cerivastatin
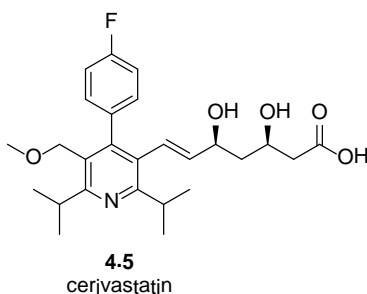
Figure 4.2 Cerivastatin for the treatment of atherosclerosis and other coronary diseases

Numerous methods have been developed to conduct the oxidative aromatization of dihydropydines to pyridines.

Ru(III)Cl 4.7 /molecular oxygen system was developed as a catalytic system for 1,4-DHP 4.6 oxidation.[105] The proposed mechanism involved single electron oxidation of DHP via Ru(III). The DHP went through radical intermediates 4.9 and 4.10 The resulting

Ru(II) 4.8 was reoxidized to Ru(III) by oxygen to turn over the catalytic cycle to afford

pyridines 4.11.(Figure 4.3)

$$Ru(II) + O_2 \xrightarrow{+H^+} Ru(III) + HO_2^{\cdot}$$

$$Ru(II) + HO_2^{\cdot} \xrightarrow{+H^+} Ru(III) + H_2O_2$$
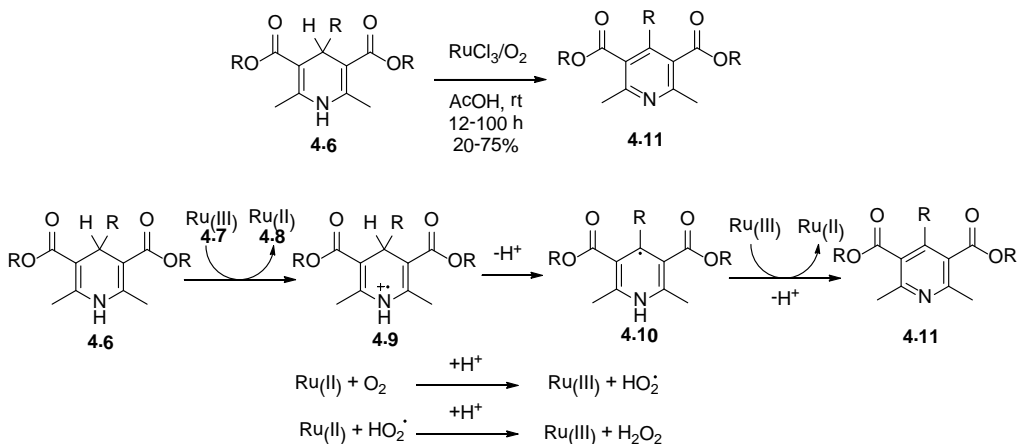
Figure 4.3 Aerobic DHP aromatization catalyzed by RuCl$_3$

A variety of Hantzsch 1,4-dihydropyridines were oxidized to the corresponding

pyridines in high yields in the presence of H6PMo9V3O40 4.12, a Keggin type

heteropolyacid, in refluxing acetic acid. In this system, terminal oxidant is believed to be

molecular oxygen. The heteropolyacid was found to be reusable.[106](Figure 4.4)
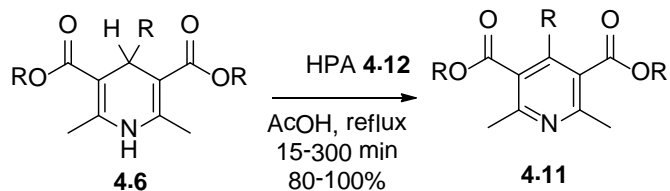
Figure 4.4 DHP oxidation in the presence of of H6PMo9V3O40

Hantzsch 1,4-dihydropyridines 4.6 and 1,3,5-trisubstituted pyrazolines 4.13 were

converted to the corresponding pyridines 4.11 and pyrazoles 4.14 efficiently by the

treatment of I2O5 in water.[107] The detailed mechanism is uncertain but believed to via

radical process with hypervalent iodine as terminal oxidant.(Figure 4.5)
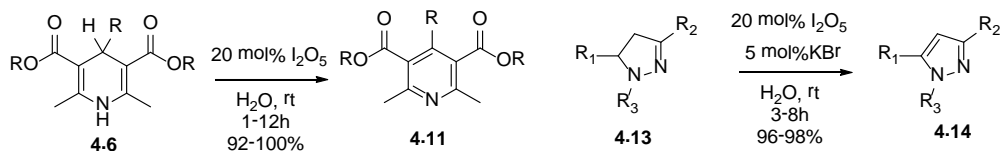
Figure 4.5 DHP oxidation with hypervalent iodine

1,3,5-Trisubstituted pyrazolines 4.13 and Hantzsch 1,4-dihydropyridines 4.6 were converted to the corresponding pyrazoles 4.14 and pyridines 4.11 effectively by the treatment of a catalytic amount of Pd/C in acetic acid at $80^\circ C$.[108] (Figure 4.6)
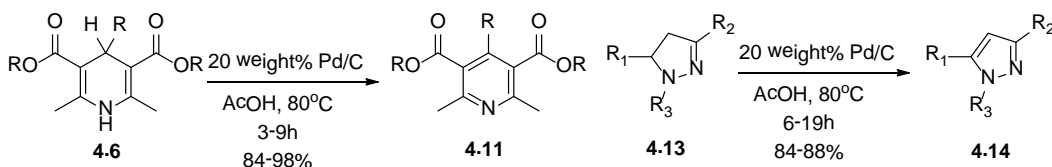
Figure 4.6 DHP oxidation catalyzed Pd/C in acetic acid

A variety of Hantzsch esters have been oxidized with potassium permanganate.[109] The author observed significant amount of dealkylation product 4.15 when the 4-substitutent of the DHP is benzyl or secondary alkyl group like CH_3CH_2. Single product 4.11 was isolated when C^4 substituent is aryl group. (Figure 4.7)

R=Aryl No **4.15** was formed
R=Benzyl or secondary alkyl group, a mixture of **4.11** and **4.15** is obtained
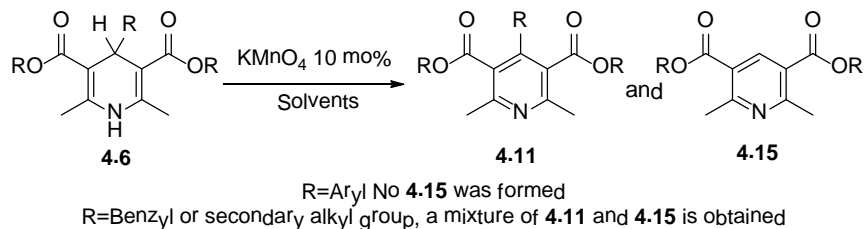
Figure 4.7 DHP oxidation catalyzed by $KMnO_4$

Photooxidation of Hantzsch 1,4-DHP by direct irradiation ($\lambda > 300$ nm) under an oxygen atmosphere.[110] Spectroscopic and electrochemical studies demonstrate that photoinduced singlet electron transfer from 1,4-DHP to molecular oxygen occurs. The

generated superoxide radical anion (O_2–·) is proposed to be responsible for photochemical oxidation. (Figure 4.8)
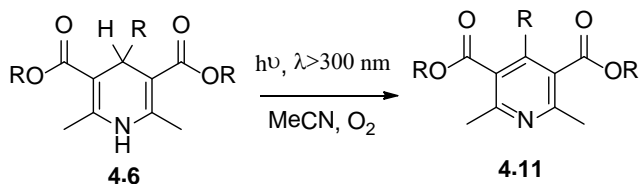
Figure 4.8 Aerobic 1, 4-DHP oxidation induced by irradiation

4.1.2 Benzothiazoline

Benzothiazoles occur naturally,[111] but numerous synthetic species display broad biological activities and are found in functional materials. Benzothiazole can be seen as the formal dehydrogenation product of benzothiazoline. The gained aromaticity of benzothiazole is the driving force for dehydrogenation to occur. Because of this, benzothiazolines have been utilized as organic reductants in many literature examples.[112]

Akiyama and coworkers have described the first example of the use of benzothiazoline 4.17 as the hydrogen source in the asymmetric transfer hydrogenation of ketimines 4.16 with catalytic amount of chiral phosphoric acid 4.20.[113] Chiral amines 4.19 were obtained in high enantioselectivity. Benzothiazole 4.18 was obtained as a byproduct. This is a simple and complementary approach that gives higher enantioselectivity in the imine reduction. (Figure 4.9)
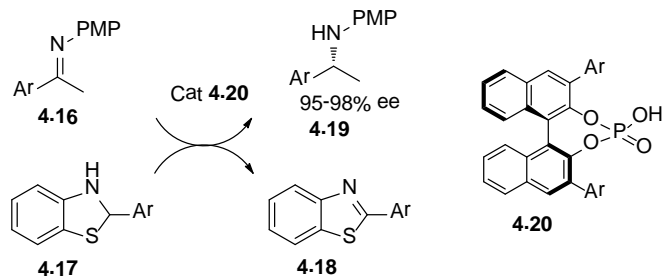
Figure 4.9 Chiral phosphoric acid catalyzed asymmetric ketimine reduction with

benzothiazoline

The same group used of 2-deuterated benzothiazoline 4.17a as a deuterium

donor in combination with a chiral phosphoric acid 4.20a, the transfer deuteration of

ketimine and R-iminoester took place smoothly to give R-deuterated amines in high

yields with excellent enantioselectivities.[114] (Figure 4.10)
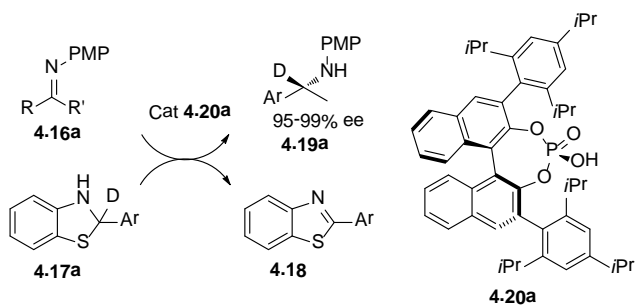
Figure 4.10 Chiral phosphoric acid catalyzed asymmetric ketimine reduction with 2-

deuterated benzothiazoline

Benzothiazole derivatives are an important class of heterocyclic compounds that

attracted strong interest due to their biological and pharmacological properties. The

benzothiazole containing compounds involved in research aimed at evaluating new drugs

that possess biological activities, such as antimicrobial, anticancer, antifungal,

anthelmintic, anti-diabetic.[115] (Figure 4.11)
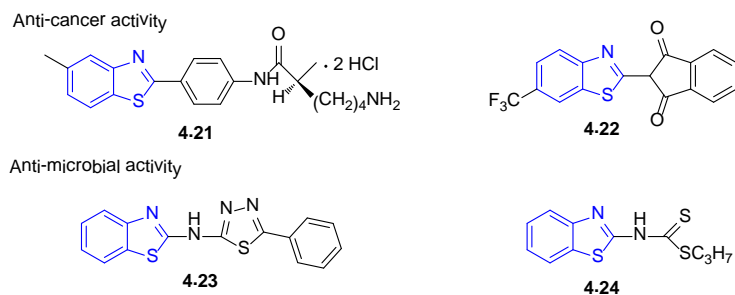
Figure 4.11 Biologically active compounds contains benzothiazole

There many ways to synthesize benzothiazoles in the literature.

Lang and coworkers developed a multi components on pot palladium-catalyzed synthesis of benzothiazoles 4.28 directly from an aryl halide 4.25, tert-butyl isocyanide 4.26 and an aminothiophenol 4.27.[116] (Figure 4.12) Experimental observations suggest that the desired process proceeds by an initial formation of imine 4.29, which cyclizes to form 4.30. 4.30 undergoes copper catalyzed C−H activation gives rise to intermediate 4.31. Oxidative addition of the iodobenzene to the palladium catalyst facilitated formation of palladium(II) species 4.32, which can undergo a transmetalation process to give compound 4.33 and regenerate the copper cocatalyst. Subsequent reductive elimination allows for formation of 2-phenyl benzothiazole 4.28.
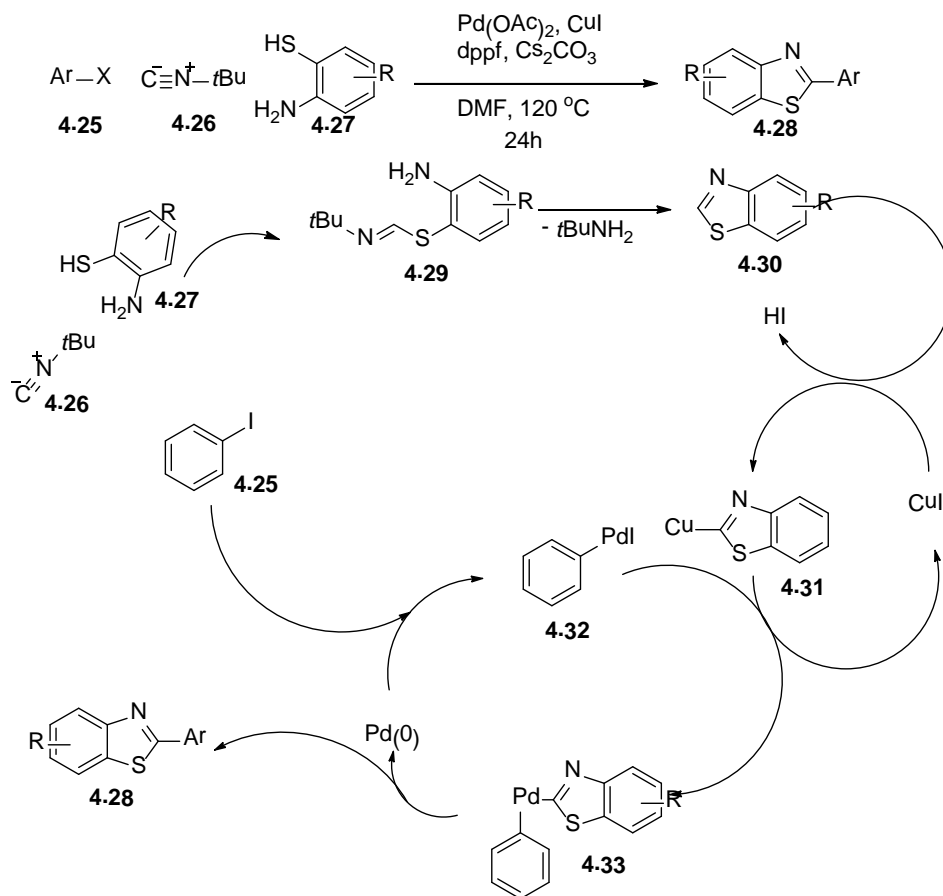
Figure 4.12 catalyzed one pot synthesis of benzothiazole from simple starting materials

A recent metal-free process for the synthesis of 2-aminobenzothiazoles 4.36 from cyclohexanones 4.34 and thioureas 4.35 has been developed using catalytic iodine and molecular oxygen as the oxidant under mild conditions.[117] (Figure 4.13)
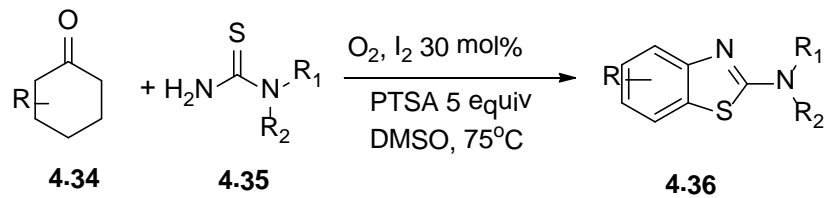
Figure 4.13 Aerobic benzothiazole synthesis catalyzed by I_2

Recently, a method was developed for the formation of 2-substituted benzothiazoles via a copper-catalyzed condensation of 2-aminobenzenethiols with nitriles.[118] (Figure 4.14) Ethanol as the environmentally friendly solvent, the inexpensive catalytic system, mild conditions combined with an operationally simple procedure render this method a valuable addition to the traditional benzothiazole synthesis.
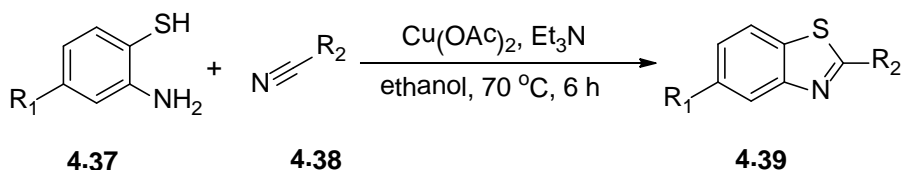
Figure 4.14 Copper catalyzed benzothiazole synthesis in ethanol

2-Aryl benzothiazole formation from aryl ketones 4.40 and 2-aminobenzenethiols 4.27 under metal- and I2-free conditions was described.[119] Various 2-aryl benzothiazoles were selectively obtained in good yields using molecular oxygen as oxidant. DMSO played an important role in this transformation. High temperature was required to obtain good yield. (Figure 4.15)
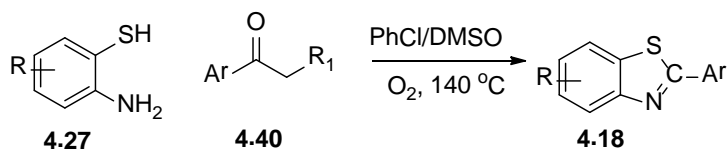
Figure 4.15 Aerobic benzothiazole synthesis in DMSO at high temperature

4.2 Flavin Catalyzed Dihydropyridine and Benzothiazoline Aromatization Reaction

In this work, a flavin catalyzed biomimetic oxidation of dihydropyridines and benzothiazolines using molecular oxygen is conducted. Biomimetic route is highlighted with red color. (Figure 4.16)
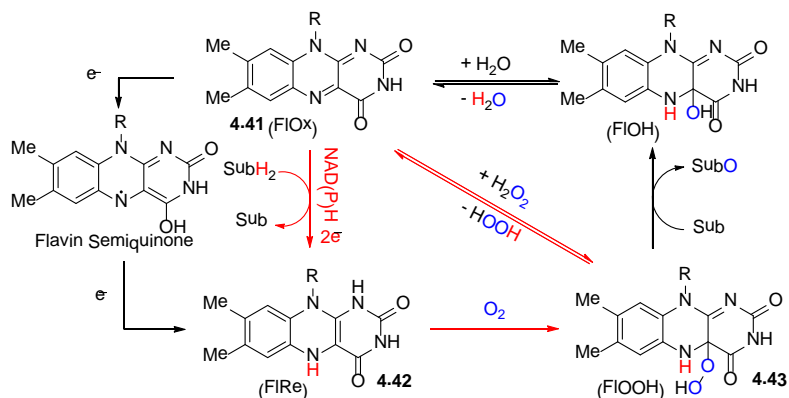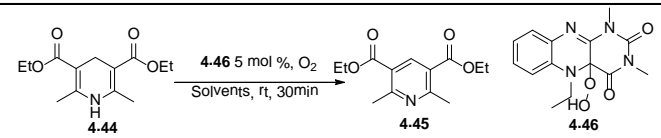
Figure 4.16 Biomimetic flavin catalyzed oxidative dehydrogenation

In organic solvents, hydroperoxyflavin 4.43 is in equilibrium with oxidized flavin 4.41 and hydrogen peroxide. (Figure 4.16) The equilibrium constant is solvent dependent in this case. To facilitate the oxidation of dihydropyridine or benzothiazoline, a solvent in which the hydroperoxyflavin 4.43 is instable will be optimal.

So we started the initial screening of common organic solvents on the aerobic oxidation of Hantzsch ester 4.44 with 5 mol % alloxazine catalyst 4.46 which has been proven to be the most active flavin catalyst in aerobic oxidation condition. (Table 4.1) Among the polar protic solvents, methanol gave the best result after 30 minutes' stirring filled with excess oxygen gas, while water showed low efficiency on pyridine formation. In fact, Burice and coworkers found that in protic solvent like water or methanol, the 4a-OOH group of 4a-hydroperoxy-3-methyllumiflavine can be easily replaced by OH- or MeO- group, and a molecule of H_2O_2 is released into solution.[120] The unexpected low yielding in water is probably because of the low solubility of DHP 4.44 in water. Polar chlorinated solvents like dichloromethane and chloroform gave good yield of pyridine, but the non-polar carbon tetrachloride had low yield. Non-polar aprotic solvents like 1,4-dioxane and toluene provided low yield of pyridine, which was in accordance with Bruice's results that in dioxane hydroperoxy-3-methyllumiflavine can be preserved for

days. Most of polar aprotic solvents gave low yields of pyridine with the exception of acetonitrile. Interestingly, in our Dakin oxidation solvent system where we used 95:5 MeCN/H_2O and one equivalent of NaHCO$_3$, the pyridine formation has not been observed after 24 hours.

Table 4.1 Initial solvent screening of alloxazine catalyzed aerobic aromatization

Entry	Solvent	Conversion(%)[a]
1	water	9
2	methanol	44
3	ethanol	19
4	*tert*-butanol	2
5	dichlormethane	58
6	chloroform	53
7	carbon tetrachloride	6
8	tetrahydrofuran	6
9	acetonitrile	33
10	ethyl acetate	1
11	acetone	2
12	dimethylformamide	1
13	1,4-dioxane	8
14	toluene	9

[a]Conversions were detected by NMR using DMSO as internal standard

A more careful solvent study was carried out among the five solvents of the best conversions. (Table 4.2) In these tests, 0.5 equivalent of oxygen was added into degassed reaction mixture and the conversion of 4.44 to 4.45 was measured by NMR. Without out addition of catalyst 4.46, no pyridine was detected. With 5 mol % of flavin catalyst 4.46, 50% conversion was detected in chloroform reaction after 30 minutes. The catalyst loading was therefore lowered to 1 mol%, so that reactions had slower rates to be compared within 30 minutes. Within the five selected solvents, although DCM and

chloroform dissolved the HEH better than others, methanol gave the best yield (26.5%)

after 30 minutes with 1 mol% alloxazine catalyst. Base on the concept of green

chemistry, methanol was selected as the solvent for the substrate study.

Table 4.2 Careful solvent study of alloxazine catalyzed aerobic aromatization

Entry	Solvent	Catalyst loading(mol%)	Conversion[a] (%)
1	Chloroform	0	0
2	Chloroform	5	50
3	Chloroform	1	22
4	Dichloromethane	1	16
5	Methanol	1	26
6	Ethanol	1	8
7	Acetonitrile	1	9

[a] Conversion was determined using NMR

With the optimized condition, we started looking into the oxidation of 1, 4-

dihydropyridines catalyzed by alloxazine catalyst 4.46 with oxygen gas as terminal

oxidant. (Figure 4.17) We were pleased to see that when the dihydropyridines C^4 position

only has hydrogen as substituent, the aromatization proceeded smoothly and cleanly at

room temperature within 90 minutes. Quantitative yield was obtained by simply

evaporating off solvent, and the purity of product was greater than 95%.
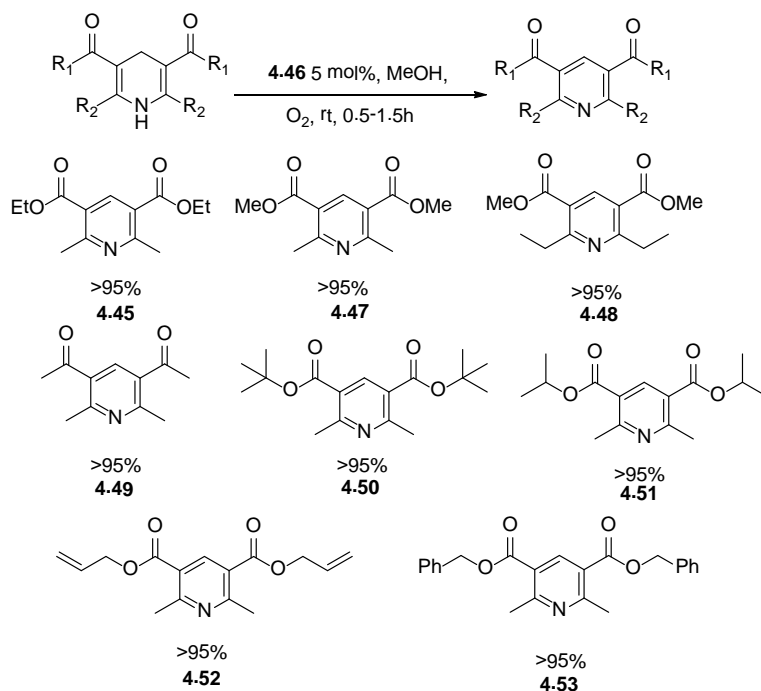
Figure 4.17 Alloxazine catalyzed dihydropyridine aromatization

Encouraged by the positive result, we tried to extend the same protocol to the tandem synthesis of pyridine starting with formaldehyde 4.54 (37 % wt in H_2O), ammonium acetate 4.56 and the corresponding acetonacetates 4.55 using air as the oxygen source. (Figure 4.18) To our delight, 1 mmol scale synthesis of pyridines can be achieved in good to excellent yield with only 2 mol % of flavin catalyst in 2 mL of methanol within 22 hours. The only exception was 4.53 since the intermediate dihydropyridine has bad solubility in methanol.
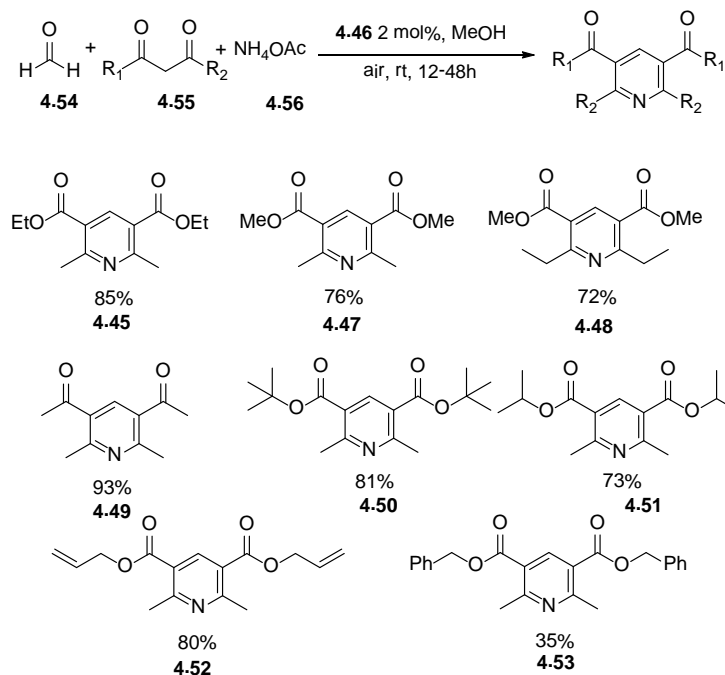
Figure 4.18 Alloxazine catalyzed multi component dihydropyridine synthesis and

aromatization process

C^4-substituted dihydropyridines (Figure 4.19) were not oxidized with alloxazine

catalyst 4.46 after long reaction time and at elevated temperatures. Ménová and Cibulka

recently described isoalloxazine catalysts 4.57 are ~10^6 times more electrophilic than

similar alloxazine species.[24] This information, combined with the redox potentials for 4.57

(E^0 = 0.388 V, −0.389 V) and 1a (E^0 = 0.109 V, −0.695 V),[121] suggest that catalyst 4.57

would accept a hydride from unreactive C^4-substituted dihydropyridines more readily than

4.46. Indeed, with 5 mol % of isoalloxazine catalyst 4.57, 4.58 formation occurred at

50°C. However, the yield was low compared to the alloxazine catalyzed oxidation (48

hours, 20%). It was also pointed out by Cibulka that by adding an acid to isoalloxazine

reactions, the elimination of H_2O from flavin pseudobase would be accelerated.[24] In our

system (Figure 4.19), when pyridine 4.58 is formed, it deprotonates hydropreoxyflavin

4.57b to form flavin hydroperoxy anion, which will not eliminate H_2O_2 to regenerate the isoalloxazinium ion 4.57. So, we imagined that the elimination of H_2O_2 from hydroperoxyflavin 4.57c to regenerate isoalloxazinium ion 4.57 would also be accelerated by an acid via similar mechanism.
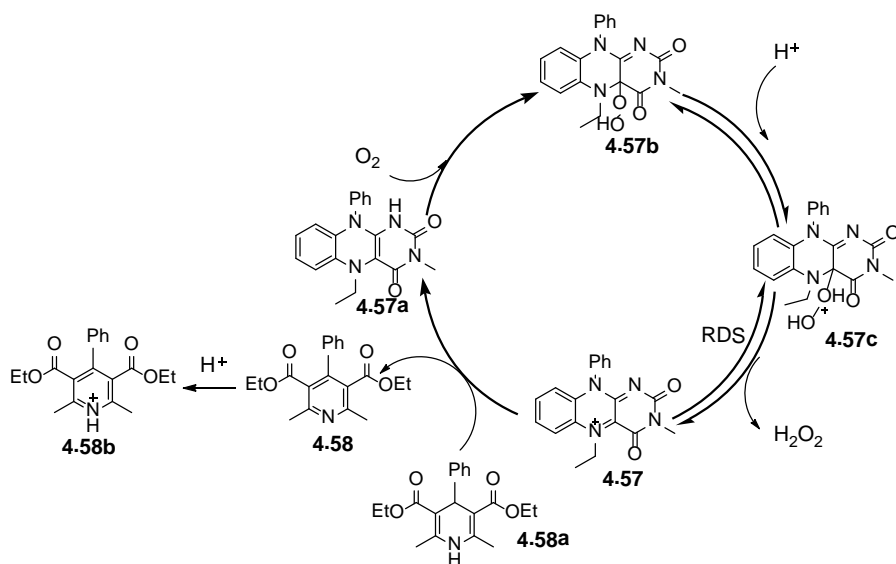
Figure 4.19 Acid mediated isoalloxazinium catalyzed aromatization mechanism

As expected, after adding 1.2 equivalent of $HClO_4$, the 4.58 formation was greatly enhanced and much shorter reaction time was required. After the consumption of the starting material, aqueous sodium carbonate was added into reaction mixture to free the protonated pyridine 4.58b. An acid screening was performed and the oxidation rate was increased with acids that have low pKa. The unexpected result of sulfuric acid is due to the strong oxidative effect of concentrated sulfuric acid itself mediated background aromatization. (Table 4.3)

Table 4.3 Acid screening with isoalloxazine 4.57 as catalyst

4.58a → 4.58

Entry	Acid	Conversion(%)	pK$_a$ of the acid
1	HClO$_4$	>95	-10.0
2	HCl	31	-8.0
3	H$_2$SO$_4$	78	-3.0
4	TFA	11.5	-0.25
5	H$_3$PO$_4$	11.5	2.12
6	HCOOH	9	3.77
7	AcOH	8	4.76

Using acidic system, we successfully oxidized a range of C^4 substituted

dihydropyridines with good to excellent yields. (Figure 4.20)
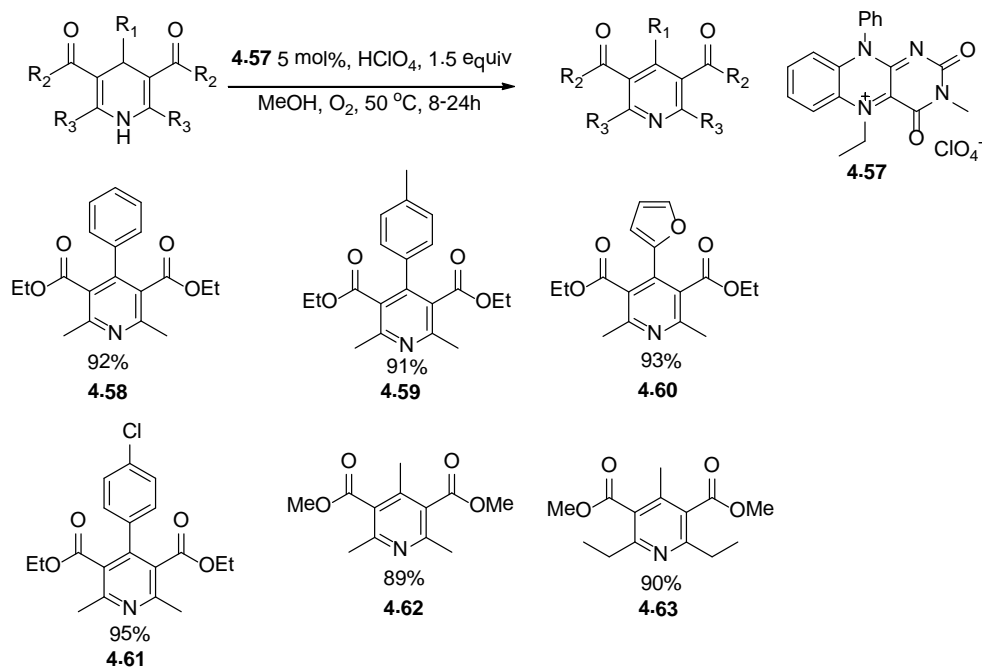
Figure 4.20 Isoalloxazine catalyzed C^4-substituted dihydropyridine aromatization

88

The initial alloxazine 4.46 catalyst system was applied to benzothiazolines. Electron rich benzothiazolines were reported to undergo autoxidation in chloroform without additional catalyst.[122] We found that acid contaminants from solvent or aldehyde oxidation enhanced the rate of benzothiazoline oxidation for electron rich substrates but also led to benzothiazoline fragmentation to amino-thiophenol and aryl aldehydes. Purification of chloroform eliminated benzothiazoline oxidation for nearly all substrates investigated in this work. In our acid free and metal-free catalytic system, control experiments without flavin catalysts were explored for all benzothiazolines that we tried. After 1.5 h, most compounds showed no detectable (<5%) benzothiazole formation, except for electron rich entries 4.69 and 4.72, which generated 20% and 25% benzothiazole conversion as background oxidation product. The alloxazine catalyzed oxidation of benzothiazolines yielded products within 1.5 h in methanol (Figure 4.21). Solvent evaporation gave products with purity greater than 95%.
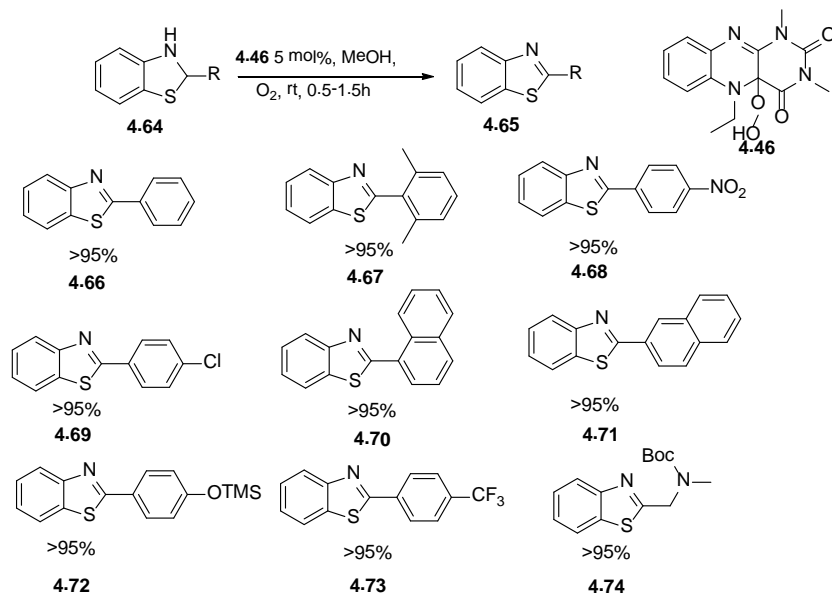
Figure 4.21 Alloxazine catalyzed benzothiazoline aromatization

On the basis of the high yields obtained by this method, a one-pot preparation of 2-substituted benzothiazoles from 2- amino-thiophenol and a range of aldehydes was sought.(Figure 4.22) A simple two-stage, one-pot operation yielded the best results. Following preparations of benzothiazolines from aminothiophenols and aldehydes in MeOH, within 6 h, flavin catalyst was added directly to the reaction without purification of the intermediate or solvent exchange.
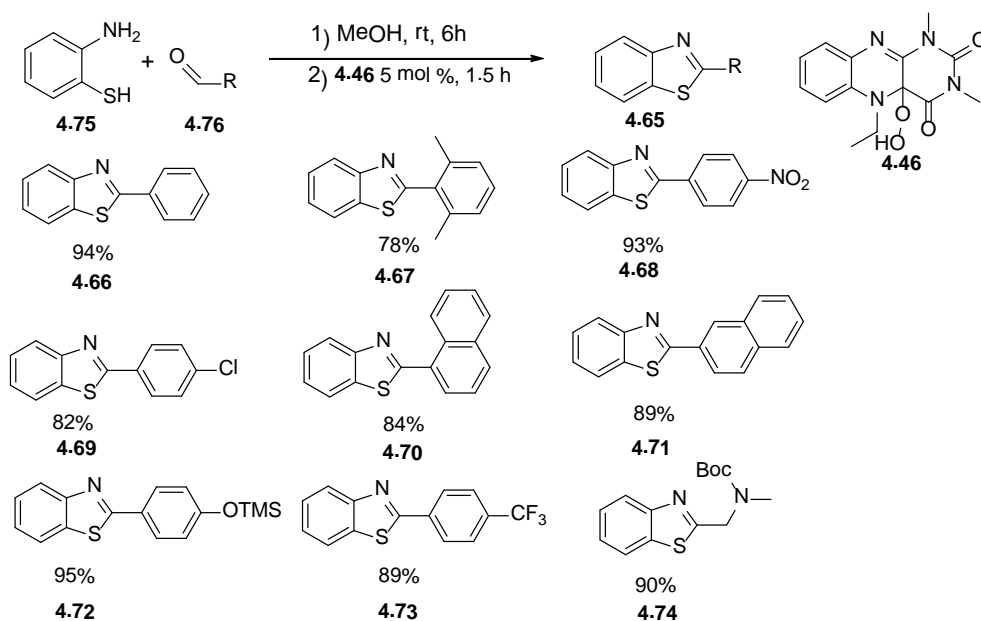
Figure 4.22 Alloxazine catalyzed two-component one pot two steps benzothiazoline aromatization

In conclusion, green and bioinspired oxidative aromatizations were developed by robust flavin organocatalysts. Flavin mimics catalyze the oxidation of dihydropyridines and benzothiazolines using oxygen as a terminal oxidant in methanol. The simple and high-yielding one-pot multicomponent synthesis of pyridines was described using 2 mol% of catalyst. Related two-stage one pot synthesis of benzothiazoles were achieved. This catalytic process is consistent with observations in the literature of flavoenzyme and

flavin mimic reactivity involving the dissociation of 4a-hydroperoxyflavins in polar protic environments, as mentioned above. Though not previously indicated in the metabolism of dihydropyridine-derived drugs, it seems chemically possible that flavoenzymes may perform the direct oxidation of various dihydropyridines drugs. Small molecule flavin mimics continue to unlock new areas of opportunity in synthesis, especially in the realm of aerobic organocatalysis. These advances are emblematic of the dynamic nature of flavin mimic catalysts and their ability to perform selective oxidations based on bioinspired method development, providing an attractive platform for efficient and sustainable oxidation research.

Appendix A

List of Abbreviations

MeCN Acetonitrile
DMF *N,N*-dimethylformamide
DMSO Dimethylsulphoxide
MeOH Methanol
EtOH Ethanol
DCM Dichloromethane
$CHCl_3$ Chloroform
TFE 2,2,2-Trifluoroethanol
Cat. Catalyst
NEt_3 Triethylamine
PTSA Para toluene sulfonic acid
KOH Potassium hydroxide
NaOH Sodium hydroxide
Na_2CO_3 Sodium carbonate
$NaHCO_3$ Sodium bicarbonate
$AlCl_3$ Aluminum chloride
$BF_3{\cdot}OEt_2$ Boron trifluoride diethyl etherate
LiCl Lithium chloride
$CaCl_2$ Calcium choride
$HClO_4$ perchloric acid
$B(OH)_3$ Boric acid
AcOH acetic acid
MeI iodomethane
$InCl_3$ Indium(III) chloride
HPLC high-performance liquid chromatography
HR-MS High-resolution mass spectrometry
GC Gas chromatography
MS Mass spectroscopy
NMR Nuclear atomic resonance
TLC Thin layer chromatography
rt Room temperature, ambient temperature
equiv Equivalent

Appendix B

General Experimental Procedure

2.10a-e general procedure:

In a 50 mL round bottom flask, *o*-phenylenediamine (3.0 mmol), alloxane monohydrate (426 mg, 3.0 mmol), boric acid (185 mg, 3.0 mmol) and 20 mL acetic acid were added. The mixture was stirred under argon at room temperature for 2 hours. During this time, solid precipitated out in the solution. The solid was collected by filtration then washed with 30 mL of acetic acid and 30 mL of diethyl ether. Product was dried further with high vacuum pump.

7,8-dichloroalloxazine (2.10a)

Yield:94% ; Yellow solid, Mp: 387-388 ℃; ^{1}H NMR (500 MHz, DMSO-d) δ 12.00 (br. s., 1 H), 11.77 (br. s., 1 H), 8.41 - 8.16 (m, 1 H), 7.95 (dd, J = 8.3, 11.2 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 160.50, 150.38, 147.53, 141.03, 140.93, 136.60, 136.51, 132.31, 116.41, 116.28, 113.44, 113.31; IR(Neat) 3055, 2894, 1738, 1706, 1575, 1563, 1456, 1448, 1341, 1188, 1139, 1120, 839, 625, 581, 498, 448, 411 cm^{-1}.

7,8-difluoroalloxazine (2.10b)

Yield: 99% ; Light blue solid, Mp: 310 - 312 ℃; ^{1}H NMR (300 MHz, DMSO-d) δ 12.08 (s, 1 H), 11.82 (s, 1 H), 8.47 (d, J = 3.4 Hz, 1 H), 8.17 (d, J = 3.8 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d) δ 160.5, 150.5, 148.2, 142.1, 138.5, 136.5, 133.7, 131.3, 131.2, 128.3; ^{19}F NMR (470 MHz, CDCl$_3$) δ -133.70 --133.35 (m, 1 F), -126.57 - -126.20 (m, 1 F) IR(Neat) 3190, 3054, 2938, 2896, 1732, 1674, 1634, 1577, 1288, 1263, 1229, 1205, 1147, 875, 588, 495, 444 cm^{-1}.

Alloxazine (2.10c)

Yield: 87%; Yellow solid, Mp: >400℃; ^{1}H NMR (500MHz, DMSO-d) δ 8.13 (d, J = 8.0 Hz, 1 H), 7.92 - 7.86 (m, 2 H), 7.79 - 7.71 (m, 1 H); ^{13}C NMR (75MHz, DMSO-d) δ 161.00, 150.67, 147.40, 143.15, 139.71, 133.87, 132.22, 130.66, 128.94, 127.50; IR(Neat) 3174, 3105, 3084, 1733, 1688, 1572, 1446, 1272, 1035, 1014, 989, 768, 705, 584, 539, 511, 427, 379 cm^{-1}.

7,8-Dimethylalloxazine (2.10d)

Yield: 95% ; Bright yellow solid, Mp: 368 - 370℃; ^{1}H NMR (500MHz, DMSO-d) δ 11.70 (br. s., 2 H), 7.86 (br. s., 1 H), 7.65 (br. s., 1 H), 2.45 (s., 3H), 2.42 (s., 3H) NMR (125 MHz, DMSO-d) (cannot obtain due to low solubility); IR(Neat) 3084, 3054, 1723, 1683, 1557, 1483, 1455, 1355, 1213, 1004, 803, 574, 525, 475, 449, 414 cm^{-1}.

7,8-dimethoxyalloxazine (2.10e)

Yield:89% ; Bright yellow solid, Mp: 364 - 366℃; ^{1}H NMR (500 MHz, DMSO-d) δ 11.74 (br. s., 1 H), 11.57 (br. s., 1 H), 7.46 (s, 1 H), 7.19 (s, 1 H), 3.98 (br. s., 3 H), 3.93 (br. s., 3 H);); ^{13}C NMR (125 MHz, CDCl$_3$) δ 161.36, 156.30, 152.24, 150.66, 146.35, 141.49, 137.15, 127.80, 107.78, 105.12, 56.96, 56.69; IR(Neat) 3073, 2935, 2846, 1690, 1555, 1502, 1434, 1372, 1344, 1291, 1236, 998, 870, 539, 501, 427 cm^{-1}. HRMS: C12H11N4O4 (Calculated = 275.0780 m/z) Found = 275.0776 m/z

2.11a-e general procedure:

Alloxanzine (3.0 mmol) and K$_2$CO$_3$ (1.38 G, 10 mmol) were added to 20 mL of dry DMF under argon. MeI (0.6 mL, 10 mmol) was then added to the above solution. The mixture was stirred at room temperature for 4 hours. DMF was removed at 80 ºC under vacuum. The resulting solid was dissolved in 20 mL of dichloromethane and 20 mL of H$_2$O then transferred into a separation funnel. The aqueous layer was washed with dichloromethane (4 x 20 mL). The combined organic phase was washed with 40 mL of brine, then dried with MgSO$_4$. Solvent was removed under reduced pressure. The crude material was purified by column chromatograph (2:98 CH$_3$OH/CH$_2$Cl$_2$).

7,8-dichloro-1,3-dimethylalloxazine (2.11a)

Yield:77% ; Light yellow solid, Mp: 248 - 250℃; ^{1}H NMR (500 MHz, CDCl3) δ 8.37 (s, 1 H), 8.12 (s, 1 H), 3.77 (s, 3 H), 3.57 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.2, 150.4, 146.2, 142.0, 139.1, 138.5, 134.0, 130.9, 130.5, 128.4, 29.8, 29.4; IR(Neat) 3078, 3038, 2948, 1720, 1674, 1597, 1552, 1490, 1355, 1294, 1211, 1189, 1110, 1065, 1017, 1002, 745, 673, 469, 445, 418, 396 cm^{-1}7,8-difluoro-1,3-dimethylalloxazine (2.11b)

Yield: 87% ; Orange solid, Mp: 196-197℃; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.09 (dd, J = 8.4, 9.8 Hz, 1 H), 7.78 (dd, J = 7.9, 10.3 Hz, 1 H), 3.81 (s, 3 H), 3.60 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 159.50, 156.49, 156.37, 154.40, 154.27, 153.14, 153.01, 151.08, 150.96, 150.56, 145.73, 141.51, 141.41, 137.19, 137.09, 129.81, 129.78, 116.27, 116.13, 113.65, 113.51, 29.78, 29.38; ^{19}F NMR (470 MHz, CDCl$_3$) δ -129.42- -129.01 (m, 1 F), -122.46- -121.71 (m, 1 F) IR(Neat) 3044, 2967, 1720, 1676, 1559, 1482, 1375, 1359, 1297, 1220, 1197, 1173, 1101, 911, 857, 744, 457, 441, 418, 398 cm^{-1}.

1,3-dimethylalloxazine (2.11c)

Yield: 97% ; Bright yellow solid, Mp: 234 - 235℃; ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.39 - 8.29 (m, 1 H), 8.08 - 8.00 (m, 1 H), 7.90 (dt, J = 1.5, 7.7 Hz, 1 H), 7.80 - 7.72 (m, 1 H), 3.83 (s,3 H), 3.61 (s, 3 H); ^{13}C NMR (75MHz, CDCl$_3$) δ 159.88, 150.80, 145.45, 143.44, 140.10, 133.93, 130.90, 129.75, 129.21, 127.92, 29.67, 29.27; IR(Neat) 1717, 1652, 1552, 1455, 1417, 1377, 1201, 1103, 1063, 810, 772, 443, 424, 405 cm^{-1}.

7,8-DiMethyl-1,3-dimethylalloxazine (2.11d)

Yield: 90% ; Bright yellow solid, Mp: 246 - 248℃; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04 (br. s., 1 H), 7.76 (br. s., 1 H), 3.78 (s, 3 H), 3.57 (s, 3 H), 2.51 (s, 3 H), 2.48 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 160.20, 150.90, 145.74, 145.11, 142.46, 140.09, 139.25, 129.54, 128.63, 126.88, 29.55, 29.19, 20.96, 20.39; IR(Neat) 3058, 3046, 2946, 2921, 2846, 1720, 1667, 1557, 1482, 1471, 1361, 1257, 1217, 873, 747, 558, 488, 467, 439, 419 cm^{-1}.

7,8-DiMethoxy-1,3-dimethylalloxazine (2.11e)

Yield:85% ; Bright yellow solid, Mp: 218 - 219℃; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.57 (s, 1 H), 7.26 (s, 1 H), 4.10 (s, 3 H), 4.04 (s, 3 H), 3.79 (s, 3 H), 3.58 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 156.68, 152.68, 150.97, 144.79, 141.87, 137.51, 126.49, 115.45, 107.57, 105.05, 56.82, 56.61, 29.47, 29.14; IR(Neat) 3079, 3006, 2942, 1714, 1663, 1549, 1248, 1230, 1202, 1060, 848, 746, 487, 457, 408 cm^{-1}. HRMS: C14H15N4O4 (Calculated = 303.1093 *m/z*) Found = 303.1088 *m/z.*

2.12a-e general procedure:

2.12c and 2.12d

2 mmol of 1,3-Dimethylalloxazine (2.11c or 2.11d) and 150 mg 10% Pd/C was added in a round bottom flask, the flask was then charged with Argon. 20 ml of degassed solvent (1:1 Ethanol/H_2O) was added under argon. The mixture was degassed 2 times using Freeze-Pump-Thaw technique with acetone and dry ice. 2 ml (36 mmol) of distilled acetaldehyde and 1.66 ml (20 mmol) of concentrated HCl was added via syringe into reaction mixture. The mixture was frozen again under vacuum. H_2 balloon was prepared to refill the reaction flask vacuum with H_2, and then reaction was warmed up to room temperature. Reaction was stirred for 2 days under H_2 atmosphere. The Pd/C was filtered off with Celite and the Celite was washed extensively with ethanol until the color of the wash became clear. During the wash, the filtrate color turned from light yellow to dark brown because of the auto oxidation of flavin by air. NH_3 was added drop-wise with stirring until the pH of the solution was adjusted to 7-8. A dark precipitate started to form while the solution was neutralized. Ethanol was removed under pressure at 30 ℃, leaving most of the water in the round bottom flask. The flask was then cooled in an ice-bath for 10 minutes, precipitating most of the product. The brown colored product was collected by filtration, and then washed with an additional 10 mL of cold water and 5 mL of cold ethanol. The product was dried under vacuum and was stable to be stored at room temperature. The NMR experiment was performed by placing 5 mG of product in an Argon-filled NMR tube with 30 mG sodium dithionite then dissolved by 0.25 mL of degassed $CDCl_3$ and 0.25 mL of degassed D_2O. The NMR tube was shaken until the color of solution turned from dark red-brown to light yellow.

2.12b

For 7,8-difluoro-1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine 2.12b, 80 psi hydrogen was applied to the reaction mixture for 2 days, instead of 1 atm pressure of hydrogen.

2.12e

For 7,8-Dimethoxy-1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine 2.12e, workup is different from the other 4 catalysts. The reaction mixture was filtered through Celite. The PH of the filtrate was adjusted to 7-8 using ammonia hydroxide solution. All of the solvent was evaporated under reduced pressure. The resulting dark brown solid was re-dissolved with DCM, insoluble salt was filtered off. The DCM of the filtrate was reduced under reduced pressure to get product as dark brown powder.

2.12a

For 7,8-Dichloro-1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine 2.12a, standard reaction solvent condition result in de-chlronation of the aromatic ring. So Dichloromethane is used as solvent instead of ethanol and water mixture. In a typical reaction, 160mg (0.5 mmol) of 7,8-Dichloro-1,3-Dimethylalloxazine and 50 mg 10% Pd/C was added in a round bottom flask, 20 ml of DCM was added to dissolve to starting material. The reaction mixture was degassed under reduced pressure while cooling with acetone and dry ice. 0.5 ml (36 mmol) of distilled acetaldehyde and 0.6 ml (5 mmol) of concentrated HCl was added via syringe into reaction mixture. H_2 balloon was prepared to refill the reaction flask vacuum with H_2, and then reaction was warmed up and stirred at room temperature. After 12 hours, the reaction is stopped. 30 ml of ethanol was added into the reaction flask to dissolve the black solid on the wall of the glass. The Pd/C was filtered off with Celite and the Celite was washed using a lot of ethanol (until the color of wash become clear). NH_3 was added drop-wise with stirring until the pH of the solution was adjusted to 7-8. Removed most of ethanol under pressure at 30 ℃, left most of water in the round bottom flask. Cool the flask in ice-bath for 10min, most of product should precipitate out. Collected the brown colored product by filtration, and then washed with additional 10 ml of cold water.

7,8-Dichloro-1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine (2.12a)

Yield:80% ; brown solid (corresponding peroxide), Mp:134-140℃ decompose; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.86 (s, 1 H), 6.61 (s, 1 H), 3.48 (q, J = 7.3 Hz, 2 H), 3.44 (s, 3 H), 3.33 (s, 3 H),

1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ157.66, 150.21, 145.06, 136.84, 134.38, 127.97, 125.86, 124.91, 122.87, 115.60, 50.22, 28.70, 28.46, 11.88 IR(Neat) 3319, 3063, 3040, 2974, 2943, 2881, 1722, 1683, 1626, 1158, 1446, 1423, 1404, 1164, 1150, 1129, 1099, 1035, 870, 746, 615, 546, 412, 396 cm^{-1}. HRMS: C14H13 N4O2Cl2 (Calculated = 339.0416 *m/z*) Found = 339.0411 *m/z*

7,8-difluoro-1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine (2.12b)

Yield:75% ; Black solid (corresponding peroxide), Mp:183 – 184℃ decompose; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.70 (dd, J = 7.7, 11.2 Hz, 1 H), 6.42 (dd, J = 7.4, 10.3 Hz, 1 H), 3.44 (s, 3 H), 3.41 (q, J = 6.9 Hz, 2H), 3.33 (s, 3 H), 1.15 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ (not obtained due to high air sensitivity) ^{19}F NMR (283MHz, CDCl$_3$) δ -141.93,-143.34; IR(Neat) 3055, 3013, 2990, 2946, 1683, 1624, 1473, 1458, 1344, 1264, 1234, 1180, 1135, 1102, 1084, 880, 747, 681, 628, 526, 456, 435, 404 cm^{-1}. HRMS: C14H13 N4O2F2 (Calculated = 307.1007 *m/z*) Found = 307.1009 *m/z.*

1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine (2.12c)

Yield 85%: ; Brown solid(corresponding peroxide), Mp: 155-160℃ decompose; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.93 - 6.81 (m, 2 H), 6.81 - 6.74 (m, 1 H), 6.59 (d, J = 7.4 Hz, 1 H), 3.46 (s, 3 H), 3.44 (q, J =6.9 Hz, 2 H) 3.33 (s, 3 H), 1.13 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.14, 150.47, 146.43, 136.33, 135.06, 125.17, 123.59, 122.62, 114.79, 99.71, 50.77, 28.79, 28.42, 11.53; IR(Neat) 3055, 2982, 2946, 2879, 1718, 1674, 1558, 1485, 1472, 1100, 1085, 1056, 1045, 744, 736, 491, 419 cm^{-1}. HRMS: C14H15N4O2 (Calculated = 271.1195 *m/z*) Found = 271.1190 *m/z.*

7,8-Dimethyl-1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine (2.12d)

Yield: 74% ; Brown solid(corresponding peroxide), Mp: 155- 160℃ decompose; ^{1}H NMR (500 MHz, CDCl3) δ 6.69 (s, 1 H), 6.33 (s, 1 H), 3.44 (s, 3 H), 3.43 (q, 2 H), 3.33 (s, 3 H), 2.11 (s, 6 H), 1.10 (t, J =6.9 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.20, 150.52, 146.41, 133.40, 133.16, 132.43, 131.79, 124.03, 116.00, 99.69, 50.83, 28.69, 28.38, 19.33, 19.18, 11.30;

IR(Neat) 2989, 2944, 1677, 1609, 1464, 1386, 1347, 1181, 1157, 1135, 1095, 1073, 1046, 750, 711, 552, 487, 423, 397, 388 cm^{-1}. HRMS: C16H19N4O2 (Calculated = 299.1508 *m/z*) Found = 299.1510 *m/z*

7,8-Dimethoxy-1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine (2.12e)

Yield:68% ; Black solid(corresponding peroxide), Mp: 85 – 88 ℃ decompose; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.59 (s, 1 H), 6.20 (s, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.46 (s, 3 H), 3.40-3.36 (q, J = 6.9 Hz, 2 H), 3.34 (s,3 H), 1.11 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ158.49, 150.54, 146.86, 146.32, 145.56, 128.09, 128.01, 107.90, 100.07, 99.23, 56.39, 56.29, 51.24, 28.80, 28.40, 11.03; IR(Neat) 3367, 3128, 2941, 1714, 1664, 1615, 1489, 1428, 1394, 1259, 1217, 1138, 1105, 985, 844, 536, 518, 485, 456, 415 cm^{-1}. HRMS: C15H23O8 (Calculated = 331.1393 *m/z*) Found = 331.1393 *m/z.*

3-methyl-6-(phenylamino)pyrimidine-2,4(1H,3H)-dione 2.17

A mixture of chlorouracil (20 mmol) and aniline (60 mmol) was stirred at 180 ℃ in a sealed tube without any solvent for 30 minutes. After cooling, the resulting solid was crushed in ester, collected by filtration, washed with water and recrystallized in ethanol to give 72% yield of white powder 2.17.

^{1}H NMR (500MHz, [D$_6$] DMSO, 25℃) δ= 10.48 (br. s., 1 H; NH), 8.24 (s, 1 H; C=CH), 7.38 - 7.31 (m, 2 H; ArH), 7.17 (d, ^{3}*J*(H,H) = 7.4 Hz, 2 H; ArH), 7.13 (t, ^{3}*J*(H,H) = 7.4 Hz, 1 H; ArH), 4.81 (d, ^{4}*J*(H,H) = 2.3 Hz, 1 H; NH), 3.03 (s, 3 H; CH3); ^{13}C NMR (75MHz, [D$_6$]DMSO, 25 ℃) δ= 163.9, 151.6, 151.2, 138.5, 130.3, 129.9, 123.0, 76.0, 26.6

3-methyl-10-phenylisoalloxane 2.19

2.17 (10mol) and nitrosobenzene (30 mmol) in a round bottom flask was added 50 mL of acetic acid. The round bottom flask was immediately merged into preheated oil bath (120 ℃) to reflux and stir for 5 minutes (prolonged heating will result in formation of complex byproducts). After 5 minutes, the reaction was cooled to room temperature then added into 200 mL of cold ether. The product was precipitated out in ether was a orange-yellow powder, which

was collected by suction filtration and washed with cold ether to give 2.19 in 70% yield as a yellow powder.

^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.35 (d, [3]J(H,H)= 7.4 Hz, 1 H; ArH), 7.71 - 7.54 (m, 5 H; ArH), 7.29 (d, [3]J(H,H)= 7.4 Hz, 2 H; ArH), 6.89 (d, [3]J(H,H)= 8.6 Hz, 1 H; ArH), 3.50 (s, 3 H; CH3); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ=159.7, 155.6, 150.0, 137.8, 135.7, 135.4, 135.1,134.3, 132.8, 130.9, 130.6, 127.6, 126.7, 117.2, 28.9.

3-methyl-5-ethyl-10-phenylisoalloxanium prechlorate 2.20

2.19 (3 mmol) and 10% Pd/C (150 mg) was added to a round bottom flask. The flask was then charged with Argon and 20 mL of degassed Ethanol/H$_2$O (1:1) under argon. The mixture was degassed two additional times using Freeze-Pump-Thaw technique with an acetone and dry ice bath. Distilled acetaldehyde (3 mL, 54 mmol) and concentrated aqueous HCl (1.66 mL, 36 mmol) was added via syringe to the reaction mixture. The mixture was frozen again under vacuum. An H$_2$ balloon was prepared to refill the reaction flask vacuum with H$_2$, and then reaction was warmed up to room temperature. The reaction was stirred for two days under H$_2$ atmosphere. The Pd/C was filtered off with Celite and the Celite was washed extensively with ethanol until the color of the wash became clear. During the wash, the filtrate color turned from light yellow to dark brown because of the auto oxidation of flavin by air. The solvent of the filtrate was then evaporated under vacuum to yield brown oil which was mixed with 12 mL of 2N HClO$_4$ and cooled to 0 ℃. 5 gram of NaClO$_4$ was added into the above acidic solution followed by 1.5 gram of NaNO$_2$. The resulting purple solution was stirred at 0 ℃ for an additional 2 hours. The product 2.20 precipitated out of the water solution and it can be collected by suction filtration and washed with water to yield 87% as purple powder.

^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 7.68 - 7.56 (m, 3 H; ArH), 7.33 (d, J = 8.0 Hz, 2 H; ArH), 6.96 - 6.92 (m, 1 H; ArH), 6.91 - 6.86 (m, 1 H; ArH), 6.65 (t, [3]J(H,H)= 7.7 Hz, 1 H; ArH), 5.93 (d, [3]J(H,H)= 8.0 Hz, 1 H; ArH), 3.54 (q, [3]J(H,H)= 6.9 Hz, 2 H; CH2), 3.28 (s, 3 H; NCH3), 1.27 (t, [3]J(H,H)= 6.9 Hz, 3 H; CH2CH3); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ=

159.0, 149.2, 143.9, 138.6, 137.1, 134.2, 131,7, 130.8, 130.4, 125.1, 123.3, 122.9, 114.3, 99.9, 50.7, 27.4, 11.2; HRMS: C19H17N4O2+Na, Calculated = 356.1238 *m/z*, Found = 356.1222 *m/z*

General Procedure for H_2O_2 based Dakin oxidation:

In a 1 dram glass vial equipped with stir bar, substrate (0.2 mmol), flavin(0.02 mmol, 0.1 equiv), 1M sodium bicarbonate aqueous solution (200 μl, 1 equiv), 35% H_2O_2 solution(5equiv, 120 μl) and 2mL solvent (MeOH/H_2O=95/5) were added. The reaction was stirred at room temperature and monitored by TLC until the disappearance of starting material. The reaction mixture was transferred to a round bottom flask and added 50 mG silica gel. The solvent was evaporated with reduced pressure. The product-silica gel was loaded on a column and purified by flash chromatography using 1:3 ethyl acetate/ hexane as eluent.

General Procedure for O_2 based Dakin oxidation:

A solution of 95:5 organic solvents/H_2O was prepared. Then an one dram glass vial was equipped with stir bar, salicylaldehyde (0.2 mmol), catalysts (5 mol%), Hantzsch Ester (1 equiv), 1 M aqueous base solution (0.2 mL), and the above solvent (2 mL). Then oxygen balloon was equipped. Reactions were stirred at room temperature for 1h. At that time, a 10 μL aliquot was taken from each reaction and dissolved in 0.5 mL of CDCl$_3$. Conversion was measured by comparing the integration of starting material signal and product signal.

Catechol 2.43a

White solid, Mp: 103 – 104 ℃. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.90 - 6.84 (m, 2 H), 6.84 - 6.74 (m, 2 H), 5.19 - 5.06 (m, 2 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 143.5, 121.4, 115.6 Flash column chromatography ethyl acetate/ hexanes, 1:3, Rf= 0.23.

3-methoxycatechol 2.43b

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.75 (dt, J = 2.3, 8.3 Hz, 1 H), 6.60 (d, J = 7.4 Hz, 1 H), 6.47 (d, J = 7.4 Hz, 1 H), 5.44 (br. s., 1 H), 5.37 (br. s., 1 H), 3.87 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 147.1, 144.2, 132.6, 119.9, 108.9, 103.2, 56.3 Flash column chromatography ethyl acetate/ hexanes, 1:3, Rf= 0.32.

4-methoxycatechol 2.43c

White solid, Mp: 56 – 57 ℃. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.76 (d, J = 8.6 Hz, 1 H), 6.50 (d, J = 2.9 Hz, 1 H), 6.34 (dd, J = 2.9, 8.6 Hz, 1 H), 5.52 (br. s., 2 H), 3.72 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 154.3, 144.7, 137.4, 116.0, 105.5, 102.6, 55.9 Flash column chromatography ethyl acetate/hexanes, 1:3, Rf= 0.27.

3-methylcatechol 2.43d

White solid, Mp: 40-43℃. ^{1}H NMR (500MHz, CDCl$_3$) δ 6.71 (s, 3 H), 5.25 (br. s., 1 H), 5.18 (br. s., 1 H), 2.26 (s, 3 H); ^{13}C NMR (125MHz, CDCl$_3$) δ 143.13, 142.20, 124.61, 123.05, 120.27, 113.07, 15.58 Flash column chromatography ethyl acetate/hexanes, 1:3, Rf= 0.5.

2,6-dimethylhydroquinone 2.43e

White solid, Mp 148-149 ℃. ^{1}H NMR (300MHz, DMSO-d6) δ 8.43 (s, 1 H), 7.38 (s, 1 H), 6.27 (s, 2 H), 2.03 (s, 6 H); ^{13}C NMR (75 MHz, DMSO-d6) δ 150.26, 145.94, 125.99, 115.09, 115.03, 17.32 Flash column chromatography ethyl acetate/ hexanes, 1:3, Rf= 0.35

1,2-naphthoquinone 2.43f

White solid, Mp 145-146 ℃. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.12 (d, J = 7.4 Hz, 1 H), 7.65 (d, J = 1.1 Hz, 1 H), 7.51 (t, J = 7.7 Hz, 1 H), 7.44 (d, J = 10.3 Hz, 1 H), 7.37 (d, J = 7.4 Hz, 1 H), 6.44 (d, J = 9.7 Hz, 1 H);); ^{13}C NMR (125 MHz, CDCl$_3$) δ 180.9, 178.9, 145.4, 135.9, 134.9, 131.7, 130.9, 130.4, 129.9, 128.1 Flash column chromatography ethyl acetate/ hexanes, 1:3, Rf= 0.25

4-nitrocatechol 2.43g

Yellow solid, Mp 173-177 ℃. ^{1}H NMR (300MHz, DMSO-d6) δ10.26 (dd, J = 4.9, 8.3 Hz, 2 H), 7.60 (dd, J = 2.6, 8.9 Hz, 1 H), 7.56 (d, J= 2.9 Hz, 1 H), 6.86 (d, J = 9.2 Hz, 1 H); NMR (75 MHz,

DMSO-d6) δ 153.43, 146.00, 140.00, 117.07, 115.55, 110.93. Flash column chromatography ethyl acetate/hexanes, 1:2, Rf= 0.3.

hydroquinone 2.43h

White solid, Mp 172-174 ℃. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.62 (s, 2 H), 6.53 (s, 4 H); ^{13}C NMR (75 MHz, DMSO-d6) δ 150.3, 116.2 Flash column chromatography ethyl acetate/hexanes, 1:3, Rf= 0.25

2-methoxyhydroquinone 2.43i

White solid, Mp 89-90℃. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.75 (d, J = 8.6 Hz, 1 H), 6.44 (d, J = 2.9 Hz, 1 H), 6.31 (dd, J = 2.9, 8.6 Hz, 1 H), 5.32 - 5.11 (m, 1H), 5.10 - 4.71 (m, 1 H), 3.84 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 149.3, 147.2, 139.6, 114.5, 106.9, 99.8, 56.0   Flash column chromatography ethyl acetate/ hexanes, 1:3, Rf= 0.22.

2,6-dimethoxy-1,4-benzenediol 2.43j

White solid, Mp 158-162℃. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.84 (s, 2 H), 3.81 (s, 6 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 186.95, 176.78, 157.41, 107.51, 56.58 Flash column chromatography ethyl acetate/hexanes, 1:3, Rf= 0.3.

2,4-dimethoxyphenol 2.43k

White solid, Mp 219-220 ℃. ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.83 (d, J = 8.9 Hz, 1 H), 6.49 (d, J = 2.8 Hz, 1 H), 6.39 (dd, J = 2.8, 8.6 Hz, 1 H), 5.34 (s, 1 H), 3.85(s, 3 H), 3.76 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.6, 147.2, 139.9, 114.2, 104.3, 99.5, 55.96, 55.9 Flash column chromatography ethyl acetate/hexanes, 1:3, Rf= 0.45

3-chlorocatechol 2.43o

White solid, Mp 48-49 ℃. ^{1}H NMR (500MHz, CDCl$_3$) δ 6.90 - 6.82 (m, 2 H), 6.81 - 6.74 (m, 1 H), 5.46 (br. s., 2 H); ^{13}C NMR (125MHz, CDCl$_3$) δ 144.93, 139.33, 121.34, 120.51, 119.86, 114.38

5-chlorocatechol 2.43p

White solid, Mp 90-91 ℃. ^{1}H NMR (500MHz, CDCl$_3$) δ 6.88 (s, 1 H), 6.78 (d, J = 1.1 Hz, 2 H), 5.44 (br. s., 1 H), 5.25 (br. s., 1 H); ^{13}C NMR (125MHz, CDCl$_3$) δ 144.28, 142.27, 125.75, 121.05, 116.23, 115.9.

3,5-dichlorocatechol 2.43q

White solid, Mp 80-82 ℃. ^{1}H NMR (500MHz, CDCl$_3$) δ 6.90 (s, 1 H), 6.86 (s, 1 H), 5.69 - 5.18 (m, 2 H); ^{13}C NMR (125MHz, CDCl$_3$) δ 145.26, 138.24, 125.99, 120.14, 120.05, 115.07.

3-bromo-5-nitrocatechol 2.43r

^{1}H NMR (500MHz, DMSO-d6) δ 11.21 - 10.55 (m, 2 H), 7.85 (d, J = 2.3 Hz, 1 H), 7.58 (d, J = 2.3 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d6) δ 150.75, 146.32, 139.88, 119.80, 109.74, 109.2.

General procedure for aerobic epoxidation:

In a 1 dram vial equipped with a stir bar, enal (0.2 mmol), flavin catalyst (3 mg, 5 mol %), pyrrolidine catalyst (13 mg, 20 mol %) and benzothiazoline (62 mg, 1.2 equivalent) were added. Then, 2 mL of freshly distilled chloroform was added to the vial. The vial was sealed and degassed at -78℃ under vacuum for 1 minute. An oxygen filled balloon was connected to the vial via a needle. The reaction was warmed up to room temperature and stirred for the time given in Table 2. During the reaction, 2-(4-nitrophenyl)benzo[d]thiazole was formed and precipitated out of the solution as white powder. When the reaction was complete (monitored by NMR), the reaction was cool at 0℃ for 5 minutes to precipitate out most of the 2-(4-nitrophenyl)benzo[d]thiazole. Then the reaction mixture was filtered through a cotton plug twice to remove the solid byproduct. The filtrate was concentrated under vacuum followed by flash column chromatography (ethyl acetate/hexanes) to give oxiranes as oily liquids. For low boiling aldehydes, after filtration, the filtrate was diluted with 2 mL methanol, cooled to 0℃.Sodium borohydride (20 mg, 2.5 equivalent) was added into the filtrate to reduce the aldehydes to corresponding alcohols. After 10 minutes, the reaction was quenched by sat. NH$_4$Cl solution. The product was extracted with dichloromethane three times, concentrated and columned to give the oxirane-alcohols.

(2S,3R)-3-Phenyl-oxirane-2-carbaldehyde 3.45a

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.20 (d, J = 5.7 Hz, 1 H), 7.42 - 7.27 (m, 5 H), 4.17 (d, J = 1.7 Hz, 1 H), 3.44 (dd, J = 1.7, 5.7 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.9, 134.3, 129.3, 128.9, 125.8, 63.0, 56.7; The enantiomeric excess of the aldehyde was determined by GC-MS on a Chromasil CPChirasil-Dex CB-column. Temperature program: 70-160 ºC, rate: 10 ºC min^{-1}, hold 10 min, major enantiomer: t_R =15.28 min, minor enantiomer t_R =15.49 min; $[a]^{25}_D$: -20.2 (c=0.01, CHCl$_3$).
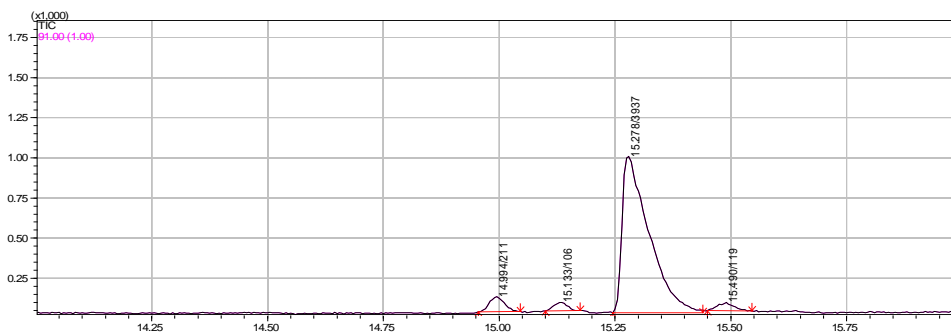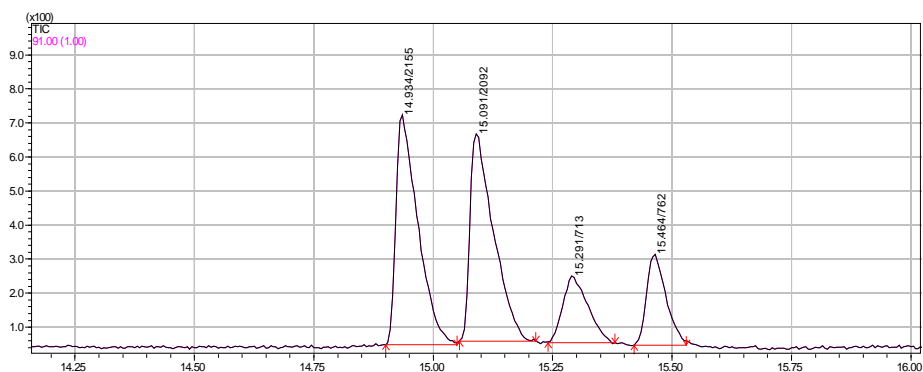
(2S,3R)-3-(2-nitrophenyl)oxirane-2-carbaldehyde 3.45b

Yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.30 (d, J = 5.7 Hz, 1 H), 8.98 (d, J = 5.2 Hz, 1 H*), 8.23 (d, J = 8.6 Hz, 1 H), 8.23 (d, J = 8.6 Hz, 1 H*), 7.93 (d, J = 8.0 Hz, 1 H*), 7.77 - 7.68 (m, 1 H), 7.77 - 7.68 (m, 1 H*), 7.63 (d, J = 7.4 Hz, 1 H), 7.59 - 7.52 (m, 1 H), 7.59 - 7.52 (m, 1 H*), 4.82 (s, 1 H), 4.82 (s, 1 H*), 3.89 (t, J = 5.2 Hz, 1 H*), 3.33 (dd, J = 2.0, 6.0 Hz, 1 H);) (* for

the (2R, 3R) isomer); ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.7, 147.5, 134.8, 131.6, 129.7, 127.2, 125.22, 61.6, 55.2; The enantiomeric excess of the corresponding alcohol was determined using HPLC with a CHIRALPAK ID (250x4.6mm i.d.) column and a 40/60 heptane/ethanol mobile phase pumped at 1mL/min, major enantiomer: t_R =7.66 min, minor enantiomer t_R =8.83 min; $[a]^{25}_D$: -28.4 (c=0.01, CHCl$_3$).
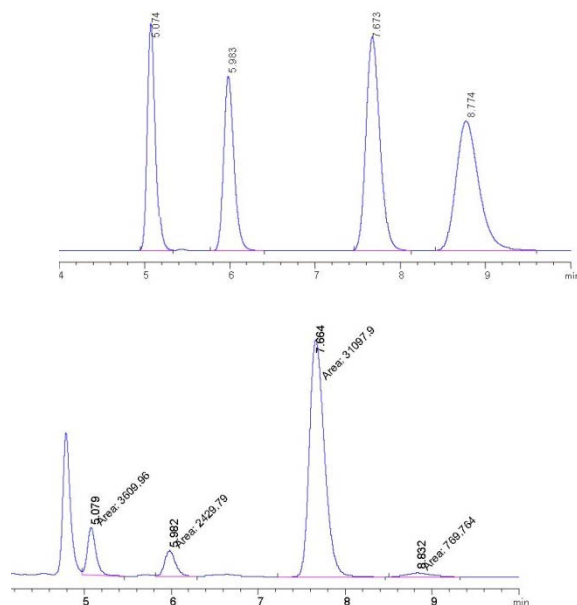
(2S,3R)-3-(4-nitrophenyl)oxirane-2-carbaldehyde 3.45c

Yellow oil. ^{1}H NMR (500 MHz, CDCl3) δ 9.22 (d, J = 5.7 Hz, 1 H), 8.25 (d, J = 8.6 Hz, 2 H), 7.49 (d, J = 8.6 Hz, 3 H), 4.28 (d, J = 1.7 Hz, 1 H), 3.44 (dd, J = 1.7, 5.7 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 195.7, 141.5, 126.7, 124.2, 62.9, 55.6. The enantiomeric excess of the corresponding alcohol was determined using HPLC with a CHIRALPAK ID (250x4.6mm i.d.) column and a 80/20 heptane/ethanol mobile phase pumped at 1mL/min. $[a]^{25}_D$: -6.7 (c =0.01, CHCl$_3$).
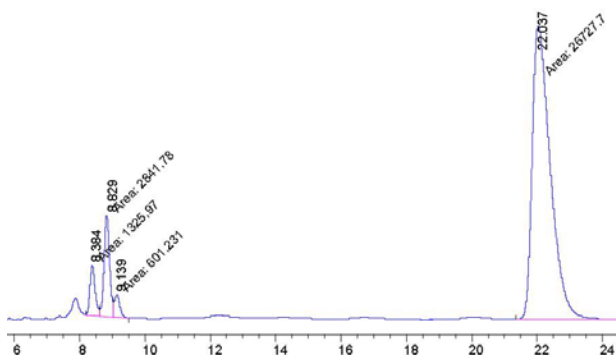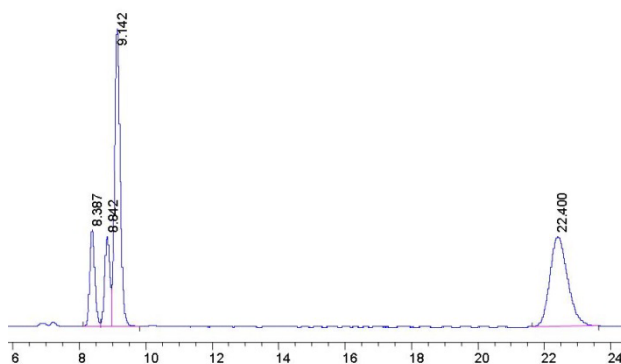
(2S,3R)-3-(4-chlorophenyl)oxirane-2-carbaldehyde 3.45d

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.19 (d, J = 5.7 Hz, 4 H), 7.36 (d, J = 8.6 Hz, 2 H), 7.23 (d, J = 8.6 Hz, 2 H), 4.15 (s, 1 H), 3.40 (dd, J = 1.4, 6.0 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 196.6, 135.2, 132.8, 129.2, 127.1, 62.9, 56.1; The enantiomeric excess of the corresponding alcohol was determined using HPLC with a CHIRALPAK IC (250x4.6mm i.d.) column coupled to a CHIRALPAK ID (250x4.6mm i.d.) column and a 96/4 heptane/ethanol mobile phase pumped at 1mL/min, major enantiomer: t_R =9.14 min, minor enantiomer: t_R =22.40 min; [a]^{25} $_D$: -34.3 (c =0.01, CHCl$_3$).
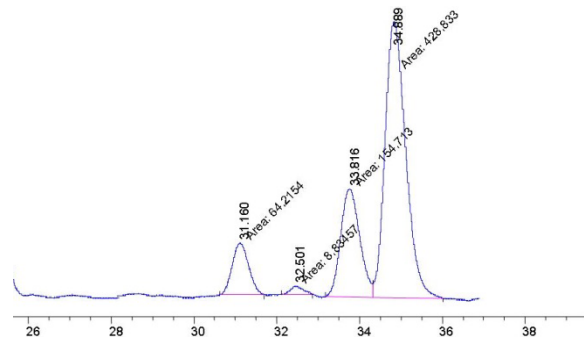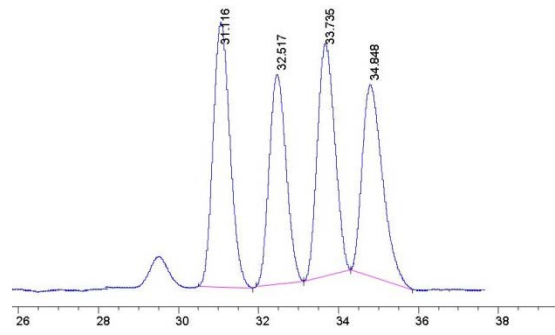
(S)-(3,3-dimethyloxiran-2-yl)methanol 3.45e

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.83 (dd, J = 4.0, 12.0 Hz, 1 H), 3.67 (dd, J = 6.3, 12.0 Hz, 1 H), 2.97 (dd, J = 4.6, 6.3 Hz, 1 H), 1.88 (br. s., 1 H), 1.33 (d, J = 17.2 Hz, 7 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 63.8, 61.6, 58.9, 24.9, 18.9; The enantiomeric excess of the corresponding alcohol was determined using GC-MS on a CHIRALDEX B-DM (20m) column. Temperature program: 100°C with a 1mL/min He carrier gas flow rate, major enantiomer: t_R =3.37 min, minor enantiomer t_R =3.19 min. $[a]^{25}_D$: +8.5 (c =0.01, CHCl$_3$).
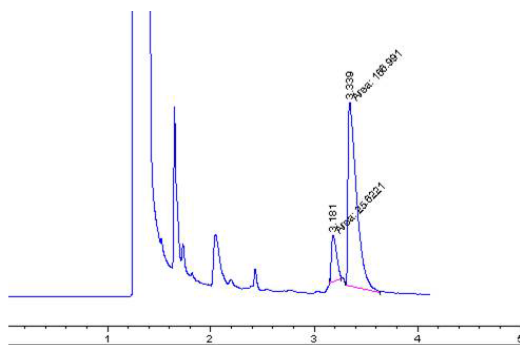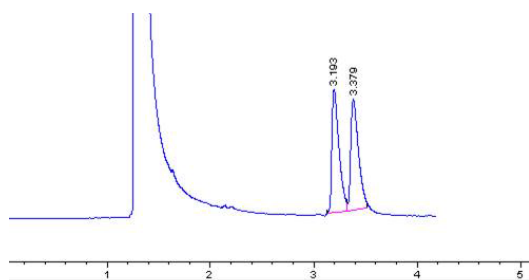
((2S,3S)-3-ethyloxiran-2-yl)methanol 3.45f

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.91 (d, J = 12.6 Hz, 1 H), 3.62 (dd, J = 2.9, 12.6 Hz, 1 H), 2.94 (d, J = 4.0 Hz, 2 H), 1.82 (br. s., 1 H), 1.66 - 1.55 (m, 2 H), 1.00 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 61.8, 58.2, 57.1, 24.7, 9.9; The enantiomeric excess of the aldehyde was determined by GC-MS on a Chromasil CPChirasil-Dex CB-column. Temperature program: 70-110 ºC, rate: 5 ºC min^{-1}, hold 10 min, major enantiomer: t_R =5.70 min, minor enantiomer t_R =5.92 min; $[a]^{25}_D$: +24.6 (c =0.01, CHCl$_3$).
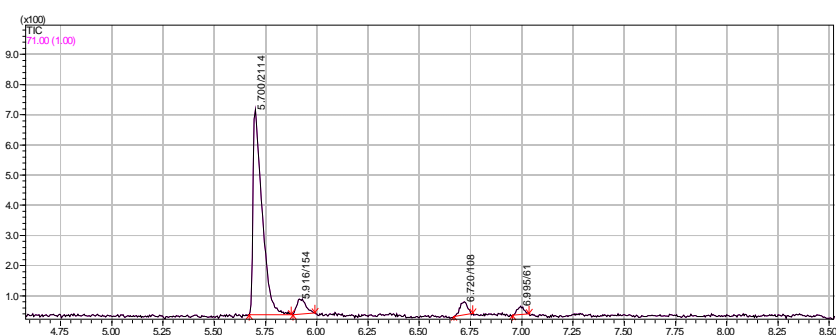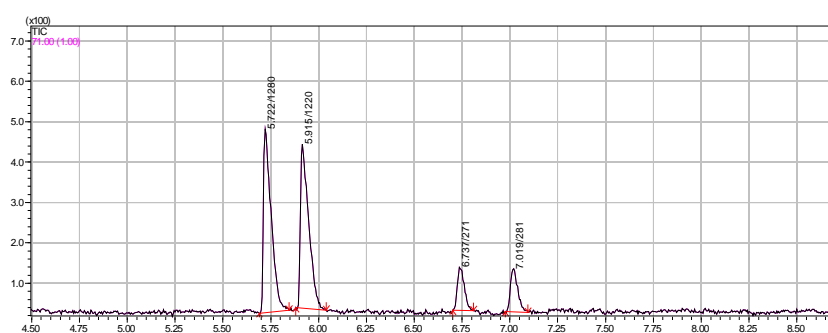
((2R,3R)-3-isopropyloxiran-2-yl)methanol 3.45g

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.89 (dd, J = 2.3, 12.6 Hz, 1 H), 3.58 (dd, J = 4.6, 12.6 Hz, 1 H), 2.98 - 2.92 (m, 1 H), 2.73 (dd, J = 2.0, 6.6 Hz, 1 H), 2.17 (br. s., 1 H), 1.63 - 1.50 (m, 1 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 62.0, 61.3, 57.7, 30.1, 19.1, 18.4; ., 1 H), 1.66 - 1.55 (m, 2 H), 1.00 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 61.8, 58.2, 57.1, 24.7, 9.9; Enantiomeric excess of the aldehyde was determined by GC-MS on a Chromasil CPChirasil-Dex CB-column. Temperature program: 50-110 ºC, rate: 5 ºC min^{-1}, hold 10 min, major enantiomer: t_R =7.75 min, minor enantiomer t_R =7.99 min; [a]^{25} $_D$: +26.2 (c =0.01, CHCl$_3$).
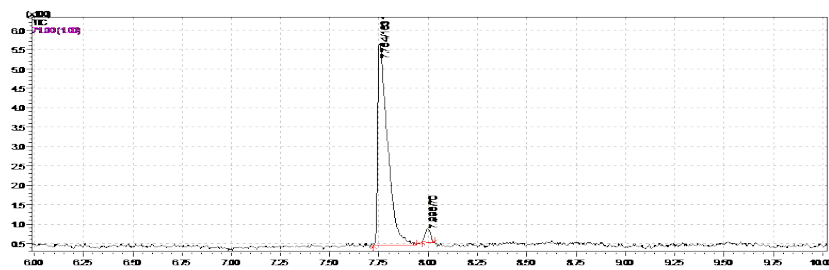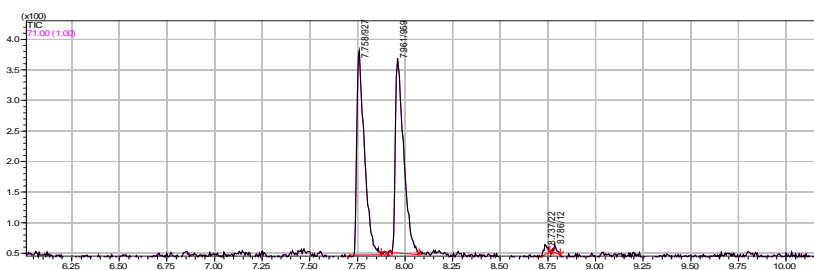
(2S,3R)-3-propyloxirane-2-carbaldehyde 3.45h

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.00 (d, J = 6.3 Hz, 1 H), 3.24 - 3.20 (m, 1 H), 3.12 (dd, J = 1.7, 6.3 Hz, 1 H), 1.68 - 1.58 (m, 2 H), 1.56 - 1.45 (m, 2 H), 0.97 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.6, 59.3, 56.88, 31.0, 27.9, 22.4, 14.0; Enantiomeric excess of the aldehyde was determined by GC-MS on a Chromasil CPChirasil-Dex CB-column. Temperature program: 50-110 ºC, rate: 5 ºC min^{-1}, hold 10 min, major enantiomer: t_R =8.78 min, minor enantiomer t_R =9.00 min; $[a]^{25}_D$: -26.5 (c =0.01, CHCl$_3$).

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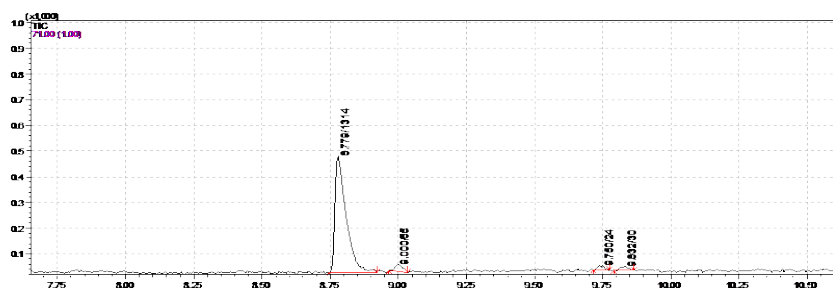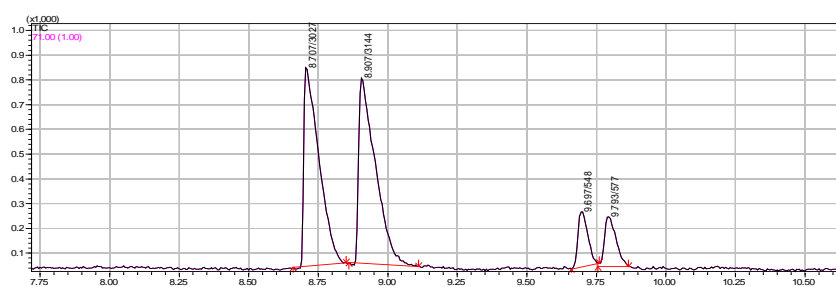
(2S,3R)-3-butyloxirane-2-carbaldehyde 3.45i

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.01 (d, J = 6.3 Hz, 1 H), 3.26 - 3.19 (m, 1 H), 3.13 (dd, J = 1.7, 6.3 Hz, 1 H), 1.73 - 1.61 (m, 2 H), 1.45 (td, J = 6.9, 13.7 Hz, 2 H), 1.41 - 1.33 (m, 2 H), 0.92 (t, J = 7.2 Hz, 3 H); Enantiomeric excess of the aldehyde was determined by GC-MS on a Chromasil CPChirasil-Dex CB-column. Temperature program: 50-150 ºC, rate: 10 ºC min^{-1}, hold 10 min, major enantiomer: t_R =7.43 min, minor enantiomer t_R =7.53 min; [a]$^{25}_D$: -20.4 (c =0.01, CHCl$_3$).
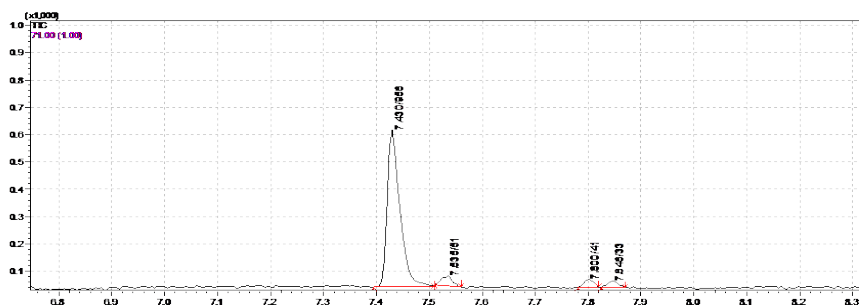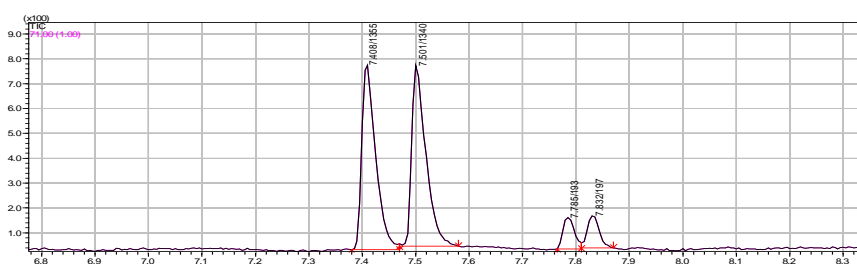
(2S,3R)-3-hexyloxirane-2-carbaldehyde 3.45j

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.01 (d, J = 6.3 Hz, 1 H), 3.25 - 3.20 (m, 1 H), 3.13 (dd, J = 1.7, 6.3 Hz, 1 H), 1.69 - 1.62 (m, 2 H), 1.50 - 1.45 (m, 2 H), 1.38 - 1.33 (m, 6 H), 0.91 - 0.85 (m, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.6, 59.3, 56.9, 31.7, 31.3, 29.0, 25.82, 22.6, 14.1; Enantiomeric excess of the aldehyde was determined by GC-MS on a Chromasil CPChirasil-Dex CB-column. Temperature program: 50-180 ºC, rate: 10 ºC min^{-1}, hold 10 min, major enantiomer: t$_R$ =18.40 min, minor enantiomer t$_R$ =18.58 min; [a]^{25} $_D$: -76.2 (c =0.01, CHCl$_3$).
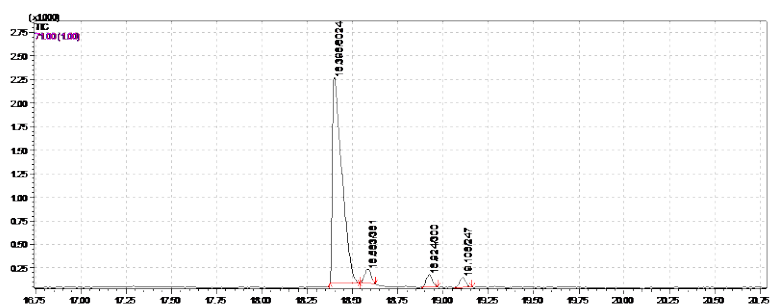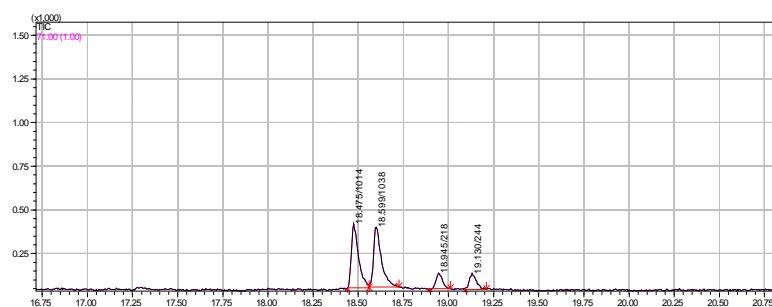
(2S,3R)-3-heptyloxirane-2-carbaldehyde 3.45k

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.98 (d, J = 6.3 Hz, 1 H), 3.24 - 3.16 (m, 1 H), 3.10 (dd, J = 2.0, 6.0 Hz, 1 H), 1.67 - 1.56 (m, 2 H), 1.51 - 1.39 (m, 3 H), 1.36 - 1.24 (m, 9 H), 0.85 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 198.6, 59.2, 56.9, 31.8, 31.3, 29.2, 29.1, 25.8, 22.7, 14.1; Enantiomeric excess of the aldehyde was determined by GC-MS on a Chromasil CPChirasil-Dex CB-column. Temperature program: 50-180 ºC, rate: 10 ºC min^{-1}, hold 10 min, major enantiomer: t$_R$ =20.71 min, minor enantiomer t$_R$ =20.83 min; [a]^{25}$_D$: -76.0 (c =0.01, CHCl$_3$).
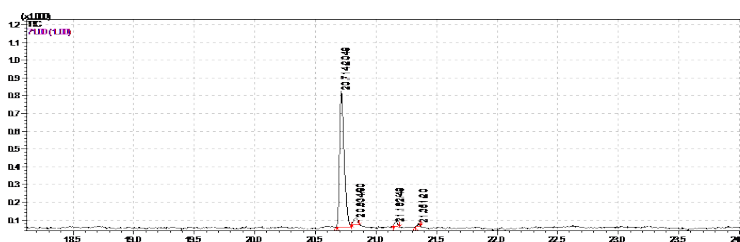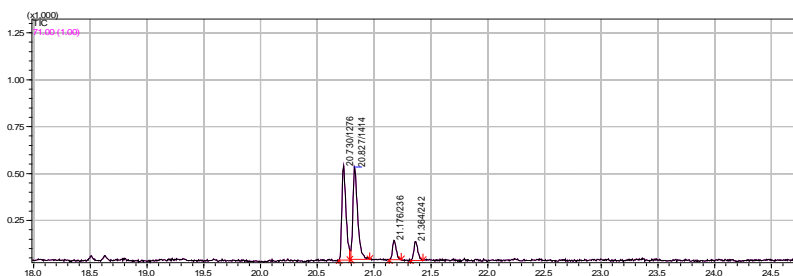
(2S,3S)-ethyl 3-formyloxirane-2-carboxylate 3.45l

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.04 (d, J = 6.3 Hz, 1 H), 4.28 (dd, J = 5.7, 6.9 Hz, 2 H), 3.73 (d, J = 1.7 Hz, 1 H), 3.61 (dd, J = 1.1, 6.3 Hz, 1 H), 1.32 (t, J = 7.2 Hz, 3 H); NMR (125 MHz, CDCl$_3$) δ 195.1, 166.3, 62.6, 57.6, 50.9, 14.1; The enantiomeric excess of the aldehyde was determined using GC-MS on a CHIRALDEX G-TA (30m) column, Temperature program: 120 °C with a 1mL/min He carrier gas flow rate; [a]^{25} $_D$: -15.6 (c =0.01, CHCl$_3$).
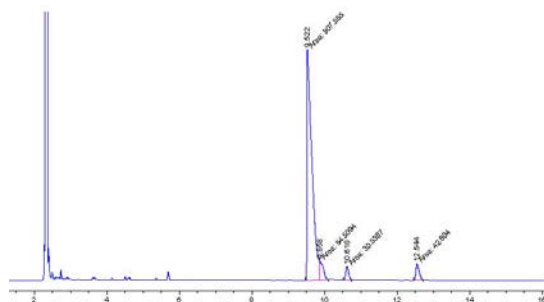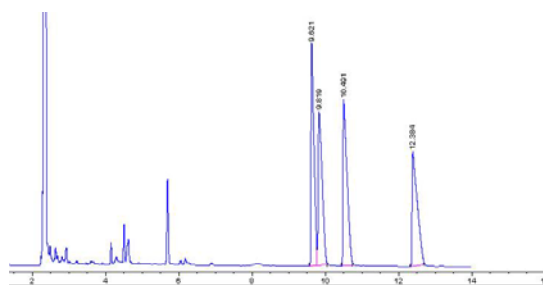
(2S, 3R)-3-Methyl-3-(4-methylpent-3-enyl)-oxirane-2-carbaldehyde 3.45m

Colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ =9.45 (d, J=5.2 Hz, 1H), 9.41 (d, J=5.1, 1H*), 5.02-5.07 (m, 1H and 1H*), 3.18 (d, J=4.6,1H), 3.13 (d, J=5.2, 1H*), 2.04-2.20 (m, 2H and 2H*), 1.65-1.85 (m, 5H and 5H*), 1.59 (s, 3H), 1.58 (s, 3H*), 1.43 (s, 3h) and 1.41(s, 3H*)(* for the (2R, 3R) isomer); The ee was determined using GC with a CHIRALDEX B-DM (20m) column at 90 °C with a 1mL/min He carrier gas flow rate. [a]^{25}$_D$: -63.8 (c =0.01, CHCl$_3$).
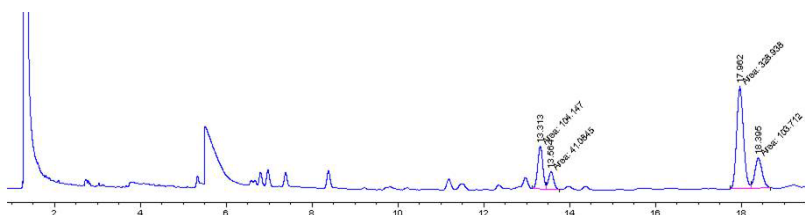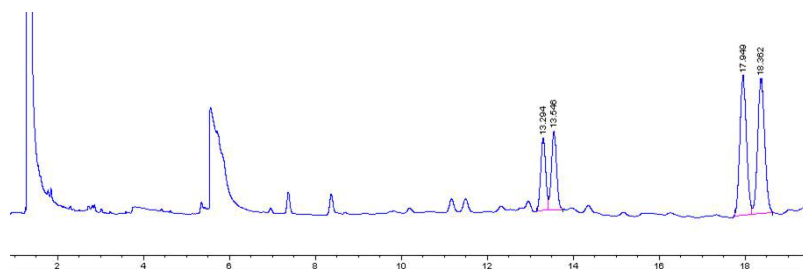
General procedure of flavin catalyzed oxidation of dihydropyridine to pyridine:

0.2 mmol of dihydropyridine , 0.01 mmol of flavin catalyst (3 mg) and 2 mL methanol was added in a 1 dram vial. The vial was filled with oxygen gas by applying an O_2 balloon via a needle. The reaction was stirred at room temperature for the time given. After the completion of reaction (followed by TLC and NMR), the reaction mixture was transferred to a small round bottom flask and the solvent was evaporated under vacuum to give pyridine as products. No column chromatography was needed since the purity of the product was higher than 95% by NMR.

General procedure of flavin catalyzed tandem synthesis of pyridine:

To a 2 dram vial, formaldehyde (37 wt% in H_2O, 1 mmol), 1, 3-dicarbonyl compound (2 mmol), ammonium acetate (1 mmol), catalyst (6 mg, 0.02 mmol, 2 mol %) and 2 mL of methanol was added. The reaction was stirred with the vial open to atmosphere at room temperature for the time given. After the complete of the reaction, the reaction mixture was dried under vacuum. Flash column chromatography (ethyl acetate/hexane) was used to purify the crude product to give pure product.

General procedure of flavin catalyzed oxidation of dihydropyridine to Pyridine

0.2 mmol of dihydropyridine, 0.01 mmol of catalyst (4.3 mg), perchloric acid (28.6mg of 70% wt $HClO_4$) and 2 mL methanol was added in a 1 dram vial. The vial was filled with oxygen gas by applying an O_2 balloon via a needle. The reaction was stirred at 50℃ for the time given. After the disappearance of the starting material, the reaction mixture was neutralized by adding 0.2 mL of saturated Na_2CO_3 solution. The solvent was evaporated under vacuum and the resulting material was directly purified by flash column chromatography (ethyl acetate/hexane) to give as pure product.

General procedure of flavin catalyzed oxidation of benzothizoline to benzothiazole

0.2 mmol of benzothiazoline, 0.01 mmol of catalyst (3 mg) and 2 mL methanol was added in a 1 dram vial. The vial was filled with oxygen gas by applying an O_2 balloon via a needle. The reaction was stirred at room temperature for the time given. After the completion of reaction (followed by TLC and NMR), the reaction mixture was transferred to a small round bottom flask and the solvent was evaporated under vacuum to give benzothiazoles as products. No column chromatography was needed since the purity of the product was higher than 95% by NMR.

General procedure of flavin catalyzed one-pot two-steps synthesis benzothiazole 12a-i

1 mmol of 2-aminothiophenol (125mg) and 1 mmol of aldehyde was mixed in 3 mL methanol in a 1.5 dram vial. The reaction was stirred at room temperature for 6 hours to ensure complete formation of corresponding benzothizolines. Then, 0.02 mmol of catalyst (15mg) was added into the reaction. At the same time, an O_2 balloon was also applied on the vial. The reaction was stirred under 1 atm oxygen for an additional 1.5 hour. After completion of the reaction, the solvent was evaporated under reduced vacuum, and the corresponding benzothiazoles were purified by flash column chromatography with silica gel.

4.45 diethyl 2,6-dimethylpyridine-3,5-dicarboxylate

White solid. M.P.: 69 - 71 ^{o}C. ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ=8.46 (s, 1H; CH), 4.20 (q, ^{3}J(H,H) = 6.9 Hz, 4H; CH2CH3), 2.63 (s, 6H; CH3), 1.23 (t, ^{3}J(H,H)= 7.4 Hz, 6H; CH2CH3); ^{13}C NMR (125MHz, [D$_1$]CHCl$_3$, 25 ℃) δ=165.6, 162.1, 140.7, 122.8, 61.19, 24.8, 14.2

4.47 dimethyl 2,6-dimethylpyridine-3,5-dicarboxylate

White solid. M.P.: 99 - 100 ^{o}C. ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.68 (s, 1 H; CH), 3.91 (s, 6 H; OCH3), 2.83 (s, 6 H; CH3); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 166.3, 162.7, 141.1, 122.7, 52.4, 25.0

4.48 dimethyl 2,6-diethylpyridine-3,5-dicarboxylate

White solid. M.P.: 99 - 100 $^{\circ}$C. ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.62 (s, 1 H; CH), 3.91 (s, 6 H; OCH3), 3.18 (q, ^{3}J(H,H)= 7.5 Hz, 4 H; C*H*2CH3), 1.28 (t, ^{3}J(H,H)= 7.4 Hz, 6 H; CH2C*H*3); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 167.38, 166.4, 141.4, 122.2, 52.4, 30.4, 13.9

4.49 1,1'-(2,6-dimethylpyridine-3,5-diyl)diethanone

White solid. M.P.: 68 - 70 $^{\circ}$C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.22 (s, 1 H; CH), 2.75 (s, 6 H; CH3), 2.61 (s, 6 H; CH3); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ=199.4, 160.4, 138.0, 130.3, 29.5, 24.9

4.50 di-tert-butyl 2,6-dimethylpyridine-3,5-dicarboxylate

White solid. M.P.: 108-109 $^{\circ}$C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.49 (s, 1 H; CH), 2.77 (s, 6 H; CH), 1.57 (s, 18 H; CH3); ^{13}C NMR (125MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 165.5, 161.2, 140.9, 124.8, 82.2, 28.3, 24.9

4.51 diisopropyl 2,6-dimethylpyridine-3,5-dicarboxylate

White solid. M.P.: 63 - 65 $^{\circ}$C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.58 (s, 1 H; CH), 5.22 (sep, ^{3}J(H,H)= 6.2 Hz, 2 H; C*H*(CH3)2), 2.79 (s, 6 H; CH3), 1.35 (d, ^{3}J(H,H)= 6.3 Hz, 12 H; CH(C*H*3)2); ^{13}C NMR (125MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 165.7, 161.8, 141.0, 123.8, 69.3, 24.8, 21.9

4.52 diallyl 2,6-dimethylpyridine-3,5-dicarboxylate[7]

White solid. M.P.: 64 - 66 $^{\circ}$C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.71 (s, 1 H; CH), 6.06 - 5.95 (m , 2 H;), 5.38 (d, J = 17.2 Hz, 2 H), 5.28 (d, J = 10.3 Hz, 2 H), 4.80 (d, J = 5.7 Hz, 4 H; CH2), 2.82 (s, 6 H; CH3); ^{13}C NMR (125MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 165.5, 162.7, 141.3, 131.8, 123.0, 119.0, 66.2, 50.7, 24.7.

4.53 dibenzyl 2,6-dimethylpyridine-3,5-dicarboxylate[11]

White solid, Mp: 87-88 ℃; ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.76 (s, 1 H; CH), 7.51 - 7.27 (m, 10 H; C6H5), 5.35 (s, 4 H; CH2), 2.85 (s, 6 H; CH3);); ^{13}C NMR (125MHz, [D$_1$]CHCl$_3$,

25 ℃) δ= 165.7, 162.8, 141.3, 135.6, 128.8, 128.4, 122.9, 67.2, 25.1; IR(Neat): 3038, 2967,

1782, 1717, 1593, 1542, 1498, 1439, 1285, 1252, 1215, 1111, 1026, 1002, 769, 749, 729, 692;

HRMS: C23H21NO4+H, Calculated = 376.1543 *m/z*, Found = 376.1525 *m/z.*

4.58 diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate

White solid. M.P.: 60 - 61 ^{o}C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 7.42 - 7.31 (m, 3 H; CH),

7.29 - 7.17 (m, 2 H; CH), 3.99 (q, ^{3}*J*(H,H)= 7.4 Hz, 4 H; C*H*2CH3), 2.59 (s, 6 H), 0.89

(t, ^{3}*J*(H,H)= 7.2 Hz, 6 H; CH2C*H*3); ^{13}C NMR (125MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 168.0, 155.5,

146.2, 136.7, 128.5, 128.2, 127.0, 61.4, 23.0, 13.6

4.59 diethyl 2,6-dimethyl-4-(p-tolyl)pyridine-3,5-dicarboxylate

White solid. M.P.: 70 - 73 ^{o}C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 7.15 (d, ^{3}*J*(H,H)= 8.0 Hz,

2 H; CH), 7.13 (d, ^{3}*J*(H,H)= 8.6 Hz, 2 H; CH), 4.02 (d, J = 7.4 Hz, 4 H; C*H*2CH3), 2.58 (s, 6 H;

CH3), 2.35 (s, 3 H; CH3), 0.94 (t, ^{3}*J*(H,H)= 7.2 Hz, 6 H; CH2C*H*3); ^{13}C NMR (125MHz,

[D$_1$]CHCl$_3$, 25 ℃) δ= 168.1, 155.3, 146.3, 138.4, 133.6, 128.9, 128.0, 127.2, 61.4, 23.0, 21.3,

13.7

4.60 diethyl 4-(furan-2-yl)-2,6-dimethylpyridine-3,5-dicarboxylate

Oil. ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 7.47 (s, 1 H; CH), 7.42 (s, 1 H; CH), 6.44 (s, 1 H;

CH), 4.18 (q, ^{3}*J*(H,H)= 7.3 Hz, 4 H; C*H*2CH3), 1.15 (t, ^{3}*J*(H,H)= 7.2 Hz, 6 H; CH2C*H*3); ^{13}C

NMR (75 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 168.2, 155.2, 143.1, 141.2, 136.7, 127.2, 120.4, 111.3,

61.7, 22.8, 13.9

4.61 diethyl 4-(4-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate

White solid. M.P.: 69 - 71 ^{o}C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 7.17 (d, ^{3}*J*(H,H)= 8.6 Hz,

2 H; CH), 6.87 (d, ^{3}*J*(H,H)= 8.6 Hz, 2 H; CH), 4.02 (q, ^{3}*J*(H,H)= 6.9 Hz, 4 H; C*H*2CH3), 3.79 (s,

3 H; CH3), 2.56 (s, 6 H; CH3), 0.96 (t, ^{3}*J*(H,H)= 7.2 Hz, 6 H; CH2C*H*3); ^{13}C NMR (75 MHz,

[D$_1$]CHCl$_3$, 25 ℃) δ= 168.2, 159.9, 155.3, 145.8, 129.5, 128.7, 127.3, 113.7, 61.4, 55.4, 22.9,

13.8.

4.62 dimethyl 2,4,6-trimethylpyridine-3,5-dicarboxylate

White solid. M.P.: 78 - 80 $^{\circ}$C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 3.50 (s, 6 H; CH3), 2.08 (s, 6 H; CH3), 1.82 (s, 3 H; CH3); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 168.9, 155.3, 142.5, 127.4, 52.5, 23.1, 17.2

4.63 dimethyl 2,6-diethyl-4-methylpyridine-3,5-dicarboxylate

Colorless oil; ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 3.90 (s, 6 H; CH3), 2.73 (d, ^3J(H,H)= 7.4 Hz, 4 H; CH2CH3), 2.20 (s, 3 H; CH3), 1.24 (t, ^3J(H,H)= 7.4 Hz, 6 H; CH2CH3); ^{13}C NMR (75 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 169.2, 160.2, 142.1, 126.9, 52.5, 29.9, 17.1, 14.0; IR(Neat): 2974, 2951, 2878, 1725, 1561, 1435, 1296, 1221, 1108, 1072, 972, 917, 832, 805, 755, 733; HRMS: C14H19NO4+H, Calculated = 266.1387m/z, Found = 266.1375m/z.

4.66 2-phenylbenzo[d]thiazole

White solid. M.P.: 113 - 114 $^{\circ}$C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.15 - 8.02 (m, 3 H; CH), 7.90 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 7.54 - 7.44 (m, 4 H; CH), 7.42 - 7.34 (m, 1 H; CH); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 168.2, 154.2, 135.2, 133.7, 131.1, 129.1, 127.7, 126.4, 125.3, 123.3, 121.7.

4.67 2-(2,6-dimethylphenyl)benzo[d]thiazole

White solid. M.P.: 123 - 124 $^{\circ}$C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.12 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 7.95 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 7.53 (t, ^3J(H,H)= 7.7 Hz, 1 H; CH), 7.48 - 7.40 (m, 1 H; CH), 7.30 - 7.26 (m, 1 H; CH), 7.14 (d, ^3J(H,H)= 7.4 Hz, 2 H; CH), 2.21 (s, 6 H; CH3); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 167.6, 153.6, 137.4, 136.4, 133.6, 129.7, 127.7, 126.1, 125.3, 123.6, 121.7, 20.3.

4.68 2-(4-nitrophenyl)benzo[d]thiazole

Yellow solid. M.P.: 225 - 226 $^{\circ}$C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.35 (d, ^3J(H,H)= 8.6 Hz, 2 H; CH), 8.27 (d, ^3J(H,H)= 8.6 Hz, 2 H; CH), 8.13 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 7.96 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 7.55 (t, ^3J(H,H)= 7.7 Hz, 1 H; CH), 7.46 (t, ^3J(H,H)= 7.5 Hz, 1 H; CH); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 164.9, 154.2, 149.1, 139.3, 135.6, 128.3, 127.0, 126.3, 124.4, 124.0, 121.9.

4.69 2-(4-chlorophenyl)benzo[d]thiazole

White solid. M.P.: 115 - 117 $^{\circ}$C. ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.06 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 8.02 (d, ^3J(H,H)= 8.6 Hz, 2 H; CH), 7.89 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 7.53 - 7.43 (m, 3 H; CH), 7.39 (t, ^3J(H,H)= 7.5 Hz, 1 H; CH); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 166.72, 154.17, 137.13, 135.15, 132.22, 129.37, 128.81, 126.59, 125.52, 123.40, 121.76.

4.70 2-(naphthalen-1-yl)benzo[d]thiazole

White solid. M.P.: 126 - 127 $^{\circ}$C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.57 (br. s., 1 H; CH), 8.21 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 8.12 (d, ^3J(H,H)= 7.4 Hz, 1 H; CH), 8.02 - 7.82 (m, 4 H; CH), 7.61 - 7.47 (m, 3 H; CH), 7.40 (t, ^3J(H,H)= 7.2 Hz, 1 H; CH); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 168.2, 154.4, 135.2, 134.7, 133.3, 131.1, 128.9, 128.0, 127.7, 127.6, 127.0, 126.5, 125.4, 124.6, 123.4, 121.8.

4.71 2-(naphthalen-2-yl)benzo[d]thiazole

White solid. M.P.: 126 - 128°C. ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 9.09 (s, 1 H; CH), 8.13 (d, ^3J(H,H)= 7.4 Hz, 1 H; CH), 8.01 (d, ^3J(H,H)= 8.6 Hz, 1 H; CH), 7.93 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 7.75 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 7.67 (t, ^3J(H,H)= 7.4 Hz, 1 H; CH), 7.58 (m, 2 H; CH), 7.28 - 7.23 (m, 2 H; CH), 7.22 - 7.13 (m, 2 H); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 160.5, 149.6, 134.1, 132.6, 132.3, 131.6, 131.3, 128.8, 128.0, 127.1, 127.1, 126.5, 126.2, 125.3, 125.0, 117.2.

4.72 2-(4-((tert-butyldimethylsilyl)oxy)phenyl)benzo[d]thiazole

Colorless oil; ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.03 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 8.6 Hz, 2 H), 7.86 (d, J = 8.0 Hz, 1 H), 7.46 (t, J = 7.4 Hz, 1 H), 7.38 - 7.32 (t, J = 7.4 Hz, 1 H), 6.94 (d, J = 8.6 Hz, 2 H), 1.01 (s, 9 H), 0.25 (s, 6 H); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ=186.0, 158.6, 154.3, 135.0, 129.2, 129.1, 126.3, 124.9, 122.9, 121.6, 120.7, 25.9, 18.4, -4.2; HRMS: C19H23NOSSi+H, Calculated = 342.1342 *m/z*, Found = 342.1323 *m/z.*

4.73 2-(4-(trifluoromethyl)phenyl)benzo[d]thiazole

White solid. M.P.: 160 - 163 °C ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 8.20 (d, ^3J(H,H)= 8.0 Hz, 2 H; CH), 8.11 (d, ^3J(H,H)= 8.6 Hz, 1 H; CH), 7.93 (d, ^3J(H,H)= 8.0 Hz, 1 H; CH), 7.75 (d, ^3J(H,H)= 8.0 Hz, 2 H; CH), 7.53 (t, ^3J(H,H)= 7.4 Hz, 1 H; CH), 7.48 - 7.37 (m, 1 H; CH); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 166.2, 154.1, 136.9, 135.3, 132.4, 127.9, 126.8, 126.13, 126.10, 125.9, 123.7, 121.9; ^{19}F NMR(283MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= -62.7

4.74 tert-butyl (benzo[d]thiazol-2-ylmethyl)(methyl)carbamate

Colorless oil; ^{1}H NMR (500 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ= 7.98 (d, J = 7.6 Hz, 1 H), 7.87 (br.s., 1 H), 7.47 (br. s., 1 H), 7.38 (br. s., 1 H), 4.89 - 4.70 (m, 2 H), 3.10 - 2.91 (m, 3 H), 1.50 (m, 9 H); ^{13}C NMR (125 MHz, [D$_1$]CHCl$_3$, 25 ℃) δ=169.87, 169.69, 155.92, 155.04, 153.12, 135.64, 135.29, 126.20, 125.26, 123.01, 121.86, 80.88, 80.62, 51.69, 50.95, 34.92, 34.82, 28.47; HRMS: C14H18N2O2S+Na, Calculated = 301.0981 m/z, Found = 301.0976

Appendix C

NMR Spectra of Compounds

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	05 Nov 2011 08:04:28		
Date Stamp	06 Nov 2011 00:15:06			File Name	C:\Users\chen\Desktop\DakinNMR\CS_diclnhflaivn_dry-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	16	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	44.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.200				

CS_diclnhflaivn_dry-1.esp

2.10a

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date		04 Nov 2011 11:47:25
Date Stamp	05 Nov 2011 03:58:02					File Name		C:\Users\chen\Desktop\DakinNMR\carbon\CS_DiclNHflavin-1.jdf
Frequency (MHz)	125.77	Nucleus		13C		Number of Transients	260	Origin	ECA 500
Original Points Count	32768	Owner		delta		Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent		DMSO-d6		Spectrum Offset (Hz)	12553.6279	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.500					

CS_DiclNHflavin-1.esp
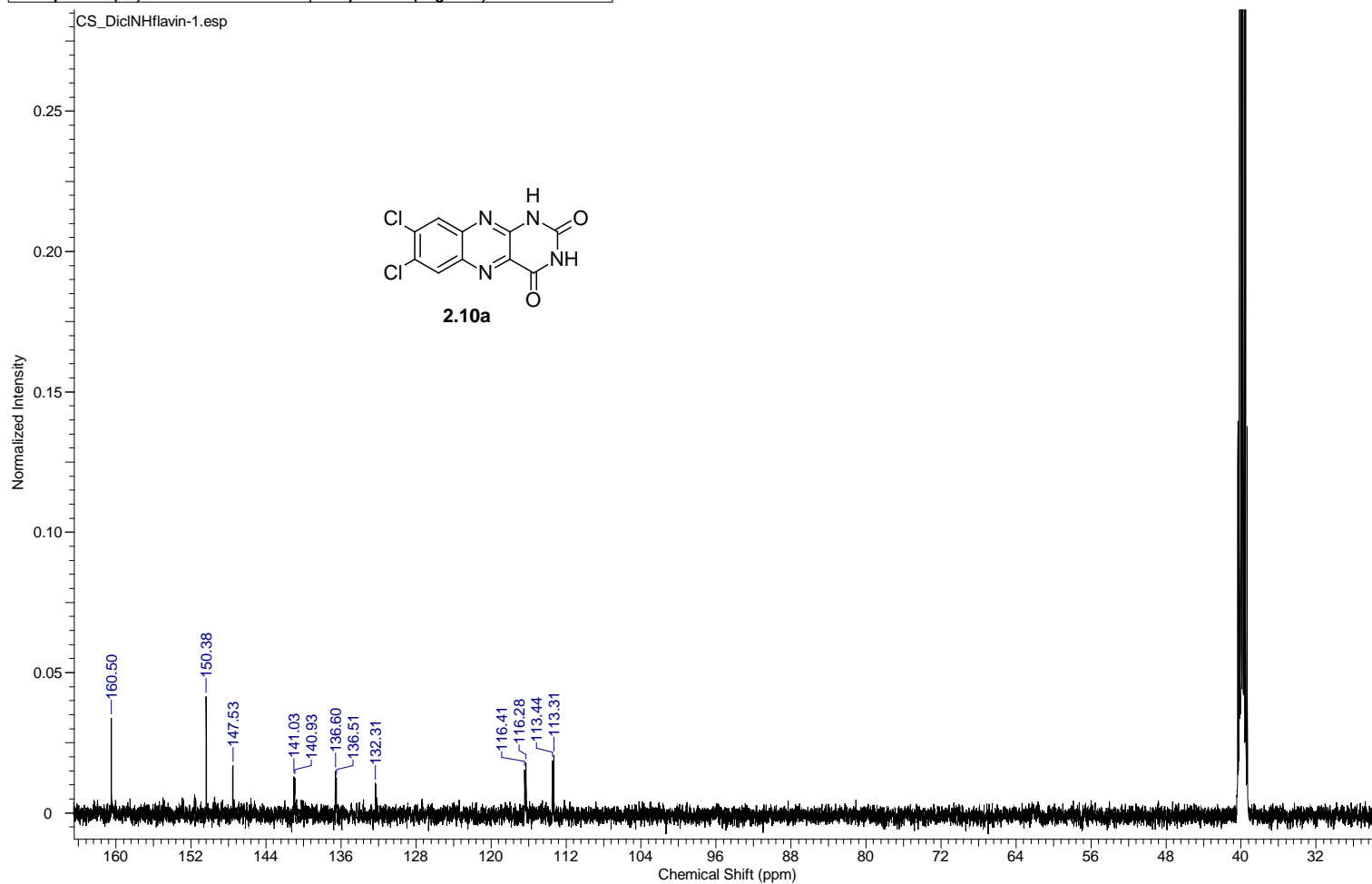
Acquisition Time (sec)	2.9072	Comment	single_pulse	Date	05 Nov 2011 08:44:44		
Date Stamp	05 Nov 2011 07:31:45			File Name	C:\Users\chen\Desktop\DakinNMR\CS_diFNHflavin_dry-1.jdf		
Frequency (MHz)	300.53	Nucleus	1H	Number of Transients	4	Origin	ECX 300
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	50.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	1502.6483	Spectrum Type	STANDARD
Sweep Width (Hz)	5635.71	Temperature (degree C)	22.100				

CS_diFNHflavin_dry-1.esp

Water

2.10b

M01(s)
M02(s)
M03(d)
M04(d)

12.08
11.82
8.47
8.46
8.18
8.16

1.00 0.93
0.89 0.87

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	04 Nov 2011 11:29:23
Date Stamp	05 Nov 2011 03:40:00					File Name	C:\Users\chen\Desktop\DakinNMR\carbon\CS_DiFNHflavin-1.jdf
Frequency (MHz)	125.77	Nucleus	13C			Number of Transients	120	Origin	ECA 500
Original Points Count	32768	Owner	delta			Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	DMSO-d6			Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.500				

CS_DiFNHflavin-1.esp

2.10b

Acquisition Time (sec)	0.2726	Comment	single_pulse	Date	30 Dec 2011 08:31:14		
Date Stamp	31 Dec 2011 01:29:18			File Name	C:\Users\chen\Desktop\DakinNMR\NMR PDF\DiF\Florine\CS_DiFNHflavin_florine-1.jdf		
Frequency (MHz)	470.62	Nucleus	19F	Number of Transients	15	Origin	ECA 500
Original Points Count	65536	Owner	delta	Points Count	65536	Pulse Sequence	single_pulse.ex2
Receiver Gain	54.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	0.0000	Spectrum Type	STANDARD
Sweep Width (Hz)	240384.63	Temperature (degree C)	21.700				

CS_DiFNHflavin_florine-1.esp

M01(m)

M02(m)

-126.39

-133.52

2.10b

1.04 1.00

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	1.7459	**Comment**	single_pulse	**Date**	05 Nov 2011 08:48:07	
Date Stamp	06 Nov 2011 00:58:45			**File Name**	C:\Users\chen\Desktop\DakinNMR\CS_diHnhflaivn_dry-1.jdf	
Frequency (MHz)	500.16	**Nucleus**	1H	**Number of Transients**	16	**Origin**	ECA 500
Original Points Count	16384	**Owner**	delta	**Points Count**	16384	**Pulse Sequence**	single_pulse.ex2
Receiver Gain	44.00	**Solvent**	DMSO-d6	**Spectrum Offset (Hz)**	2500.7996	**Spectrum Type**	STANDARD
Sweep Width (Hz)	9384.38	**Temperature (degree C)**	22.100				

CS_diHnhflaivn_dry-1.esp

2.10c

Acquisition Time (sec)	0.8336	**Comment**		single pulse decoupled gated NOE		**Date**	05 Nov 2011 08:59:41
Date Stamp	06 Nov 2011 01:10:19				**File Name**		C:\Users\chen\Desktop\DakinNMR\CS_diHNHflavin_dry-1.jdf
Frequency (MHz)	125.77	**Nucleus**	13C		**Number of Transients**	260	**Origin**	ECA 500
Original Points Count	32768	**Owner**	delta		**Points Count**	32768	**Pulse Sequence**	single_pulse_dec
Receiver Gain	50.00	**Solvent**	DMSO-d6		**Spectrum Offset (Hz)**	12576.5293	**Spectrum Type**	STANDARD
Sweep Width (Hz)	39308.18	**Temperature (degree C)**	22.700					

CS_diHNHflavin_dry-1.esp

2.10c

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	01 Dec 2011 13:28:21		
Date Stamp	02 Dec 2011 06:24:38			File Name	F:\Dakin NMR\CS_DiMeNhflavin_proton-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	6	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	48.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.100				

CS_DiMeNhflavin_proton-1.esp

2.10d

Acquisition Time (sec)	2.9072	Comment	single_pulse	Date	17 Nov 2011 16:44:17		
Date Stamp	17 Nov 2011 16:16:38			File Name	C:\Users\chen\Desktop\DakinNMR\NMR PDF\DiMeO\CS_DiMethoxyNHflavin-1.jdf		
Frequency (MHz)	300.53	Nucleus	1H	Number of Transients	15	Origin	ECX 300
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	46.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	1502.6483	Spectrum Type	STANDARD
Sweep Width (Hz)	5635.71	Temperature (degree C)	22.000				

CS_DiMethoxyNHflavin-1.esp

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	06 Nov 2011 08:18:49		
Date Stamp	07 Nov 2011 01:14:57			File Name	C:\Users\chen\Desktop\DakinNMR\CS_DiClNMeFlavin_500HMz-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	4	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	42.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.200		

CS_DiClNMeFlavin_500HMz-1.esp

2.11a

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	06 Nov 2011 08:25:30
Date Stamp	07 Nov 2011 01:21:38					File Name	C:\Users\chen\Desktop\DakinNMR\carbon\CS_diClNMeFlaivn_500HMz_copy-1.jdf
Frequency (MHz)	125.77	Nucleus	13C			Number of Transients	180	Origin	ECA 500
Original Points Count	32768	Owner	delta			Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d					Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18			Temperature (degree C)	22.600		

CS_diClNMeFlaivn_500HMz_copy-1.esp

2.11a

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	06 Nov 2011 08:04:19
Date Stamp	07 Nov 2011 01:00:27			File Name		C:\Users\chen\Desktop\DakinNMR\carbon\CS_diFNMeFlaivn_500HMz-1.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	1000	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	22.800	

CS_diFNMeFlaivn_500HMz-1.esp

2.11b

CS_diFNMeFlaivn_500HMz-1.esp

Acquisition Time (sec)	0.2726	Comment		single_pulse	Date		30 Dec 2011 08:26:09		
Date Stamp	31 Dec 2011 01:24:13								
File Name	C:\Users\chen\Desktop\DakinNMR\NMR PDF\DiF\Florine\CS_DiFNMeFlavin_Florine-1.jdf						Frequency (MHz)	470.62	
Nucleus	19F	Number of Transients	36		Origin	ECA 500	Original Points Count	65536	
Owner	delta	Points Count	65536		Pulse Sequence	single_pulse.ex2	Receiver Gain	56.00	
Solvent	CHLOROFORM-d				Spectrum Offset (Hz)	0.0000	Spectrum Type	STANDARD	
Sweep Width (Hz)	240384.63	Temperature (degree C)	21.800						

CS_DiFNMeFlavin_Florine-1.esp

Acquisition Time (sec)	2.9074	Comment	single_pulse	Date	24 Apr 2010 07:54:17		
Date Stamp	24 Apr 2010 07:38:58						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\NMR300M 072010\300MHZ\proton\CS_1043_SM-6.jdf						
Frequency (MHz)	300.53	Nucleus	1H	Number of Transients	11	Origin	ECX 300
Original Points Count	13107	Owner	delta	Points Count	13107	Pulse Sequence	single_pulse.ex2
Receiver Gain	48.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	1502.6483	Spectrum Type	STANDARD
Sweep Width (Hz)	4508.15	Temperature (degree C)	21.000				

CS_diHNMeflavin.esp

2.11c

M05(s) 3.83
M06(s) 3.61
7.26
M01(m)
M03(td)
M04(m)
M02(m)
1.59
8.36 8.33 8.02 8.02 7.91 7.90 7.79 7.76
1.00 0.94 0.98 0.97
2.88 2.89
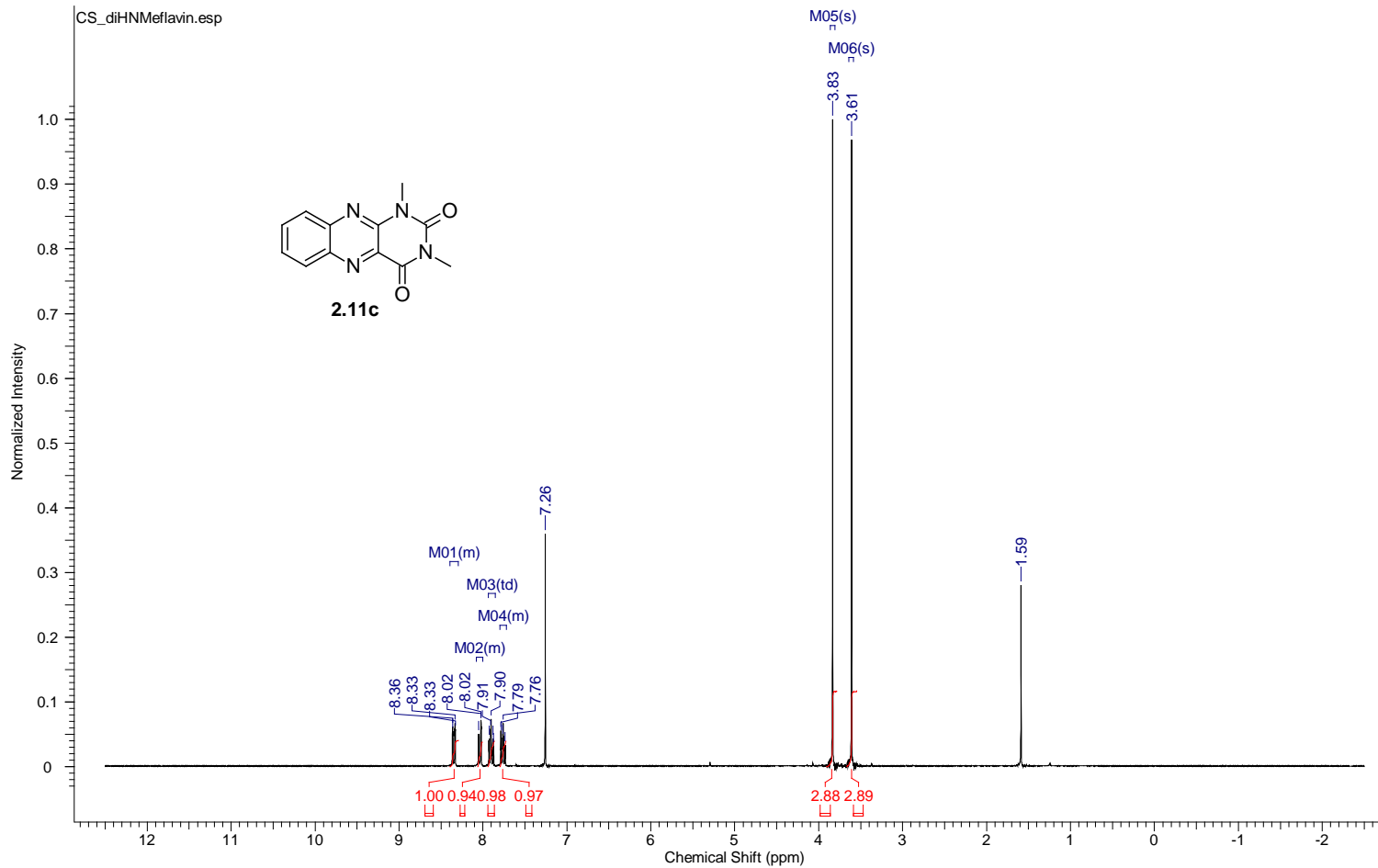
Acquisition Time (sec)	2.0840	Comment		single pulse decoupled gated NOE		Date		28 Sep 2009 17:27:29
Date Stamp	29 Sep 2009 10:36:52			File Name		C:\Users\chen\Desktop\DakinNMR\CS_1043_copy-2.jdf		
Frequency (MHz)	125.76	Nucleus	13C	Number of Transients	340	Origin		Eclipse+ 500
Original Points Count	65536	Owner	delta	Points Count	65536	Pulse Sequence		single_pulse_dec
Receiver Gain	28.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)		12575.7109
Spectrum Type	STANDARD	Sweep Width (Hz)	31446.54	Temperature (degree C)	28.200			

CS_diHNMeflavin_carbon.esp

2.11c

159.88 150.80 145.45 143.44 140.10 133.93 130.90 129.21 127.92 29.67

Normalized Intensity

Chemical Shift (ppm)

CS_diMeNMeFlaivn_500HMz-1.esp

2.11d

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	16 Nov 2011 14:09:18		
Date Stamp	17 Nov 2011 07:05:29						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz112511\aaron\proton\CS_DimethoxyNMeFlaivn-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	11	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	48.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.300				

CS_DiMethoxyNMeflavin-1.esp

2.11e

Acquisition Time (sec)	1.3841	Comment	single pulse decoupled gated NOE		Date	17 Nov 2011 16:31:49
Date Stamp	17 Nov 2011 16:04:10					
File Name	C:\Users\chen\Desktop\DakinNMR\NMR PDF\DiMeO\CS_DiMethoxyNMeflavin-1_carbon.jdf				Frequency (MHz)	75.57
Nucleus	13C	Number of Transients	1000	Origin	ECX 300	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	7556.8232	Spectrum Type	STANDARD	Sweep Width (Hz)	23674.24
Temperature (degree C)	22.300					

CS_DiMethoxyNMeflavin-1_carbon.esp

2.11e

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date		27 Dec 2011 08:48:32	
Date Stamp	28 Dec 2011 01:46:35			File Name		C:\Users\chen\Desktop\DakinNMR\NMR PDF\DiCl\CS_2293_12h_DiClNEtflavin-1.jdf	
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	16	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	56.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	21.700		

CS_2293_12h_DiClNEtflavin-1.esp

2.12a

M03(q)
M04(s)
M05(s)

3.44
3.33

M06(t)
1.17

7.26
M01(s)
6.86
M02(s)
6.61

3.48
3.47
3.50

1.18
1.16

0.71 0.68

2.15 2.72 3.09

3.02

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	28 Dec 2011 03:08:52
Date Stamp	28 Dec 2011 14:19:10			File Name	G:\Dakin NMR\carbon\CS_2293_DiClNEtflavin-1.jdf		
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	10000	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	22.500		

CS_2293_DiClNEtflavin-1_carbon.esp

2.12a

Peaks: 157.66, 150.21, 145.06, 136.84, 134.38, 127.97, 125.86, 124.91, 122.87, 115.60, 50.22, 28.70, 28.46, 11.88

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	22 Nov 2011 09:21:58		
Date Stamp	23 Nov 2011 02:18:12			File Name	C:\Users\chen\Desktop\DakinNMR\NMR PDF\DiF\CS_DIFNEtflavin_good-5.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	16	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	56.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000		

CS_DIFNEtflavin_good-5.esp

2.12b

Acquisition Time (sec)	0.2307	Comment	single_pulse	Date	07 Dec 2011 11:35:52		
Date Stamp	07 Dec 2011 11:07:56						
File Name	C:\Users\chen\Desktop\DakinNMR\NMR PDF\DiF\Florine\CS_DifNEtFlavin_reduced_F-1.jdf					Frequency (MHz)	282.78
Nucleus	19F	Number of Transients	196	Origin	ECX 300	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse.ex2	Receiver Gain	30.00
Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	0.0000	Spectrum Type	STANDARD
Sweep Width (Hz)	142045.45	Temperature (degree C)	26.000				

CS_DifNEtFlavin_reduced_F-1.esp

2.12b
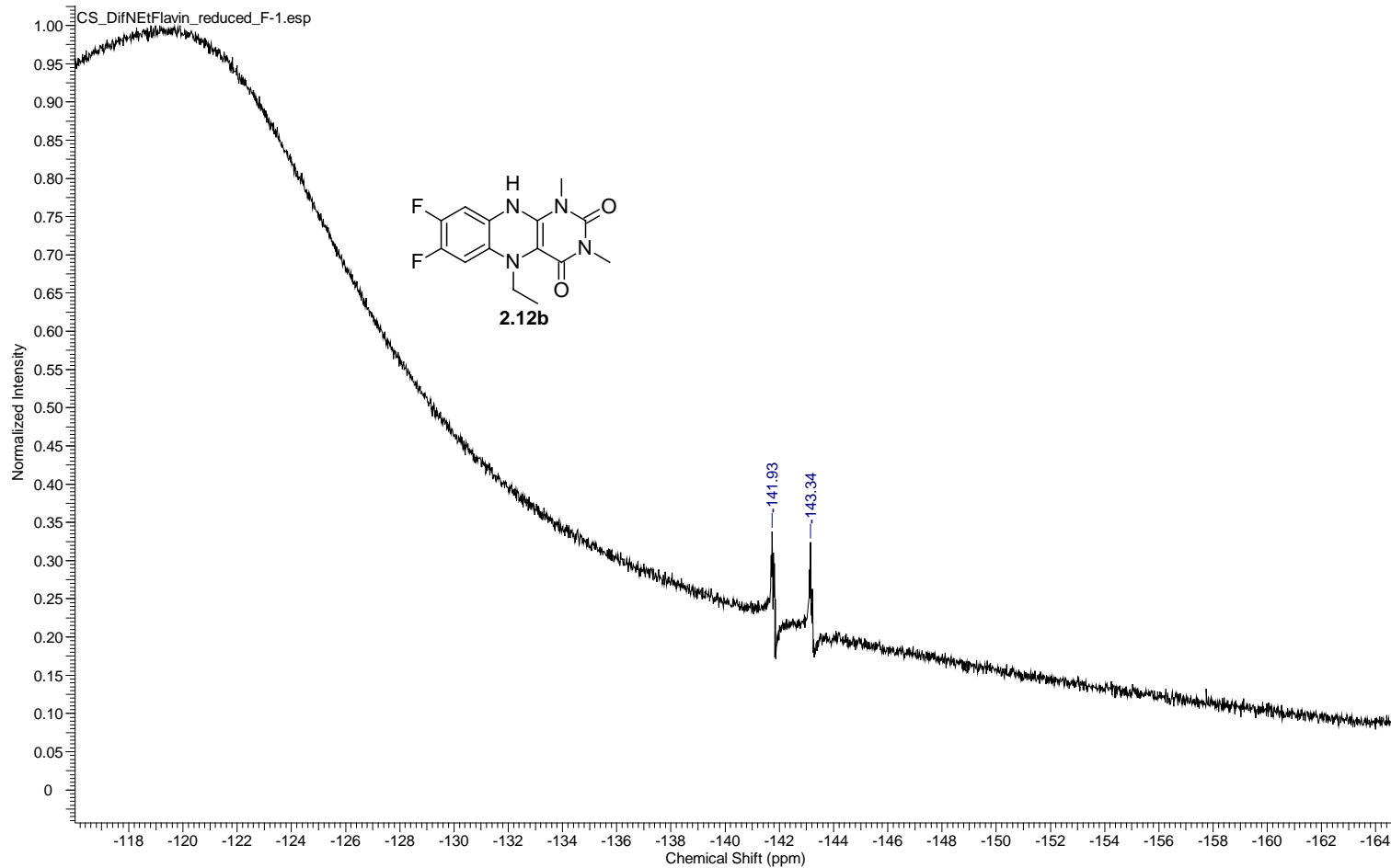
Acquisition Time (sec)	2.9072	Comment	single_pulse	Date	05 Nov 2011 12:38:42		
Date Stamp	05 Nov 2011 11:25:43			File Name	C:\Users\chen\Desktop\DakinNMR\CS_DiHNEtFlavin_reduced-1.jdf		
Frequency (MHz)	300.53	Nucleus	1H	Number of Transients	24	Origin	ECX 300
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	46.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	1502.6483
Spectrum Type	STANDARD	Sweep Width (Hz)	5635.71	Temperature (degree C)	22.400		

CS_DiHNEtFlavin_reduced-1.esp

2.12c

7.26 6.90 6.87 6.87 6.86 6.79 6.76 6.61 6.58 4.70 3.47 3.45 3.40 3.34

3.20 1.00 0.61 8.07

Chemical Shift (ppm)

Normalized Intensity
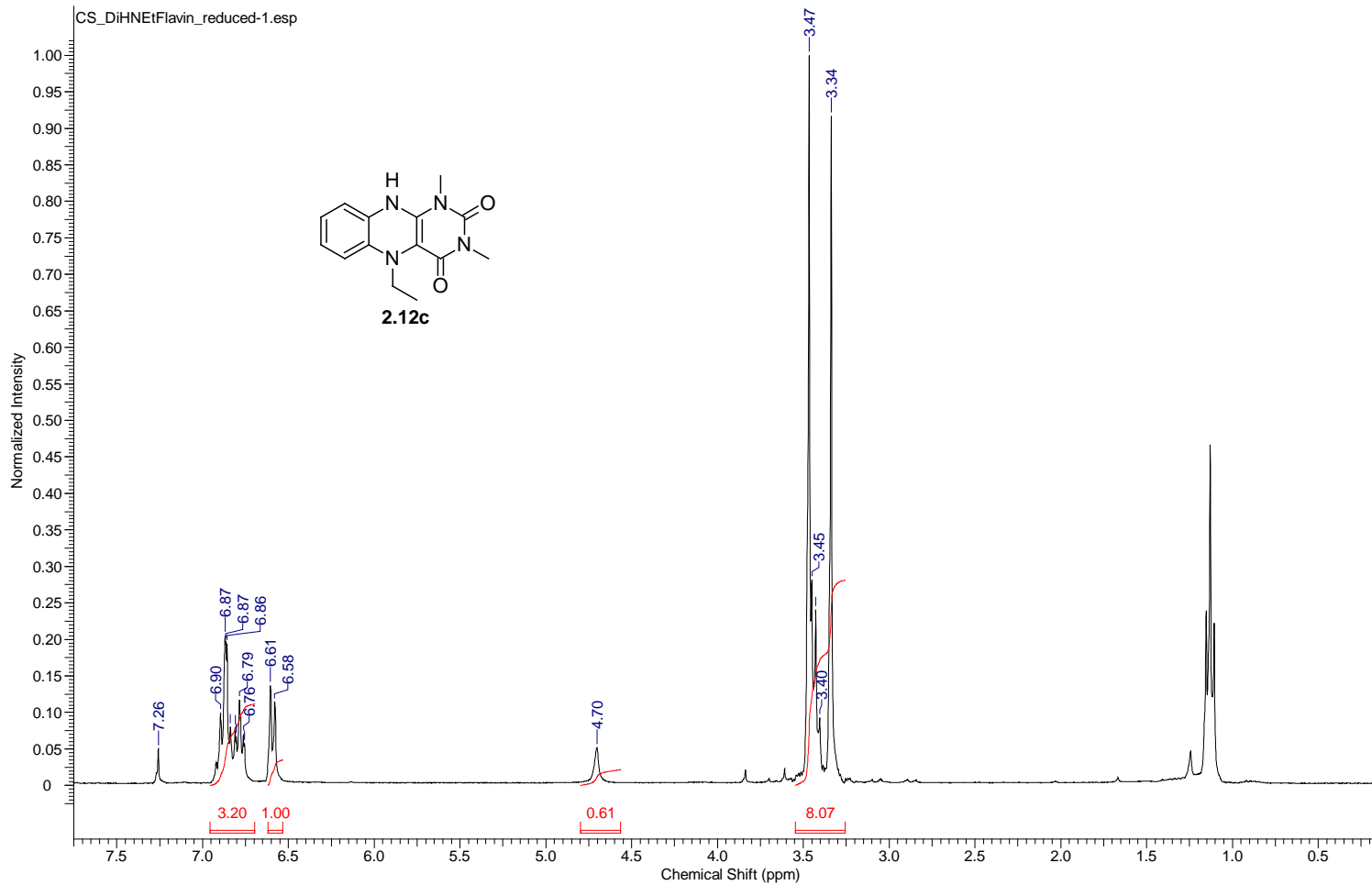
Acquisition Time (sec)	1.3841	Comment		single pulse decoupled gated NOE		Date	05 Nov 2011 14:47:18
Date Stamp	05 Nov 2011 13:34:18					File Name	C:\Users\chen\Desktop\DakinNMR\carbon\CS_DiHNEtFlavin_reduced_carbon.jdf
Frequency (MHz)	75.57	Nucleus	13C	Number of Transients	3000	Origin	ECX 300
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	7556.8232
Spectrum Type	STANDARD	Sweep Width (Hz)	23674.24	Temperature (degree C)	22.500		

CS_DiHNEtFlavin_reduced_carbon.esp

2.12c

Peaks: 158.14, 150.47, 146.43, 136.33, 135.06, 125.17, 123.59, 122.62, 114.79, 99.71, 50.77, 28.79, 28.42, 11.53

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date		17 Sep 2011 12:27:59	
Date Stamp	18 Sep 2011 04:40:32			File Name		C:\Users\chen\Desktop\DakinNMR\CS_2159_dimethylethylflavin_reduced-1.jdf	
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	5	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	54.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000		

CS_2159_dimethylethylflavin_reduced-1.esp

2.12d

Acquisition Time (sec)	1.3841	Comment		single pulse decoupled gated NOE	Date		06 Nov 2011 10:36:31
Date Stamp	06 Nov 2011 10:09:01				File Name		F:\Dakin NMR\carbon\CS_diMeNEtflavin_reduced_again-1.jdf
Frequency (MHz)	75.57	Nucleus	13C		Number of Transients	3000	Origin	ECX 300
Original Points Count	32768	Owner	delta		Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d				Spectrum Offset (Hz)	7556.8232
Spectrum Type	STANDARD	Sweep Width (Hz)	23674.24		Temperature (degree C)	22.100		

CS_diMeNEtflavin_reduced_again-1.esp

2.12d

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	28 Nov 2011 16:55:19
Date Stamp	29 Nov 2011 09:51:35					
File Name	C:\Users\chen\Desktop\DakinNMR\NMR PDF\DiMeO\CS_DiMethoxyNEtFlaivn_carbon-1.jdf				Frequency (MHz)	125.77
Nucleus	13C	Number of Transients	390	Origin	ECA 500	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18
Temperature (degree C)	22.200					

CS_DiMethoxyNEtFlaivn_carbon-1.esp

2.12e

Peaks: 158.49, 150.54, 146.86, 146.32, 145.56, 128.09, 128.01, 107.90, 100.07, 99.23, 56.39, 56.29, 51.24, 28.80, 28.40, 11.03

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	15 May 2012 08:49:43		
Date Stamp	16 May 2012 01:06:18						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz051012\aaron\proton\CS_3197_2ndbatch-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	16	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	46.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000				

CS_3197_2ndbatch-1.jdf

2.17

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	14 May 2012 09:01:18
Date Stamp	15 May 2012 01:17:52					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz051012\aaron\carbon\CS_3197_carbon-1.jdf				Frequency (MHz)	125.77
Nucleus	13C	Number of Transients	120	Origin	ECA 500	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	DMSO-d6	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18
Temperature (degree C)	22.600					

CS_3197_carbon-1.jdf

2.17

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	15 May 2012 12:06:10		
Date Stamp	16 May 2012 04:22:45						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz051012\aaron\proton\CS_3198_crudeproduct-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	13	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	54.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.200				

CS_3198_crudeproduct-1.jdf

2.19

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	05 Nov 2010 01:17:07
Date Stamp	05 Nov 2010 11:51:28					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\NMR 12 28 2010\500mhz110810\aaron\carbon\CS_1168-2.jdf					
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	5000	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.400				

CS_1168-2.jdf

2.19

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	19 May 2012 11:54:31		
Date Stamp	20 May 2012 04:11:08						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz051012\aaron\proton\CS_3201_reduced-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	10	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	56.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000				

CS_3201_reduced-1.esp

2.20

M02(d) 7.26

M08(s) 3.28

M09(t) 1.26 1.24

M03(m)

M05(t)

M01(m) 7.66 7.64 7.63 7.61 7.34

M04(m) 6.95 6.93 6.91 6.89 6.67 6.65 6.64

M06(d) 5.94 5.92

4.71

M07(q) 3.56 3.55 3.53 3.52

1.56 1.28

Normalized Intensity

3.23 2.19 1.01 1.00 0.94   0.94   2.04 2.98   3.00

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	23 Oct 2012 07:58:01
Date Stamp	23 Oct 2012 18:11:24			File Name		G:\500MHz101512\aaron\carbon\CS_4193_recrys_carbon-1.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	500	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	23.000		

CS_4193_recrys_carbon-1.esp

2.20

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	01 Dec 2011 09:01:22		
Date Stamp	02 Dec 2011 01:57:39			File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\CS_catechol_product-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	4	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	48.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000		

CS_catechol_product-1.esp

2.43a

M02(m)

M01(m)

M03(m)

Normalized Intensity

6.86 6.83 6.88 6.82 6.81 7.26 6.88 6.81 5.14 5.13 5.10

0.05 2.00 1.98 1.96

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	01 Dec 2011 09:02:41
Date Stamp	02 Dec 2011 01:58:57					File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\CS_catechol_carbon-2.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	30	Origin	ECA 500
Original Points Count	26214	Owner	delta	Points Count	26214	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	31444.86	Temperature (degree C)	22.300		
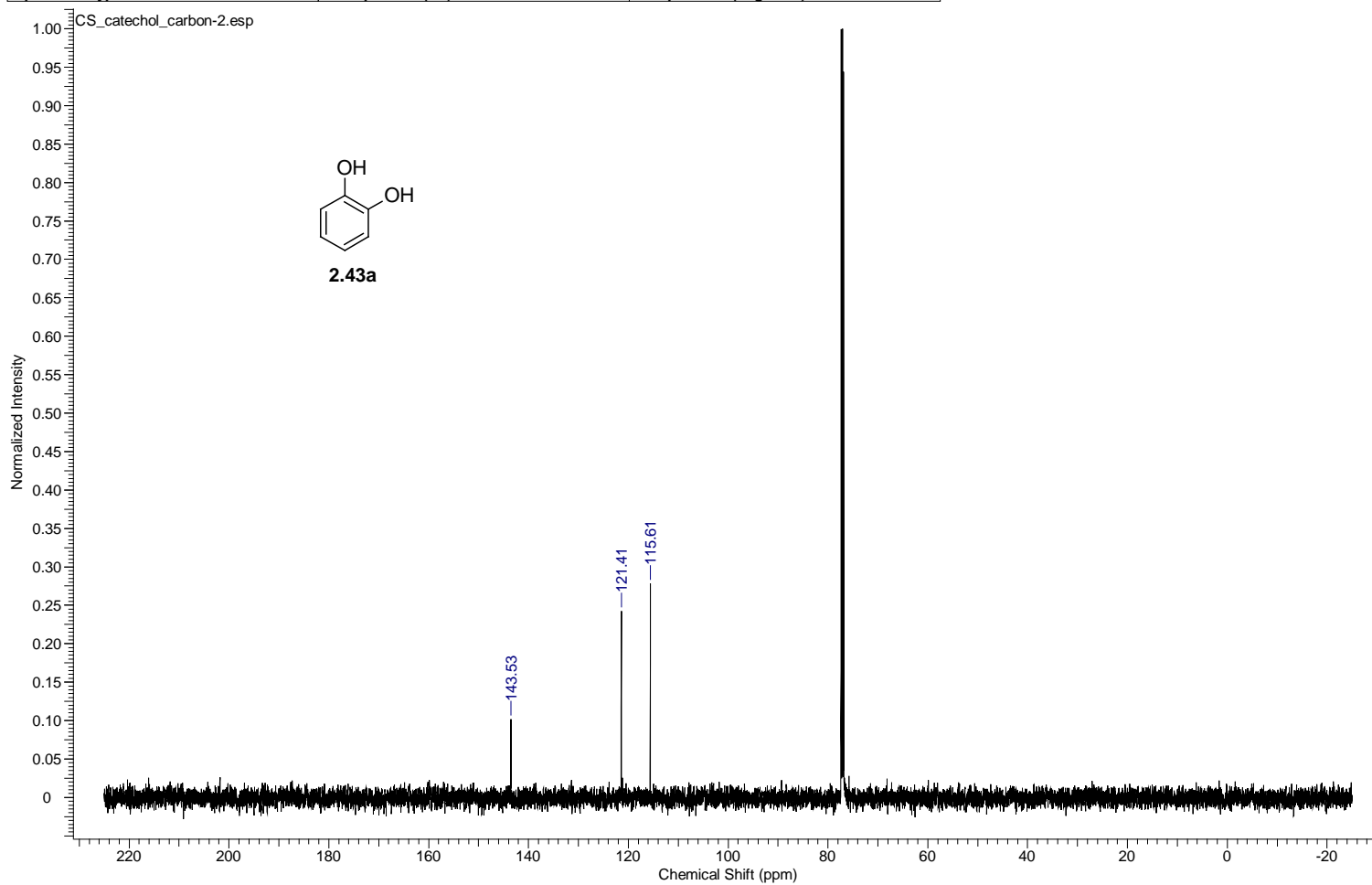
Acquisition Time (sec)	1.7460	Comment	single_pulse	Date	28 Oct 2011 11:19:01		
Date Stamp	29 Oct 2011 03:28:44			File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\MSH_1072-7.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	4	Origin	ECA 500
Original Points Count	13107	Owner	delta	Points Count	13107	Pulse Sequence	single_pulse.ex2
Receiver Gain	40.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	7506.82	Temperature (degree C)	22.200		

MSH_1072-7.esp

M06(s)

M01(td)
M03(d)
M02(d)
M05(br. s.)
M04(br. s.)

7.25
7.25
6.77
6.77
6.75
6.75
6.73
6.60
6.59
6.48
6.46
5.44
5.37
3.87
1.25

0.97 0.96 0.96   1.95   3.00

2.43b

Chemical Shift (ppm)

Normalized Intensity

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	28 Oct 2011 11:19:55
Date Stamp	29 Oct 2011 03:30:29				File Name		C:\Users\chen\Desktop\DakinNMR\substrate study\MSH_1072-1.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	40	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	22.500		

MSH_1072-1.esp

2.43b

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	19 Nov 2011 12:01:09		
Date Stamp	20 Nov 2011 04:57:22			File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\CS_2224_product-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	7	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	40.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000		

CS_2224_product-1.esp

M04(s)

3.72

OH

OH

O

2.43c

Normalized Intensity

M01(d) M03(dd)

M02(d)

6.77
6.75
6.50
6.49

6.35
6.34
6.33
6.33

7.26

M05(br. s.)

5.52

1.00 0.01 1.02 1.00   1.75   2.99

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	19 Nov 2011 12:03:24
Date Stamp	20 Nov 2011 04:59:37			File Name		C:\Users\chen\Desktop\DakinNMR\substrate study\CS_2224_product_copy-1.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	50	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d		Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	22.400		

CS_2224_product_copy-1.esp

2.43c

Peaks: 154.31, 144.73, 137.37, 116.01, 105.50, 102.57, 55.92

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	15 Dec 2011 11:11:23		
Date Stamp	16 Dec 2011 04:09:21			File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\MSH_198_product-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	13	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	44.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.300		

MSH_198_product-1.esp

2.43d

174

MSH_198_product_carbon-1.esp

2.43d

Acquisition Time (sec)	2.9072	Comment	single_pulse	Date	13 Dec 2011 16:46:58		
Date Stamp	13 Dec 2011 16:18:57			File Name	F:\Dakin NMR\sustract\CS_13dimethylhydroquinone-2.jdf		
Frequency (MHz)	300.53	Nucleus	1H	Number of Transients	4	Origin	ECX 300
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	46.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	1502.6483	Spectrum Type	STANDARD
Sweep Width (Hz)	5635.71	Temperature (degree C)	22.000				

CS_13dimethylhydroquinone-2.esp

2.43e

M04(s)

DMSO

2.03

M03(s)

6.27

Water

M01(s)

8.43

M02(s)

7.38

1.00   0.96   1.94   5.55

Normalized Intensity

Chemical Shift (ppm)

176

2.43e

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	13 Dec 2011 12:48:03		
Date Stamp	14 Dec 2011 05:46:00						
File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\SubstrateNMRPDF\CS_napthylcatechol-1.jdf				Frequency (MHz)	500.16	
Nucleus	1H	Number of Transients	7	Origin	ECA 500	Original Points Count	16384
Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2	Receiver Gain	54.00
Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	21.900				

1,2-Naphthoquinone.esp

2.43f

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	27 Dec 2011 10:05:12
Date Stamp	28 Dec 2011 03:03:15			File Name		C:\Users\chen\Desktop\DakinNMR\substrate study\napthaquinone_again-1.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	2000	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	22.400		

1,2-Naphthoquinone_carbon.esp

2.43f

Peaks: 180.99, 178.94, 145.45, 135.93, 134.89, 131.75, 130.99, 130.37, 129.94, 128.07

Normalized Intensity

Chemical Shift (ppm)

179

4nitrocatechol_proton.esp

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	28 Jan 2012 11:35:55		
Date Stamp	29 Jan 2012 04:35:18			File Name	G:\500MHz012512\aaron\proton\CS_3052_product_proton-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	16	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	46.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	21.900				

OH
OH
NO₂

2.43g

DMSO

M03(dd)
M02(d)
M01(d)
M04(dd)

7.56
7.56
6.87
6.85
7.61
7.59
10.27
10.25
10.24

Water

1.85
0.97 0.96 1.00

Acquisition Time (sec)	2.9072	Comment	single_pulse	Date	01 Dec 2010 08:55:33		
Date Stamp	01 Dec 2010 08:40:57			File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\CC_1018_product_DMSO-1.jdf		
Frequency (MHz)	300.53	Nucleus	1H	Number of Transients	6	Origin	ECX 300
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	38.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	1502.6483	Spectrum Type	STANDARD
Sweep Width (Hz)	5635.71	Temperature (degree C)	20.800				

CS_2182_product_hydroquione.esp

M02(s)
6.53

M01(s)
8.62

Water

2.43h

1.94

4.00

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	1.3841	Comment	single pulse decoupled gated NOE		Date	01 Dec 2010 09:10:38
Date Stamp	01 Dec 2010 08:56:02					
File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\CS_2182_product_hydroquinone_carbon.jdf				Frequency (MHz)	75.57
Nucleus	13C	Number of Transients	330	Origin	ECX 300	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	DMSO-d6	Spectrum Offset (Hz)	7556.8232	Spectrum Type	STANDARD	Sweep Width (Hz)	23674.24
Temperature (degree C)	21.200					

CS_2182_product_hydroquinone_carbon.jdf

2.43h

Acquisition Time (sec)	1.7460	Comment	single_pulse	Date	18 Nov 2011 11:40:20		
Date Stamp	19 Nov 2011 04:35:36			File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\CS_2188_product_redo-3.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	5	Origin	ECA 500
Original Points Count	13107	Owner	delta	Points Count	13107	Pulse Sequence	single_pulse.ex2
Receiver Gain	44.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	7506.82	Temperature (degree C)	22.200		

CS_2188_product_redo-3.esp

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date		18 Nov 2011 11:41:42
Date Stamp	19 Nov 2011 04:37:54					File Name		C:\Users\chen\Desktop\DakinNMR\substrate study\CS_2188_product-1.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	50	Origin		ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence		single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)		12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	22.500			

CS_2188_product-1.esp

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	15 Dec 2011 10:58:11		
Date Stamp	16 Dec 2011 03:56:09			File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\MSH_197_product-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	4	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	44.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.200		

MSH_197_product-1.esp

187

MSH_197_product_carbon-1.esp

2.43j

Acquisition Time (sec)	2.9072	Comment	single_pulse	Date	01 Dec 2010 12:10:57		
Date Stamp	01 Dec 2010 11:56:21			File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\CS_2214_column_yellowoil-1.jdf		
Frequency (MHz)	300.53	Nucleus	1H	Number of Transients	10	Origin	ECX 300
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	30.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	1502.6483
Spectrum Type	STANDARD	Sweep Width (Hz)	5635.71	Temperature (degree C)	21.100		

CS_2214_column_yellowoil-1.esp

2.43k

M05(s) 3.85
M06(s) 3.76
M01(d) 6.85, 6.82
M02(d) 6.50, 6.49
M03(dd) 6.41, 6.40, 6.38, 6.37
M04(s) 5.34

Integrations: 1.00, 0.94, 1.00, 0.93, 2.96, 2.97

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	01 Dec 2010 13:00:48
Date Stamp	02 Dec 2010 06:08:34				File Name	C:\Users\chen\Desktop\DakinNMR\substrate study\CS_2214_column_product-1.jdf
Frequency (MHz)	125.77	Nucleus	13C		Number of Transients	1000	Origin	ECA 500
Original Points Count	32768	Owner	delta		Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d		Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	21.800	

CS_2214_column_product-1.esp

2.43k

Acquisition Time (sec)	1.7459	**Comment**	single_pulse	**Date**	09 May 2012 13:20:51		
Date Stamp	10 May 2012 05:37:24						
File Name	C:\Users\chen\Desktop\DakinNMR\Aerobic Dakin Oxdiation\Substrate NMR\RAW data\CS_3194_3chlorocatechol_proton-1.jdf						
Frequency (MHz)	500.16	**Nucleus**	1H	**Number of Transients**	4	**Origin**	ECA 500
Original Points Count	16384	**Owner**	delta	**Points Count**	16384	**Pulse Sequence**	single_pulse.ex2
Receiver Gain	46.00	**Solvent**	CHLOROFORM-d	**Spectrum Offset (Hz)**	2500.7996	**Spectrum Type**	STANDARD
Sweep Width (Hz)	9384.38	**Temperature (degree C)**	22.400				

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	09 May 2012 13:24:50
Date Stamp	10 May 2012 05:41:23						
File Name	C:\Users\chen\Desktop\DakinNMR\Aerobic Dakin Oxdiation\Substrate NMR\RAW data\CS_3194_3chlorocatechol_carbon-1.jdf						
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	100	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.900				

CS_3194_3chlorocatechol_carbon-1.jdf

2.43o

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	08 May 2012 08:06:03		
Date Stamp	09 May 2012 00:22:34						
File Name	C:\Users\chen\Desktop\DakinNMR\Aerobic Dakin Oxdiation\Substrate NMR\RAW data\CS_3191_5chlorocatechol_proton.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	16	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	46.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.600				

CS_5chlorocatechol_proton-1.esp

2.43p

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	08 May 2012 08:09:53
Date Stamp	09 May 2012 00:26:25					
File Name	C:\Users\chen\Desktop\DakinNMR\Aerobic Dakin Oxdiation\Substrate NMR\RAW data\CS_3191_5chlorocatechol_carbon.jdf					
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	100	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	23.100				

CS_3191_5chlorocatechol_carbon.jdf

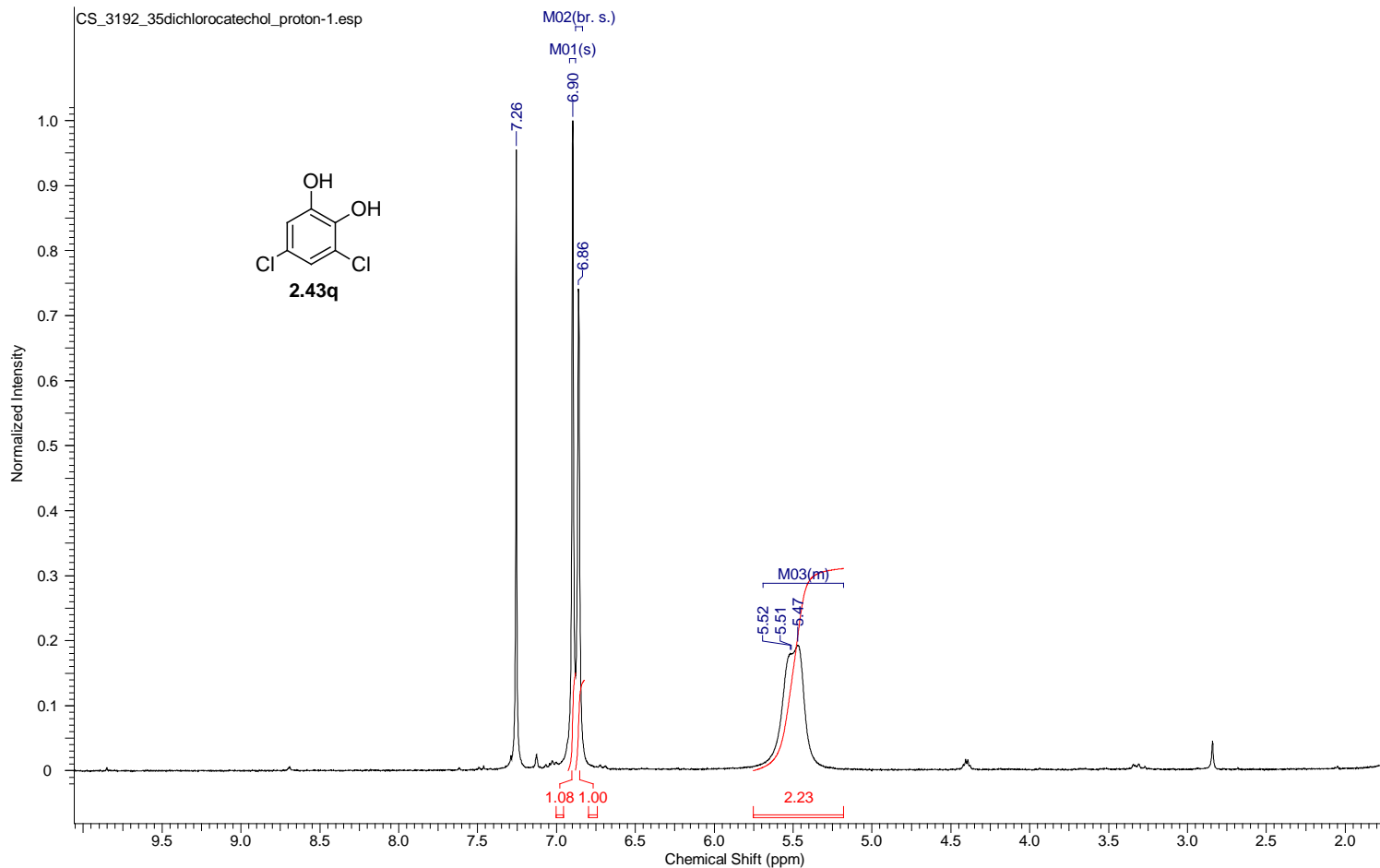| Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	09 May 2012 12:36:30		
Date Stamp	10 May 2012 04:53:02						
File Name	C:\Users\chen\Desktop\DakinNMR\Aerobic Dakin Oxdiation\Substrate NMR\RAW data\CS_3192_35dichlorocatechol_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	7	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.300				

CS_3192_35dichlorocatechol_proton-1.esp

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	09 May 2012 13:12:38
Date Stamp	10 May 2012 05:29:10					
File Name	C:\Users\chen\Desktop\DakinNMR\Aerobic Dakin Oxdiation\Substrate NMR\RAW data\CS_3192_35dichlorocatechol_carbon-1.jdf					
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	1000	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	23.000			

CS_3192_35dichlorocatechol_carbon-1.jdf

2.43q

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	01 May 2012 10:04:51		
Date Stamp	02 May 2012 02:21:20						
File Name	C:\Users\chen\Desktop\DakinNMR\Aerobic Dakin Oxdiation\Substrate NMR\RAW data\CS_3127_3bromo5nitrocatechol_proton.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	11	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	50.00	Solvent	DMSO-d6	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000				

CS_3127_3bromo5nitrocatechol_proton.esp

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE			Date	10 Aug 2012 12:52:59
Date Stamp	11 Aug 2012 05:11:37						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz083012\aaron\carbon\CS_4113_product_carbon-1.jdf						
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	70	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.400				

CS_4113_product_carbon-1.esp

3.45a

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	03 Sep 2012 09:31:51		
Date Stamp	04 Sep 2012 01:50:39						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz083012\aaron\proton\CS_4140_proton-1.jdf			Frequency (MHz)	500.16		
Nucleus	1H	Number of Transients	8	Origin	ECA 500	Original Points Count	16384
Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2	Receiver Gain	50.00
Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000				

CS_4140_proton-1.esp

3.45b

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	31 Aug 2012 11:21:37		
Date Stamp	01 Sep 2012 03:40:23						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz083012\aaron\proton\CS_4141_product_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	7	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	48.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.200				

CS_4141_product_proton-1.esp

3.45c

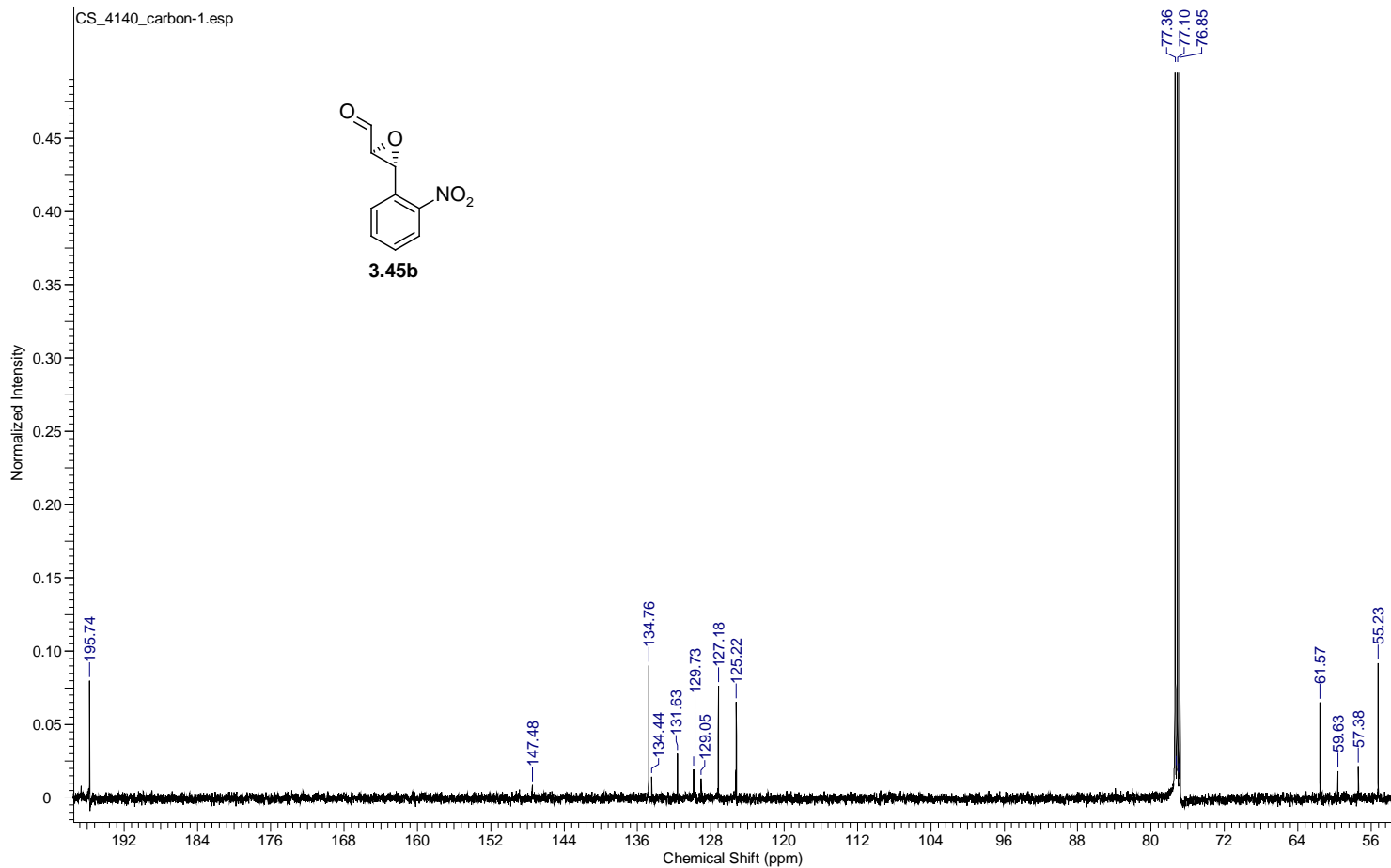| Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	31 Aug 2012 11:24:05
Date Stamp	01 Sep 2012 03:42:51					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz083012\aaron\carbon\CS_4141_carbon_copy-1.jdf			Frequency (MHz)	125.77	
Nucleus	13C	Number of Transients	60	Origin	ECA 500	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18
Temperature (degree C)	22.600					

CS_4141_carbon_copy-1.jdf

3.45c

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	15 Nov 2012 08:13:37		
Date Stamp	16 Nov 2012 01:00:25			File Name	G:\500MHz111612\aaron\proton\CS_4209_proton-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	16	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	20.800		

CS_4209_proton-1.esp

3.45d

M02(d)
M03(d)
7.26

M01(d)
9.19
9.18

7.37
7.35
7.24
7.22

M04(s)
4.15

M05(dd)
3.41
3.40

1.55

0.93   2.01 2.14   1.01 0.93

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	14 Nov 2012 07:23:43
Date Stamp	15 Nov 2012 00:10:30				File Name	G:\500MHz111612\aaron\carbon\CS_4209_product_carbon-1.jdf
Frequency (MHz)	125.77	Nucleus	13C		Number of Transients	20	Origin	ECA 500
Original Points Count	32768	Owner	delta		Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d				Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	21.200		

CS_4209_product_carbon-1.esp

3.45d

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	21 Nov 2012 07:14:11		
Date Stamp	22 Nov 2012 00:01:53			File Name	G:\500MHz111612\aaron\proton\CS_4211_reduced_column_1_proton-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	10	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	42.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	21.000		

CS_4211_reduced_column_1_proton-1.esp

3.45e

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	12 Nov 2012 10:15:14		
Date Stamp	13 Nov 2012 03:02:00			File Name	G:\500MHz111612\aaron\proton\CS_4207_reduced_product_proton-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	10	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	40.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	21.100		

CS_4207_reduced_product_proton-1.esp

3.45f

M06(t)
1.00

M04(br. s.)
M05(m)
1.01
0.98

M03(d)
2.94
2.93

M02(dd)
M01(d)
3.92
3.90
3.63
3.63
2.95

1.61
1.60
1.62
1.59
1.82
1.04
0.21

0.93 0.99 1.78 1.05 2.24 3.00

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	12 Nov 2012 10:17:33
Date Stamp	13 Nov 2012 03:04:20					File Name	G:\500MHz111612\aaron\carbon\CS_4207_reduced_product_carbon-1.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	60	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	21.500		

CS_4207_reduced_product_carbon-1.esp

3.45f

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	10 Nov 2012 12:34:08		
Date Stamp	11 Nov 2012 05:20:54			File Name	G:\500MHz111612\aaron\proton\CS_4206_reduced_product_proton-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	16	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	30.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	21.100		

CS_4206_reduced_product_proton-1.esp

3.45g

M08(d)
M07(d)
M03(m)
M01(dd)
M02(dd)
M04(dd)
M05(br. s.)
M06(m)

1.01, 0.99, 0.95, 0.94
3.91, 3.90, 3.88
3.60, 3.59, 3.58, 3.57
2.96, 2.95, 2.95
2.74, 2.73, 2.72
2.17
1.58, 1.57, 1.55, 1.54, 1.53, 1.23

0.94 0.95 0.90 0.92 0.83 0.99 2.84 3.00

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	10 Nov 2012 12:36:08
Date Stamp	11 Nov 2012 05:22:53			File Name	G:\500MHz111612\aaron\carbon\CS_4206_reduced_carbon-1.jdf	
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	50	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	21.500		

CS_4206_reduced_carbon-1.esp

3.45g

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	20 Aug 2012 12:13:47
Date Stamp	21 Aug 2012 04:32:29			File Name	G:\500MHz083012\aaron\proton\CS_4120_column_2-1.jdf
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	9	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	36.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.100

CS_4120_column_2-1.esp

3.45h

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	20 Aug 2012 12:18:53
Date Stamp	21 Aug 2012 04:37:34				File Name	G:\500MHz082412\aaron\carbon\CS_4120_carbon-1.jdf	
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	130	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	22.700		

CS_4120_carbon-1.esp

3.45h

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	21 Feb 2013 12:57:16		
Date Stamp	22 Feb 2013 05:40:26						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz022213\aaron\proton\CS_c7_epoxide_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	5	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	42.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	20.700				

CS_c7_epoxide_proton-1.esp

3.45i

216

217

CS_4120_carbon_heptenal_copy-1.esp

3.45i

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	22 Aug 2012 10:42:01		
Date Stamp	23 Aug 2012 03:00:43			File Name	G:\500MHz082412\aaron\proton\CS_4119_proton_2-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	6	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.200		

CS_4119_proton_2-1.esp

3.45j

219

CS_4119_carbon-2.esp

3.45j

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	21 Aug 2012 12:32:15		
Date Stamp	22 Aug 2012 04:50:57						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz083012\aaron\proton\CS_4118_proton-1.jdf			Frequency (MHz)	500.16		
Nucleus	1H	Number of Transients	7	Origin	ECA 500	Original Points Count	16384
Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2	Receiver Gain	24.00
Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	21.800				

CS_4118_proton-1.esp

3.45k

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date		21 Aug 2012 12:34:04
Date Stamp	22 Aug 2012 04:52:46							
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz082412\aaron\carbon\CS_4118_carbon-1.jdf					Frequency (MHz)		125.77
Nucleus	13C	Number of Transients	40	Origin	ECA 500	Original Points Count		32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain		50.00
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)		39308.18
Temperature (degree C)	22.200							

CS_4118_carbon-1.esp

3.45k

Acquisition Time (sec)	1.7459	**Comment**	single_pulse	**Date**	05 Dec 2012 10:07:12		
Date Stamp	06 Dec 2012 02:55:00			**File Name**	G:\500Mhz120912\aaron\proton\CS_4216_proton_x-1.jdf		
Frequency (MHz)	500.16	**Nucleus**	1H	**Number of Transients**	16	**Origin**	ECA 500
Original Points Count	16384	**Owner**	delta	**Points Count**	16384	**Pulse Sequence**	single_pulse.ex2
Receiver Gain	44.00	**Solvent**	CHLOROFORM-d			**Spectrum Offset (Hz)**	2500.7996
Spectrum Type	STANDARD	**Sweep Width (Hz)**	9384.38	**Temperature (degree C)**	21.100		

CS_4216_proton_x-1.esp

3.45l

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	08 Sep 2012 13:08:09
Date Stamp	09 Sep 2012 05:26:58					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_4117_4151_carbon_copy-1.jdf					
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	120	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.600				

CS_4117_4151_carbon_copy-1.esp

3.45l

Acquisition Time (sec)	1.7459	Comment		single_pulse	Date		15 Nov 2012 08:20:41		
Date Stamp	16 Nov 2012 01:07:29								
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz111612\aaron\proton\CS_4210_proton-1.jdf						Frequency (MHz)		500.16
Nucleus	1H	Number of Transients		7	Origin	ECA 500	Original Points Count		16384
Owner	delta	Points Count		16384	Pulse Sequence	single_pulse.ex2	Receiver Gain		34.00
Solvent	CHLOROFORM-d				Spectrum Offset (Hz)	2500.7996	Spectrum Type		STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	20.800						

CS_4210_proton-1.esp

3.45m

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	15 Nov 2012 08:25:55
Date Stamp	16 Nov 2012 01:12:43					
File Name		C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz111612\aaron\carbon\CS_4210_carbon-1.jdf			Frequency (MHz)	125.77
Nucleus	13C	Number of Transients	140	Origin	ECA 500	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18
Temperature (degree C)	21.400					

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	10 May 2012 12:49:29		
Date Stamp	11 May 2012 05:06:02						
File Name	C:\Users\chen\Desktop\DakinNMR\Aerobic Dakin Oxdiation\Substrate NMR\RAW data\CS_3134_HEHpyridine_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	3	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	16.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.300				

CS_3134_HEHpyridine_proton-1.esp

4.45

M03(s) —2.63

M04(m) —1.23

M02(q) 4.21 4.19

M01(s) —8.46

—1.21

1.24

4.22 4.18

2.61

0.93   3.88   6.00   5.90

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	10 May 2012 12:50:27
Date Stamp	11 May 2012 05:07:00						
File Name	C:\Users\chen\Desktop\DakinNMR\Aerobic Dakin Oxdiation\Substrate NMR\RAW data\CS_3134_HEHpyridine_carbon-1.jdf						
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	20	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.500				

CS_3134_HEHpyridine_carbon-1.jdf

4.45

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	22 Sep 2012 09:10:41		
Date Stamp	23 Sep 2012 01:29:37						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\proton\CS_194_oxidation_produt_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	3	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	36.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000				

CS_194_oxidation_produt_proton-1.esp

CS_194_oxidation_product_carbon-1.esp

230

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	22 Sep 2012 09:16:22		
Date Stamp	23 Sep 2012 01:35:18						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\proton\CS_195_oxidation_produt_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	4	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	32.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000				

CS_195_oxidation_produt_proton-1.esp

4.48

Acquisition Time (sec)	0.8336	**Comment**	single pulse decoupled gated NOE		**Date**	22 Sep 2012 09:06:31
Date Stamp	23 Sep 2012 01:25:27					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_193_oxidation_product_carbon-1.jdf					
Frequency (MHz)	125.77	**Nucleus**	13C	**Number of Transients** 40	**Origin**	ECA 500
Original Points Count	32768	**Owner**	delta	**Points Count** 32768	**Pulse Sequence**	single_pulse_dec
Receiver Gain	50.00	**Solvent**	CHLOROFORM-d	**Spectrum Offset (Hz)** 12576.5293	**Spectrum Type**	STANDARD
Sweep Width (Hz)	39308.18	**Temperature (degree C)** 22.300				

CS_193_oxidation_produt_carbon-1.esp

4.49

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	22 Sep 2012 09:22:07		
Date Stamp	23 Sep 2012 01:41:03						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\proton\CS_196_oxidation_produt_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	5	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	26.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.100				

CS_196_oxidation_produt_proton-1.esp

4.50

M03(s) —1.57

M02(s) —2.77

M01(s) —8.49

0.90   6.00   17.68

Chemical Shift (ppm)

Normalized Intensity

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	22 Sep 2012 09:23:24
Date Stamp	23 Sep 2012 01:42:19					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_196_oxidation_product_carbon-1.jdf					
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	30	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.400				

CS_196_oxidation_product_carbon-1.esp

4.50

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	24 Sep 2012 13:18:32
Date Stamp	25 Sep 2012 05:37:29			File Name		G:\500MHz092012\aaron\carbon\CS_212_oxidation_product_carbon-1.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	30	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	22.400		

CS_212_oxidation_product_carbon-1.esp

4.51

239

CS_197_oxidation_product_proton-1.esp

4.52

M07(s) 2.82
M06(s) 3.44
M04(d)
M05(d) 4.80
M03(d) 4.79
M01(s) 8.71
M02(m)
6.03 6.01 6.00 5.99 5.98 5.40 5.29 5.27
2.81

0.01 1.00 0.00   1.98 2.01 1.98 4.05   3.36 6.39

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	24 Sep 2012 13:06:39
Date Stamp	25 Sep 2012 05:25:35						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_197_oxidation_product_carbon-1.jdf						
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	30	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.400				

CS_197_oxidation_product_carbon-1.esp

4.52

241

CS_199_oxidation_product_carbon-1.esp

4.53

242

243

CS_4168_column_proton-1.esp

4.58

Acquisition Time (sec)	0.8336		Comment	single pulse decoupled gated NOE			Date	26 Sep 2012 13:25:53
Date Stamp	27 Sep 2012 05:44:50							
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_4168_product_carbon-1.jdf							
Frequency (MHz)	125.77		Nucleus	13C		Number of Transients	40	Origin	ECA 500
Original Points Count	32768		Owner	delta		Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00		Solvent	CHLOROFORM-d		Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18		Temperature (degree C)	22.300					

CS_4168_product_carbon-1.esp

4.58

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	27 Sep 2012 08:47:58		
Date Stamp	28 Sep 2012 01:06:56						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\proton\CS_4164_product_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	4	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	40.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.200				

CS_4164_product_proton-1.esp

4.59

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	27 Sep 2012 08:47:07
Date Stamp	28 Sep 2012 01:06:05					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_4164_product_carbon-1.jdf					
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	50	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.400				

CS_4164_product_carbon-1.esp

4.59

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	23 Oct 2012 11:35:34		
Date Stamp	24 Oct 2012 03:36:42			File Name	G:\500MHz101512\aaron\proton\CS_4192_2_proton-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	4	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	34.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.900		

CS_4192_2_proton-1.esp

4.60

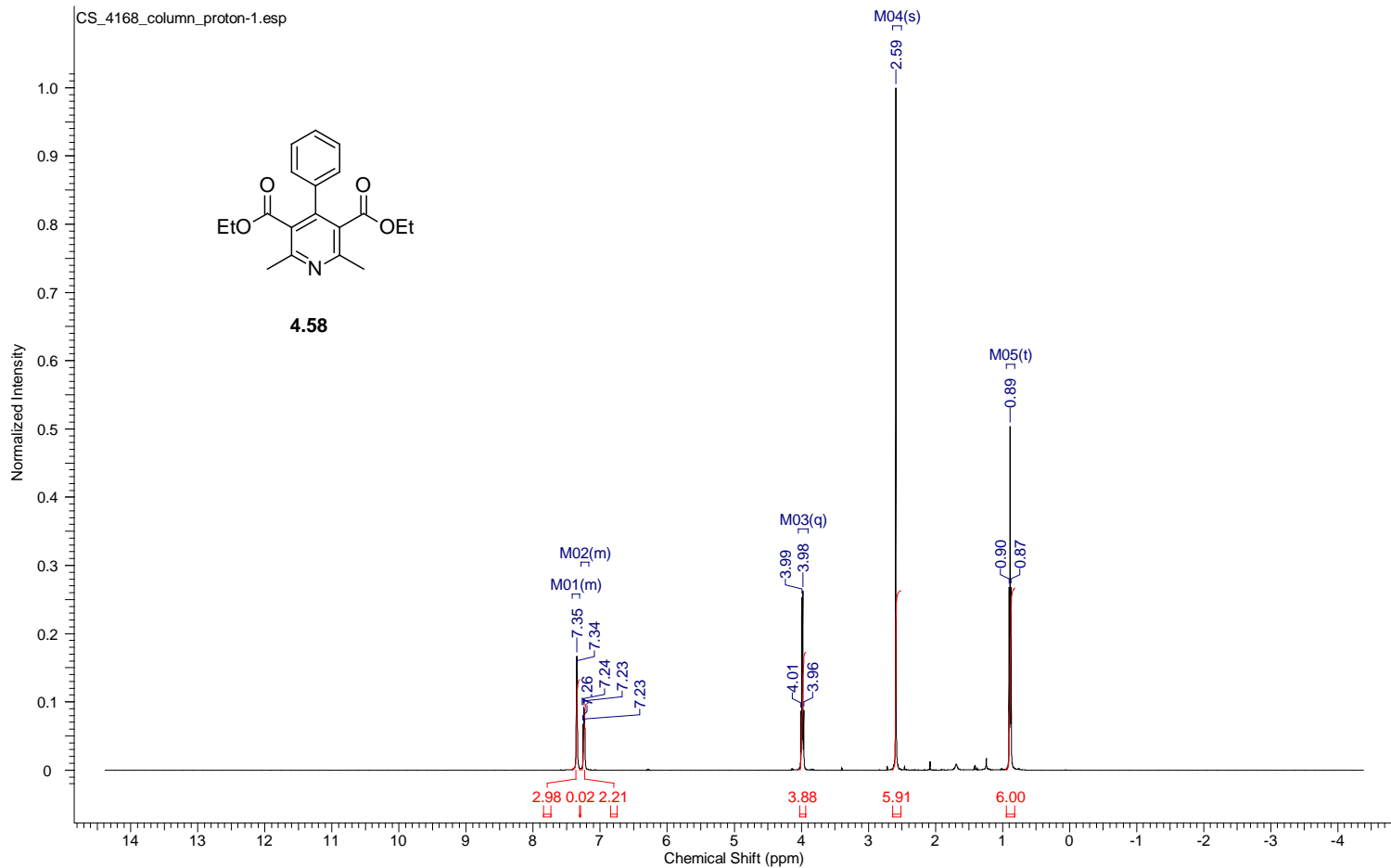| Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE	Date	23 Oct 2012 11:36:52
Date Stamp	24 Oct 2012 03:38:01				File Name	G:\500MHz101512\aaron\carbon\CS_4192_2_carbon-1.jdf
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	30	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d		Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	23.100	

CS_4192_2_carbon-1.esp

4.60

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	19 Oct 2012 10:26:01		
Date Stamp	20 Oct 2012 02:27:08			File Name	G:\500MHz101512\aaron\proton\CS_4192_4_proton_500-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	10	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	30.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	21.000		

CS_4192_4_proton_500-1.esp

4.61

Acquisition Time (sec)	1.3841	Comment		single pulse decoupled gated NOE	Date	16 Oct 2012 11:37:13
Date Stamp	16 Oct 2012 11:22:45				File Name	G:\500MHz101512\carbon\CS_4192_4_carbon-1.jdf
Frequency (MHz)	75.57	Nucleus	13C	Number of Transients 70	Origin	ECX 300
Original Points Count	32768	Owner	delta	Points Count 32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d		Spectrum Offset (Hz)	7556.8232
Spectrum Type	STANDARD	Sweep Width (Hz)	23674.24	Temperature (degree C) 22.100		

CS_4192_4_carbon-1.esp

4.61

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	19 Oct 2012 10:35:24		
Date Stamp	20 Oct 2012 02:36:31			File Name	G:\500MHz101512\aaron\proton\CS_4194_2_proton_500-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	4	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	30.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	21.100		

CS_4194_2_proton_500-1.esp

M01(s)
3.50

M02(s)
2.08

1.82

4.62

6.00   6.04 3.00

Chemical Shift (ppm)

Normalized Intensity

Acquisition Time (sec)	1.3841	Comment	single pulse decoupled gated NOE		Date	16 Oct 2012 11:27:15
Date Stamp	16 Oct 2012 11:12:46			File Name	G:\500MHz101512\carbon\CS_4194_3_carbon-1.jdf	
Frequency (MHz)	75.57	Nucleus	13C	Number of Transients	50	Origin	ECX 300
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	7556.8232
Spectrum Type	STANDARD	Sweep Width (Hz)	23674.24	Temperature (degree C)	22.500		

CS_4194_3_carbon-1.esp

4.63

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	28 Sep 2012 09:26:58		
Date Stamp	29 Sep 2012 01:45:56						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\proton\CS_4169_1_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	5	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	40.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000		

CS_4169_1_proton-1.esp

4.66

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date		28 Sep 2012 09:28:37
Date Stamp	29 Sep 2012 01:47:35							
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_4169_1_carbon-1.jdf					Frequency (MHz)		125.77
Nucleus	13C	Number of Transients	40	Origin	ECA 500	Original Points Count		32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain		50.00
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)		39308.18
Temperature (degree C)	22.300							

CS_4169_1_carbon-1.esp

4.66

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date		28 Sep 2012 09:34:20		
Date Stamp	29 Sep 2012 01:53:18							
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\proton\CS_4169_2_proton-1.jdf							
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	4	Origin	ECA 500	
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2	
Receiver Gain	40.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996	
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000			

CS_4169_2_proton-1.esp

4.67

M07(s)
—2.21

M04(m)
M03(t)
M06(d)
M05(m)
M01(d)
—7.15
—7.13
M02(d)
—8.13
—8.11
—7.96
—7.94
—7.44
—7.28

—2.61

0.99 0.97 1.011.03 1.04 1.99   6.28

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	**Comment**	single pulse decoupled gated NOE		**Date**	28 Sep 2012 09:36:19
Date Stamp	29 Sep 2012 01:55:17					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_4169_2_carbon-1.jdf				**Frequency (MHz)**	125.77
Nucleus	13C	**Number of Transients**	50	**Origin**	ECA 500	**Original Points Count**	32768
Owner	delta	**Points Count**	32768	**Pulse Sequence**	single_pulse_dec	**Receiver Gain**	50.00
Solvent	CHLOROFORM-d	**Spectrum Offset (Hz)**	12576.5293	**Spectrum Type**	STANDARD	**Sweep Width (Hz)**	39308.18
Temperature (degree C)	22.400					

CS_4169_2_carbon-1.esp

4.67

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	10 Aug 2012 11:51:50		
Date Stamp	11 Aug 2012 04:10:28						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz083012\aaron\proton\CS_4113_oxizedbenzothiazoline-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	6	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	48.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	22.100				

CS_4113_oxizedbenzothiazoline-1.esp

4.68

M02(d)
M03(d)
M01(d) M04(d)
8.34
8.27

M06(t)
7.26

8.36
8.26

M05(t)
8.14
8.12
7.96
7.95
7.55
7.46

7.57
7.45

Normalized Intensity

2.10 2.151.09 1.03 1.10 1.00

Chemical Shift (ppm)

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	10 Aug 2012 11:57:23
Date Stamp	11 Aug 2012 04:16:01					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500HMz081312\aaron\carbon\CS_4113_oxidzedbenzothiazoline_carbon-1.jdf					
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	140	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	22.600				

CS_4113_oxidzedbenzothiazoline_carbon-1.esp

4.68

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	28 Sep 2012 09:40:33		
Date Stamp	29 Sep 2012 01:59:31						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\proton\CS_4169_4_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	3	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	44.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000		

CS_4169_4_proton-1.esp

4.69

Chemical Shift (ppm)

1.00 1.81 0.98 3.01 1.04

Acquisition Time (sec)	0.8336		Comment	single pulse decoupled gated NOE		Date	28 Sep 2012 09:43:16
Date Stamp	29 Sep 2012 02:02:14						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_4169_4_carbon-1.jdf					Frequency (MHz)	125.77
Nucleus	13C		Number of Transients	70	Origin	ECA 500	Original Points Count	32768
Owner	delta		Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	CHLOROFORM-d		Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18
Temperature (degree C)	22.500						

CS_4169_4_carbon-1.esp

4.69

Acquisition Time (sec)	1.7459	**Comment**	single_pulse	**Date**	28 Sep 2012 09:47:47		
Date Stamp	29 Sep 2012 02:06:45						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\proton\CS_4169_5_proton-1.jdf						
Frequency (MHz)	500.16	**Nucleus**	1H	**Number of Transients**	5	**Origin**	ECA 500
Original Points Count	16384	**Owner**	delta	**Points Count**	16384	**Pulse Sequence**	single_pulse.ex2
Receiver Gain	40.00	**Solvent**	CHLOROFORM-d			**Spectrum Offset (Hz)**	2500.7996
Spectrum Type	STANDARD	**Sweep Width (Hz)**	9384.38	**Temperature (degree C)**	22.100		

4.70

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	28 Sep 2012 09:49:47
Date Stamp	29 Sep 2012 02:08:45					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_4169_5_carbon-1.jdf				Frequency (MHz)	125.77
Nucleus	13C	Number of Transients	50	Origin	ECA 500	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18
Temperature (degree C)	22.400					

CS_4169_5_carbon-1.esp

4.70

168.22 154.36 135.24 134.72 133.29 131.09 128.94 127.99 127.69 127.57 127.00 126.50 125.36 124.55 123.35 121.76

Normalized Intensity

Chemical Shift (ppm)

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	28 Sep 2012 09:54:00		
Date Stamp	29 Sep 2012 02:12:58						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\proton\CS_4169_6_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	5	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	54.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.100		

CS_4169_6_proton-1.esp

4.71

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	28 Sep 2012 10:37:27
Date Stamp	29 Sep 2012 02:56:25					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz092012\aaron\carbon\CS_4169_6_carbon-1.jdf				Frequency (MHz)	125.77
Nucleus	13C	Number of Transients	1200	Origin	ECA 500	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18
Temperature (degree C)	22.700					

CS_4169_6_carbon-1.esp

4.71

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	23 Jan 2013 10:51:12		
Date Stamp	24 Jan 2013 03:34:09						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz012913\aaron\proton\CS_4252_proton-1.jdf			Frequency (MHz)	500.16		
Nucleus	1H	Number of Transients	5	Origin	ECA 500	Original Points Count	16384
Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2	Receiver Gain	30.00
Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	9384.38	Temperature (degree C)	21.000				

CS_4252_proton-1.esp

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE			Date	23 Jan 2013 10:53:43
Date Stamp	24 Jan 2013 03:36:40						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz012913\aaron\carbon\CS_4252_carbon-1.jdf					Frequency (MHz)	125.77
Nucleus	13C	Number of Transients	60	Origin	ECA 500	Original Points Count	32768
Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec	Receiver Gain	50.00
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18
Temperature (degree C)	21.400						

CS_4252_carbon-1.esp

Acquisition Time (sec)	1.7459	Comment	single_pulse	Date	13 Oct 2012 13:08:04		
Date Stamp	14 Oct 2012 05:27:09			File Name	G:\500MHz101512\aaron\proton\CS_4191_product_proton-1.jdf		
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	5	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	44.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	2500.7996
Spectrum Type	STANDARD	Sweep Width (Hz)	9384.38	Temperature (degree C)	22.000		

Acquisition Time (sec)	0.8336	Comment		single pulse decoupled gated NOE		Date	13 Oct 2012 13:10:34
Date Stamp	14 Oct 2012 05:29:38			File Name	G:\500MHz101512\aaron\carbon\CS_4191_carbon-1.jdf		
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	60	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	12576.5293
Spectrum Type	STANDARD	Sweep Width (Hz)	39308.18	Temperature (degree C)	22.400		

CS_4191_carbon-1.esp

4.73

Acquisition Time (sec)	0.2726	Comment	single_pulse	Date	13 Oct 2012 13:11:39		
Date Stamp	14 Oct 2012 05:30:44			File Name	G:\500MHz101512\aaron\proton\CS_4191_F-1.jdf		
Frequency (MHz)	470.62	Nucleus	19F	Number of Transients	3	Origin	ECA 500
Original Points Count	65536	Owner	delta	Points Count	65536	Pulse Sequence	single_pulse.ex2
Receiver Gain	52.00	Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	0.0000
Spectrum Type	STANDARD	Sweep Width (Hz)	240384.63	Temperature (degree C)	22.200		

CS_4191_F-1.esp

−62.74

4.73
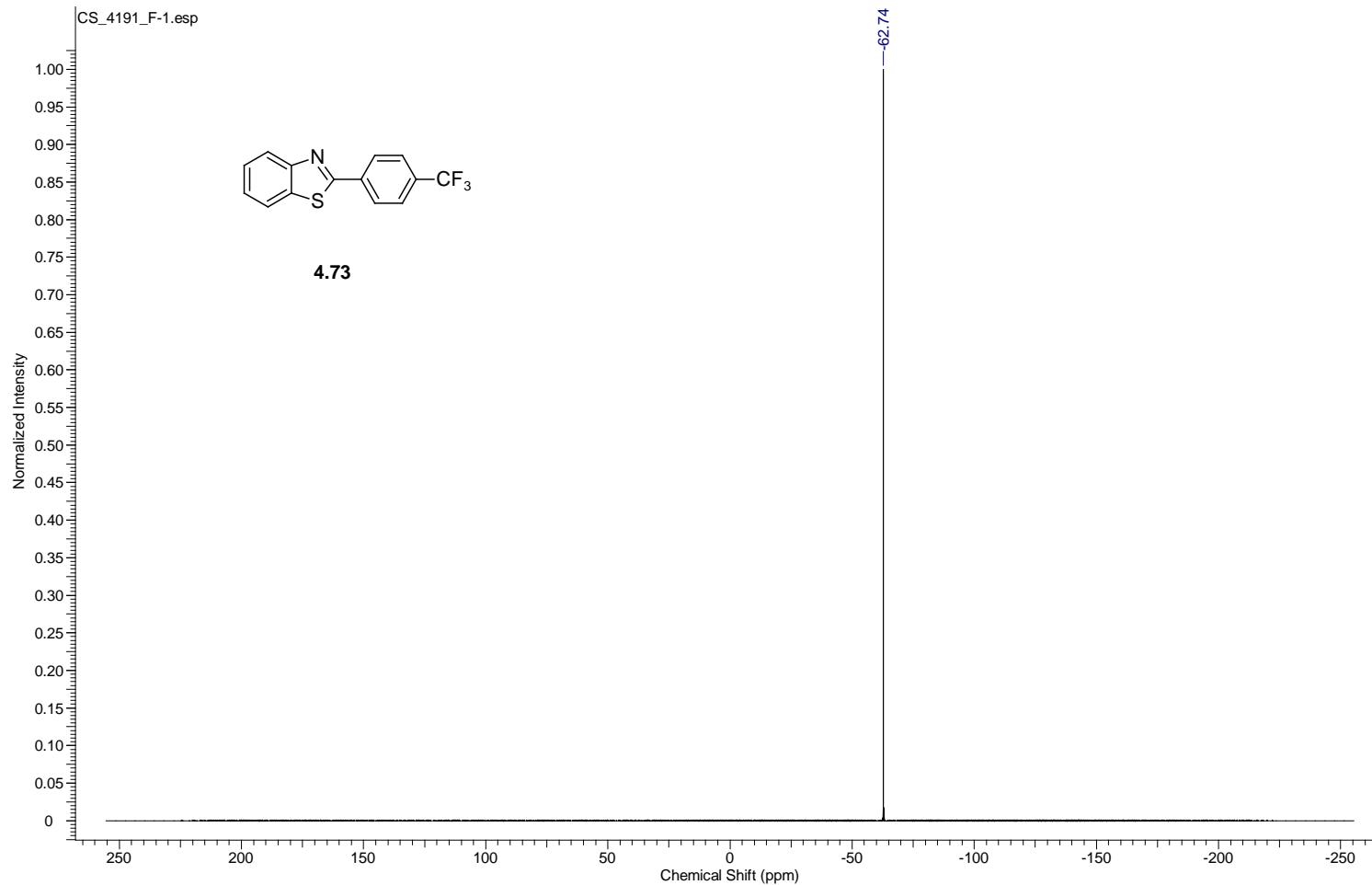
Acquisition Time (sec)	1.3081	Comment	single_pulse	Date	26 Jan 2013 08:14:12		
Date Stamp	27 Jan 2013 00:57:10						
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz012913\aaron\proton\CS_4253_column_proton-1.jdf						
Frequency (MHz)	500.16	Nucleus	1H	Number of Transients	14	Origin	ECA 500
Original Points Count	16384	Owner	delta	Points Count	16384	Pulse Sequence	single_pulse.ex2
Receiver Gain	36.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	2500.7996	Spectrum Type	STANDARD
Sweep Width (Hz)	12525.05	Temperature (degree C)	20.900				

CS_4253_column_proton-1.esp

4.74

Acquisition Time (sec)	0.8336	Comment	single pulse decoupled gated NOE		Date	26 Jan 2013 08:50:12
Date Stamp	27 Jan 2013 01:33:10					
File Name	C:\Users\chen\Desktop\study\Foss\Shuai's Data\NMR DATA\500MHz012913\aaron\carbon\CS_4253_column_carbon-1.jdf					
Frequency (MHz)	125.77	Nucleus	13C	Number of Transients	1000	Origin	ECA 500
Original Points Count	32768	Owner	delta	Points Count	32768	Pulse Sequence	single_pulse_dec
Receiver Gain	50.00	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	12576.5293	Spectrum Type	STANDARD
Sweep Width (Hz)	39308.18	Temperature (degree C)	21.400				

CS_4253_column_carbon-1.esp

4.74

References

1. Massey, V. *Biochem. Soc. Trans.* 2000, *28*, 283-296.

2. Kuhn, R.; Reinemund, K.; Weygand, F. *Ber.* 1934, *67*, 1460-1463

3. Karrer, P.; Schöpp, K.; Benz, F. *Helv. Chim. Acta.* 1935, *18*,426-429

4. Theorell, H. *Biochem. Z.* 1935, *275*, 344-346

5. Bruice, T. B. *Acc. Chem. Res.* 1980, *13*, 256-262

6. Gelalcha F. G. *Chem. Rev.* 2007, *107*, 3338-3361

7. Sono, M.; Roach, M. P.; Coulter, E. D.; Dawson, J. H. *Chem. Rev.* 1996, *96*, 2841-2887

8. Donoghue, N. A.; Norris, D. B.; Trudgill, P. W. *Eur. J. Biochem.* 1976, *63,* 175-192

9. Malito, E.; Alfieri, A.; Fraaije, M. W.; Mattevi, A. *Proc. Natl. Acad. Sci. USA* 2004, *101*, 13157-13162

10. Torres Pazmino D. E.; Baas, J. B.; Janssen, D. B.; Fraaije, M. W. *Biochemistry*, 2008, *47*, 4082-4093

11. List, B. *Chem. Rev.* 2007, *107*, 5414-5415

12. Murahashi, S.-I.; Oda, T.; Masui, Y. *J. Am. Chem. Soc.* 1989, *111*, 5002-5003

13. Imada, Y.; Iida, H.; Ono, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* 2003, *125*, 2868-2869

14. Lindén, A. A.; Krüger, L.; Bảckvall, J.-E. *J. Org. Chem.* 2003, *68*, 5890-5896

15. Lindén, A. A.; Johansson, M.; Hermanns, N.; Bảckvall, J.-E. *J. Org. Chem.* 2006, *71*, 3849-3853

16. Baxová, L.; Cibulka, R.; Hampl, F. *J. Mol. Catal. A: Chem.* 2007, *277*, 53-60

17. Marsh, B. J.; Carbery, D. R. Tetrahedron Lett. 2010, *51*, 2362-2365

18. Zurek, J.; Cibulka, R.; Dvoráková, H.; Svoboda, J. Tetrahedron Lett. 2010, 51, 1083-1086

19. Shinkai, S.; Yamaguchi, T.; Manabe, O.; Toda, F. *J. Chem. Soc. Chem Commun.* 1988, *21*, 1399-1401.

20. Jurok, R.; Cibulka, R.; Dvoráková, H.; Hampl, F.; Hodačová, J. *Eur. J. Org. Chem.* 2010, *27*, 5217–5224

21. Mojr, V.; Herzig, V.; Budesinsky, M.; Cibulka, R.; Kraus, T. *Chem. Commun.* 2010, *46*, 7599–7601

22. Iida, H.; Iwahana, S.; Mizoguchi, T.; Yashima, E. *J. Am. Chem. Soc.* 2012, *134*, 15103-15113

23. Bergstad, K.; Bàckvall, J.-E. *J. Org. Chem.* 1998, *63*, 6650-6655

24. Ménová, P.; Cibulka, R. *J. Mol. Catal. A: Chem.* 2012, *363*, 362-370

25. Mazzini, C. Lebreton, J.; Furstoss, R. *J. Org. Chem.* 1996, *61*, 8-9

26. Murahashi, S.-I.; Ono, S.; Imada, Y. *Angew. Chem.* 2002, *114*, 2472-2474

27. Imada, Y.; Iida, H.; Murahashi, S.-I.; Naota, T. *Angew. Chem. Int. Ed.* 2005, *44*, 1704-1706

28. Jayapaul, J.; Hodenius, M.; Arns, S.; Lederle, W.; Lammer, T.; Comba, P.; Kiessling, F.; Gaetjens, J. Biomaterials. 2011, *32*, 5863-5871

29. Nöll, G.; Trawöger, S.; Sanden-Flohe, M. V.; Dick, B.; Grininger, M. ChemBioChem 2009, *10*, 834 –837.

30. Baeyer, A.; Villiger, V. *Ber. Dtsch. Chem. Ges.* 1899, *32*, 3625-3631

31. Brink, G.-J. T.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* 2004, *104,* 4105-4123

32. Strukul, G. *Angew. Chem. Int. Ed.* 1998, *37*, 1198-1209

33. Schrader, S.; Dehmlow, E. V. *Org. Prep. Proc. Int.* 2000, *32*, 125-134

34. Kaneda, K.; Ueno, S.; Imanaka, T.; Shimotsuma, E.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* 1994, *59*, 2915-2919

35. Fukuda, O.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* 2001, *42*, 3479-3482

36. Carlqvist, P.; Eklund, R.; Brinck, T. *J. Org. Chem.* 2001, *66*, 1193-1199

37. Yoneda, F.; Sakuma, Y.; Ichiba, M.; Shinomura, K. *J. Am. Chem. Soc.* 1976, *98*, 830-835

38. Xu, S.; Wang, Z.; Li, Y.; Zhang, X.; Wang, H.; Ding, K. *Chem. Eur. J.* 2010, *16*, 3021 -3035

39. Yamazaki, S. *Chem. Lett.*1997, *12*, 127-128

40. Bernini, R.; Coratti, A.; Provenzano, G.; Fabrizib, G.; Tofanic, D. *Tetrahedron*, 2005, *61*, 1821-1825

41. Silva, E. T. D.; Caamara, C. A.; Antunes, O. A. C.; Barreiro, E. J.; Fraga, C. A. M. *Synth. Commun.* 2008, *38*, 784–788

42. Kaballm, G. W.; Reddy, N. K.; Narayana, C. *Tetrahedron Lett.*, 1992, *33*, 865-866.

43. Roy, A.; Reddya, K. R.; Mohanta, P. K.; Ila, H.; Junjappat, H. *Synth. Commun.* 1999, *29*, 3781-3791

44. Varma, R. S.; Naicker, K. P. *Org. Lett.* 1999, *1*, 189-191

45. Murray, A. T.; Matton, P.; Fairhurst, N. W. G.; John, M. P.; Carbery, D. R. *Org. Lett.* 2012, *14*, 3656–3659

46. Kuran, W.; Mazanek, E. *J. Organomet. Chem.* 1990, *384*, 13-17

47. Lavilla, R. *J. Chem. Soc., Perkin Trans. 1 VL -* 2002, 1141-1156.

48. Zheng, C.; You, S.-L. *Chem. Soc. Rev.* 2012, *41*, 2498-2518

49. Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* 2011, *13*, 1084-1105

50. Kaneda, K.; Haruna, S.; Imanaka, T.; Hamamoto, M.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* 1992, *33*, 6827–6830

51. Bolm, C.; Schlingloff, G.; Weickhardt, K. *Tetrahedron Lett.* 1993*, 34,* 3405-3408

52. Kaneda, K.; Ueno, S.; Imanaka, T.; Shimotsuma, E.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* 1994, *59*, 2915-2917

53. Murthy, Y. V. S. N.; Massey, V. *J. Biol. Chem.* 1998, *273*, 8975–8982

54. Minidis, A. B.; Bäckvall, J. E*. Chem-Eur J.* 2001, *7*, 297–302

55. Li, X.-L.; Fu, Y. J. Mol. *Struc.-THEOCHEM* 2008, *856,* 112-118

56. Jacobsen, E. N.; Taylor, M. S. *Angew. Chem. Int. Ed.* 2006, *45*,1521–1539

57. Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* 2007, *107*, 5713–5743

58. Melchiorre, P. *Angew. Chem. Int. Ed.* 2012, *51*, 9748-9770

59. Lelais, G.; MacMillan, D. W. C. Aldrichimica Acta. 2006, *39*, 79-87

60. Weitz, E.; Scheffer, A. *Chem. Ber.* 1921, *54*, 2327

61. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* 1980, *102*, 5974-5978

62. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* 1990, *112*, 2801–2803

63. Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* 1997, *119*, 11224-11235

64. Bunton, C. A.; Minkoff, G. J. *J. Chem. Soc.* 1949, 665-670

65. Pluim, H ; Wynberg, H. *J. Org. Chem.* 1980, *45*, 2498-2504

66. Lygo, B.; Wainwright, P. G. *Tetrahedron* 1999, *55*, 6289-6295

67. Corey, E. J.; Zhang, F.-Y. *Org. Lett.* 1999, *1*, 1287-1291

68. Arai, S.; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* 1998, *39*, 7563-7565

69. Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed.* 1980, *19*, 929-933

70. Colonna, S.; Molinari, H.; Banfi, S.; Juliá, S.; Masana, J.; Alvarez, A. *Tetrahedron* 1983, *39*, 1635-1641

71. Elston, C. L.; Jackson, R. F. W.; MacDonald, S. J. F.; Murray, P. J. *Angew. Chem. Int. Ed.* 1997, *36*, 410-414

72. Jacques, O.; Richards, S. J.; Jackson, R. F. W. *Chem. Commun.* 2001, 2712-2716

73. Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* 2005, *127*, 6964-6968

74. Lee, S.; MacMillan, D. W. C. *Tetrahedron* 2006, *62*, 11413-11420

75. Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* 2012, *105*, 2329–2364

76. Budnik, R. A.; Kochi, J. K. *J. Org. Chem.* 1976, *41*, 1384-1391

77. Punniyamurthy, T.; Bhatia, B.; Reddy, M. M.; Maikap, G. C.; Iqbal, J. *Tetrahedron* 1997, *53*, 7649-7656

78. Nam, W.; Baek, S. J.; Lee, K. A.; Ahn, B. T.; Muller, J. G.; Burrows, C. J.; Valentine, J. S. *Inorg. Chem.* 1996, *35*, 6632-6638

79. Imagawa, K.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* 1994, 527-532

80. Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* 1994, *67*, 2248-2253

81. Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. *Chem. Lett.* 1992, 2231-2236

82. Bhattacharjee, S.; Anderson, J. A. *Chem. Commun.* 2004, 554-558

83. Rhodes, B.; Rowling, S.;Tidswell, P.; Woodward, S.; Brown, S. M. *J. Mol. Catal. A: Chem.* 1997, *116*, 375-379

84. Ito, Y. N.; Katsuki, T. *Bull. Chem. Soc. Jpn.* 1999, *72*, 603-607

85. Katsuki, T. *J. Synth. Org. Chem. Jpn.* 1995, *53*, 940-944

86. Jacobsen, E. N. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, Germany, 1993

87. Bryliakov, K. P.; Kholdeeva, O. A.; Vanina, M. P.; Talsi, E. P. *J. Mol. Catal. A: Chem.* 2002, *178*, 47-52

88. Kawai, H.; Okusu, S.; Yuan, Z.; Tokunaga, E.; Yamano, A.; Shiro, M.; Shibata, N. *Angew. Chem. Int. Ed.* 2013, *52*, 2221-2225

89. Cui, L.; Furuhashi, S.; Tachikawa, Y.; Tada, N.; Miura, T.; Itoh, A. *Tetrahedron Lett.* 2013, *54*, 162-165

90. Minami, A.; Shimaya, M.; Suzuki, G.; Migita, A.; Shinde, S. S.; Sato, K.; Watanabe, K.; Tamura, T.; Oguri, H.; Oikawa, H. *J. Am. Chem. Soc.* 2012, *134* , 7246-7249

91. Katsuyama, Y.; Harmrolfs, K.; Pistorius, D.; Li, Y; Müller, R. *Angew. Chem. Int. Ed.* 2012, *51*, 9437-9440

92. Mueller, N. J.; Stueckler, C.; Hall, M.; Macheroux, P.; Faber, K. *Org. Biomol. Chem.* 2009, *7*, 1115-1119

93. Zhao, G.-L.; Ibrahem, I.; Sundén, H.; Córdova, A. *Adv. Synth. Catal.* 2007, *349*, 1210-1224

94. Yang, J.; Hechavarria Fonseca, M.; List, B. *Angew. Chem. Int. Ed.* 2004, *43*, 6660-6662.

95. Zhu, C.; Falck, J. R. *Chemcatchem* 2011, *3*, 1850-1851

96. Zheng, C.; You, S.-L. *Chem. Soc. Rev.* 2012, *41*, 2498-2518

97. Aziz, F.; Mirza, G. A. *Talanta* 1964, *11*, 889-892

98. Massey, V. *J. Biol. Chem.* 1994, *269*, 22459-22462.

99. Hantzsch, A. *Justus Liebigs Ann. Chem.* 1882, *215*, 1-82

100. Kumar, A.; Maurya, R. A.; Sharm, S. *Bioorg. Med. Chem. Lett.* 2009, *19*, 4432-4436

101. Love, B.; Goodman, M.; Snader, K.; Tedeschi, R.; Macko, E. *J. Med. Chem.* 1974, *17*, 956-965

102. Bossert, F.; Meyer, H.; Wehinger, E*. Angew. Chem. Int. Ed. Engl.* 1981, *20*, 762-769

103. Guengerich, F. P.; Brian, W. R.; Iwasaki, M.; Sari, M. A.; Baarnhielm, C.; Berntsson, P. *J. Med. Chem.* 1991, *34*, 1838-1844

104. Bischhoff, H.; Angerbauer, R.; Bender, E.; Bischoff, J. A.; Petzinna, D.; Pfitzner, J.; Porter, M. C.; Schmidt, D.; Thomas, G. *Atherosclerosis* 1997, *135*, 119

105. Mashraqui, S. H.; Kamik, M. A. *Tetrahedron Lett.* 1998, *39*, 4895-4898

106. Heravi, M. M.; Derikvand, F.; Hassan-Pour, S.; Bakhtiari, K.; Bamoharram, F. F.; Oskooie H. A. *Bioorg. Med. Chem. Lett.* 2007, *17*, 3305-3309

107. Chai, L.; Zhao, Y.; Sheng, Q.; Liu, Z-Q. *Tetrahedron Lett.* 2006, *47*, 9283-9285

108. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* 2002, *4*, 3955-3957

109. Eynde, J.-J. V.; D'Oraxio, R.; Haverbeke, Y. V. *Tetrahedron* 1994, *50*, 2419-2484

110.   Wang, D.; Liu, Q; Chen, B.; Zhang, L.; Tung, C.; Wu, L. *Chinese. Sci. Bull.* 2010, *55*, 2855–2858

111.   Le Bozec, L.; Moody, C. J. *Aust. J. Chem.* 2009, *62*, 639−647

112.   Zhu, C; Falck, J. R. *ChemCatChem* 2011, *3*, 1850-1851

113.   Zhu, C.; Akiyama, T. *Org. Lett.* 2009, *11*, 4180-4183

114.   Sakamoto, T.; Mori, K.; Akiyama, T. *Org. Lett.* 2012, *14*, 3312-3315

115.   Yadav, G. S.; Senthilkumar, G. P. *Int. J. Pharm. Drug Dev. Res.* 2011, *3*, 1-7

116.   Bochatay, V. N.; Boissarie, P. J.; Murphy, J. A.; Suckling, C. J.; Lang, S. *J. Org. Chem.*, 2013, *78*, 1471-1477

117.   Zhao, J.; Huang, H.; Wu, W.; Chen, H.; Jiang, H. Org. Lett. 2013, *15*, 2604-2607

118.   Sun, Y.; Jiang, H.; Wu, W.; Zeng, W.; Wu, X. *Org. Lett.*, 2013, 15, 1598-1601

119.   Liao, Y.; Qi, H.; Chen, S.; Jiang, P.; Zhou, W.; Deng, G.-J*. Org. Lett.* 2012, *14*, 6004−6007

120.   Kemal, C.; Bruice, T. C. *Proc. Nat. Acad. Sci. USA* 1976, *73*, 995-999

121.   Imada, Y.; Iida, H.; Ono, S.; Masui, Y.; Murahashi, S.-I. *Chem. Asian J.* 2006, *1*, 136−147

122.   Lynn, M. A.; Carlson, L. J.; Hwangbo, H.; Tanski, J. M.; Tyler, L. A. *J. Mol. Struct.* 2012, *1011*, 81−93

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