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Single-Electron Transfer Radical Activations and Reactions Enabled by Carbene Organic Catalysts and Organic Reagents

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ABSTRACT

This thesis focuses on exploring new single-electron transfer reaction modes enabled by *N*-heterocyclic carbene (NHC) organocatalysts and organic reagents. It contains four parts:

Chapter 1 gives brief introductions to the development of radical reactions mediated by common radical initiators, photoredox catalysis, transition metal catalysts, electronchemistry and organocatalysts. This chapter also shows the challenges in organocatalyzed single-electron transfer reactions, especially, the limitations in NHC-catalyzed single-electron transfer reactions.

Chapter 2 describes a NHC-catalyzed SET process that allows for highly enantioselective entry into *β*-hydroxyl esters that are widely found in natural products and bioactive molecules. The mechanistic study demonstrates the generation of multiple radical intermediates in this catalytic reaction.

Chapter 3 shows an unusual trimerization of enones via a formal [2+2+2] process, which is enabled by NaO*t*Bu and NHC. This study provides a new avenue in using NaO*t*Bu and combined NHC/NaO*t*Bu to generate radical intermediates from enones.

Chapter 4 introduces a one-pot approach to synthesis of sulfoxides from alkenes and alkynes, this process is metal-free and no over-oxidatition of sulfoxides to sulfones is observed. N-fluorobenzenesulfonimide (NFSI) is used to enable radical generation for thiol-ene/yne reaction and subsequent selective oxidation of sulfides *in situ* to sulfoxides.

PUBLICATIONS

1. N-Heterocyclic Carbene-Catalyzed Radical Reactions for Highly Enantioselective β-Hydroxylation of Enals
__Yuexia Zhang__, Yu Du, Zhijian Huang, Jianfeng Xu, Xingxing Wu, Yuhuang Wang, Ming Wang, Song Yang, Richard D. Webster, Yonggui Robin Chi
J. Am. Chem. Soc., **2015**, *137*, 2416.

2. Sulfoxidation of Alkenes and Alkynes with NFSI as a Radical Initiator and Selective Oxidant
__Yuexia Zhang__, Zeng Rong Wong, Xingxing Wu, Sherman J. L. Lauw, Xuan Huang, Richard D. Webster, Yonggui Robin Chi
Chem. Commun., **2017**, *53*, 184.

3. Trimerization of Enones under Air Enabled by NHC/ NaO*t*Bu via a SET Radical Pathway
__Yuexia Zhang__, Xingxing Wu, Lin Hao, Zeng Rong Wong, Sherman J. L. Lauw, Song Yang, Richard D. Webster, Yonggui Robin Chi
Org. Chem. Front., **2017**, *4*, 467.

4. Polyhalides as Efficient and Mild Oxidants for Oxidative Carbene Organocatalysis by Radical Process
Xingxing Wu, __Yuexia Zhang__, Yuhuang Wang, Jie Ke, Martin Jeret, Rambabu N. Reddi, Song Yang, Bao-An Song, Yonggui Robin Chi
Angew. Chem. Int. Ed., **2017**, *56*, 2942.

5. Enantioselective Nucleophilic β-Carbon-Atom Amination of Enals: Carbene-Catalyzed Formal [3+2] Reactions
Xingxing Wu, Bin Liu, __Yuexia Zhang__, Martin Jeret, Honglin Wang, Pengcheng Zheng, Song Yang, Bao-An Song, Yonggui Robin Chi
Angew. Chem. Int. Ed., **2016**, *55*, 12280.

6. Construction of Fused Pyrrolidines and β-Lactones by Carbene-Catalyzed C-N, C-C, and C-O Bond Formations
Xingxing Wu, Lin Hao, __Yuexia Zhang__, Maiti Rakesh, Rambabu N. Reddi, Song Yang, Bao-An Song, Yonggui Robin Chi
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6. Asymmetric Access to the Smallest Enolate Intermediate via Organocatalytic Activation of Acetic Ester
Shaojin Chen, *Lin Hao*, ***Yuexia Zhang***, *Bhoopendra Tiwari*, Yonggui Robin Chi
Org. Lett., **2013**, *15*, 5822.

7. Carbene-catalysed Reductive Coupling of Nitrobenzyl Bromides and Activated Ketones or Imines via Single-electron-transfer Process
Bao-Sheng Li, Yuhuang Wang, Rupert S.J. Proctor, ***Yuexia Zhang****, Richard D. Webster, Song Yang, Baoan Song, Yonggui Robin Chi*
Nat. Commun., **2016**, *7*, 12933.

8. Carbene-Catalyzed Reductive Coupling of Nitrobenzyl Bromide and Nitroalkene via Single-Electron-Transfer (SET) Process and Formal 1,4-Addition
Yuhuang Wang, Yu Du, Xuan Huang, Xingxing Wu, ***Yuexia Zhang****, Song Yang, Yonggui Robin Chi*
Org. Lett., **2017**, *19*, 632.

ABBREVIATIONS

Ac	acetate
acac	acetylacetone
AIBN	2,2'−azo *bis*isobutyronitrile
Boc	*tert*−butyloxycarbonyl
Bu	butyl
Bn	benzyl
bpy	bipyridine
Bz	benzoyl
9-BBN	9-borabicyclo(3.3.1)nonane
Cbz	benzyloxycarbonyl
CV	cyclic voltammetry
DABCO	1,4−diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
DIBAL	diisobutylaluminum hydride
DIEA	N,N-diisopropylethylamine
DMAP	4−dimethylaminopyridine
DMEDA	N,N'-dimethylethanediamine
DMF	dimethylformamide
DMPO	5,5-dimethyl-pyrroline N-oxide
DMSO	dimethylsulfoxide

EA	ethyl acetate
EE	ethyl ether
EPR	electron paramagnetic resonance
equiv	equivalent
ESI	electrospray ionization
ET	electron transfer
Fc	ferrocene
FG	functional group
GC	gas chromatography
HAT	hydrogen atom transfer
HPLC	high performance liquid chromatography
HRMS	high−resolution mass spectrometry
IPA	isopropyl alcohol
i-Pr	isopropyl
IR	infrared
LC-MS	liquid chromatography-mass spectrometry
Mes	mesityl
mp	melting point
NFSI	N-fluorobenzenesulfonimide
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
OAc	acetocy
OTf	trifluoromethanesulfonate
por	porphyrinato
RT	room temperature

SET	single-electron transfer
SOMO	singly occupied molecular orbital
TBHP	*tert*-butyl hydroperoxide
*t*Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCN	trimethylsilyl cyanide
TPP	thiamine pyrophosphate
V-50	2,2'-azobis(2-methylpropionamidine)dihydrochloride
V-70	2,2'-azobis(4-methoxyl-2,4-dimethylvaleronitrile)

α	alpha
β	beta
γ	gamma
μ	micro
π	pi
η	eta
ω	omega
σ	sigma

Chapter 1

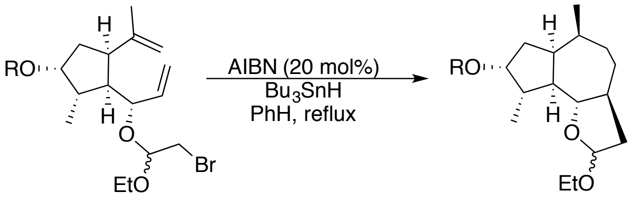
Introduction

Introduction

The radical reaction has become an important synthetic tool in organic synthesis as radical reactions can achieve the reactions where electron-pair transfer reactions fail. A lager number of free radical reactions have been disclosed in the past several decades. In a radical reaction, the key point focus is radical generation, in other words, how to initiate the radical reaction. There are several known methods for generation of radicals up to this point, including: (1) using radical initiators; (2) photoinduced electron transfer; (3) transition metal-promoted radical reactions; (4) electrochemically initiated radical reactions; (5) organocatalysis-enabled radical reactions.

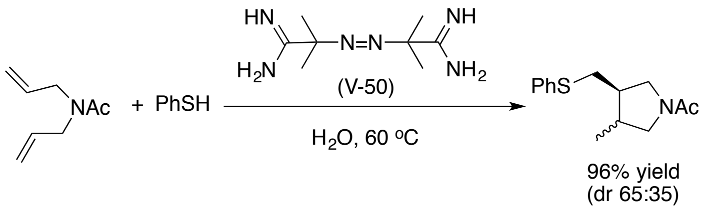
1.1 Radical initiators-induced radical reactions

The homolytic cleavage of a covalent bond in radical initiators will produce the radicals. Azo compounds and peroxides are two kinds of radical initiators which are most widely used in organic synthesis. 2,2'-azobisisobutyronitrile (AIBN) is often used to initiate the radical reactions in combination with trialkyltin hydrides or tri(trimethylsilyl)silane.[1] Lee *et. al* utilized the AIBN together with trialkyltin hydrides to construct the seven-membered and five-membered rings via one step in total synthesis of (+)-Cladantholide (Scheme 1.1).[2]



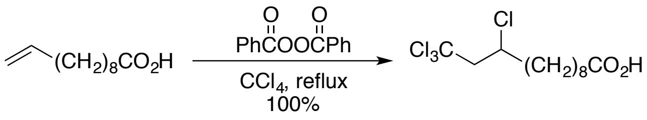
Scheme 1.1 Cyclization using AIBN

Other azo compounds such as 2,2'-azobis(4-methoxyl-2,4-dimethylvaleronitrile) (**V-70**)[3] and 2,2'-azobis(2-methylpropionamidine)dihydrochloride (**V-50**) were also used as effective initiators; it’s worth noting that the **V-50** is a hydrophilic radical initiator as it has an amidine group (Scheme 1.2).[4]

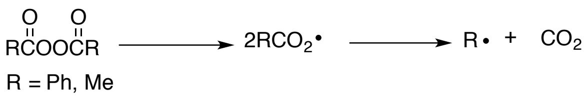


Scheme 1.2 V-50-mediated radical cyclization reaction in water

Peroxides will undergo cleavage of the O-O bond to produce the acyloxy radicals and alkoxyl radicals upon heating. Benzoyl peroxide is on the list of mostly used peroxide radical initiators; it was used as an efficient radical initiator in the trichloromethyl chlorination of alkenes (Scheme 1.3).[5] Such a peroxide would give benzoyloxy radical via cleavage of peroxide bond, the benzoyloxy radical further decomposing to release carbon dioxide and phenyl radical (Scheme 1.4).

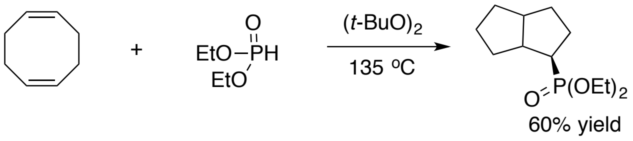


Scheme 1.3 Benzoyl peroxide-induced radical addition reaction



Scheme 1.4 Decomposition of peroxyldicarbonates

Di-*tert*-butyl peroxide is another well-known peroxide. It generates the *tert*-butoxyl radical (the *tert*-butoxyl radical will decompose into acetone and methyl radical), which reacts with diethyl phosphonate via hydrogen atom transfer (HAT) to afford the phosphonate radical, and the phosphonate radical undergoes addition to one of the double bonds of *cis*, *cis*-1,5-cyclooctadiene followed by radical cascade reaction to yield the corresponding diethyl *exo*, *cis*-bicyclo[3.3.0]octane-2-phosphonate in 60% yield (Scheme 1.5).[6]



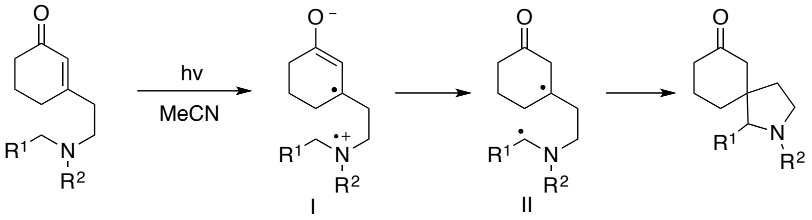
Scheme 1.5 Radical addition reaction using *tert*-butyl peroxide

1.2 Radical reactions involved photoredox catalysis

Photochemistry has already attracted much attention because of its availability, safety and environmental friendliness. The target of photocatalysis is development of artificial catalytic systems for the conversion of light into storable chemical fuels. Photoinduced electron transfer processes usually involve an electron donor, an electron acceptor and an electronic excitation. Radical-ions generated during the electron transfer steps can be transformed directly in the radical reactions, such as coupling reaction, single bond fragmentation and cyclization. Especially, the visible-light photoredox catalysis is emerging as powerful tool due to its natural abundance and fascinating potential of applications.

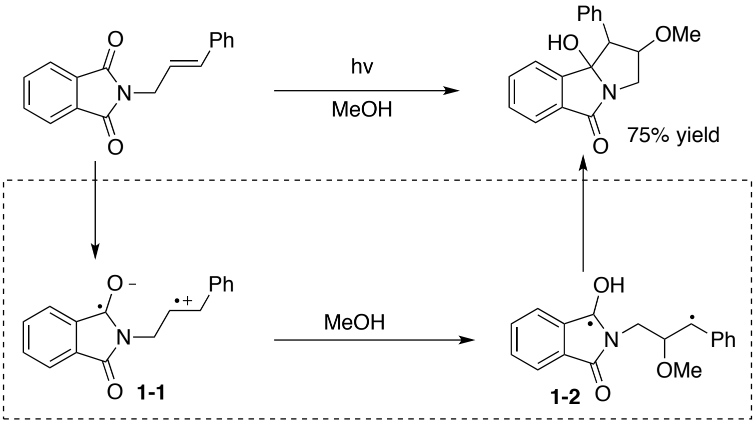
1.2.1 Photoinduced radical reactions without photocatalysts

Mariano studied the direct photocyclization of amine-enone, in which amine served as electron donor and enone served as electron acceptor.[7] When the donor-acceptor pair belongs to the same molecule, intramolecular single-electron transfer (SET) from the amine donor to the cyclohexanone results in the formation of intermediate **I** bearing of carbon-centered radical and nitrogen-centered radical cation, and a sequential intramolecular proton transfer process leads to formation of a zwitterionic biradical **II**, and lastly the spiro N-heterobicyclic product is produced via intramolecular radical-radical coupling reaction (Scheme 1.6).



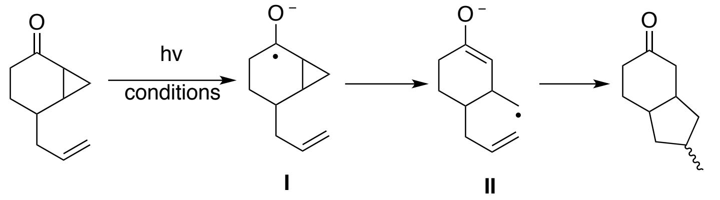
Scheme 1.6 Photocyclization reactions of (aminoalkyl)cyclohexenones

The photoinduced intramolecular electron transfer also occurs between olefin double and excited phthalimide carbonyl group. In 1981, Maruyama and co-workers reported a intramolecular photoinduced cyclization between two chromophores in the cases of N-(2-alkenyl)phthalimides (Scheme 1.7).[8] The N-alkylphthalimide undergoes intramolecular electron transfer from olefin to the carbonyl group to yield radical ions **1-1**, which leads to biradical intermediate **1-2** via reaction with MeOH. The two radical centers combine to form a new C-C bond and result in the cyclization product in 75% yield. The solvent MeOH is very essential to the reaction, because the olefin radical cation can be trapped owing to the highly nucleophilic character of methanol.



Scheme 1.7 Photochemical solvent-incorporated cyclization reactions

Mattay[9] and Cossy[10] independently reported the photoinduced fragmentation-cyclization reaction of bicycle [3.1.0]hexanones bearing a suitable unsaturated side chain using triethylamine as the electron donor (Scheme 1.8). Photochemically induced electron transfer from trimethylamine to carbonyl group resulted in the radical ion intermediate **I** which underwent ring opening of cyclopropyl moiety to form intermediate **II**, radical cyclization of intermediate **II** followed by acceptance of another single electron from triethylamine and protonation to give bicyclic product. Increasing the loading of electron donor trimethylamine dramatically increased the yield of product, and the presence of Li^+ stabilized the radical ion **II**.



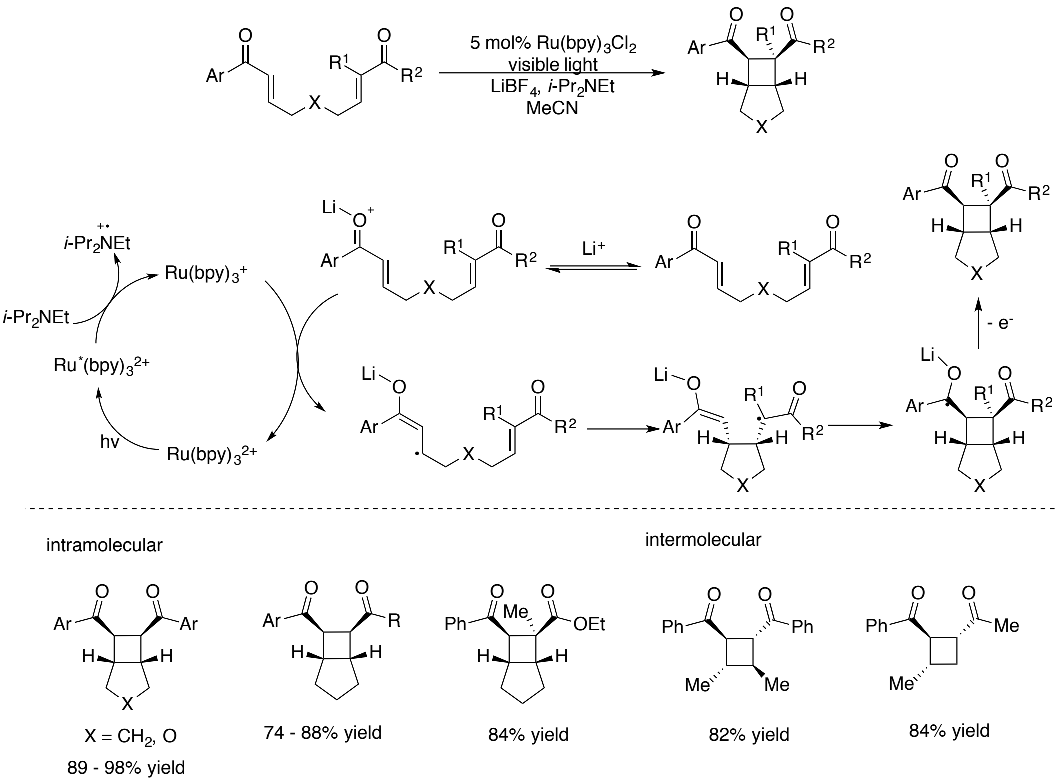
Mattay's condition: 4 equiv Et_3N, CH_3CN, 300 nm hv 23% yield

Cossy's condition: 10 equiv Et_3N, 1equiv $LiClO_4$,CH_3CN, 300 nm hv 70% yield

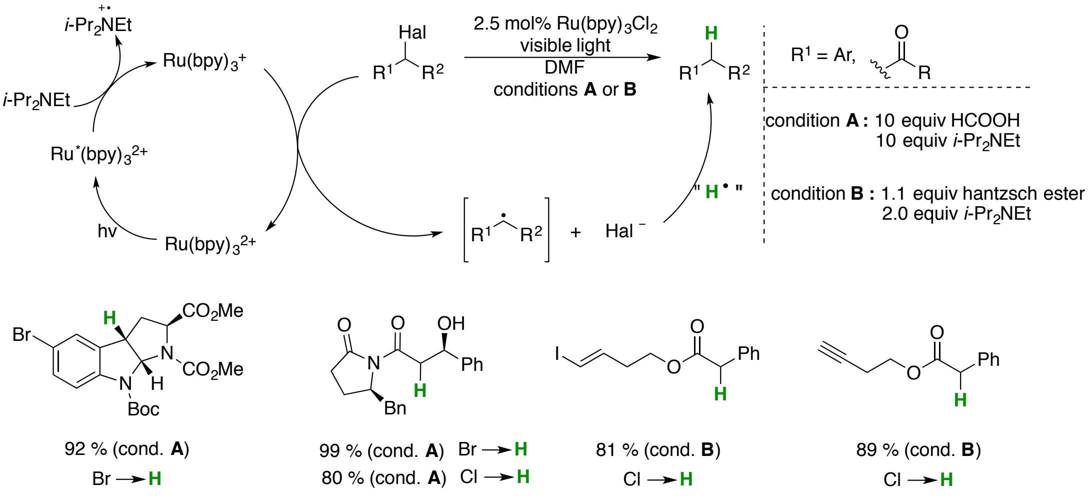
Scheme 1.8 Photoinduced ring opening and cyclization

1.2.2 Photocatalytic radical reactions using $Ru(bpy)_3^{2+}$ as photocatalyst

$Ru(bpy)_3^{2+}$ is widely used in photochemistry because of its special photophysical and chemical properities.[11] Yoon and co-workers carried out studies on visible-light photocatalytic [2+2] cycloaddition reactions of enones enabled by $Ru(bpy)_3^{2+}$; intramolecular and intermolecular [2+2] cycloadditions both proceed smoothly (Scheme 1.9).[12] Ethyldiisopropylamine is used as electron donor to generate the reductive Ru^+ species from the excited state Ru^{2+*}, the Li^+ applied in the reactions plays dual roles: improving the solubility of reactants in MeCN and serving as a mild Lewis acid to activate the enones. However, a limitation of such photocatalytic [2+2] cycloadditions is that at least one of the enones must be aryl enone no matter in cases of intramolecular cycloadditions or intermolecular cycloadditions.



Scheme 1.9 Photocatalysis of formal [2+2] cycloadditions of enones

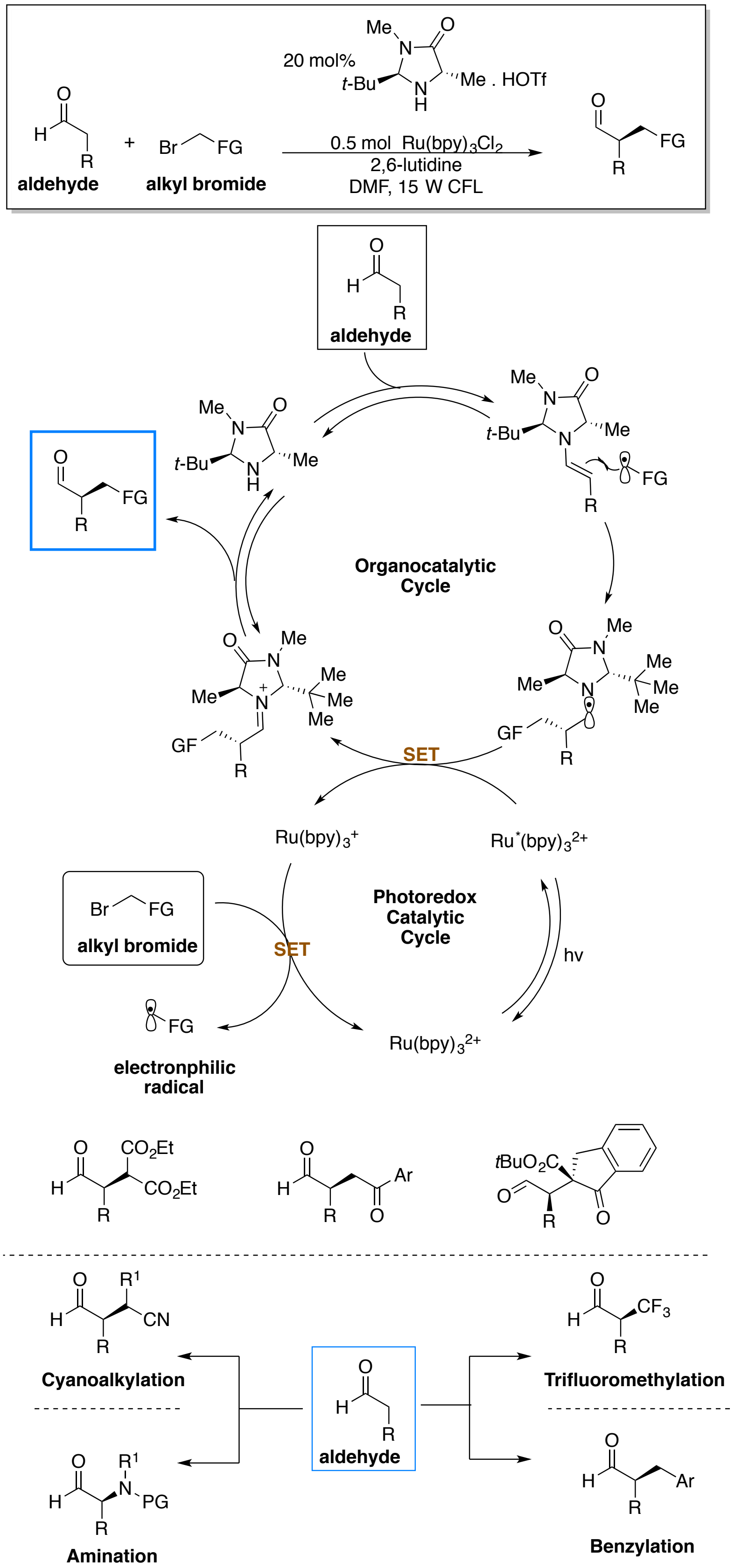


Scheme 1.10 Photoredox-catalyzed reductive dehalogenation reactions

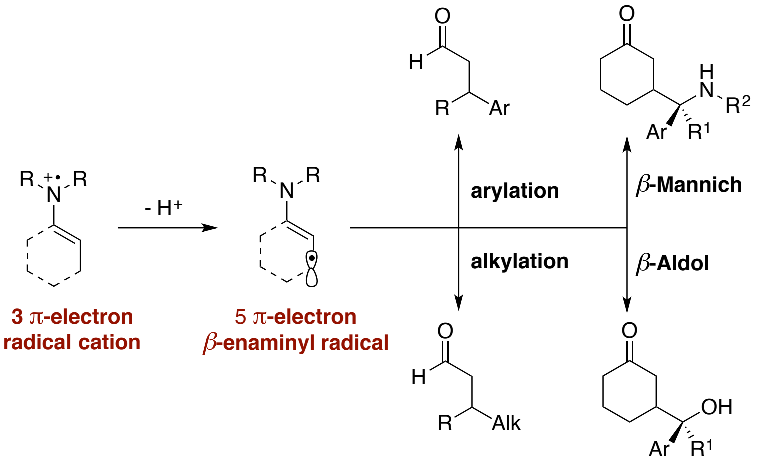
$Ru(bpy)_3^{2+}$-mediated photochemical reductive dehalogenation reactions of α-aryl and α-carbonyl derivatives proceed under mild conditions and tolerate a number of different hydrogen sources such as formic acid and Hantzsch ester derivatives.[13] Additionally, the reduced products tolerating variant functional groups can be obtained in excellent yields with superior chemoselectivity (Scheme 1.10).

The MacMillan group combined photoredox catalysis with amine-catalyzed SOMO type organocatalysis to develop new reaction modes and achieved great success in photoredox-catalyzed α-functonlization reactions of aldehydes. In 2008, their group developed the asymmetric α-alkylation of aldehydes using the dual photoredox organocatalysis (Scheme 1.11).[14] The chiral imidazolidinone catalyst allows for the radical attacking the enamine in a highly enantioselective fashion, both organocatalytic cycle and photoredox catalytic cycle interact to yield the α-alkylated aldehydes with high enantioselectivities, in this process no sacrificial electron donor is needed. A wide range of asymmetric α-functionalization reactions were achieved using this mechanistic platform, such as cyanoalkylation,[15] amination,[16] trifluoromethylation[17] and benzylation (Scheme 1.11).[18]

MacMillan and co-workers also applied the photoredox and organocatalysis activation mode into enanotioselective β-carbonyl functionalizations (Scheme 1.12).[19] The electrophilic 3π-electron SOMO intermediates[20] formed via single-electron oxidation of enamine undergo β-deprotonation to generate the 5π-electron β-enaminyl radical intermediates. These β-enaminyl radicals provide direct access to enantioenriched β-functionalized carbonyl products via asymmetric radical-radical couplings. The 5π-electron β-enaminyl radical activation platform has been expanded to couplings with catalytically generated alkyl and aryl radicals to accomplish formal β-alkylation and arylation products, respectively. The strategy also offers access to β-aldol and β-Mannich reactions through coupling reactions of β-enaminyl radical with ketyl (from ketones) and α-amino (from imines) radicals (Scheme 1.12).



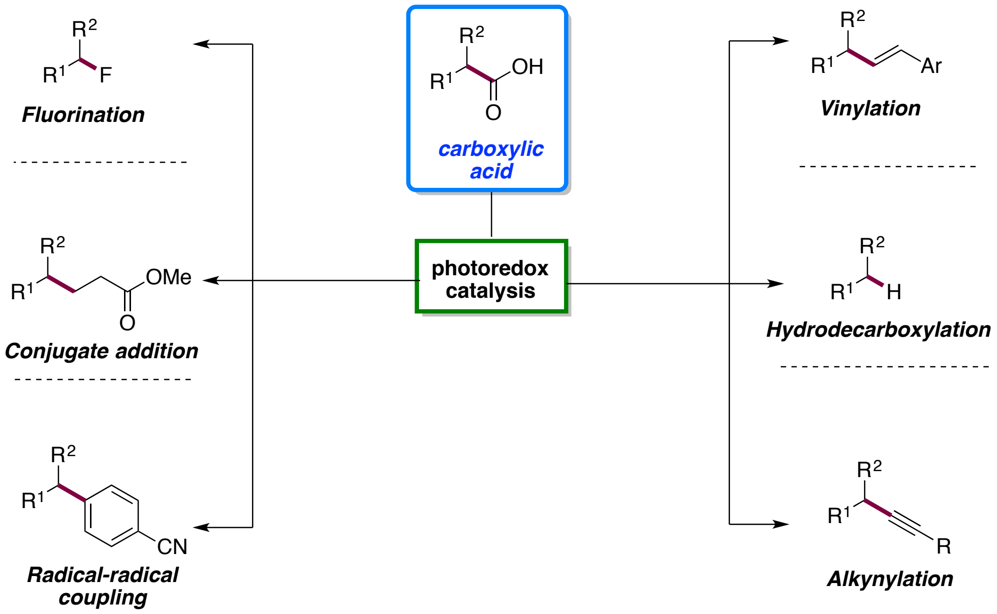
Scheme 1.11 Asymmetric α-functionalization of aldehydes via dual photoredox organocatalysis



Scheme 1.12 Direct β-functionalization of saturated carbonyl compounds through the merger of photoredox and organocatalysis

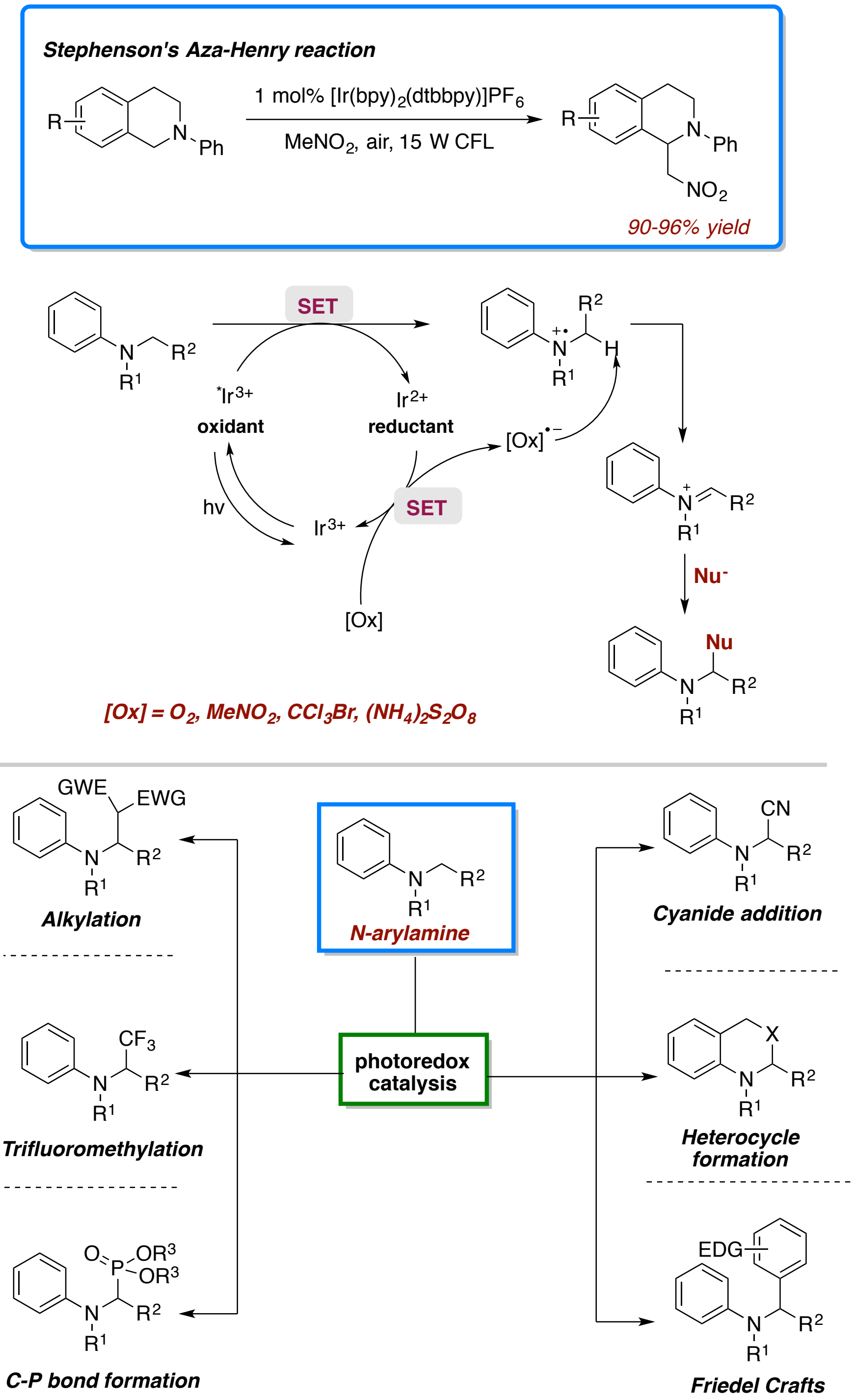
1.2.3 Photocatalytic radical reactions using Ir(bpy)$_3^{2+}$ as photoredox catalyst

Ir polypyridyl complexes also have been demonstrated as efficient photoredox catalysts. Carboxylic acids are readily available and bench-stable compounds, and have been exploited as carbon-centered radical precursors in photoredox catalysis as demonstrated by Sammis, MacMillan and others. Oxidation of the carboxylic acids leads to desired alkyl radical species via extrusion of CO_2. Except for simple alkyl radicals, a wide range of α-oxyl and benzylic radicals can be accessed using this strategy. In addition, α-amino radicals can be generated from amino acid derivatives with this activation mode. As a result, a variety of redox neutral transformations were achieved using carboxylic acids as substrates, such as hydrodecarboxylation[21] and radical-radical coupling reactions[22] as well as decarboxylative vinylnations,[23] fluorinations,[24] alkynylations[25] and conjugate additions (Scheme 1.13).[26]



Scheme 1.13 Photoredox-catalyzed decarboxylative transformations

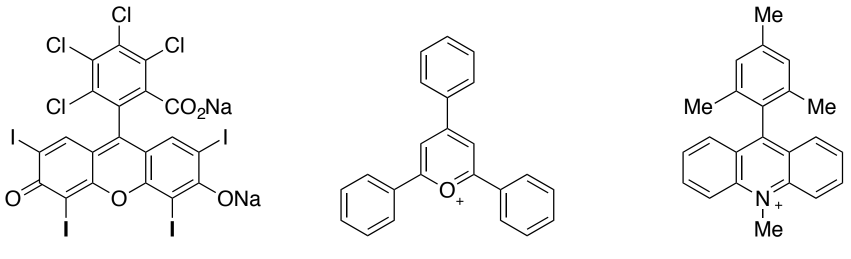
Functionalization and construction of nitrogen heterocycles remains an attractive research area as the nitrogen heterocycles represent a privileged motif in natural products and biologically active compounds. Photoredox catalysis was demonstrated to be successful in selective α-functionalization of amines. In 2010, Stephenson and co-workers disclosed a photoredox-catalyzed aza-Henry reaction (Scheme 1.14).[27] In this process, single-electron transfer from an amine to excited state of Ir photocatalyst to generate an amine radical cation with reduction of photocatalyst Ir^{3+} to Ir^{2+}, subsequently, deprotonation of the relatively acidic α-amino C-H bond by a radical anion derived from oxidant results in an α-amino radical, which is oxidized by the oxidant immediately into the iminium ion. A nucleophile attacks the iminium ion to afford the α-functionalized product. In this transformation, the oxidant is necessary and not only is used to oxidize the Ir^{2+} to Ir^{3+}, its corresponding reductive product also serves as base to deprotonate the acidic α-amino C-H bond. A variety of compounds such as molecular oxygen, $MeNO_2$, CCl_3Br and $(NH_4)_2S_2O_8$ can be used as oxidants in this process. The nucleophilic coupling partner has been extended to cyanide,[28] electron-rich aromatics,[29] malonates,[30] trifluoromethyl anion[28] and phosphonates (Scheme 1.14).[31]



Scheme 1.14 Photoredox-catalyzed oxidative α-amino functionalization

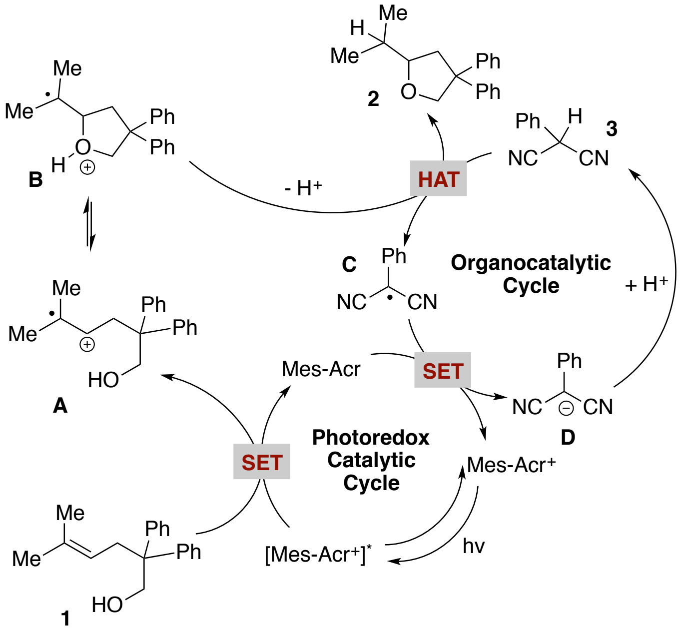
1.2.4 Photocatalytic radical reactions using organic dyes as photoredox catalysts

Organic dyes, such as Rose Bengal, TPP$^+$ and Mes-Acr$^+$, are also used as catalysts for conversion of visible light into chemical energy in the photoredox catalysis (Figure 1.1).[32]



Rose Bengal **TPP$^+$** **Mes-Acr$^+$**

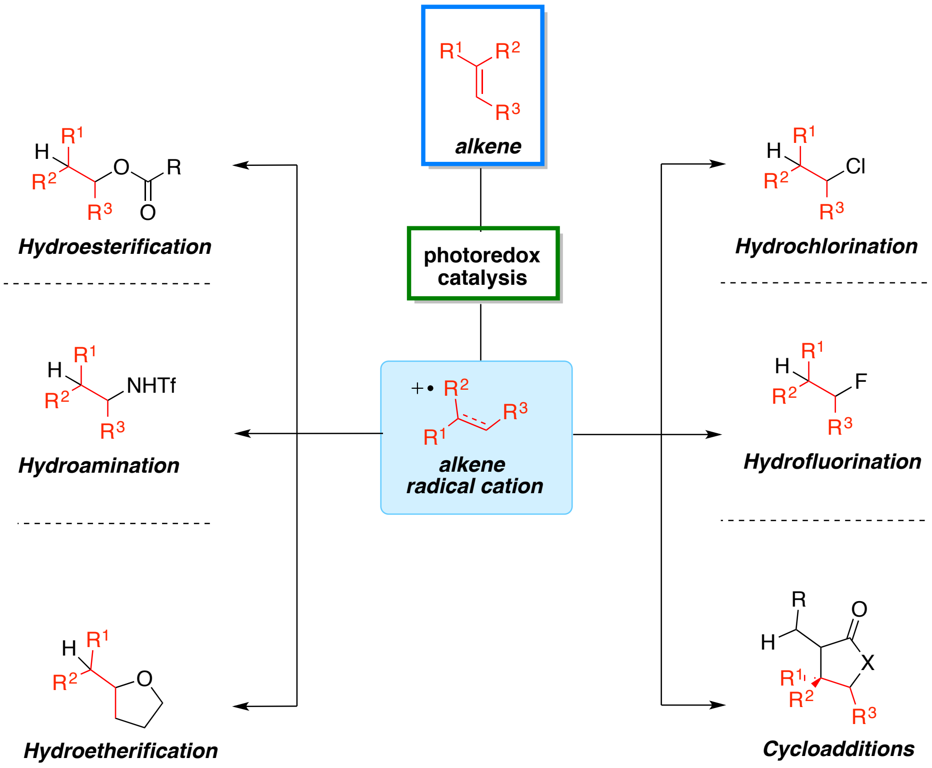
Figure 1.1 Organic dyes used as photoredox catalysts



Scheme 1.15 Intramolecular anti-Markovnikov hydroetherification of alkenols

Nicewicz group has achieved great success in hydrogen atom transfer (HAT) reactions utilizing the organic dynes as photoredox catalysts. In 2012, Nicewicz and co-workers disclosed the intramolecular anti-Markovnikov hydroetherification of alkenes via a two-component single electron photoredox system; 9-mesityl-10-

methylacridinium perchlorate ([Mes-Acr]ClO_4) was employed as photoredox catalyst in this transformation (Scheme 1.15).[33] The alkene **1** undergoes single-electron transfer to excited Mes-Acr$^+$ to deliver to radical cation **A** with the reduction of excited Mes-Acr$^+$ to Mes-Acr. This highly electrophilic species **A** proceeds intramolecular alcohol attack to give radical **B**, which undergoes a HAT from 2-phenylmalonitrile **3** (the HAT catalyst used in this strategy) and releases a proton to deliver the tetrahydrofuran **2**. The resulted 2-phenylmalonitrile radical **C** can be readily reduced to anion **D** by photoredox catalyst Mes-Acr, protonation of anion **D** regenerates the HAT catalyst.

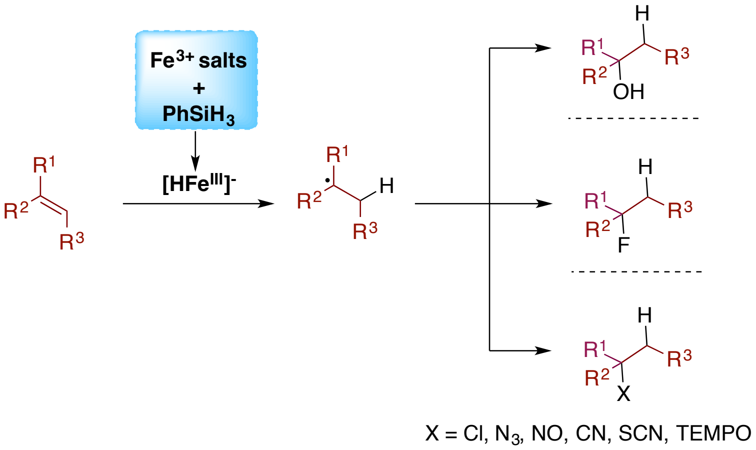


Scheme 1.16 Dual photoredox HAT catalysis for alkene functionalizations

Following this success, Nicewicz extended this photoredox HAT strategy to various alkene functionalizations using the Mes-Acr as photoredox catalyst in combination with the HAT catalyst (such as 2-phenylmalonitrile or thiophenol derivatives). These alkene functionalizations include hydrofluorination,[34] hydrochlorination,[34] hydroacetoxylation[35] and hydroamination,[36] as well as a range of radical crossover cycloadditions (Scheme 1.16).[37]

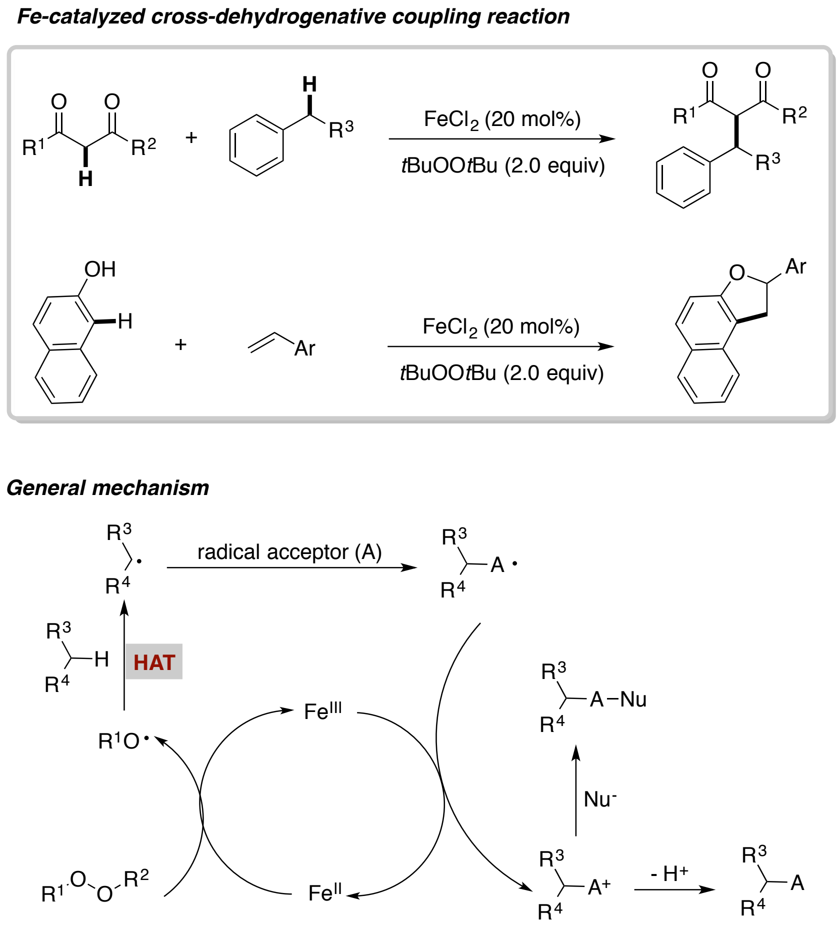
1.3 Transition metal-catalyzed radical reactions

Transition metals can serve as catalysts in radical chemistry. Iron is a cheap, readily available and environment-friendly metal. Iron salts have been successfully used as catalysts in radical chemistry. Fe(acac)$_3$ can generate Fe^{III}-hydrido complex in situ in combination with phenylsilane as a reducing reagent, with the Fe^{III}-hydrido complex having been employed as ideal catalyst in catalytic reductive alkene coupling reactions.[38] The radical intermediate generated from alkene via H-atom transfer from Fe^{III}-hydrido complex to alkenes can be oxidized by various oxidants to give alcohols, haloalkanes, nitriles and isothiocyanates, as well as TEMPO ethers (Scheme 1.17).[39]



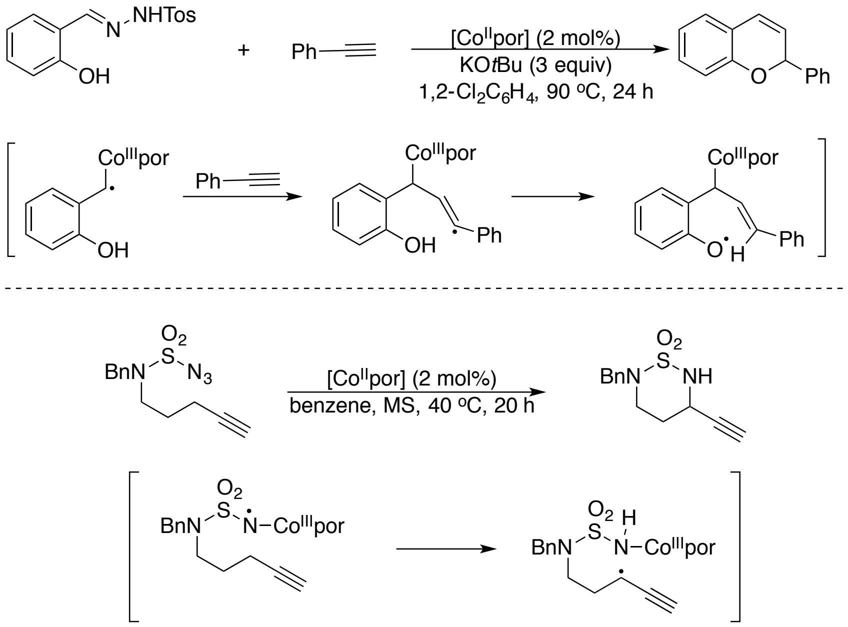
Scheme 1.17 Fe-mediated radical alkene functionalization

Fe catalysts are also used in conjugation with peroxides or hydroperoxides in radical reactions. In these cases, Fe^{II} salt reacts with the peroxide R^{1}OOR^2 to lead to alkoxyl radical R^{1}O$^\cdot$ and the corresponding Fe^{III}OR^2. The reactive alkoxyl radical R^{1}O$^\cdot$ then abstracts a hydrogen atom from substrate to result in carbon-centered radical which further reacts with radical acceptor to generate an adduct radical. The adduct radical is oxidized by Fe^{III} to afford the adduct cation, which undergoes deprotonation or reaction with a nucleophile to release the final product (Scheme 1.18).[40] For example, di-tert-butylperoxide was used in combination with $FeCl_2$ to initiate the radical reactions of β–diketones or β–ketoesters with diarylmethanes and cyclic alkylbenzenes.[41] Under the similar conditions, benzofuran derivatives are prepared via the radical reactions of β–naphthol with styrenes (Scheme 1.18).[42]



Scheme 1.18 Cross-dehydrogenative coupling reaction enabled by Fe and peroxide and general mechanism

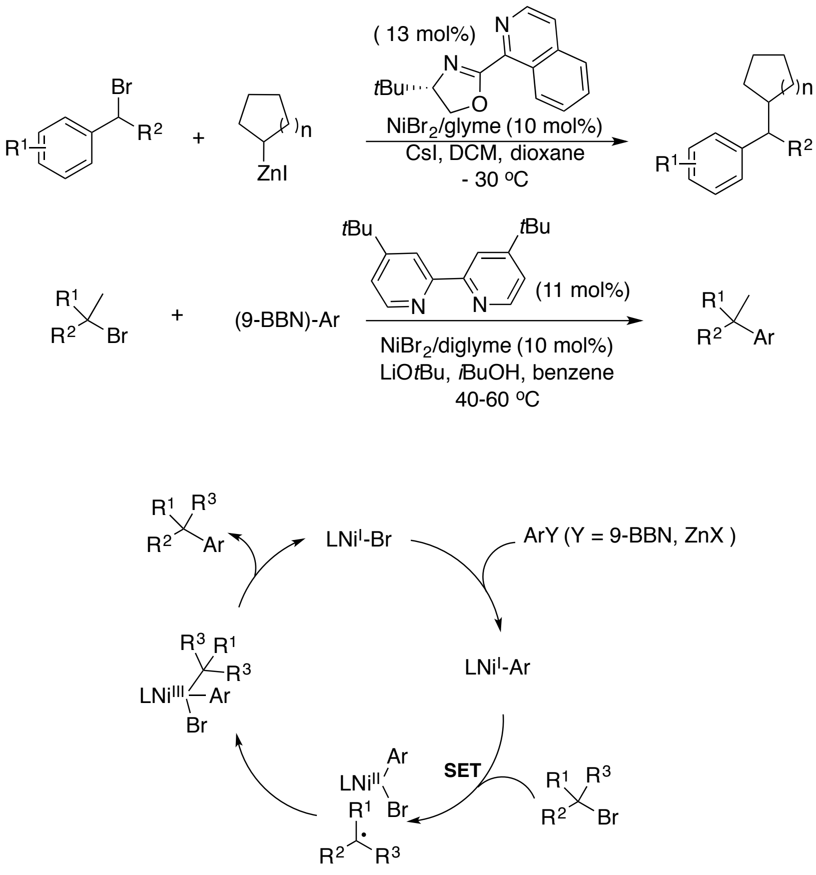
$[Co^{II}por]$ complex has been employed as catalyst in radical reactions of N-tosylhydrazones and azides (Scheme 1.19). In the case of N-tosylhydrazone, N-tosylhydrazone can generate diazo compound in situ under basic condition. [Co^{II}por] complex reacts with diazo compound to lead to cobalt (III)-carbene radical upon N_2 fragmentation, which undergoes radical addition to terminal alkyne to form vinyl radical intermediate. Phenoxyl radical is produced via 1,6-H transfer from the hydroxyl group to vinyl carbon radical, followed by 6-*endo*-cyclization to afford chromene product under regeneration of Co^{II} catalyst.[43] When come to the reactions of azides, they undergo the similar pathway. Co-complexed N-centered radical generated via reaction of [Co^{II}por] complex with azide upon liberation of N_2, undergoes 1,6-H transfer to yield carbon radical. This carbon radical then undergoes homolytic substitution at the nitrogen atom to yield the final product with the regeneration of Co^{II} catalyst.[44]



Scheme 1.19 Radical reactions enabled by Co^{II} metalloradical catalysis

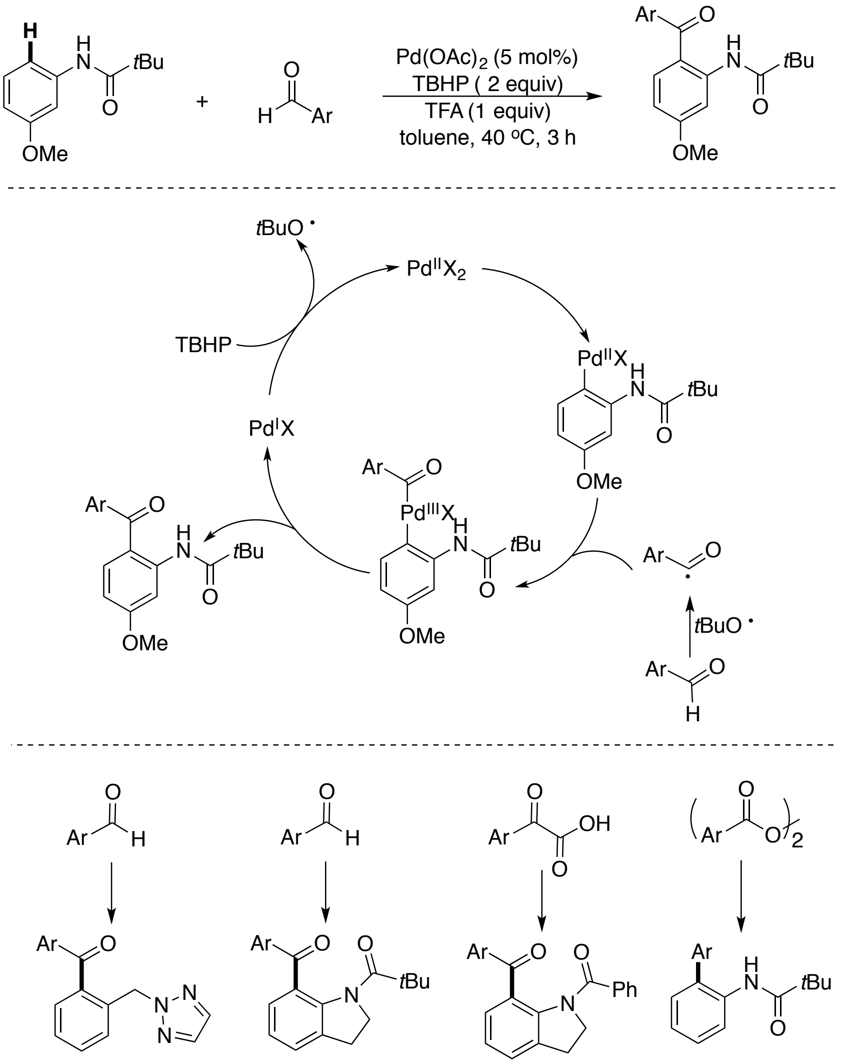
The Ni^{I} complex can generate the radical intermediates from alkyl halides via electron transfer (ET) processes. The Fu group disclosed the Ni-catalyzed Negishi and

Suzuki-type cross-coupling with alkyl bromides, in such cases, LNi^{I}Br first undergoes transmetalation with arylzinc or (9-BBN)-aryl compounds to produce LNi^{I}Ar complex, this LNi^{I}Ar complex forms the LNi^{II}ArBr species via SET to alkyl bromide, along with the generation of the corresponding carbon radical, and LNi^{II}ArBr reacts with the carbon radical to give Ni^{III} complex, which undergoes reductive elimination to yield the coupling product with regeneration of LNi^{I}Br back into catalytic cycle (Scheme 1.20).[45]



Scheme 1.20 Ni-catalyzed Negishi- and Suzuki-type cross-coupling with alkyl bromide and general catalytic cycle

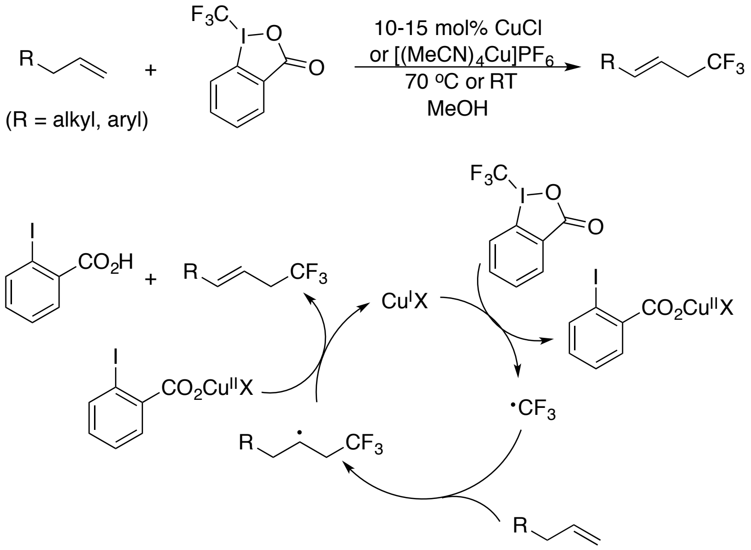
Radical arene C-H functionalization can be achieved by using Pd catalysis, *tert*-butyl hydroperoxide (TBHP) is usually used as a stoichiometric oxidant in this transformation. For instance, in the case of direct C-H activation and functionalization



Scheme 1.21 Pd-catalyzed direct arene C-H activation and functionalization

of N-arylamide with acyl radical (generated from aldehyde), $Pd(OAc)_2$ is used as catalyst and TBHP is used as oxidant (Scheme 1.21).[46] $Pd^{II}X_2$ ($X = CF_3CO_2$) reacts with N-arylamide first to give aryl$Pd^{II}X$ intermediate, which undergoes addition reaction with acyl radical to lead to an acylaryl$Pd^{III}X$ complex. At this moment, it's worth mentioning that the acyl radical is generated from the starting aldehyde by hydrogen abstraction of *tert*-butoxyl radical. The acylaryl$Pd^{III}X$ complex undergoes reductive elimination to release the targeted coupling product along with $Pd^{I}X$. The $Pd^{I}X$ is oxidized by TBHP to $Pd^{II}X_2$ with generation of *tert*-butoxyl radical (Scheme 1.21). The amide group is often used as the directing group in such transformation. Ketones are successfully prepared by C-H activation and functionalization of corresponding arenes using aldehyde as acyl radical source (Scheme 1.21).[47] α-Keto acids can also generate acyl radicals for trapping aryl$Pd^{II}X$ intermediate via oxidative decarboxylation (Scheme 1.21).[48] When diaroyl peroxide is used, aryl radical can be generated, which reacts with aryl$Pd^{II}X$ complex to yield the biaryl as the final product (Scheme 1.21).[49]

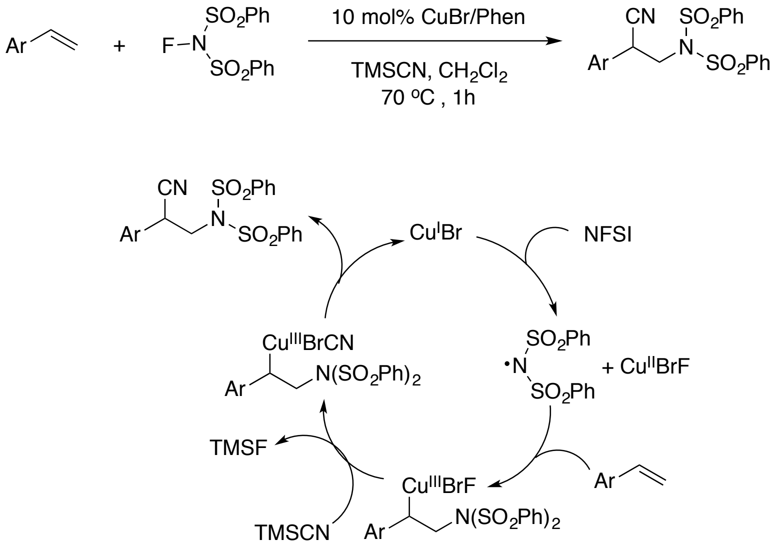
Cu catalyst is used in radical trifluoromethylation of alkenes as studied by Buchwald[50] and Wang groups.[51] Single-electron transfer from Cu^I salt to Togni reagent to give Cu^{II} carboxylate and CF_3 radical, and the CF_3 radical then adds to alkene to afford carbon radical, which undergoes SET to Cu^{II} carboxylate followed by deprotonation to produce the trifluoromethylation product and regenerate the Cu^I salt (Scheme 1.22).



Scheme 1.22 Cu-catalyzed radical alkene trifluoromethylation with Togni reagent

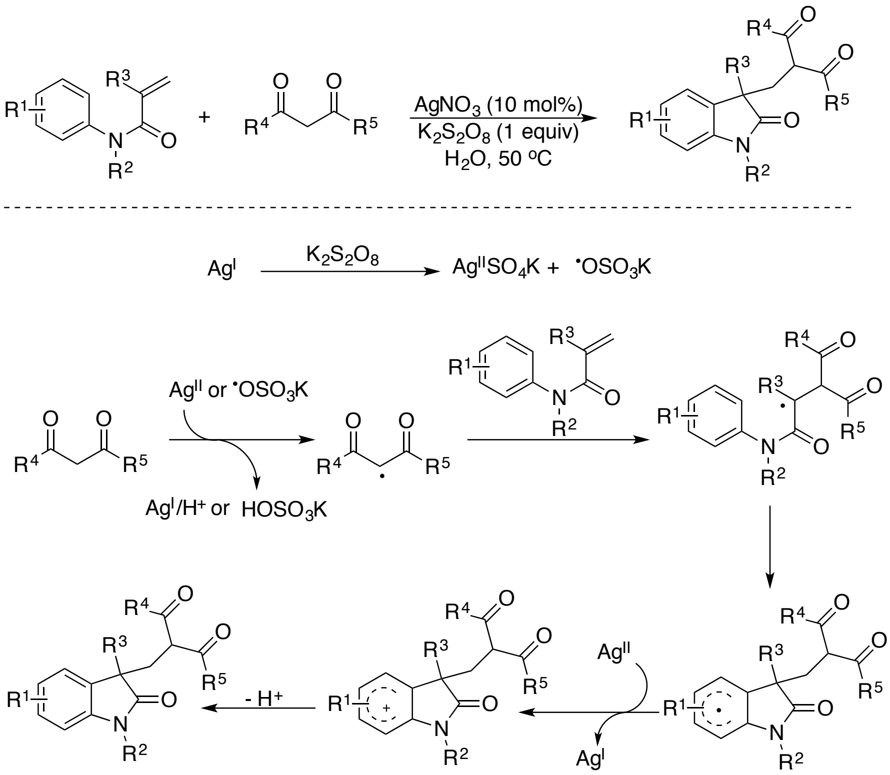
Cu catalysis is also used to generate N-centered radicals from oxaziridines[52] and N-fluorosulfonimide (NFSI).[53] Here we take Cu-catalyzed styrene amidocyanation with NFSI as an example;[53a] Cu^I catalyst reacts with NFSI to give an amidyl radical, with

Cu^{I} oxidized to Cu^{II} at the same time. Amidyl radical adds to alkene and then is trapped by Cu^{II} to generate RCu^{III}BrF complex, which reacts with TMSCN to afford RCu^{III}BrCN complex, and the RCu^{III}BrCN complex proceeds via reductive elimination to give amidocyanation product along with reduced Cu^{I} catalyst (Scheme 1.23).



Scheme 1.23 Cu-catalyzed amidocyanation of styrene with NFSI

Silver catalyst is mostly used for the oxidation of radicals in radical chemistry. In the oxidative coupling reactions of N-alkyl-N-methyl-acrylamide with β-diketones and β-ketoesters, AgNO$_3$ is used as a catalyst and K$_2$S$_2$O$_8$ is used as an oxidant (Scheme 1.24).[54] K$_2$S$_2$O$_8$ oxidizes the Ag^{I} to Ag^{II} and generates $^{\cdot}$OSO$_3$K radical. β-Dicarbonyl derivative undergoes SET to Ag^{II} or HAT to $^{\cdot}$OSO$_3$K radical to result in carbon radical, which adds to the C-C double bond of acrylamide to form a new carbon radical. The resulted new carbon radical cyclizes to lead to cyclohexadienyl radical, which is further oxidized by Ag^{II} to provide cyclohexadienyl cation. Deprotonation eventually yields the targeted product.

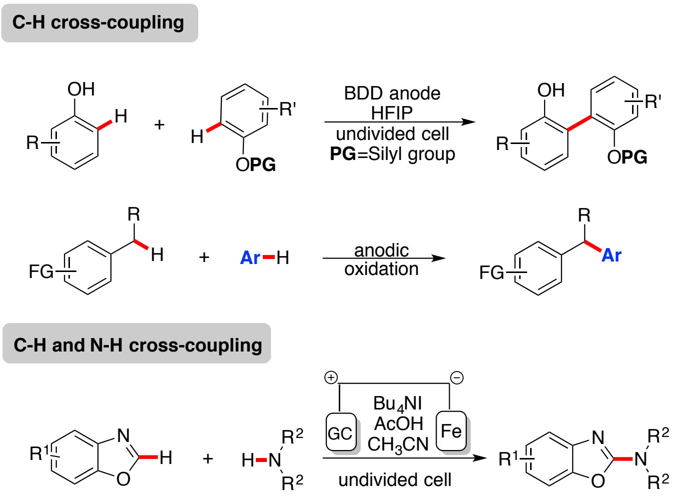


Scheme 1.24 Ag-catalyzed radical cascade reactions

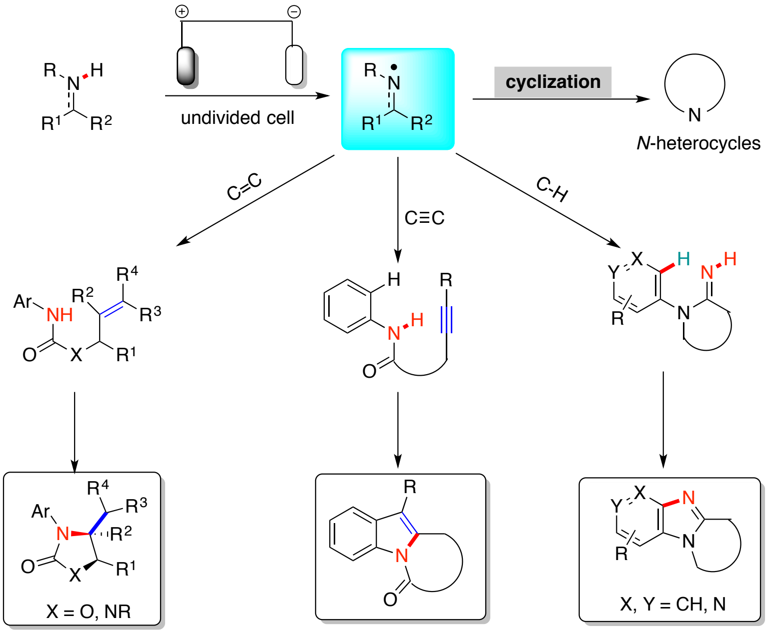
1.4 Electrochemically initiated radical reactions

Electrochemistry has been used to generate radicals for construction the carbon-carbon and carbon-heteroatom bonds. Waldvogel,[55] Yoshida,[56] Zeng and Little[57] *et. al* successfully employed the electrochemical method to realize the cross-coupling between C-H and C-H, as well as the cross-coupling between C-H and N-H (Scheme 1.25). Horn and Rosen realized the electrochemical allylic C-H oxidation.[58]

Xu ultilized the electrochemistry to generate the nitrogen-centered radicals which under intramolecular reactions with carbon-carbon double bond, carbon-carbon triple bond or C-H to prepare a variety of heterocycles (Scheme 1.26).[59] Very recently, Lei developed an electrocatalytic protocol for dehydrogenative C-H/S-H cross-coupling.[60]



Scheme 1.25 Electrochemistry-enabled C-H functionalizations

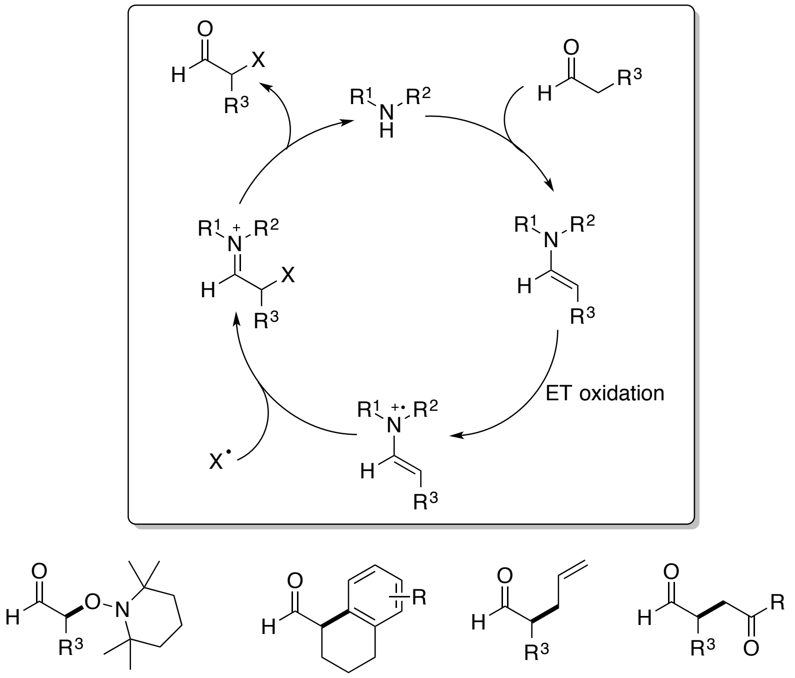


Scheme 1.26 Xu's electrochemical generation of nitrogen-centered radicals for reactions

1.5 Organocatalyzed radical reactions

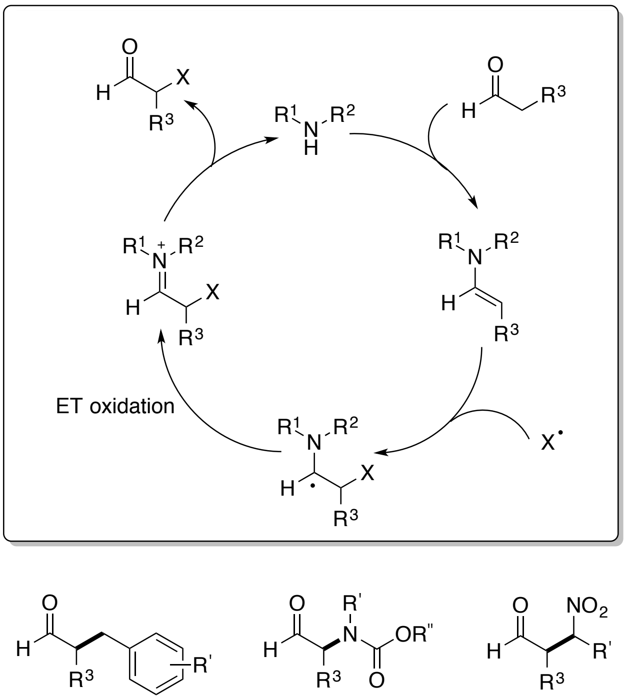
1.5.1 Amines as catalysts

An amine catalyst can condense with aldehyde to generate an enamine in situ, the enamine proceeding via single-electron transfer to an external oxidant to give enamine radical cation, which further reacts with various radical trapping reagents such as TEMPO,[61] arenes[62] or electron-rich alkenes[63] to yield the α-functionalized iminium ions, with eventual hydrolysis to yield the products and regenerate the amine catalyst (Scheme 1.27).



Scheme 1.27 Amine-catalyzed radical reactions via enamine radical cations

In the absence of oxidant, the in situ generated enamines serve as electron-rich alkenes and show high reactivity towards benzyl radicals,[64] carbamoyl radicals,[16] as well as α-nitroalkyl radicals,[65] with the resulting α-amiyl radicals undergo single-electron oxidation to form iminium ions, and subsequent hydrolysis of iminium ions affording the α-benzylated, α-aminated, and α-nitroalkylated products (Scheme 1.28).

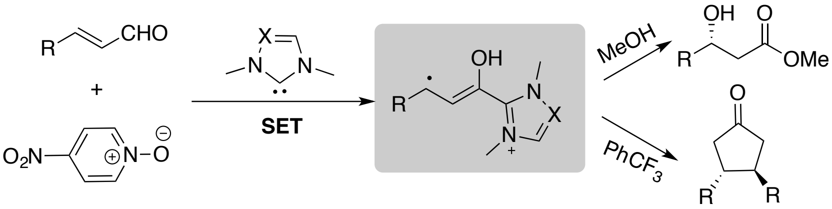


Scheme 1.28 Amine-catalyzed radical reactions: enamines as radical acceptors

1.5.2 Radical reactions with N-heterocyclic carbenes as catalysts

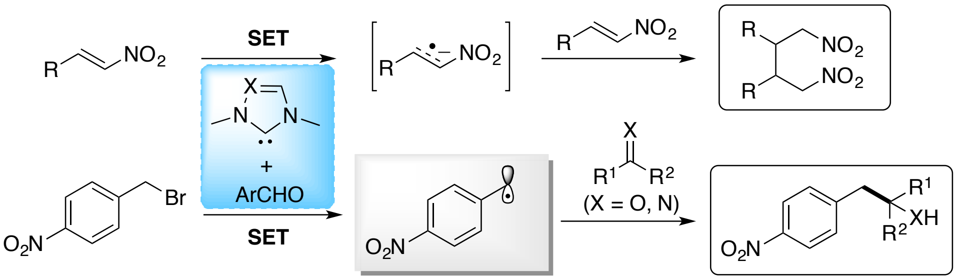
N-Heterocyclic carbenes (NHCs)-catalyzed electron pair reactions have been well developed in last decades, however, the radical chemistry catalyzed by NHCs is still in its infancy, and few reactions have been reported so far. The first example NHC-catalyzed SET reaction was reported by Studer in 2008, using TEMPO as the oxidant to yield the TEMPO ester finally.[66]

Rovis and co-workers found that homoenolate equivalent could lose one electron to electron-deficient nitroarene to form radical cation intermediate. β-hydroxyl ester and cyclopentanone products are both accessible when applying this strategy with alternative solvents (Scheme 1.29).[67]



Scheme 1.29 Rovis's NHC-catalyzed radical reactions

Our group discovered that the Breslow intermediate derived from NHC and aldehyde can be used as an efficient single-electron reductant to generate radicals from nitroalkenes[68] or nitrobenzyl bromides;[69] these radicals react with activated ketones/imines or upon homocoupling to afford the reductive products (Scheme 1.30).



Scheme 1.30 Our group's NHC-catalyzed reductive coupling reactions involved SET

1.6 Summary and research designs

Radical chemistry has received tremendous attention since 1980s, and a broad range of radical reactions has been developed with various ways to generate radicals to date, from the use of azo compounds and peroxides radical initiators, photoredox catalysis, transition-metal catalysts to organocatalysts. Among them, organocatalyzed radical reaction lacks general exploration, especially NHC-catalyzed radical reaction.

NHCs have been applied to the study of paired electron chemistry between NHC-bound nucleophile and a variety of electrophiles, and significant progress has been achieved in such field. However, when examining single-electron chemistry involving NHC catalysis, there are only few examples we can discuss. The NHC-catalyzed radical reaction remains a challenging research area, needing much effort to explore. Therefore, we aimed at developing novel radical activations and reactions enabled by NHC catalysis.

With limited successful pioneering work in the field of radical reactions catalyzed by NHCs, as well as the unique ability of NHCs to target restricted functional groups, such as aldehyde and activated carboxylic acid derivatives, we will launch our work from two aspects: (1) search for suitable electron acceptors that could receive the single electron form NHC-bound intermediates to form radical intermediates; (2) combine NHC with other reagents to initiate the radical reactions of no NHC-bound compounds.

1.7 References

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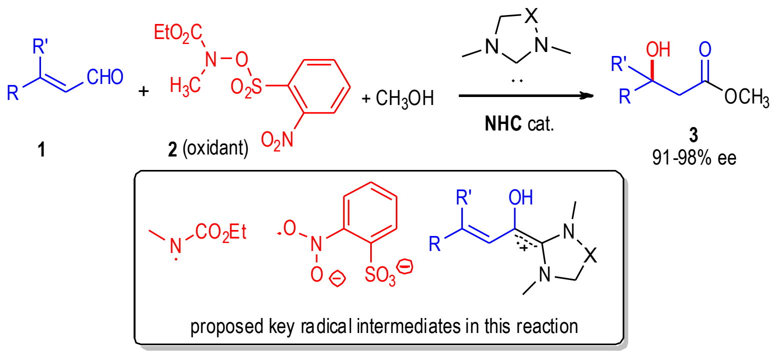
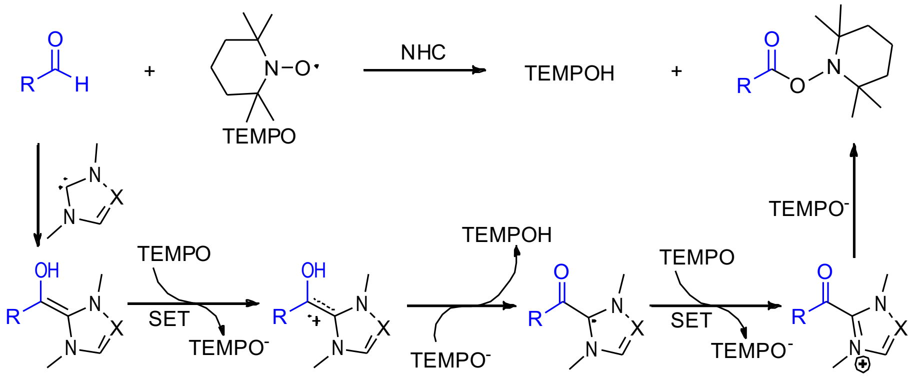
Chapter 2

N-Heterocyclic Carbene-Catalyzed Radical Reactions for Highly Enantioselective β-Hydroxylation of Enals



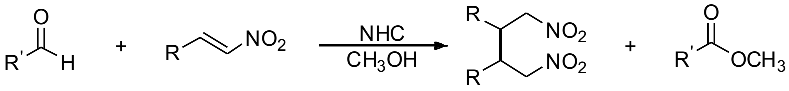
2.1 Introduction

N-heterocyclic carbene organocatalysis have gained increasing attention in the past two decades, with a broad range of reactions have been invented via acyl anion, enolate, and homoenolate equivalents.[1] All these discrete reactive species proceed via a pair of electron transfer. Reactions involving single-electron transfer (SET) have important applications in organic synthesis, since the SET process[2] can provide valuable opportunities for activation chemical bonds or functionalization of molecules which are not easy to achieve via electron pair chemistry. Indeed, the NHC-enabled SET processes in the living systems have been studied, and it has been proved that thiamine pyrophosphate (TPP)-mediated generation of acetyl-CoA and CO_2 via oxidative decarboxylation of pyruvate proceeds via SET processes.[3] However, NHC-catalyzed SET reactions in synthetic chemistry have been rarely-explored. In 2008, Studer reported NHC-catalyzed oxidation of aldehydes to corresponding TEMPO esters utilizing TEMPO as an oxidant (Scheme 2.1).[4] The authors suggested that the reaction is achieved by two steps of SET from Breslow intermediate to TEMPO.

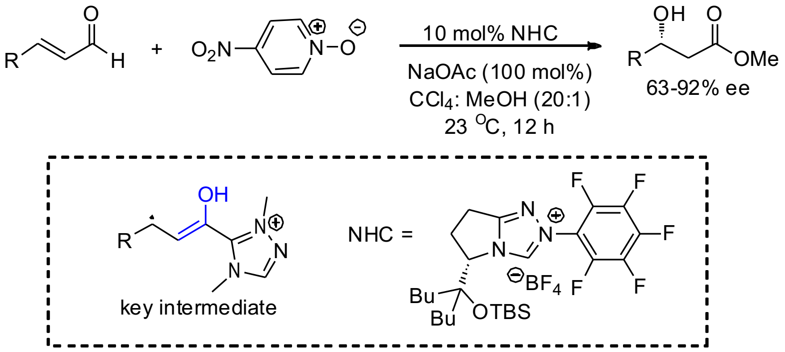


Scheme 2.1 NHC-catalyzed oxidation of aldehydes via SET process

From 2013, our laboratory has been involved in the development of NHC-catalyzed new reaction modes which rely on the single-electron transfer process. In 2014, our group reported the reductive β,β-coupling of nitroalkenes via NHC-catalyzed radical reaction (Scheme 2.2).[5] The presence of nitroalkene-derived radical anion was verified by electron paramagnetic resonance (EPR). Very recently, Rovis and co-workers reported carbene-catalyzed β-hydroxylation of enals via SET processes using nitropyridine N-oxide as an oxidant (Scheme 2.3).[6]



Scheme 2.2 NHC-catalyzed reductive β,β-coupling of nitroalkenes



Scheme 2.3 NHC-catalyzed β-hydroxylation of enals using 4-nitropyridine N-oxides

We hypothesized that Breslow intermediate **A** could undergo SET to generate a homoenolate β-carbon-centered radical cation **B** (Figure 2.1). Meanwhile, dinitrobenzenesulfonic carbamate **2a**, first reported by MacMillan as a N-centered radical precursor,[7] receives this electron to yield a radical **C** that then undergoes a subsequent combination with the radical **B** to form NHC-bound ester intermediate **D** with the generation of a C-N covalent bond. The intermediate **D** can be readily captured by alcohol to yield β-amino ester **E**. However, we didn't get β-amino ester **E** in our study, but obtained β-hydroxyl ester **3** instead. We were encouraged by the results to envision that this carbene-mediated transformation could be developed for useful reactions, presumably through a radical pathway. β-hydroxyl esters are important building blocks and ubiquitous subunits present in a large range of biologically active compounds and natural products (Figure 2.2),[8,9] and the main approaches to such products are transition metal-catalyzed reactions, such as aldol reactions,[10] Reformatskii reactions[11] and hydrogenations[12]. Organocatalytic preparation of β-hydroxyl esters has not been well studied.[13]

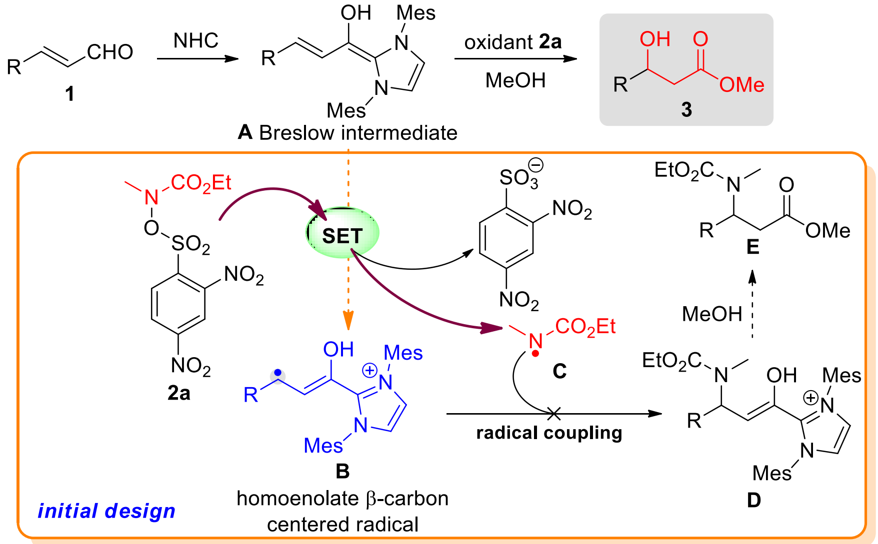


Figure 2.1 Our work and the initial design to access NHC-catalyzed radical reaction via SET process

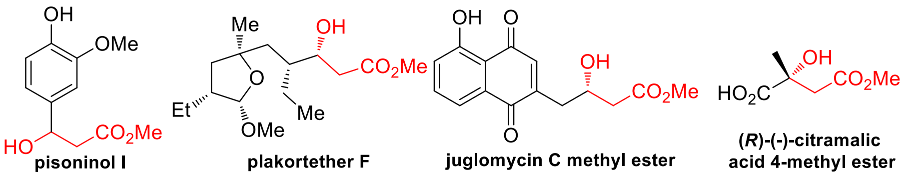


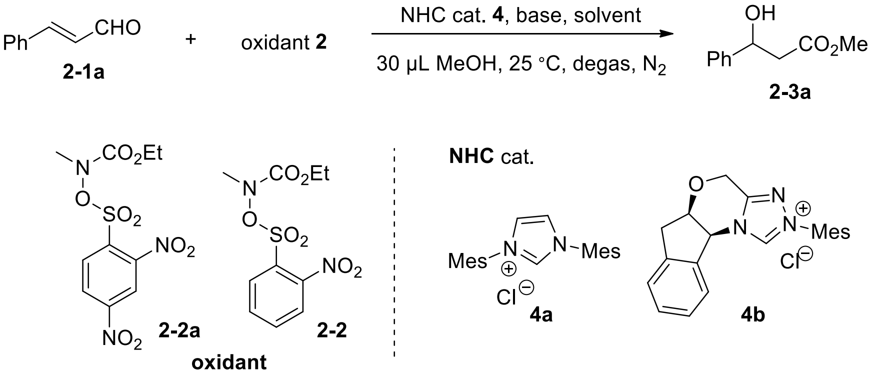
Figure 2.2 Natural products and bioactive molecules containing β-hydroxyl ester unit

2.2 Results and discussion

2.2.1 Condition optimization

In the initial study, we used cinnamaldehyde **2-1a** and dinitrobenzenesulfonic carbamate **2-2a** as model substrates to try the reaction. When the reaction was carried out in THF at room temperature under N_2 atmosphere using achiral imidazolium **4a** as catalyst and K_2CO_3 as base, the β-hydroxyl ester **2-3a** was obtained in an encouraging yield of 32% (Table 2.1, entry 1). Then we switched the catalyst to chiral catalyst **4b**, the β-hydroxyl ester **2-3a** was isolated in both low yield and enantioselectivity (25% yield and 12% ee) (Table 2.1, entry 2). We found that the oxidant **2-2** is more suitable for this β-hydroxylation reaction, both of yield and enantioselectivity were improved, particularly, the ee was increased to 96% (Table 2.1, entry 3).

Table 2.1 Initial study



Entry	NHC	Base	Solvent	Yield (%)[b]	ee (%)[c]
1	30 mol% **4a**	K_2CO_3	THF	32	-
2	20 mol% **4b**	K_2CO_3	THF	25	12
3[d]	20 mol% **4b**	K_2CO_3	THF	31	96

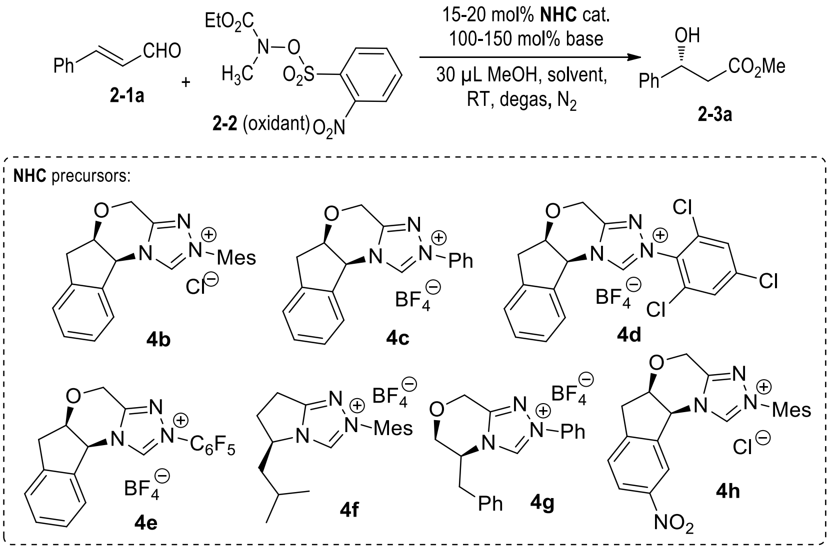
[a] Unless otherwise noted, reactions were carried out at rt using **2-1a** (0.1 mmol), **2-2a** (0.05 mmol), catalyst (0.01 mmol), base (0.05 mmol), and 1.5 mL of solvent, MeOH was added 30

min later. [b]Obtained by ^{1}H NMR analysis using 1,3,5-trimethoxylbenzene as an internal standard. [c]Determined by chiral HPLC analysis. [d]**2-2** was used as the oxidant.

2.2.1.1 Catalyst screening for asymmetric β-hydroxylation of enals

After we obtained the results above, we began to turn our efforts to screening the effect of catalysts. Changed the catalyst into chiral catalyst **4c**, the desired product was isolated in similar yield but decreased ee (92%) (Table 2.2, entry 2). The electron-deficient carbenes (e.g **4d**, **4e**) are not available to this reaction, not producing any desired product (Table 2.2, entries 3 and 4). Other catalysts, such as **4f** and **4g**, could provide higher yield of product but the enantioselectivity was poor (Table 2.2, entries 5 and 6). **4h** gave similar result as **4b**, however, **4h** is more difficult to prepare when compared with **4b**, so we chose **4b** for further optimization.

Table 2.2 Catalyst screening



Entry	NHC	Base	Solvent	Yield (%)[b]	ee (%)[c]
1	20 mol% **4b**	K_2CO_3	THF	31	96
2	20 mol% **4c**	K_2CO_3	THF	31	92
3	20 mol% **4d**	K_2CO_3	THF	0	-

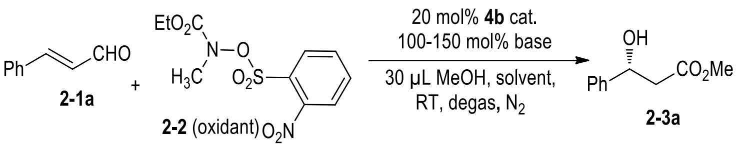
4	20 mol% **4e**	K_2CO_3	THF	0	-
5	20 mol% **4f**	K_2CO_3	THF	46	88
6	20 mol% **4g**	K_2CO_3	THF	53	77
8	20 mol% **4h**	K_2CO_3	THF	30	96

[a] Reactions were conducted with **2-1a** (0.1 mmol, 2.0 equiv.), oxidant **2-2** (0.05 mmol, 1.0 equiv.), and base (1.0 equiv.) in 1.5 mL solvent, MeOH was added via a needle 30 min later after the reaction started. [b] Obtained by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined via HPLC analysis on a chiral stationary.

2.2.1.2 Solvent screening for asymmetric β-hydroxylation of enals

We next studied the effect of solvent on reaction outcomes. In general, non-polar solvents (such as DCE, hexane and pentane) had a strong tendency to improve the yield (Table 2.3, entries 2, 5 and 7). However, the enantioselectivity dropped. Other non-polar solvents (e.g EE and cyclohexane) led to a slight increase in yield but a slight decrease in enantioselectivity (Table 2.3, entries 4 and 6). Polar solvent CH_3CN resulted in low yield and moderate enantioselectivity (24 % yield, 80% ee) (Table 2.3, entry 3). Toluene was the best choice, yielding good yield and excellent enantioselectivity (Table 2.3, entry 8).

Table 2.3 Solvent screening



Entry	NHC	Base	Solvent	Yield (%)[b]	ee (%)[c]
1	20 mol% **4b**	K_2CO_3	THF	31	96
2	20 mol% **4b**	K_2CO_3	DCE	67	90
3	20 mol% **4b**	K_2CO_3	CH_3CN	24	80

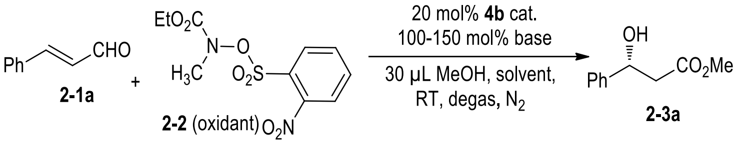
4	20 mol% **4b**	K_2CO_3	EE	40	92
5	20 mol% **4b**	K_2CO_3	hexane	62	66
6	20 mol% **4b**	K_2CO_3	cyclohexane	39	89
7	20 mol% **4b**	K_2CO_3	pentane	57	86
8	20 mol% **4b**	K_2CO_3	toluene	61	96

[a]Reactions were conducted with of **2-1a** (0.1 mmol, 2.0 equiv.), oxidant **2-2** (0.05 mmol, 1.0 equiv.), and base (1.0 equiv.) in 1.5 mL solvent, MeOH was added via a needle 30 min later after the reaction started. [b]Obtained by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c]Determined via HPLC analysis on a chiral stationary.

2.2.1.3 Base screening for asymmetric β-hydroxylation of enals and further optimization

Finally, we screened the bases and found that K_2CO_3 is the best choice (Table 2.4, entries 1-7), and that when increasing the loading of K_2CO_3 to 1.5 equivalents, the yield jumped to 79% with no effect on the enantioselectivity (Table 2.4, entry 8). It is very interesting that the yield is improved to 98% when the methanol was added at the very beginning (Table 2.4, entry 9). When the loading of catalyst was decreased to 15 mol%, the yield dropped slightly (Table 2.4, entry 10). Notably, the yield of the product is based on oxidant **2-2**, two equivalents of enal **2-1a** were used in the reaction, one equivalent of the enal was converted to the corresponding α,β-unsaturated ester.

Table 2.4 Base screening and further optimization



Entry	NHC	Base	Solvent	Yield (%)[b]	ee (%)[c]

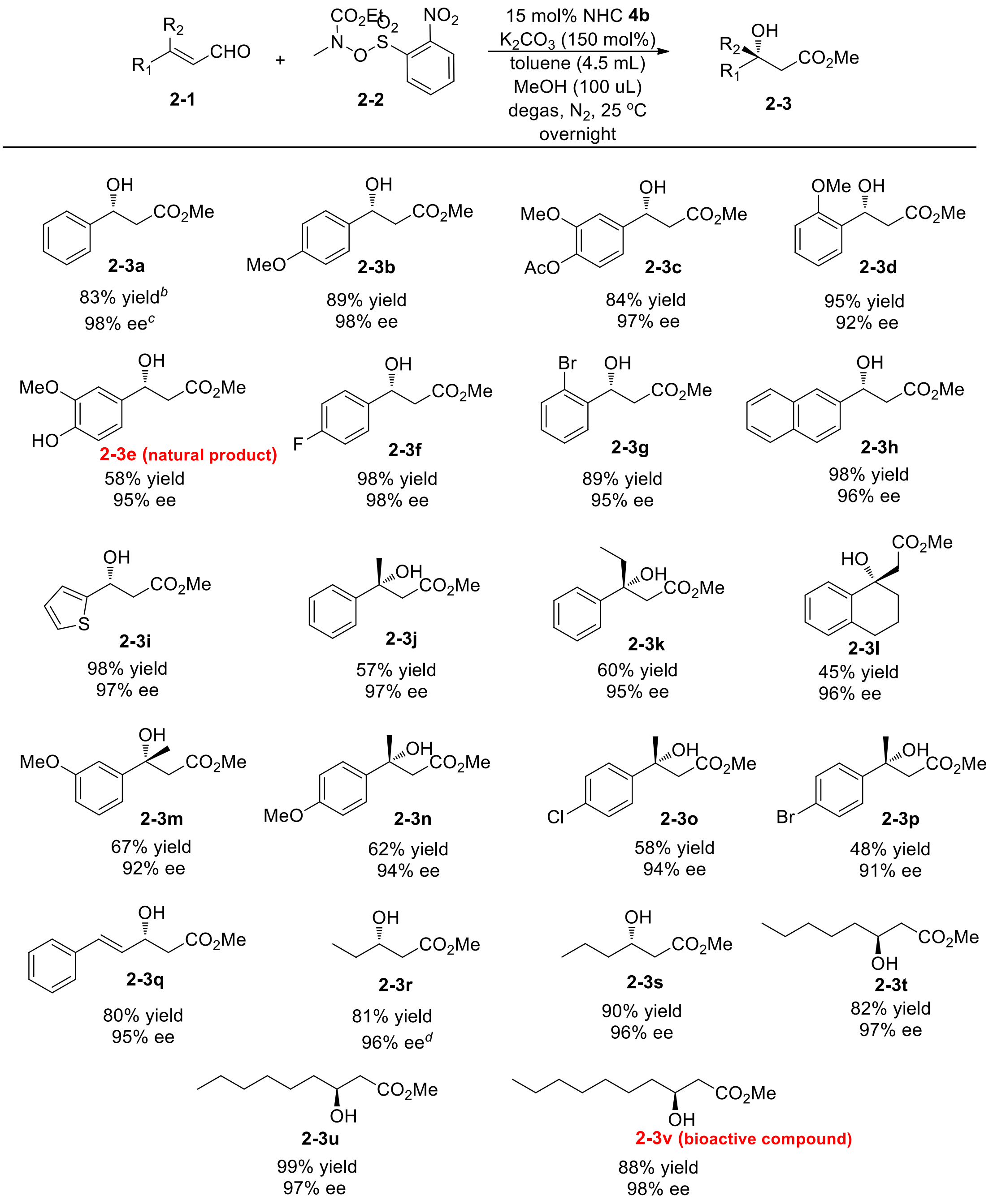
1	20 mol% **4b**	K_2CO_3	toluene	61	96
2	20 mol% **4b**	Cs_2CO_3	toluene	34	95
3	20 mol% **4b**	K_3PO_4	toluene	58	85
4	20 mol% **4b**	Na_2CO_3	toluene	31	97
5	20 mol% **4b**	DBU	toluene	25	94
6	20 mol% **4b**	DIEA	toluene	31	89
7	20 mol% **4b**	Et_3N	toluene	19	94
8[d]	20 mol% **4b**	K_2CO_3	toluene	79	96
9[d,e]	20 mol% **4b**	K_2CO_3	toluene	98 (95)	97
10[d,e]	15 mol% **4b**	K_2CO_3	toluene	89 (87)	97

[a] Reactions were conducted with of **2-1a** (0.1 mmol, 2.0 equiv.), oxidant **2-2** (0.05 mmol, 1.0 equiv.), and base (1.0 equiv.) in 1.5 mL solvent, MeOH was added via a needle 30 min later after the reaction started. [b] Obtained by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, isolated yields after chromatography are in parentheses. [c] Determined via HPLC analysis on a chiral stationary. [d] 1.5 equivalents of base were used. [e] The methanol was added at the same time as other substrates and reagents.

2.2.2 Substrate scope

With our optimal conditions in hand, we examined the scope of this new asymmetric β-hydroxylation of enals (Table 2.5). We were pleased to find that a variety of enals are tolerated. The enals with different substituents on the phenyl rings afford the corresponding β-hydroxyl esters in good yields and excellent enantioselectivities (84 - 98% yield, 92 - 98% ee). It should be noted that natural product Pisoninol **I** (**2-3e**)[8] was prepared in one step in this transformation with moderate yield and excellent enantiocontrol (58% yield, 95% ee). Naphthyl and furyl-substituented enals are also suitable substrates for this reaction, affording **2-3h** and **2-3i** in 98% yield, 96% ee and 98% yield, 97% ee, respectively. The β-hydroxyl esters with a quaternary stereo center (**2-3j** to **2-3p**) were successfully prepared using this method, which were isolated in moderate yields and high ee.

Table 2.5 The Scope of Asymmetric β-hydroxylation of Enals[a]



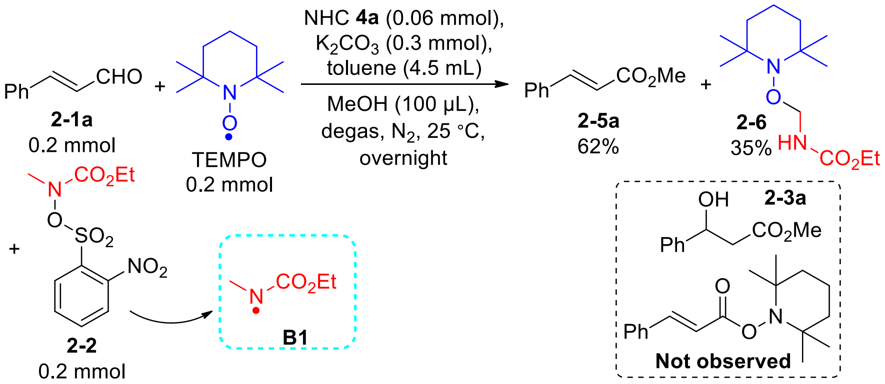
[a] Reactions were conducted with 2.0 equiv. of **2-1** (0.4 mmol), 1.0 equiv. of **2-2** (0.2 mmol), and

1.5 equiv. of base in 4.5 mL toluene at room temperature. [b]Isolated yields after chromatography. [c]Determined by chiral HPLC analysis. [d]Determined by chiral HPLC analysis after 3,5-dinitrobenzoylation.

Substrates bearing alkyl groups as well as long chains at the β-position could be smoothly converted to their corresponding products (**2-3q** to **2-3v**) in good to excellent yields and excellent enantiocontrol (80 - 99% yield, 95 - 98% ee). It is worth mentioning that the β-hydroxyl esters with long alkyl chain are useful compounds with bioactivity or are natural products. For instance, **2-3v** is a bioactive compound which has effect on the membrane of human erythrocytes.[9]

2.3 Mechanistic study

2.3.1 TEMPO trapping experiment

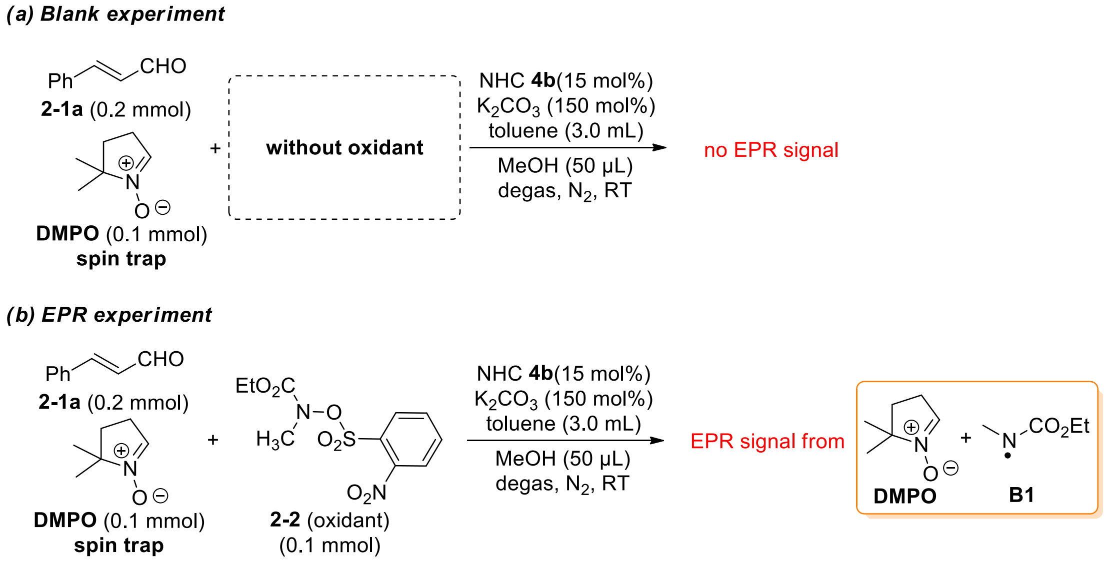


Scheme 2.4 TEMPO trapping experiment

We then moved to conduct some mechanistic studies. We felt that the addition of TEMPO as a carbon-radical trapping reagent to our reaction system might terminate any radical intermediate. Experimentally, we indeed found that by adding 1.0 equivalent of TEMPO to the model reaction, the formation of **2-3a** was completely suppressed, α,β-unsaturated ester **2-5a** was obtained in 62% yield, and compound **2-6** was isolated in 35% yield (Scheme 2.4). The mechanism for production of compound **2-6** is still unclear; according to the study of MacMillan, the generation of N-centered radical **B1** from oxidant **2-2** is possible.[7] However, the pathway for yielding compound **2-6** from TEMPO and radical **B1** was unclear. On the other hand, the TEMPO trapping has provided strong evidence for a radical mechanism.

2.3.2 EPR experiment

The existence of N-centered radical **B1** is detected by EPR. N-centered radical **B1** is a very reactive radical; in other words, the half-life of radical **B1** is too short to detect with EPR. In fact, we didn't observe any signal from EPR when spin trap was not added. When we added 1.0 equivalent of spin trap DMPO[14] into the reaction system, fortunately, we observed strong signal from EPR, which was confirmed as the adduct from DMPO and radical **B1** (Figure 2.3).



Scheme 2.4 EPR experiment

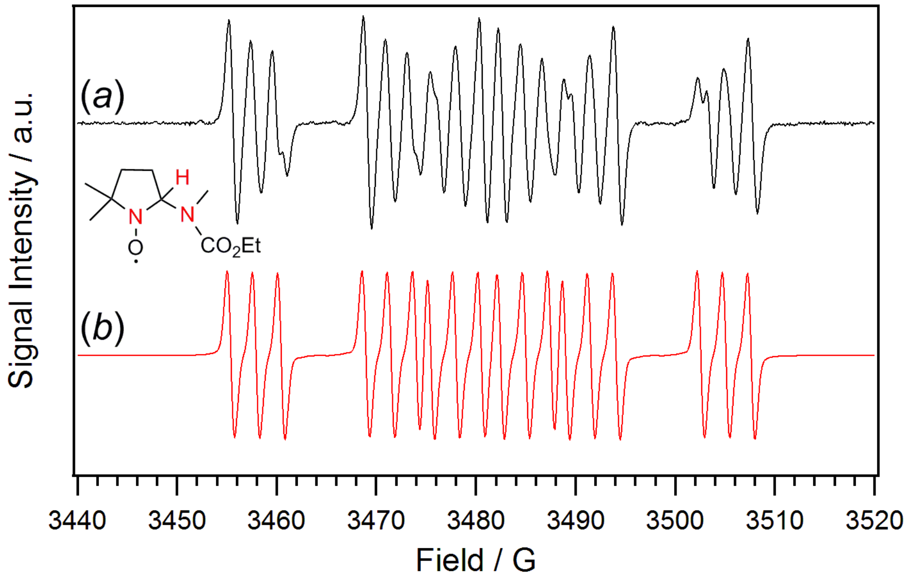
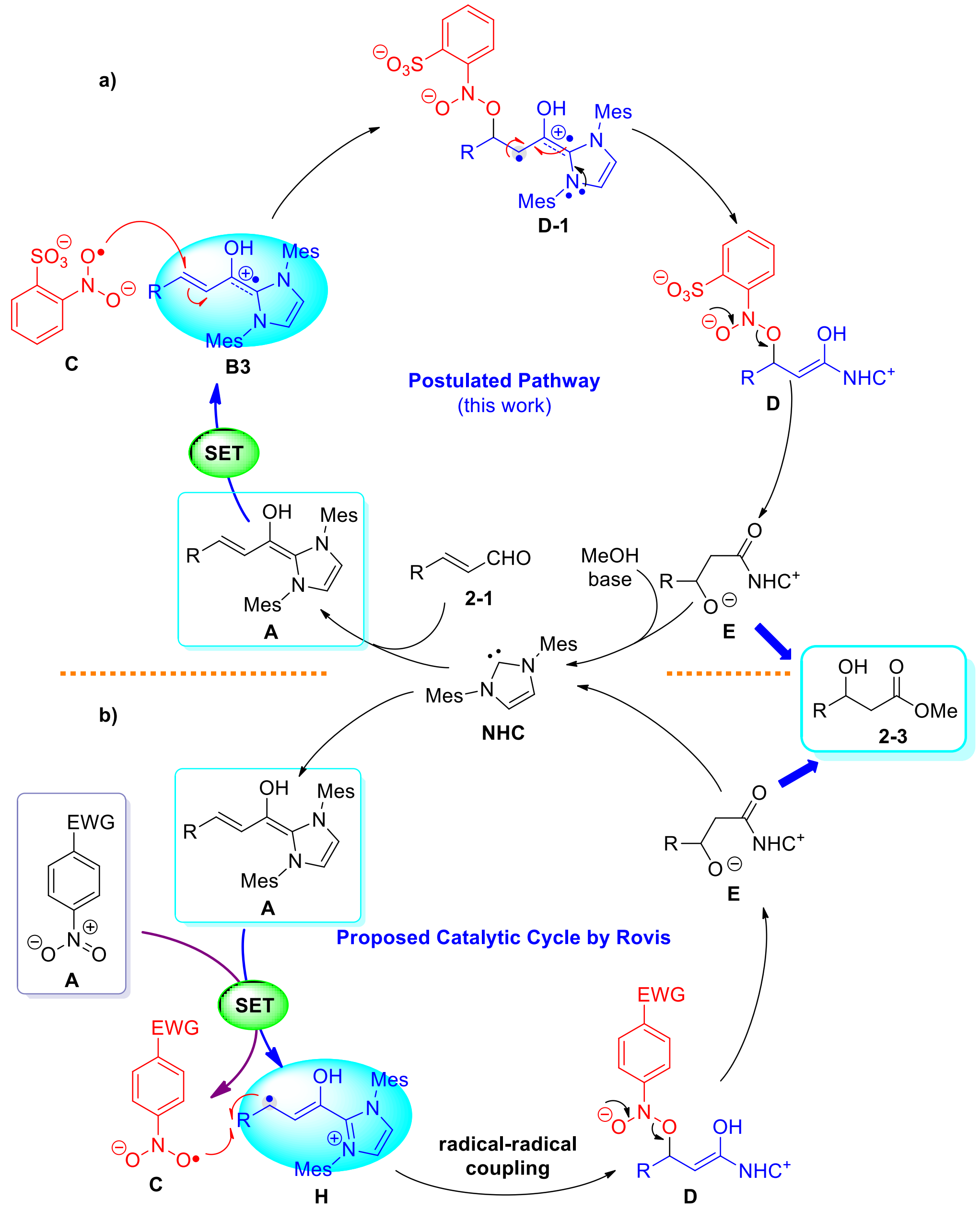


Figure 2.3. (Black line) EPR spectra of the radical derived from trapping **B1** with DMPO at 22(±2) °C in toluene according to the reaction in Scheme 2. (Red line) Simulated EPR spectrum based on hyperfine coupling constants of 1N = 13.55 G, 1N = 2.53 G, 1H = 20.10 G, and with a line width of 0.75 G.

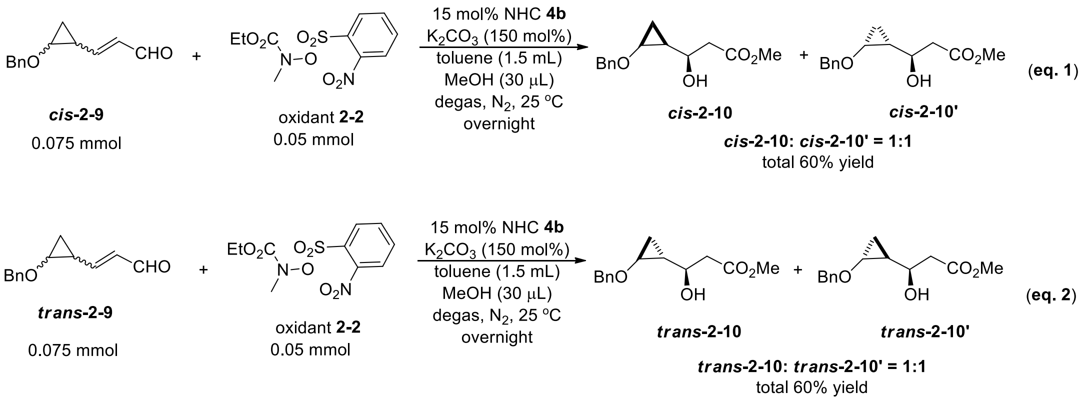
2.3.3 Radical clock experiment

There are some different details between our postulated mechanism and that proposed by Rovis and co-workers. In our reactions, the Breslow intermediate **A** undergoes a single-electron oxidation by nitrobenzenesulfonic acid group to furnish Breslow-centered radical cation **B3** which was well studied by Studer.[4] The radical **B3** is an electrophilic species which behaves as a Michael acceptor to react with an O-centered radical **C** as the termination step (Scheme 2.5a). Rovis postulated that the new C-O covalent bond in intermediate **E** was constructed through the combination of the O-centered radical **C** and a homoenolate β-position centered radical **H** (Scheme 2.5b).[6] Below we report the results of our mechanistic investigations through "radical clock" experiments, which are not consonant with the last process.



Scheme 2.5 Potential radical-radical coupling mechanism

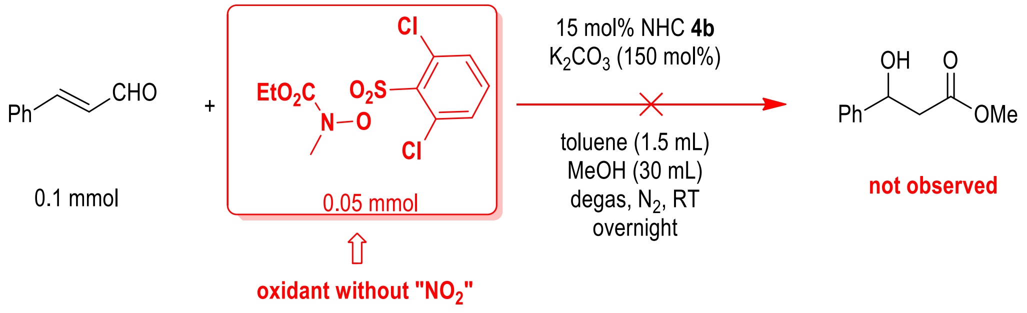
When the *cis*-/*trans*-cyclopropyl-substituted enals **2-9** were utilized in our reaction system, the relative configurations of the cyclopropyl in the final ester products (**2-10**) were retained. Specifically, when the *cis*-**2-9** was used, we isolated two diastereomers of *cis*-**2-10** in 28% and 32% yield (Scheme 2.6, eq. 1); similarly, we obtained a mixture of diastereomers of *trans*-**2-10** in 60% yield (the ratio is 1:1) when the *trans*-**2-9** was used as the substrate (Scheme 2.6, eq. 2). These observations were not consonant with the postulated homoenolate β-carbon centered radical **H** (Scheme 2.5b), which should undergo ring opening/closing prior to productive C-O bond formation, and would lead to the thermodynamically more stable *trans*-**2-10** no matter which enal (*cis*- or *trans*-**2-9**) used (Scheme 2.6, eq. 2).



Scheme 2.6 “Radical clock” experiments

2.3.4 Experiment to probe the “O” source

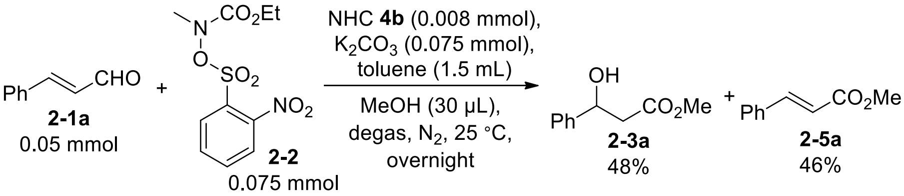
In order to establish the source of “O”, we prepared the similar oxidant with two chloride substutites on the phenyl ring instead of nitro group, and we didn’t observe the formation of β-hydroxyl ester **2-3a** (Scheme 2.7). The result indicated that the oxygen in hydroxyl group of product may originate from the nitro group of oxidant **2-2**.



Scheme 2.7 Experiment to probe the “ O ” source

2.3.5 Control experiment

We carried out the reaction with excess of oxidant **2-2**, and isolated 48% of **2-3a** together with 46% **2-5a** (Scheme 2.8). This indicated that half of enal was converted to desired product **2-3a** and half was over-oxidized into α,β-unsaturated ester.



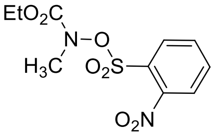
Scheme 2.8 Control experiment

2.3.6 Cyclic voltammogram

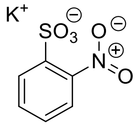
We isolated **B2** from our reaction system in around 5% yield, and we confirmed its structure by X-ray. Then we tested the cyclic voltammograms of oxidant **2-2** and **B2** (Figure 2.4).

Compound **2-2** can be reduced in two voltammetric processes. The first reduction process is chemically irreversible and occurs at a peak potential (E_p^{red}) of -1.235 V *vs.* Fc/Fc$^+$ (Fc = ferrocene). The process is deemed chemically irreversible because no corresponding oxidation peak was observed when the scan direction was reversed at approximately -1.5 V *vs.* Fc/Fc$^+$ (red dashed line in Figure 2.4). A small pre-wave occurs before the first reduction process at -1.020 V, which is believed to be due to a product of electrode fouling as the pre-wave shifted in potential when a platinum rather than GC electrode was used. Furthermore, it was observed that process 1 decreased in current magnitude when multiple scans were performed without polishing the electrode between each scan, which is also supportive of fouling/adsorption phenomena. When the voltammetric scan was extended to more negative potentials, a second voltammetric process was detected for compound **2-2** with a reductive peak potential of -1.865 V *vs.* Fc/Fc$^+$ and a corresponding oxidation peak (E_p^{ox}) at -1.735 V *vs.* Fc/Fc$^+$ when the scan direction was switched at approximately -2.25 V *vs.* Fc/Fc$^+$. Based on the separation between the E_p^{red} and E_p^{ox} peaks, the half-wave potential ($E^r_{1/2}$) (which approximates the formal electrode potential, E^o_f) of the second process is -1.800 V *vs.* Fc/Fc$^+$ [$E^r_{1/2} = (E_p^{red}+E_p^{ox})/2 \approx E^o_f$). It is unusual to observe a chemical reversible process that occurs at a higher potential than a chemically irreversible process during CV measurements on a single molecule. However, such an effect can occur in certain circumstances, such as; (*i*) when the initially reduced compound reacts rapidly to form a new compound, which then undergoes further reduction at more negative potentials in a chemically reversible process (an electrochemical ECE mechanism, where "E" signifies an electron transfer and "C" signifies a chemical step), or (*ii*) when the reduction processes occur at two non-electronically communicating sites within the same molecule, so the individual electron transfer steps occur separately to one another (an electrochemical EE mechanism).

CVs of compound **B2** indicate the presence of a reductive process at E_p^{red} = -1.835 V *vs.* Fc/Fc$^+$. When the scan direction was reversed at approximately -2.25 V *vs.* Fc/Fc$^+$, a comparatively small oxidative process was detected at -1.635 V *vs.* Fc/Fc$^+$. An E_p^{ox}/E_p^{red} ratio <<1 for the reduction process indicates that the reduced species is reactive and is unable to be completely re-oxidized back to the starting material on the voltammetric timescale. The oxidation process that is detected at -1.175 V *vs.* Fc/Fc$^+$ is only observed when the scan is applied in the negative potential direction first so as to reduce the starting material, and is likely to be associated with the oxidation of a product of the initial reduction. It was also observed that the shape of the reduction process for compound **B2** was unusual, appearing too sharp for a purely diffusion controlled process. Furthermore, when multiple CV scans were performed without polishing the electrode surface, the peak current decreased dramatically between each scan indicating that the reduced compound (or products of the reduction) were adsorbing on the electrode surface. When comparing the voltammograms of compounds **2-2** and **B2**, it can be observed that both display a reductive process at approximately -1.8 V *vs*. Fc/Fc$^+$. Since both compounds share the nitrobenzene structure, it is possible that the reduction occurs at the nitro functionality.



2-2 (oxidant)



B2

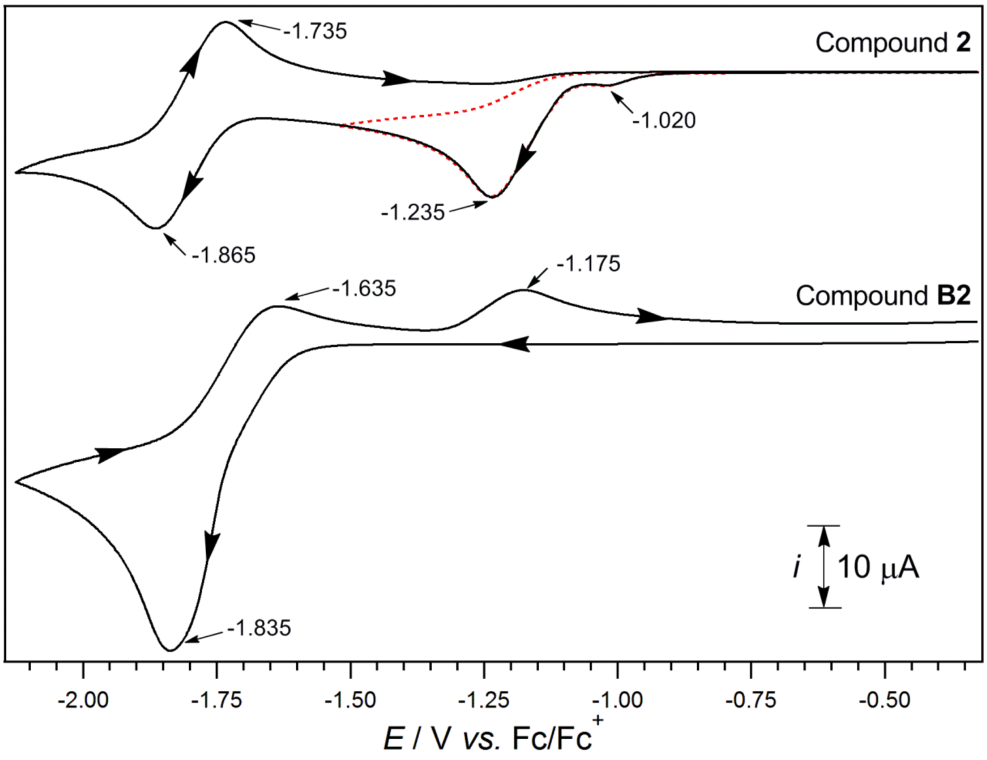
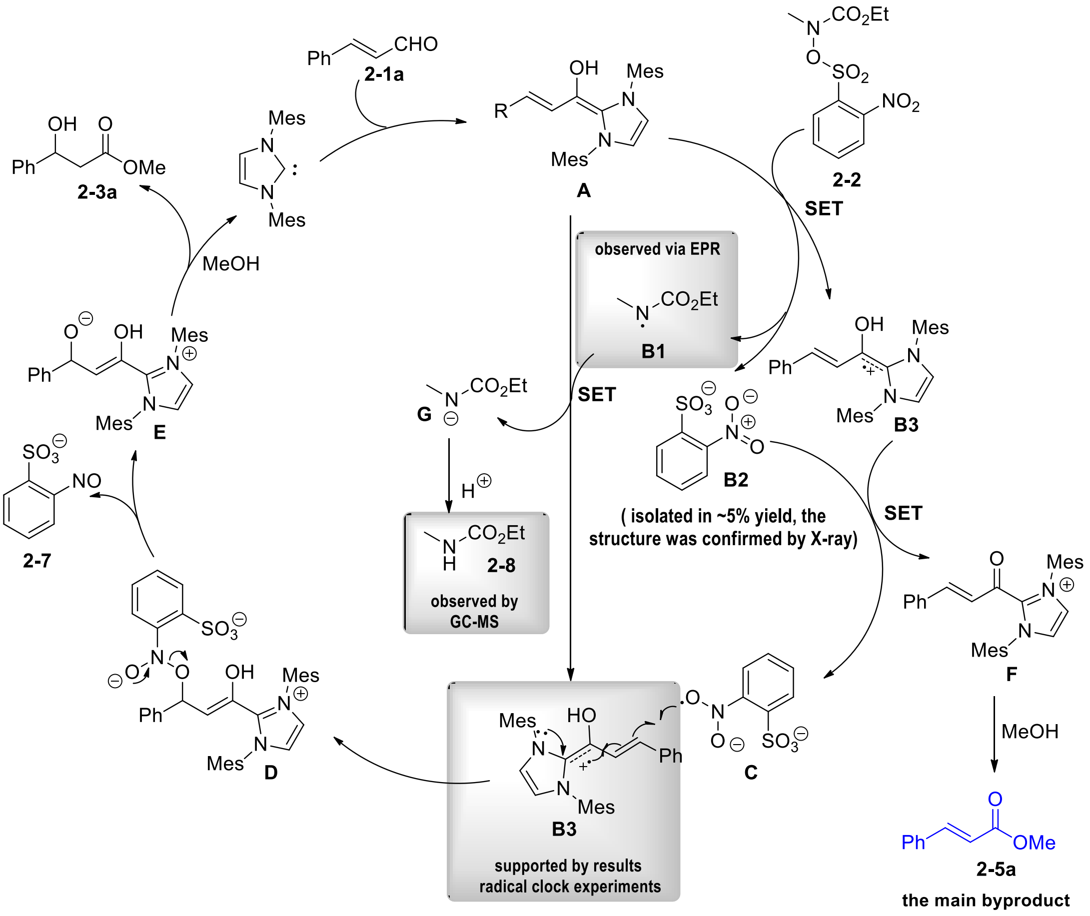


Figure 2.4 Cyclic voltammograms of 20 mM analytes obtained in DMSO containing 0.2 M Bu_4NPF_6 at a 1 mm diameter planar glassy carbon (GC) electrode and at a scan rate of 0.1 V s^{-1} at 22 °C. Peak potentials are reported to the nearest 5 mV.

2.3.7 Proposed reaction pathway

Based on the results of the above experiments, a postulated pathway is illustrated in Scheme 2.9. Our reaction proceeds firstly by formation of the Breslow intermediate **A**, which undergoes a single-electron oxidation enabled by carbamate **2-2** to form Breslow-derived radical cation **B3** and a N-centered radical **B1**, at the same time releasing one molecule of **B2**. Rapid transfer of the second single electron from **B3** to **B2** yields α,β-unsaturated acyl azolium **F** and O-centered radical **C**. After this, radical **C** reacts with another radical cation **B3** which is generated by transferring of single electron from another molecule of **A** to radical **B1**, to provide intermediate **D**. The resulting intermediate **D** subsequently collapses with cleavage of N-O bond to furnish nitrobenzenesulfonic acid salt and NHC-bounded ester intermediate **E**, followed by protonation and methoxylation to release the desired β-hydroxyl ester product **2-3a** and regenerate the carbene which returns back into the catalytic cycle. The α,β-unsaturated acyl azolium **F** produced in this reaction is intercepted with methanol to yield the α,β-unsaturated ester **2-5a**. That explains why we isolated α,β-unsaturated ester as the major byproduct in this transformation. The imine **2-8** produced by protonation of anion **G**, which is generated from radical **B1** by abstraction of anther single electron from anther Breslow intermediate **A**, is observed by GC-MS.



Scheme 2.9 Proposed mechansim

2.4 Summary

In conclusion, we have developed a novel NHC-catalyzed approach to β-hydroxyl esters via a radical pathway. A wide range of β-hydroxyl esters were prepared in good to excellent yields and excellent enantiocontrol. Natural product Pisoninol I and some compounds with bioactivities are also prepared one step in good yields and excellent ee utilizing this method. The mechanism was studied and provided the evidence suggesting the radical process.

2.5 Experimental section

2.5.1 General information

Chemicals and solvents:

Commercially available materials purchased from Alfa Aesar or Aldrich were used as received. HPLC grade solvents (toluene and methanol) were used without further purification.

Nuclear magnetic resonance (NMR):

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV400 (100 MHz) spectrometer.

HRMS, IR, Optical rotations and others:

High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. IR spectra were recorded on a Shimadzu IRPrestige-21 FT-IR spectrometer as neat thinfilms between NaCl plates. Optical rotations were measured using a 1 mL cell with a 1 cm path length on a Jasco P1030 digital polarimeter and are reported as follows: $[\alpha]^t_D$. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

Electron paramagnetic resonance (EPR):

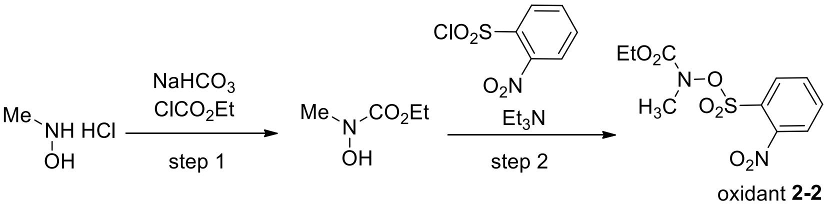
Continuous wave X-band EPR spectra was obtained with a Bruker ELEXSYS E500 EPR spectrometer in a silica flat cell. In each case the modulation amplitude = 0.1-0.2 G, sweep time = 30 s, microwave power = 0.2 mW (corresponding to attenuation = 25 dB, which was sufficiently high to avoid power saturation at $T = 22 \pm 2\ ^{\circ}$C), time constant = 10 milliseconds and 10 accumulated spectra were obtained. ESR studies were carried out by using reaction mixtures after stirring for 45~60 min.

Cyclic voltammogram:

Cyclic voltammetry (CV) experiments were conducted with a computer controlled Metrohm Autolab PGSTAT 100 with an ADC fast scan generator. Working electrodes were 1 mm diameter planar platinum (Pt) and glassy carbon (GC) disks (eDAQ Pte Ltd), used in conjunction with a Pt wire auxiliary electrode (Metrohm) and an Ag wire miniature reference electrode (eDAQ Pte Ltd) connected to the test solution *via* a salt bridge containing 0.5 M *n*-Bu_4NPF_6 in CH_3CN. Accurate potentials were obtained using ferrocene as an internal standard that was added to the solution at the completion of the measurements. All solutions were deoxygenated prior to CV experiments by purging with high purity argon gas which was also flowed over the top of the solutions during measurements.

2.5.2 Preparation of oxidant 2-2

Oxidant **2-2** was prepared following a reported procedure.[7]



Step 1: To a solution of *N*-methylhydroxylamine hydrochloride (5.0 g, 60 mmol) in THF (100 mL) and H_2O (10 mL) was added $NaHCO_3$ (10.0g, 120 mmol, 2.0 equiv) and ethylchloroformate (6.3 mL, 66 mmol, 1.1 equiv). The resulting suspension was stirred overnight at room temperature, then diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in *vacuo* to yield the ethyl hydroxyl(methyl)carbamate as a colorless oil, which was used without further purification.

Step 2: To a stirred solution of ethyl hydroxyl(methyl)carbamate (3.0 g, 28.5 mmol, 1.0 equiv) in CH_2Cl_2 (200 mL) at 0 ^{o}C was added Et_3N (5.1 mL, 37.1 mmol, 1.3 equiv) and 2-nitrobenzenesulfonyl chloride (6.6 g, 29.9 mmol, 1.05 equiv). The resulting organic was stirred at 0 ^{o}C for 5h, then diluted with 0.5 M aqueous citric acid (100 mL) and extracted with CH_2Cl_2 (2×100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated in *vacuo* to yield the crude product, which was washed with Et_2O on a sintered funnel to yield oxidant **2-2** as a white solid. **^{1}H NMR**: (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.89 – 7.82 (m, 2H), 7.79 – 7.74 (m, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.35 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR**: (100MHz, $CDCl_3$) δ 157.0, 135.7, 132.9, 131.8, 127.4, 124.7, 63.6, 40.6, 13.9; **HRMS**: (ESI) $[M+H]^+$ calcd. for $C_{10}H_{13}N_2O_7S$, 305.0443 found, 305.0444.

2.5.3 General procedures

2.53.1 General procedure for catalytic enantioselective *β*-hydroxylation of enals (Table 2.5)

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1** (0.4 mmol, 2.0 equiv) and oxidant

2-2 (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography to obtain product **2-3**.

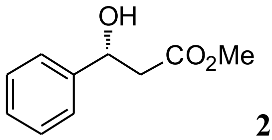
2.5.3.2 Experimental procedures for Scheme 2.6

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (2.8 mg, 15 mol%), K_2CO_3 (10.4 mg, 1.5 equiv), *cis*-**2-9** (16.2 mg, 0.075 mmol, 1.5 equiv), and oxidant **2-2** (15.2 mg, 0.05 mmol, 1.0 equiv). The tube was closed after addition of toluene (1.5 mL) and MeOH (30 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain products *cis*-**2-10** and *cis*-**2-10'.**

2.5.3.3 Experimental procedures for Scheme 2.8

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (2.8 mg, 15 mol%), K_2CO_3 (10.4 mg, 1.5 equiv), *trans*-cinnaldehyde (6.6 mg, 0.05 mmol, 1.0 equiv), and oxidant **2-2** (22.8 mg, 0.075 mmol, 1.5 equiv). The tube was closed after addition of toluene (1.5 mL) and MeOH (30 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain products **2-5a** and **2-3a**.

2.5.4 Characterization of products[15]



2-3a

(*R*)-methyl 3-hydroxy-3-phenylpropanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1a** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 µL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain product **2-3a** 30.0 mg, colorless oil, 83% yield, 97% ee.

Opt. Rot.: $[\alpha]^{23}_{D}$ (*c* 2.40, $CHCl_3$): +47.6

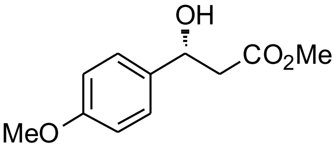
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 4H), 7.31 – 7.26 (m, 1H), 5.15 – 5.11 (m, 1H), 3.72 (s, 3H), 3.22 (d, *J* = 3.2 Hz, 1H), 2.77 (dd, *J* = 16.0, 8.8 Hz, 1H), 2.71 (dd, *J* = 16.0, 4.0 Hz, 1H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.7, 142.5, 128.5, 127.8, 125.6, 70.3, 51.9, 43.1;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{10}H_{13}O_3$, 181.0865 found, 181.0857;

IR (film): ν_{max} 3433 (OH), 2955, 2924, 1728 (C=O), 1439, 756 cm^{-1}

HPLC: 97% *ee* (*R*) - isomer as determined by HPLC (IA, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 36.2 min, *tr(S)* = 40.0 min.



2-3b

(*R*)-methyl 3-hydroxy-3-(4-methoxyphenyl)propanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1b** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 µL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain product **2-3b** 37.2 mg, colorless oil, 89% yield, 98% ee.

Opt. Rot.: $[\alpha]^{23}_{D}$ (*c* 3.00, $CHCl_3$): +47.3

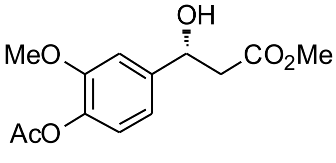
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 6.90 – 6.86 (m, 2H), 5.08 (dt, *J* = 9.2, 3.2 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.16 (d, *J* = 3.2 Hz, 1H), 2.76 (dd, *J* = 16.0, 9.2 Hz, 1H), 2.67 (dd, *J* = 16.0, 3.6 Hz, 1H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.7, 159.2, 134.7, 126.9, 113.9, 69.9, 55.2, 51.8, 43.11;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{11}H_{15}O_4$, 211.0970 found, 211.0967;

IR (film): ν_{max} 3433 (OH), 2953, 2922, 1732 (C=O), 1514, 1248 cm^{-1}

HPLC: 98% *ee* (*R*) - isomer as determined by HPLC (OD-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 62.3 min, *tr(S)* = 68.2 min.



2-3c

(*R*)-methyl 3-(4-acetoxy-3-methoxyphenyl)-3-hydroxypropanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1c** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 3/1) to obtain product **2-3c** 45.0 mg, pale yellow oil, 84% yield, 97% ee.

Opt. Rot.: $[\alpha]^{23}_{D}$ (*c* 3.37, $CHCl_3$): +31.1

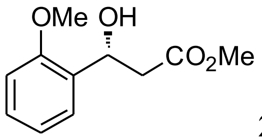
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 1.6 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.14 – 5.09 (m, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.31 (d, *J* = 2.8 Hz, 1H), 2.76 (dd, *J* = 16.4, 8.4 Hz, 1H), 2.70 (dd, *J* = 16.4, 4.8 Hz, 1H), 2.30 (s, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.7, 169.0, 151.1, 141.5, 139.1, 122.7, 117.7, 109.7, 70.0, 55.8, 51.9, 43.2, 20.6;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{13}H_{17}O_6$, 269.1025 found, 269.1025;

IR (film): ν_{max} 3472 (OH), 3017, 2951, 1763 (C=O), 1736 (C=O), 1508, 1219, 756 cm^{-1}

HPLC: 97% *ee* (*R*) - isomer as determined by HPLC (ID, 95/5 hexanes/i-PrOH, 0.7 ml/min) *tr(R)* = 96.8 min, *tr(S)* = 114.1 min.



2-3d

(*R*)-methyl 3-hydroxy-3-(2-methoxyphenyl)propanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1d** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain product **2-3d** 39.7 mg, colorless oil, 95% yield, 92% ee.

Opt. Rot.: $[\alpha]^{23}_D$ (*c* 3.14, $CHCl_3$): +29.6

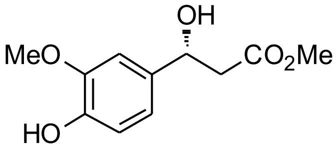
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.28 – 7.23 (m, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.39 – 5.33 (m, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.43 (d, *J* = 5.6 Hz, 1H), 2.83 (dd, *J* = 16.0, 3.6 Hz, 1H), 2.71 (dd, *J* = 16.0, 9.2 Hz, 1H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.0, 156.0, 130.4, 128.6, 126.5, 120.8, 110.3, 66.6, 55.2, 51.7, 41.5;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{11}H_{15}O_4$, 211.0970 found, 211.0969;

IR (film): ν_{max} 3445 (OH), 2953, 1732 (C=O), 1493, 1244 cm^{-1}

HPLC: 92% *ee* (*R*) - isomer as determined by HPLC (IA, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 41.7 min, *tr(S)* = 44.5 min.



2-3e

(*R*)-methyl 3-hydroxy-3-(4-hydroxy-3-methoxyphenyl)propanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1e** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 3/1) to obtain product **2-3e** 26.0 mg, yellow oil, 58% yield, 95% ee.

Opt. Rot.: [α]$^{24}_{D}$ (*c* 1.83, $CHCl_3$): +30.8

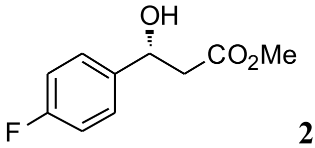
^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.66 (s, 1H), 5.07 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.89 (s, 3H), 3.73 (s, 3H), 3.18 (s, 1H), 2.77 (dd, *J* = 16.0, 9.2 Hz, 1H), 2.69 (dd, *J* = 16.0, 3.6 Hz, 1H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.8, 146.6, 145.2, 134.6, 118.6, 114.2, 108.2, 70.2, 55.9, 51.9, 43.3;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{11}H_{15}O_5$, 227.0919 found, 227.0913;

IR (film): ν_{max} 3441 (OH), 2955, 2924, 1728 (C=O), 1516, 1273, 1034, 756 cm^{-1}

HPLC: 95% *ee* (*R*) - isomer as determined by HPLC (ID, 95/5 hexanes/i-PrOH, 0.7 ml/min) *tr(R)* = 111.7 min, *tr(S)* = 153.9 min.



2-3f

(*R*)-methyl 3-(4-fluorophenyl)-3-hydroxypropanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1f** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain product **2-3f** 39.0 mg, colorless oil, 98% yield, 98% ee.

Opt. Rot.: [α]$^{24}_{D}$ (*c* 2.20, $CHCl_3$): +52.7

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.07 – 7.00 (m, 2H), 5.12 – 5.09 (m, 1H), 3.72 (s, 3H), 3.32 (d, *J* = 3.2 Hz, 1H), 2.74 (dd, *J* = 16.4, 8.8 Hz, 1H), 2.68 (dd, *J* = 16.4, 4.4 Hz, 1H);

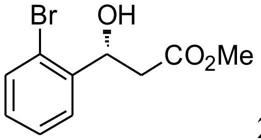
^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.6, 162.3 (d, *J* = 244.3 Hz), 138.2 (d, *J* = 3.0 Hz), 127.3 (d, *J* = 8.0 Hz), 115.4 (d, *J* = 21.0 Hz), 69.6, 51.9, 43.1;

^{19}F NMR: (376 MHz, $CDCl_3$) -114.6 – -114.68 (m, 1F);

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{10}H_{12}FO_3$, 199.0770 found, 199.0771;

IR (film): ν_{max} 3443 (OH), 2955, 1732 (C=O), 1512, 1225, 839 cm^{-1}

HPLC: 98% *ee* (*R*) - isomer as determined by HPLC (OD-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(S)* = 36.6 min, *tr(R)* = 46.3 min.



2-3g

(*R*)-methyl 3-(2-bromophenyl)-3-hydroxypropanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1g** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain product **2-3g** 46.0 mg, colorless oil, 89% yield, 95% ee.

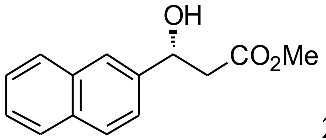
Opt. Rot.: $[\alpha]^{24}_D$ (*c* 2.36, $CHCl_3$): +70.8

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.52 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.17 – 7.12 (m, 1H), 5.45 (dt, *J* = 9.6, 2.8 Hz, 1H), 3.75 (s, 3H), 3.52 (d, *J* = 3.6 Hz, 1H), 2.88 (dd, *J* = 16.4, 2.4 Hz, 1H), 2.57 (dd, *J* = 16.4, 9.6 Hz, 1H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.8, 141.4, 132.6, 129.1, 127.8, 127.3, 121.4, 69.2, 51.9, 41.3;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{10}H_{12}BrO_3$, 258.9970 found, 258.9958;

HPLC: 95% *ee* (*R*) - isomer as determined by HPLC (ID, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 38.2 min, *tr(S)* = 51.3 min.



2-3h

(*R*)-methyl 3-hydroxy-3-(naphthalen-2-yl)propanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1h** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain product **2-3h** 45.0 mg, pale yellow solid, 98% yield, 96% ee.

Opt. Rot.: $[\alpha]^{24}_D$ (*c* 2.10, $CHCl_3$): +47.4

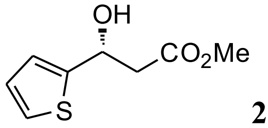
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.83 – 7.81 (m, 4H), 7.50 – 7.43 (m, 3H), 5.32 – 5.27 (m, 1H), 3.72 (s, 3H), 3.37 (d, *J* = 3.2 Hz, 1H), 2.89 – 2.76 (m, 2H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.7, 139.8, 133.2, 133.0, 128.4, 128.0, 127.6, 126.2, 126.0, 124.4, 123.6, 70.4, 51.9, 43.1;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{14}H_{15}O_3$, 231.1021 found, 231.1022;

IR (film): ν_{max} 3454 (OH), 2954, 2925, 1732 (C=O), 752 cm^{-1}

HPLC: 96% *ee* (*R*) - isomer as determined by HPLC (ID, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 91.6 min, *tr(S)* = 161.5 min.



2-3i

(*R*)-methyl 3-hydroxy-3-(thiophen-2-yl)propanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1i** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain product **2-3i** 36.0 mg, yellow oil, 97% yield, 97% ee.

Opt. Rot.: $[\alpha]^{24}_{D}$ (*c* 2.40, $CHCl_3$): +33.4

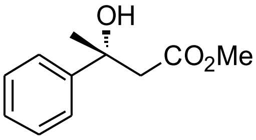
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 4.4, 1.6 Hz, 1H), 6.98 – 6.95 (m, 2H), 5.40 – 5.35 (m, 1H), 3.73 (s, 3H), 3.45 (d, *J* = 4.0 Hz, 1H), 2.93 – 2.81 (m, 2H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.2, 146.2, 126.7, 124.8, 123.6, 66.5, 51.9, 43.0;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_8H_{11}O_3S$, 187.0429 found, 187.0428;

IR (film): ν_{max} 3453 (OH), 3017, 2955, 1728 (C=O), 1439, 756 cm^{-1}

HPLC: 97% *ee* (*R*) - isomer as determined by HPLC (ID, 95/5 hexanes/i-PrOH, 0.7 ml/min) *tr(R)* = 30.6 min, *tr(S)* = 34.8 min.



2-3j

(*R*)-methyl 3-hydroxy-3-phenylbutanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1j** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 µL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 8/1) to obtain product **2-3j** 22.0 mg, colorless oil, 57% yield, 97% ee.

Opt. Rot.: $[\alpha]^{25}_{D}$ (*c* 0.20, $CHCl_3$): +4.5

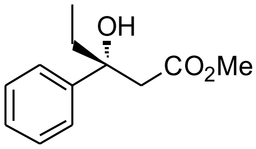
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 2H), 7.36 – 7.31 (m, 2H), δ 7.26 – 7.21 (m, *J* 1H), 4.32 (s, 1H), 3.61 (s, 3H), 2.99 (d, *J* = 16.0 Hz, 1H), 2.81 (d, *J* = 16.0 Hz, 1H), 1.55 (s, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.1, 146.8, 128.3, 126.9, 124.4, 72.7, 51.7, 46.2, 30.6;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{11}H_{15}O_3$, 195.1021 found, 195.1017;

IR (film): ν_{max} 3501 (OH), 2978, 2955, 1715 (C=O), 1439, 1179, 700 cm^{-1}

HPLC: 97% *ee* (*R*) - isomer as determined by HPLC (OJ-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 43.7 min, *tr(S)* = 53.2 min.



2-3k

(*R*)-methyl 3-hydroxy-3-phenylpentanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1k** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 µL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 8/1) to obtain product **2-3k** 24.9 mg, colorless oil, 60% yield, 95% ee.

Opt. Rot.: $[\alpha]^{25}_{D}$ (*c* 1.16, $CHCl_3$): -14.1

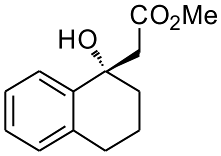
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 2H), 7.35 – 7.31 (m, 2H), 7.25 – 7.21 (m, 1H), 4.28 (s, 1H), 3.57 (s, 3H), 2.98 (d, *J* = 16.0 Hz, 1H), 2.81 (d, *J* = 16.0 Hz, 1H), 1.86 – 1.73 (m, 2H), 0.76 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.4, 145.1, 128.1, 126.7, 125.1, 75.1, 51.7, 44.7, 35.8, 7.7;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{12}H_{17}O_3$, 209.1178 found, 209.1171;

IR (film): ν_{max} 3474 (OH), 2970, 2953, 1715 (C=O) cm^{-1}

HPLC: 95% *ee* (*R*) - isomer as determined by HPLC (OJ-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 25.6 min, *tr(S)* = 38.9 min.



2-3l

(*S*)-methyl 2-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)acetate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1l** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 µL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 8/1) to obtain product **2-3l** 20.0 mg, colorless oil, 45% yield, 96% ee.

Opt. Rot.: $[\alpha]^{25}_{D}$ (*c* 0.70, $CHCl_3$): +24.0

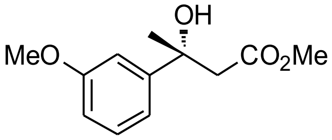
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.24– 7.15 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 3.89 (s, 1H), 3.73 (s, 3H), 3.92 – 2.75 (m, 4H), 2.12 – 2.06 (m, 1H), 2.01 – 1.95 (m, 2H), 1.85 – 1.70 (m, 1H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.9, 140.6, 136.5, 128.9, 127.4, 126.4, 126.3, 71.1, 51.8, 45.8, 36.3, 29.4, 20.0;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{13}H_{17}O_3$, 221.1178 found, 221.1174;

IR (film): ν_{max} 3491 (OH), 2924, 2851, 1721 (C=O), 1215, 756 cm^{-1}

HPLC: 96% *ee* (*S*) - isomer as determined by HPLC (OJ-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(S)* = 55.1 min, *tr(R)* = 63.0 min.



2-3m

(*R*)-methyl 3-hydroxy-3-(3-methoxyphenyl)butanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1m** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain product **2-3m** 30.0 mg, colorless oil, 67% yield, 92% ee.

Opt. Rot.: $[\alpha]^{24}_{D}$ (*c* 1.10, $CHCl_3$): -17.0

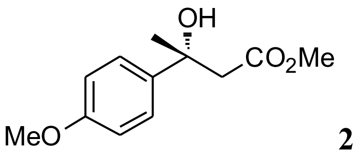
^{1}H NMR: (400 MHz, CDCl$_3$) δ 7.24 (t, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.78 (dd, *J* = 8.0, 2.4 Hz, 1H), 4.33 (s, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 2.99 (d, *J* = 16.0 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H), 1.53 (s, 3H);

^{13}C NMR: (100 MHz, CDCl$_3$) δ 173.1, 159.6, 148.7, 129.3, 116.7, 112.2, 110.5, 72.6, 55.2, 51.8, 46.0, 30.6;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{12}H_{17}O_4$, 225.1127 found, 225.1120;

IR (film): ν_{max} 3501 (OH), 2953, 1715 (C=O), 1601, 1435, 1288, 1177, 1045 cm^{-1}

HPLC: 92% *ee* (*R*) - isomer as determined by HPLC (OD-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(S)* = 24.8 min, *tr(R)* = 28.7 min.



2-3n

(*R*)-methyl 3-hydroxy-3-(4-methoxyphenyl)butanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1n** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 8/1) to obtain product **2-3n** 27.8 mg, colorless oil, 62% yield, 94% ee.

Opt. Rot.: $[\alpha]^{26}_D$ (*c* 0.60, CHCl$_3$): -1.7

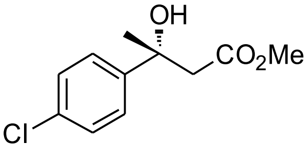
^{1}H NMR: (400 MHz, CDCl$_3$) δ 7.38 – 7.34 (m, 2H), 6.88 – 6.84(m, 2H), 4.27 (s, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 2.96 (d, *J* = 16.0 Hz, 1H), 2.78 (d, *J* = 16.0 Hz, 1H), 1.53 (s, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.2, 158.4, 139.0, 125.6, 113.6, 72.4, 55.2, 51.7, 46.3, 30.7;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{12}H_{17}O_4$, 225.1127 found, 225.1120;

IR (film): ν_{max} 3495 (OH), 2955, 2918, 2849, 1717 (C=O), 1514, 1250, 1179, 756 cm^{-1}

HPLC: 94% *ee* (*R*) - isomer as determined by HPLC (OJ-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 81.1 min, *tr(S)* = 102.2 min.



2-3o

(*R*)-methyl 3-(4-chlorophenyl)-3-hydroxybutanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1o** (0.4 mmol, 2.0 equiv) and oxidant **2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 8/1) to obtain product **2-3o** 26.6 mg, colorless oil, 58% yield, 94% ee.

Opt. Rot.: $[\alpha]^{26}_{D}$ (*c* 1.41, $CHCl_3$): -8.1

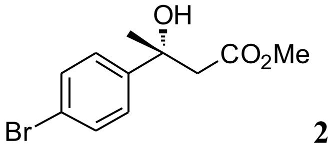
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.32 – 7.28 (m, 2H), 4.37 (s, 1H), 3.62 (s, 3H), 2.96 (d, *J* = 16.0 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H), 1.52 (s, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.0, 145.4, 132.7, 128.4, 126.0, 72.4, 51.9, 45.9, 30.6;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{11}H_{14}ClO_3$, 229.0631 found, 229.0625;

IR (film): ν_{max} 3491 (OH), 2928, 1715 (C=O), 1489, 1439, 1177, 1094, 1013 cm^{-1}

HPLC: 94% *ee* (*R*) - isomer as determined by HPLC (OJ-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 28.5 min, *tr(S)* = 30.1 min.



2-3p

(*R*)-methyl 3-(4-bromophenyl)-3-hydroxybutanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1p** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 8/1) to obtain product **2-3p** 26.4 mg, colorless oil, 48% yield, 91 % ee.

Opt. Rot.: $[\alpha]^{26}_{D}$ (*c* 1.63, $CHCl_3$): -6.9

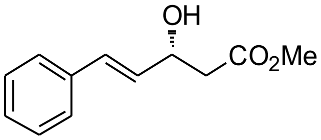
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.34 – 7.30 (m, 2H), 4.37 (s, 1H), 3.62 (s, 3H), 2.95 (d, *J* = 16.4 Hz, 1H), 2.79 (d, *J* = 16.0 Hz, 1H), 1.51 (s, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.0, 146.0, 131.4, 126.3, 120.9, 72.4, 51.9, 45.8, 30.6;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{11}H_{14}BrO_3$, 273.0126 found, 273.0128;

IR (film): ν_{max} 3495 (OH), 2928, 1717 (C=O), 1215, 1177, 1007, 756 cm^{-1}

HPLC: 91% *ee* (*R*) - isomer as determined by HPLC (OD-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(R)* = 18.2 min, *tr(S)* = 20.9 min.



2-3q

(*R,E*)-methyl 3-hydroxy-5-phenylpent-4-enoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1q** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (hexanes/EtOAc, 5/1) to obtain product **2-3q** 33.0mg, colorless oil, 80% yield, 95% ee.

Opt. Rot.: $[\alpha]^{25}_D$ (*c* 2.09, $CHCl_3$): +16.5

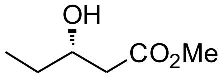
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 2H), 7.33 – 7.29 (m, 2H), 7.27 – 7.22 (m, 1H), 6.66 (dd, *J* = 16.0, 0.8 Hz, 1H), 6.22 (dd, *J* = 16.0, 6.4 Hz, 1H), 4.76 – 4.70 (m, 1H), 3.73 (s, 3H), 3.05 (d, *J* = 4.0 Hz, 1H), 2.71 – 2.59 (m, 2H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.6, 136.4, 130.8, 129.8, 128.6, 127.8, 126.5, 68.8, 51.8, 41.3;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{12}H_{15}O_3$, 207.1021 found, 207.1013;

IR (film): ν_{max} 3445 (OH), 3024, 2952, 1732 (C=O), 1439, 752 cm^{-1}

HPLC: 95% *ee* (*R*) - isomer as determined by HPLC (IA, 96/4 hexanes/i-PrOH, 0.7 ml/min) *tr(R)* = 23.2 min, *tr(S)* = 24.9 min.



2-3r

(*S*)-methyl 3-hydroxypentanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1r** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 µL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (pentane/ether, 1/1) to obtain product **2-3r** 21.0 mg, colorless oil, 81% yield, 96% ee.

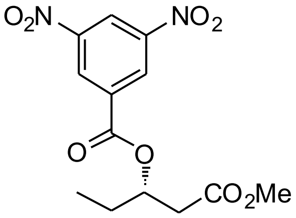
Opt. Rot.: $[\alpha]^{25}_{D}$ (*c* 2.00, $CHCl_3$): +26.9

^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.98 – 3.91 (m, 1H), 3.72 (s, 3H), 2.86 (d, *J* = 3.6 Hz, 1H), 2.53 (dd, *J* = 16.4, 2.8 Hz, 1H), 2.42 (dd, *J* = 16.4, 8.8 Hz, 1H), 1.60 – 1.43 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.5, 69.3, 51.7, 40.7, 29.4, 9.8;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_6H_{13}O_3$, 133.0865 found, 133.0864;

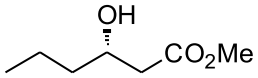
HPLC: 96% *ee* (*S*) - isomer after 3,5-dinitrobenzoylation of **2-3r** as determined by HPLC (AD-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(S)* = 61.6 min, *tr(R)* = 66.1 min.



(*S*)-1-methoxy-1-oxopentan-3-yl 3,5-dinitrobenzoate

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (t, *J* = 2.0 Hz, 1H), 9.14 (d, *J* = 2.0 Hz, 2H), 5.57 – 5.51 (m, 1H) 3.69 (s, 3H), 2.82 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.74 (dd, *J* = 16.0, 4.8 Hz, 1H), 1.89 – 1.82 (m, 2H), 1.02 (t, *J* = 7.6 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 161.9, 148.7, 134.0, 129.4, 122.4, 74.6, 52.0, 38.3, 27.0, 9.5.



2-3s

(*S*)-methyl 3-hydroxyhexanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1s** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (pentane/ether, 1/1) to obtain product **2-3s** 26.3 mg, colorless oil, 90% yield, 96% ee.

Opt. Rot.: $[\alpha]^{24}_{D}$ (*c* 1.40, $CHCl_3$): +27.2

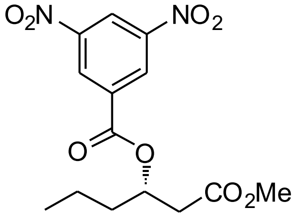
^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.06 – 3.99 (m, 1H), 3.72 (s, 3H), 2.79 (d, *J* = 4.8 Hz, 1H), 2.52 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.42 (dd, *J* = 16.4, 8.8 Hz, 1H), 1.55 – 1.34 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.5, 67.7, 51.7, 41.1, 38.6, 18.6, 13.9;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_7H_{15}O_3$, 147.1021 found, 147.1020;

IR (film): ν_{max} 3415 (OH), 2959, 2934, 1728 (C=O) cm^{-1}

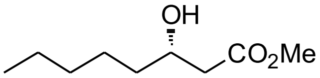
HPLC: 96% *ee* (*S*) - isomer after 3,5-dinitrobenzoylation of **2-3s** as determined by HPLC (AD-H, 99/1 hexanes/i-PrOH, 0.5 ml/min) *tr(S)* = 84.9 min, *tr(R)* = 93.5 min.



(*S*)-1-methoxy-1-oxohexan-3-yl 3,5-dinitrobenzoate

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (t, *J* = 2.0 Hz, 1H), 9.13 (d, *J* = 2.0 Hz, 2H), 5.64 – 5.57(m, 1H), 3.69 (s, 3H), 2.81 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.74 (dd, *J* = 16.0, 4.8 Hz, 1H), 1.89 – 1.70 (m, 2H), 1.49 – 1.38 (m, 2H), 0.98 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 161.9, 148.7, 134.0, 129.4, 122.4, 73.3, 52.0, 38.8, 36.1, 18.5, 13.7.



2-3t

(*S*)-methyl 3-hydroxyoctanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1t** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (pentane/ether, 1/1) to obtain product **2-3t** 28.2 mg, colorless oil, 82% yield, 97% ee.

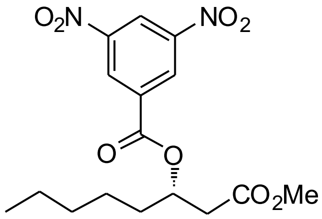
Opt. Rot.: $[\alpha]^{25}_D$ (*c* 0.70, $CHCl_3$): +38.9

^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.06 – 3.96 (m, 1H), 3.72 (s, 3H), 2.86 (d, *J* = 4.0 Hz, 1H), 2.52 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.41 (dd, *J* = 16.4, 8.8 Hz, 1H), 1.56 – 1.25 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.5, 68.0, 51.7, 41.1, 36.5, 31.7, 25.1, 22.6, 14.0;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_9H_{19}O_3$, 175.1334 found, 175.1324;

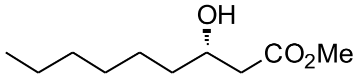
HPLC: 97% *ee* (*S*) - isomer after 3,5-dinitrobenzoylation of **2-3t** as determined by HPLC (AD-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(S)* = 42.7 min, *tr(R)* = 61.0 min.



(*S*)-1-methoxy-1-oxooctan-3-yl 3,5-dinitrobenzoate

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.23 (t, *J* = 2.0 Hz, 1H), 9.13 (d, *J* = 2.0 Hz, 2H), 5.62 – 5.55(m, 1H), 3.69 (s, 3H), 2.81 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.74 (dd, *J* = 16.0, 4.8 Hz, 1H), 1.89 – 1.72 (m, 2H), 1.40 – 1.25 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, CDCl$_3$) δ 170.5, 161.9, 148.7, 134.0, 129.4, 122.4, 73.6, 52.0, 38.8, 34.0, 31.4, 24.8, 22.4, 13.9.



2-3u

(*S*)-methyl 3-hydroxynonanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K$_2$CO$_3$ (41.4 mg, 1.5 equiv), enal **2-1u** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 μL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N$_2$ and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (pentane/ether, 1/1) to obtain product **2-3u** 37.0 mg, colorless oil, 99% yield, 97% ee.

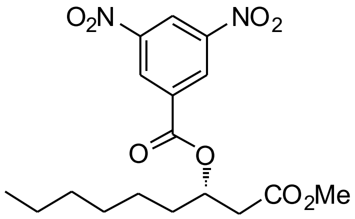
Opt. Rot.: $[\alpha]^{25}_{D}$ (*c* 1.95, CHCl$_3$): +27.1

^{1}H NMR: (400 MHz, CDCl$_3$) δ 4.06 – 3.94 (m, 1H), 3.71 (s, 3H), 2.91 (s, 1H), 2.52 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.41 (dd, *J* = 16.4, 9.2 Hz, 1H), 1.55 – 1.25 (m, 10H), 0.88 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.4, 68.0, 51.7, 41.1, 36.5, 31.7, 29.1, 25.4, 22.5, 14.0;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{10}H_{21}O_3$, 189.1491 found, 189.1485;

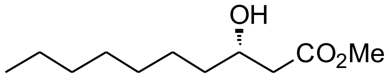
HPLC: 97% *ee* (*S*) - isomer after 3,5-dinitrobenzoylation of **2-3u** as determined by HPLC (AD-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(S)* = 40.4 min, *tr(R)* = 60.5 min.



(*S*)-1-methoxy-1-oxononan-3-yl 3,5-dinitrobenzoate

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (t, *J* = 2.0 Hz, 1H), 9.13 (d, *J* = 2.0 Hz, 2H), 5.62 – 5.55(m, 1H), 3.69 (s, 3H), 2.81 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.74 (dd, *J* = 16.0, 4.8 Hz, 1H), 1.90 – 1.72 (m, 2H), 1.40 – 1.25 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170. 5, 161.9, 148.7, 134.0, 129.4, 122.4, 73.6, 52.0, 38.8, 34.0, 31.6, 28.9, 25.1, 22.5, 14.0.



2-3v

(*S*)-methyl 3-hydroxydecanoate

To a dry Schlenk tube equipped with a magnetic stir bar, was added catalyst **4b** (11.0 mg, 15 mol%), K_2CO_3 (41.4 mg, 1.5 equiv), enal **2-1v** (0.4 mmol, 2.0 equiv) and oxidant **2-2** (60.8 mg, 0.2 mmol, 1.0 equiv). The tube was closed after addition of toluene (4.5 mL) and MeOH (100 µL). The resulting mixture was degassed (two freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The reaction mixture was then directly applied to silica gel chromatography (pentane/ether, 1/1) to obtain product **2-3v** 35.0 mg, colorless oil, 88% yield, 98% ee.

Opt. Rot.: $[\alpha]^{26}_{D}$ (c 1.40, $CHCl_3$): +21.0

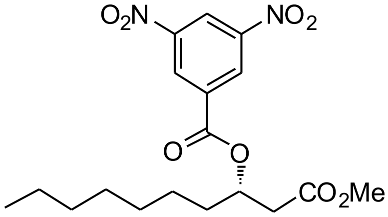
^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.04 – 3.97 (m, 1H), 3.72 (s, 3H), 2.97 (bs, 1H), 2.52 (dd, J = 16.4, 3.2 Hz, 1H), 2.41 (dd, J = 16.4, 9.2 Hz, 1H), 1.57 – 1.25 (m, 12H), 0.88 (t, J = 6.8 Hz, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 173.5, 68.0, 51.7, 41.1, 36.5, 31.8, 29.4, 29.2, 25.5, 22.6, 14.1;

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{11}H_{23}O_3$, 203.1647 found, 203.1646;

IR (film): ν_{max} 3449 (OH), 2928, 2855, 1732 (C=O), 1439, 1169 cm^{-1}

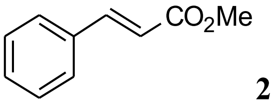
HPLC: 98% *ee* (*S*) - isomer after 3,5-dinitrobenzoylation of **2-3v** as determined by HPLC (AD-H, 98/2 hexanes/i-PrOH, 0.5 ml/min) *tr(S)* = 37.4 min, *tr(R)* = 54.8 min.



(*S*)-1-methoxy-1-oxodecan-3-yl 3,5-dinitrobenzoate

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (t, J = 2.0 Hz, 1H), 9.13 (d, J = 2.0 Hz, 2H), 5.62 – 5.55(m, 1H), 3.69 (s, 3H), 2.81 (dd, J = 16.0, 8.0 Hz, 1H), 2.74 (dd, J = 16.0, 4.8 Hz, 1H), 1.88 – 1.74 (m, 2H), 1.39 – 1.26 (m, 10H), 0.87 (t, J = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 161.9, 148.7, 134.0, 129.4, 122.3, 73.5, 52.0, 38.7, 34.0, 31.7, 29.2, 29.0, 25.2, 22.6, 14.0.

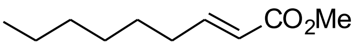


2-5a

Methyl cinnamate

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.70 (d, J = 16.0 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.40 – 7.37 (m, 3H), 6.44 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 167.3, 144.7, 134.2, 130.2, 128.8, 127.9, 117.7, 51.6.

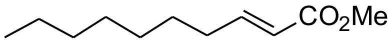


2-5u

(*E*)-methyl non-2-enoate

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.02 – 6.93 (m, 1H), 5.84 – 5.79 (m, 1H), 3.73 (s, 3H), 2.23 – 2.16 (m, 2H), 1.47 – 1.41 (m, 2H), 1.35 – 1.25 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, CDCl$_3$) δ 167.2, 149.8, 120.8, 51.3, 32.2, 31.6, 28.8, 28.0, 22.5, 14.0;

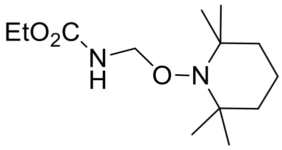


2-5v

(*E*)-methyl dec-2-enoate

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.02 – 6.93 (m, 1H), 5.84 – 5.79 (m, 1H), 3.73 (s, 3H), 2.23 – 2.16 (m, 2H), 1.47 – 1.41 (m, 2H), 1.33 – 1.25 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, CDCl$_3$) δ 167.2, 149.8, 120.8, 51.3, 32.2, 31.7, 29.1, 29.0, 28.0, 22.6, 14.0;



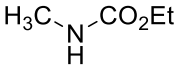
2-6

Ethyl (((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)carbamate

^{1}H NMR: (400 MHz, CDCl$_3$) δ 5.46 (s, 1H), 4.82 (d, *J* = 7.2 Hz, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.60 – 1.51 (m, 1H), 1.47 – 1.39 (m, 4H), 1.35 – 1.30 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.18 (s, 6H), 1.09 (s, 6H);

^{13}C NMR: (100 MHz, CDCl$_3$) δ 156.2, 77.5, 61.0, 59.6, 39.7, 33.2, 20.1, 17.1, 14.5;

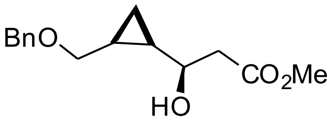
HRMS: (ESI) [M+H]$^+$ calcd. for $C_{13}H_{27}N_2O_3$, 259.2022 found, 259.2019.



2-8

Ethyl methylcarbamate

MS: ***m/z* (%)**: 58 (100), 74 (54), 75 (58), 103(41).



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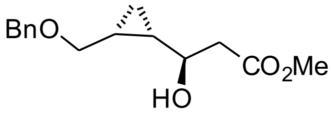


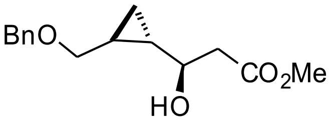
***cis* -2-10 and *cis* -2-10'**

^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.38 – 7.27 (m, 5H), 4.55 (s, 2H), 3.94 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.80 (s, 1H), 3.71 (s, 3H), 3.69 – 3.64 (m, 1H), 3.24 (t, *J* = 10.8 Hz, 1H), 2.69 (dd, *J* = 14.8, 8.0 Hz, 1H), 2.60 (dd, *J* = 14.8, 4.4 Hz, 1H), 1.37 – 1.31 (m, 1H), 1.26 – 1.11(m, 1H), 0.84 – 0.78 (m, 1H), 0.29 (q, *J* = 5.2 Hz, 1H);

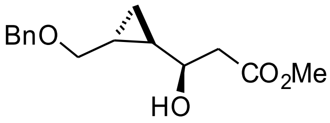
^{13}**C NMR** (100 MHz, CDCl$_3$) δ 172.1, 137.4, 128.5, 127.9, 127.9, 73.1, 71.0, 69.5, 51.6, 41.5, 22.8, 15.1, 8.9;

^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.36 – 7.27 (m, 5H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 3.74 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.71 (s, 3H), 3.68 – 3.62 (m, 1H), 3.23 (t, *J* = 10.0 Hz, 1H), 2.94 – 2.89 (m, 2H), 2.61 (dd, *J* = 16.4, 9.2 Hz, 1H), 1.33 – 1.25 (m, 1H), 1.11 – 1.00 (m, 1H), 0.89 – 0.84 (m, 1H), 0.41 (dd, *J* = 10.8, 5.2 Hz, 1H);

^{13}**C NMR** (100 MHz, CDCl$_3$) δ 173.4, 138.1, 128.4, 127.8, 127.7, 73.0, 70.5, 68.7, 51.7, 41.7, 21.7, 15.6, 8.3.



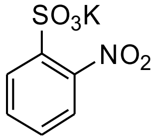
and



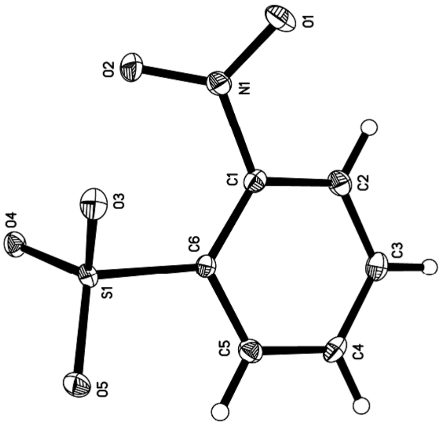
***trans*-2-10 and *trans*-2-10'**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 10H), 4.54 – 4.50 (m, 4H), 3.70 (s, 3H), 3.69 (s, 3H), 3.51 – 3.41 (m, 2H), 3.38 – 3.26 (m, 5H), 2.86 (s, 1H), 2.78 (d, *J* = 3.2 Hz, 1H), 2.70 – 2.54 (m, 4H), 1.77 (s, 1H), 1.32 – 1.25 (m, 1H), 1.22 – 1.15 (m, 1H), 1.10 – 1.00 (m, 2H), 0.91 – 0.84 (m, 2H), 0.71 – 0.66 (m, 1H), 0.55 – 0.46 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.94, 172.85, 138.44, 138.41, 135.61, 132.90, 131.79, 128.35, 127.66, 127.52, 124.68, 73.11, 72.54, 72.48, 71.46, 71.19, 51.71, 41.18, 41.08, 22.90, 22.75, 16.84, 16.00, 8.53, 7.71.



B2



^{1}H NMR (400 MHz, D_2O) δ 8.03 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.80 – 7.70 (m, 3H);

^{13}C NMR (100 MHz, D_2O) δ 147.3, 134.8, 132.7, 132.6, 128.9, 123.9;

^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, *J* = 7.2 Hz, 1H), 7.67 – 7.60(m, 3H);

^{13}C NMR (100 MHz, CD_3OD) δ 149.7, 138.6, 132.3, 132.3, 130.5, 124.4;

LC-MS: $[M+K]^+$ = 279.95

IR (KBr): ν_{max} 1538 ($-NO_2$), 1351 ($-NO_2$), 1242 ($-SO_3^-$), 1209 ($-SO_3^-$), 1080 ($-SO_3^-$), 1031 ($-SO_3^-$), 857($-NO_2$), 784, 740, 665 ($-SO_3^-$), 619($-SO_3^-$) cm^{-1}

2.7 References

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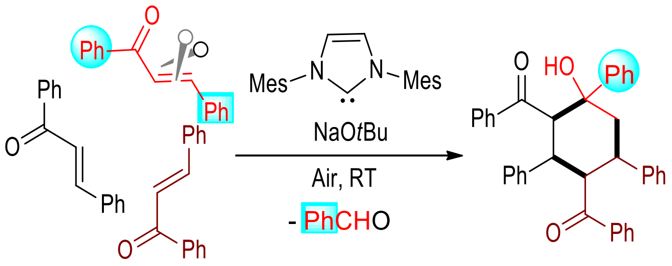
Chapter 3

Trimerization of Enones under Air Enabled by NHC/ NaOtBu via a SET Radical Pathway

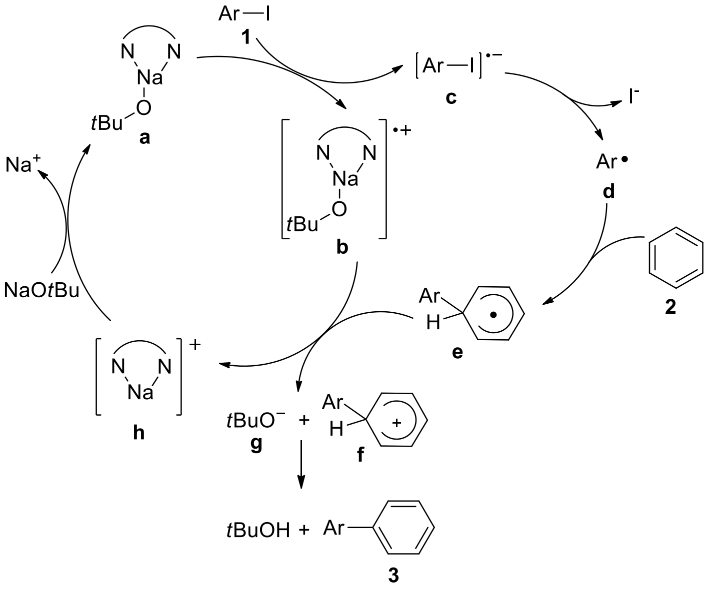


- **NHC/NaO*t*Bu-Assisted SET**
- **SET Radical Reaction**
- **C-C Bond Cleavage**
- **Unusual Trimerization**

3.1 Introduction

Alkali metal *tert*-butoxides such as KO*t*Bu, NaO*t*Bu and LiO*t*Bu are commonly used as strong inorganic bases. However, it's worth mentioning that these commercially available compounds are also used as electron-donors in some single-electron transfer (SET) reactions. The first alkali metal *tert*-butoxides-enabled SET reaction was reported by Stowell in 1981, who found that KO*t*Bu/ LiO*t*Bu reacted with trityl chloride or bromide to yield trityl radical (as detected by EPR) in THF at room temperature.[1]

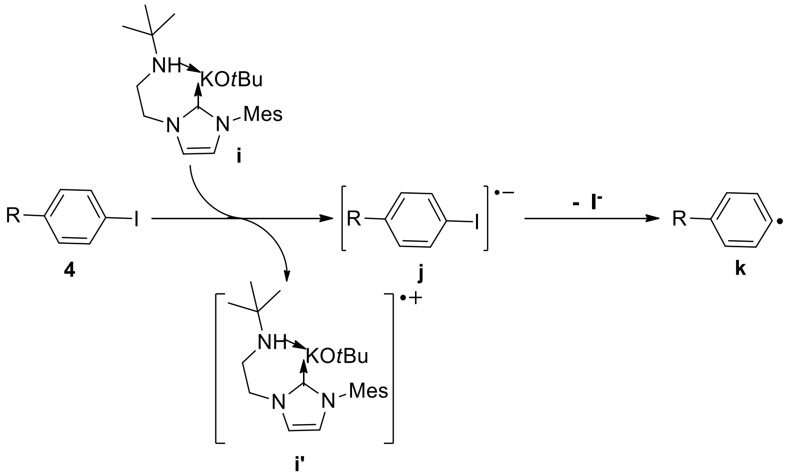
The study on alkali metal *tert*-butoxides-engaged SET reactions received unprecedented attention from 2010 onwards, and many research results were reported.[2] Shi *et. al* reported the cross coupling of aryl halides and arenes in the presence of 3.0 equivalents KO*t*Bu and 40 mol% 1,10-phenanthroline at high temperature (100 ^{o}C),[2b] however, the results were described as organocatalytic direct C-H activation at that time. Later on, Shirakawa and Hayashi published their research results: NaO*t*Bu-mediated cross-coupling of aryl halides and arenes with the aid of 1,10-phenanthroline derivative, and they also proposed the SET reaction pathway for such reactions for the first time (Scheme 3.1).[2c] NaO*t*Bu and 1,10-phenanthroline derivative forms the adduct **a**, which serves as the electron donor to transfer single electron to aryl iodine **1** to generate the radical anion **c** and radical cation **b**. Aryl radical **d** is generated via release an iodine anion from radical anion **c**, **d** adds to benzene **2** to yield cyclohexadienyl radical **e**, which gives cation **f** by single electron oxidation. Deprotonation of **f** by **g** produces the desired coupling product **3**. On the other hand, radical cation **b** is transferred to cation **h** via obtaining single electron followed by release a molecule of *t*BuO^{-} , with further reaction of NaO*t*Bu with **h** to regenerate the complex **a**. Lei and co-workers reported the similar results using N,N'-dimethylethane-1,2-diamine (DMEDA) and KO*t*Bu.[2d]



Scheme 3.1 Shirakawa and Hayashi proposed SET reaction pathway

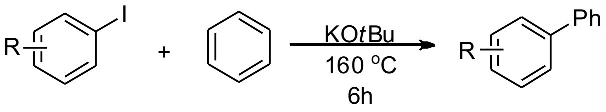
In 2012, Ong and co-workers reported the biaryl coupling between aryl halides and benzene or pyridine promoted by KO*t*Bu/NaO*t*Bu and amino-linked N-heterocyclic carbenes. Amino-linked N-heterocyclic carbenes enhance the SET process from alkali metal *tert*-butoxides to aryl halides (Scheme 3.2).[2j] Single-electron transfer from the complex **i** formed by KO*t*Bu and amino-linked N-heterocyclic carbene to aryl halide **4** affords radical anion **j**, with the generation of radical cation **i'**. Radical anion **j** transforms to the key intermediate radical **k** by release I^-.

Wilden found that the biaryl coupling reaction can also occur in the absence of bidentate nitrogen-containing compounds such as 1,10-phenanthroline and DMEDA (Scheme 3.3a).[2n] The author demonstrated that the bidentate ligands previously used for alkali metal could lead to a chelate, which enable the electron transfer to aryl halides to initiate the radical coupling reaction with arenes. In fact, there is a dynamic equilibrium in metal ion and alkoxide between essentially covalent and charge separated species, when the degree of dissociation between the group 1 metal cation and the alkoxide is sufficient enough to allow electron transfer to aryl halides, the radical coupling reaction can occur without any additives or ligands (Scheme 3.3b).

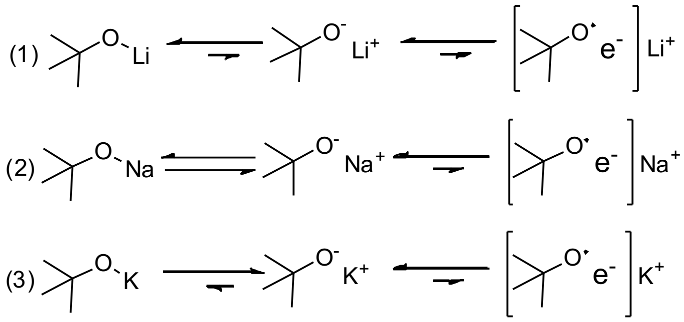


Scheme 3.2 Amino-linked N-heterocyclic carbene enhanced SET from KO*t*Bu to aryl halides

(a) Additives free KO*t*Bu-mediated biaryl coupling reaction

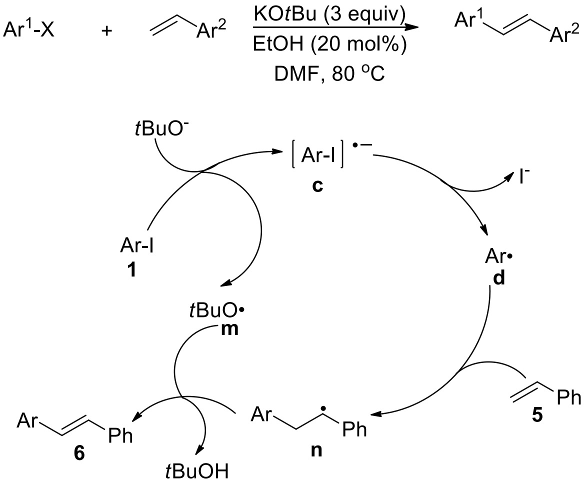


(b) Cationic dissociationof alkali metal tert-butoxides



Scheme 3.3 KO*t*Bu-mediated biaryl coupling reaction in the absence of additives

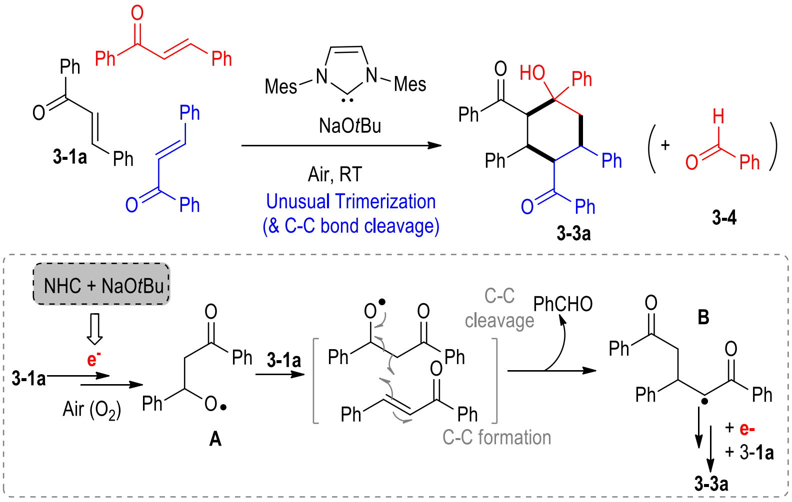
In 2011, Hayashi *et. al* expanded such *tert*-butoxide-promoted radical reaction strategy to coupling of aryl halides and styrene derivatives.[2g] No bidentate nitrogen-containing additive was used, instead trace amount of EtOH was used as additive to give higher yield. DMF was determined to be the only suitable solvent that affords the desired homolytic aromatic substitution product (Scheme 3.4). One-electron transfer from butoxide to aryl iodine **1** to give radical anion **c** and alkoxy radical **m**. **c** loses an I^- to lead to aryl radical **d**, which adds to the strene **5** to afford radical **n**, SET from **n** to **m** followed by deprotonation to yield product **6** and *t*BuOH.



Scheme 3.4 Hayashi reported KO*t*Bu-mediated Mizoroki–Heck-Type reaction

3.2 Results and discussion

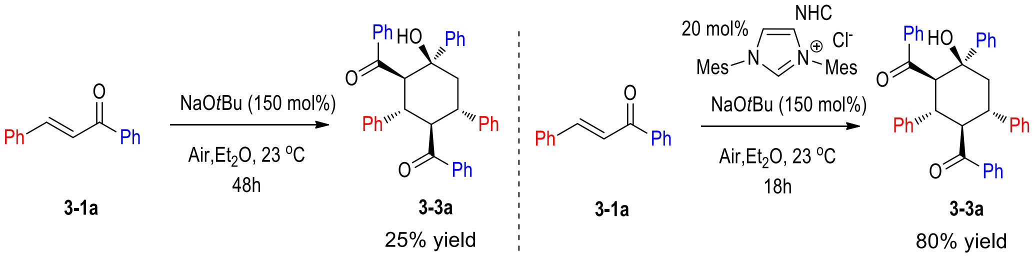
We found that alkali metal *tert*-butoxides can also initiate the radical process of enones, which were used for radical [2+2] and [2+3] dimerizations initiated by metals, photocatalysis or electronchemistry.[3] In this work, N-heterocyclic carbene (NHC) and NaO*t*Bu were used to enable the SET process of enones to afford the unusual [2+2+2] product (Scheme 3.5). The SET process from NHC/NaO*t*Bu to enone (**3-1a**) under air to afford intermediate **A**, which reacts with another molecule of enone to give intermediate **B**. Intermediate **B** undergoes further reactions with **3-1a** to lead to trimerization product **3-3a**. In this process (from **A** to **B**), one C-C bond is cleaved with the release of an aldehyde **3-4** that was experimentally verified.



Scheme 3.5 Our NHC/NaO*t*Bu-enabled unusual [2+2+2] trimerization of enones via radical pathway

3.2.1 Condition optimization

In the initial study, we carried out the reaction with enone **3-1a** as substrate in the absence of NHC and the product **3-3a** was isolated in 25% yield after 48 h, addition of NHC dramatically improved the yield within shorter reaction time (Scheme 3.6).



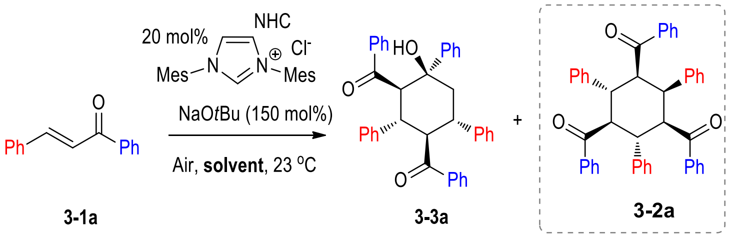
Scheme 3.6 The influence of NHC on the reaction outcomes

3.2.1.1 Solvent screening

We studied the effect of solvents on the reaction outcomes (see table 3.1). In general, diethyl ether (Et_2O) is the best choice compared with other solvents, leading to 80%

yield of **3-3a** together with 11% yield of **3-2a** after 18 h (table 3.1, entry 1). It's worth mentioning that **3-2a** was only prepared by accident under electrolysis by Fournier when he studied the effect of counter ions on the outcomes of electroreduction of chalcone.[4] Toluene and acetonitrile (CH_3CN) are also good solvents for this trimerization reaction, giving 65% and 71% yield of **3-3a**, respectively (table 3.1, entries 2 and 3). In addition, traces of **3-2a** was formed when these two solvents were used. THF and 1,4-dioxane leaded to moderate yields of **3-3a** (table 3.1, entries 4 and 5), and hexane yielded 45% yield of **3-3a** as well as 30% yield of **3-2a** (table 3.1, entry 6). When DCM was used, only 29% yield of **3-3a** was isolated (table 3.1, entry 7).

Table 3.1. Solvent screening for trimerization of chalcone (**3-1a**)^a



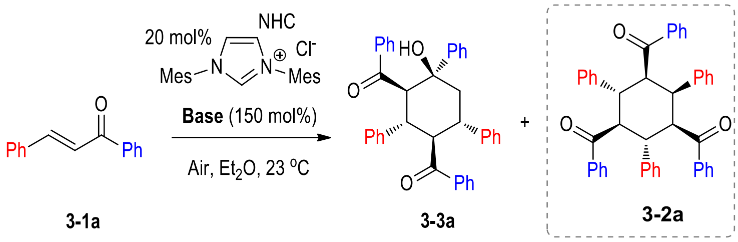
Entry	Solvent	t (h)	Yield of **3-3a** (%)^b	Yield of **3-2a** (%)^b
1	Et_2O	18	80	11
2	toluene	36	65	trace
3	CH_3CN	24	71	trace
4	1,4-dioxane	24	57	20
5	THF	24	55	4
6	hexane	24	45	30
7	DCM	24	29	20

^{a} Reaction conditions: NHC (20 mol %), NaO*t*Bu (1.5 equiv.), **3-1a** (0.1 mmol) and solvent (1.5 mL). ^{b} Isolated yield.

3.2.1.2 Base screening

According to the results from base screening, we can conclude that only the alkali metal *tert*-butoxides NaO*t*Bu and KO*t*Bu gave the trimerization product **3-3a** and **3-2a** (table 3.2, entries 1 and 2). This is easy to understand, because only alkali metal *tert*-butoxides can initiate the radical reactions as the literatures reported. Therefore, other bases can't give any product, no matter if it's an organic base or inorganic base, and their basicity plays no role (table 3.2, entries 3-10). These results also suggest that this reaction may proceed via SET process.

Table 3.2. Base screening for trimerization of chalcone (**3-1a**)[a]

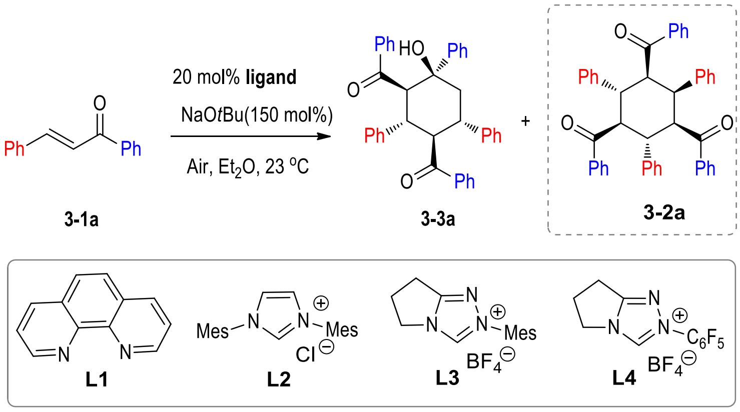


Entry	Base	*t* (h)	Yield of **3-3a** (%)[b]	Yield of **3-2a** (%)[b]
1	NaO*t*Bu	18	80	11
2	KO*t*Bu	48	30	17
3[c]	Mg(O*t*Bu)$_2$	48	0	0
4[c]	Al(O*t*Bu)$_3$	48	0	0
5[c]	NaOH	48	0	0
6[c]	NaOMe	48	0	0
7[c]	KOMe	48	0	0
8[c]	K_2CO_3	48	0	0
9[c]	DBU	48	0	0
10[c]	Et_3N	48	0	0

[a] Reaction conditions: NHC (20 mol %), base (1.5 equiv.), **3-1a** (0.1 mmol) and Et_2O (1.5 mL). [b] Isolated yield. [c] No reaction.

3.2.1.3 Ligand or additive screening

Table 3.3. Ligand or additive screening for trimerization of chalcone (**3-1a**) [a]



Entry	Ligand	*t* (h)	Yield of **3-3a** (%)[b]	Yield of **3-2a** (%)[b]
1	**L1**	24	59	14
2	**L2**	18	80	11
3	**L3**	24	24	14
4	**L4**	24	0	19

[a] Reaction conditions: ligand (20 mol %), NaO*t*Bu (1.5 equiv.), **3-1a** (0.1 mmol) and Et_2O (1.5 mL). [b] Isolated yield.

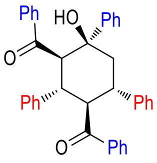
In this reaction, we use imidazolium **L2** as the ligand or additive (table 3.3, entry 2). We also tried other ligands: other triazolium NHCs such as **L3** and **L4** give very low yields (table 3.3, entries 3-4), the 1,10-phenanthroline used by other researchers in alkali metal tert-butoxides-mediated SET reaction afford 59% yield of **3-3a** and 14% yield of **3-2a** (table 3.3, entry 1).

3.2.2 Substrate scope

With an optimized set of conditions in hand, we screened a variety of enones (Table 4.4) by first varying the α -substituents. Reactions of enones bearing an electron-rich or electron-deficient α -aryl substituent proceeded smoothly to give the corresponding products in good yields (**3-3b** to **3-3d**). Moreover, naphthyl and heteroaryl substituted enones are also tolerated, despite the low yield for the furyl-substituted enone (**3-3e**, **3-3f**). When we studied the effect of the β -aryl substituent we found that the reaction outcome did not depend on the electron-withdrawing or donating nature of the α -substituents (**3-3g** to **3-3l**), though the enones bearing an electron-donating substituent needed much longer reaction time (**3-3j** to **3-3l**), with the naphthyl group and heteroaryl groups generally affording good yields (**3-3m**, **3-3n**). We also explored varying both phenyl groups and discovered that enones with other aryl substituents at both positions are good substrates, giving the corresponding 1,2,3,4,5-pentasubstituted cyclohexanols in good to excellent yields (**3-3o** to **3-3s**).

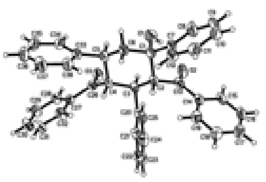
Interestingly, reactions employing aliphatic enone and 3-azachalcone did not yield the desired 1,2,3,4,5-pentasubstituted cyclohexanols (Scheme 3.7). Aliphatic enone **3-1t** gave 4,5-diphenyl-3-acetylcyclohexanone **3-3t** as the product.[3b] 3-azachalcone affords dimer **3-3u** in 63% yield through head-to-tail orientation cycloaddition due to the cation-π interaction.[5]

Table 3.4. Substrate Scope.[a]

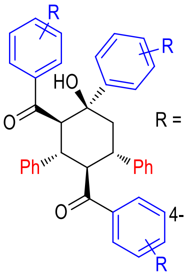


3-3a

24 h, 80% yield[b]



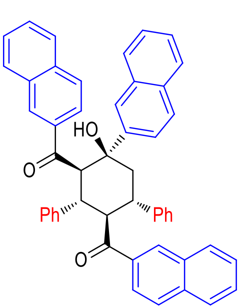
X-ray structure of 3-**3a**



R = 4-Cl, 3-**3b**, 24h, 65% yield

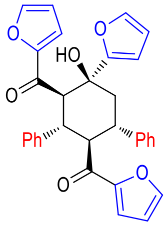
4-Br, 3-**3c**, 24h, 62% yield

4-OMe, 3-**3d**, 24h, 77% yield



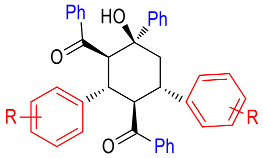
3-3e

19h, 63% yield



3-3f

24h, 36% yield



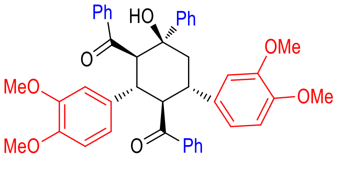
R = 4-Cl, 3-**3g**, 24h, 58% yield

4-Br, 3-**3h**, 25h, 50% yield

3-Br, 3-**3i**, 25h, 68% yield

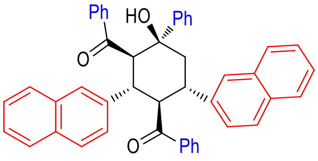
4-OMe, 3-**3j**, 36h, 45% yield

4-Me, 3-**3k**, 48h, 67% yield



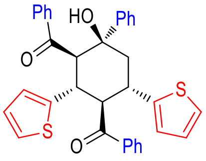
3-3l[c]

4d, 49% yield



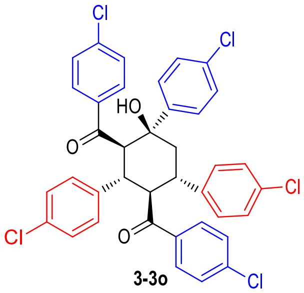
3-3m[c]

3d, 86% yield



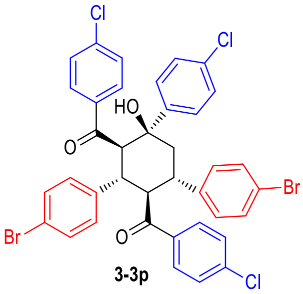
3-3n

3d, 73% yield



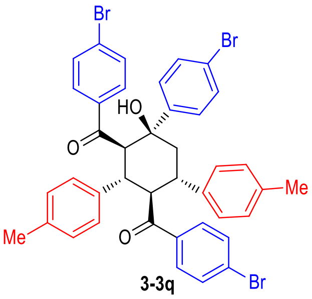
3-3o

5h, 98% yield



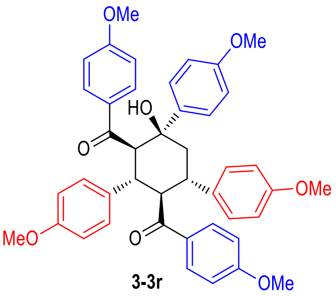
3-3p

18h, 73% yield



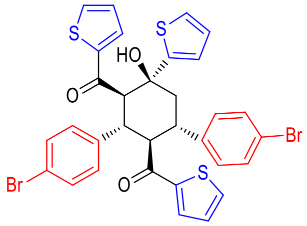
3-3q

2d, 60% yield



3-3r

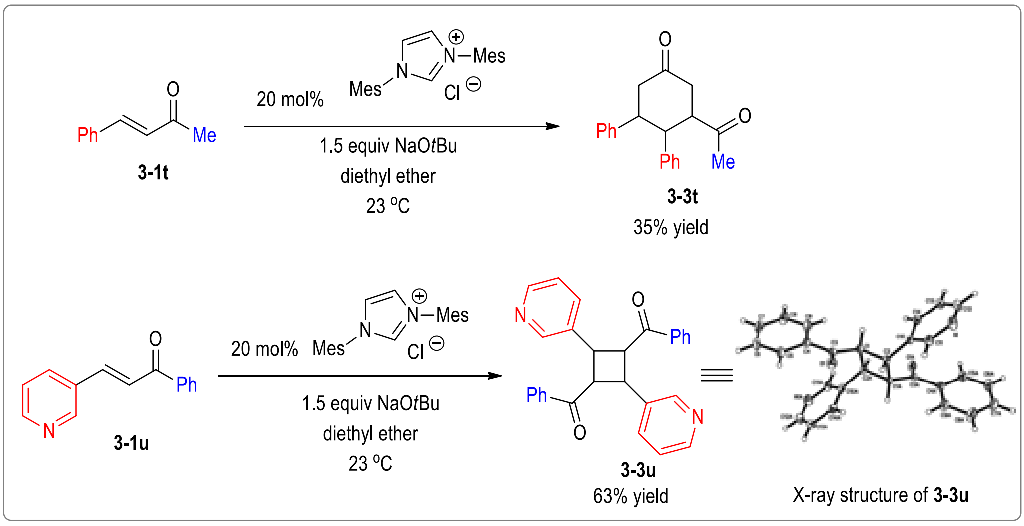
4d, 65% yield



3-3s

6h, 66% yield

[a] Unless otherwise noted, the reactions were conducted in 4 mL vials with 0.2 mmol enones, 20 mol% NHC precursor **L2** and 1.5 equivalents of NaO*t*Bu in 3 mL diethyl ether. The reaction mixture was stirred at room temperature (23 °C) under air till the enones were fully converted monitored by TLC. [b] Isolated yield. [c] 0.2 mL THF was added.

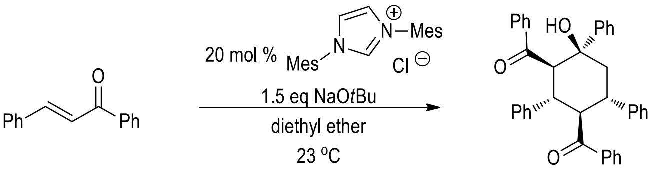


Scheme 3.7 Special examples

3.3 Mechanistic study

In order to study the mechanistic pathway, several control experiments were performed (Table 3.5). Firstly, the reaction is partially inhibited by TEMPO. When 1.0 equivalent of TEMPO was added, the product yield dropped to 16% (table 3.5, entry 1), no product was isolated when 3.0 equivalents of TEMPO was added (table 3.5, entry 2). Secondly, we discovered that molecular oxygen is necessary for this reaction, as there was no reaction when oxygen is not present (table 3.5, entry 3). However, when the reaction was carried out under pure oxygen, no **3-3a** was formed. That may be ascribed to the high concentration of oxygen, as the reduction potential of **3-1a** was found to be greater than the reduction potential of O_2 by approximately 500 mV (reduction potential of O_2 is -1.25 V vs. Fc/Fc^+),[6] when the reaction took place under air, the concentration of **3-1a** was largely greater than oxygen and **3-1a** would obtain the one electron from NHC-NaO*t*Bu; while when the reaction was conducted under pure oxygen, the oxygen will get the one electron and the reaction is suspended. All the above are suggestive that the reaction may proceed via a radical pathway that involves oxygen.

Table 3.5. Control experiments



3-3a

entry	conditions	Yield of **3-3a** (%)
1	under air , 1.0 equiv. TEMPO	16%
2	under air, 3.0 equiv. TEMPO	0
3	degassing, under N_2 atmosphere	0
4	degassing then insert O_2 (balloon)	0

To further verify our assumed radical pathway, we conducted electron paramagnetic resonance (EPR) spectroscopic analysis of the reaction mixture of **3-1a** in diethyl ether containing 20 mol% of NHC and 1.5 equiv. of NaO*t*Bu. An exchange broadened and persistent radical signal was obtained at room temperature with a *g*-value of 2.0050 (Fig. 3.1). It indicated that a radical anion was involved in the reaction process.

In order to confirm the identity of the radical detected by EPR, we conducted the cyclic voltammogram study. Cyclic voltammetry experiments performed on **3-1a** showed that it could be reduced at approximately -1.85 V *vs.* ferrocene$^{0/+}$ (Figure 3.2). However, the chemical irreversible nature of the voltammetric reduction process indicated that the radical anion form of **3-1a** (intermediate **I** in Scheme 3.7) could not be the long-lived radical that was detected via the EPR experiments (Fig. 3.1), as the CV experiments indicate that it is relatively short-lived (lifetime << 1 s). Therefore, the radical anion detected by EPR in figure 3.1 maybe the intermediate **II** in Scheme 3.7, which is generated via radical intermediate **I** reacting with oxygen.

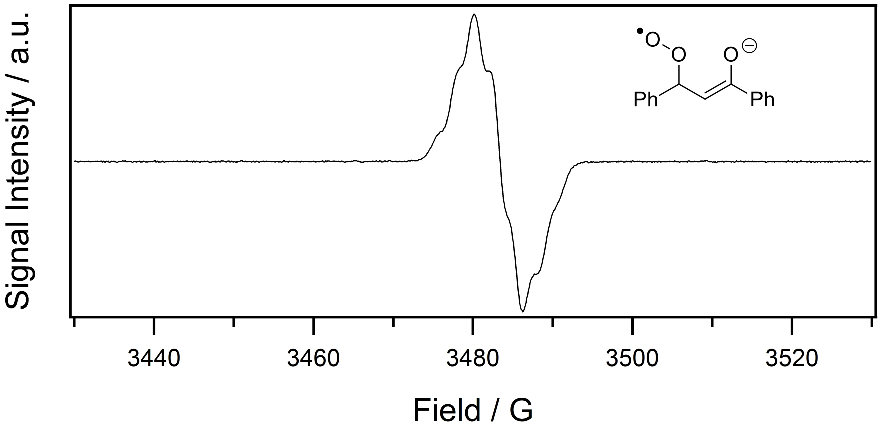


Figure 3.1. Continuous wave X-band room-temperature EPR spectrum of the reaction mixture of 20 mol% NHC precursor A, 1.5 equiv. of NaO*t*Bu and chalcone 1a in diethyl ether. The modulation amplitude = 0.2 G and sweep time = 30 s.

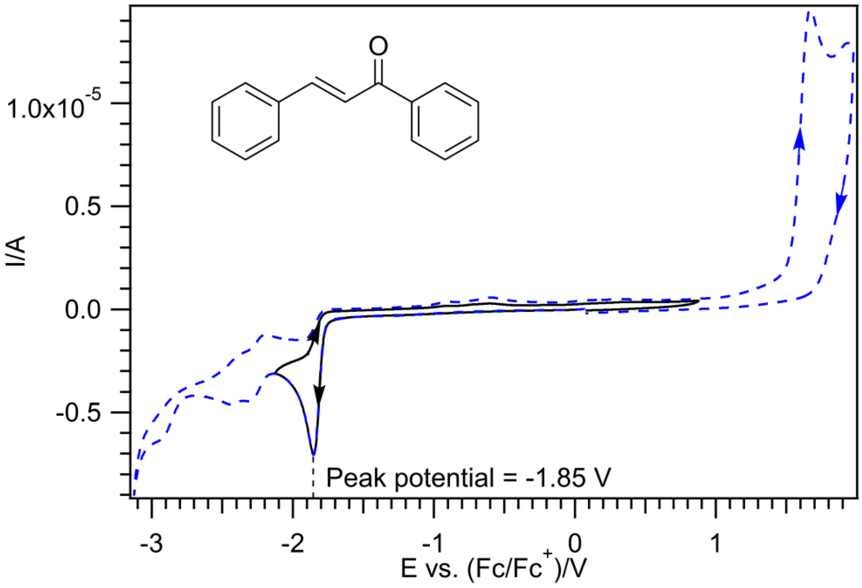
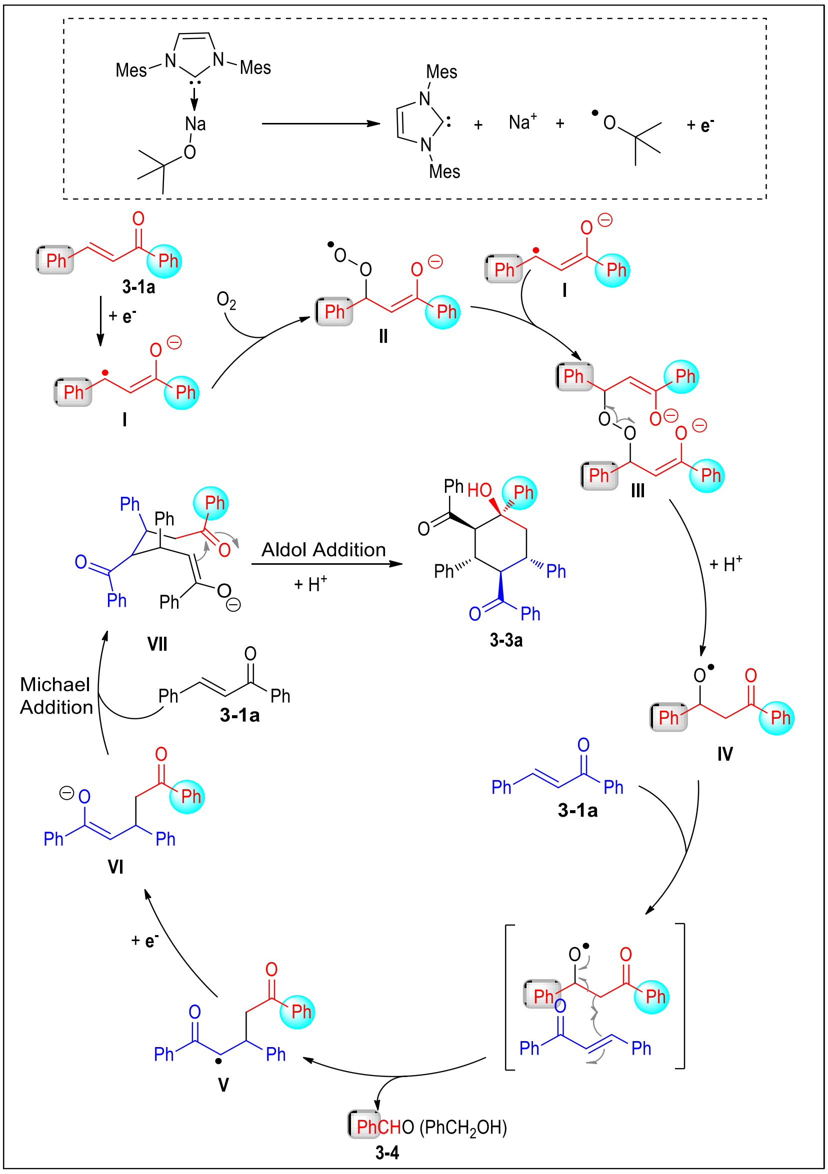


Figure 3.2. Cyclic voltammogram of 5 mM of **3-1a** recorded at a 1 mm diameter planar circular glassy carbon electrode in acetonitrile containing 0.2 M *n*-Bu_4NPF_6 as the supporting electrolyte, at a scan rate of 0.1 mV s^{-1} and at 22 ± 2 °C.

A detailed description of our radical [2+2+2] cycloaddition of enones triggered by the NHC and NaO*t*Bu (1.5 equivalents of NaO*t*Bu was used in our reaction) is presented in Scheme 3.7. Our proposed mechanism begins with carbene assisting to remove a single electron of NaO*t*Bu,[2g, 2n] giving an alkoxy radical which collapses via a variety of well-known decomposition pathways such as H-atom abstraction or β-scission process.[7] Meanwhile, the chalcone **3-1a** obtains one electron to give radical anion **I** which subsequently reacts with molecular oxygen to generate radical intermediate **II**.[8,9] Intermediate **III** is formed after radical intermediate **II** reacts with another molecule of intermediate **I**, followed by the cleavage of the peroxide bond and protonation to yield O-centered radical intermediate **IV,** which reacts with anther molecule of chalcone **3-1a** to generate intermediate **V** along with the corresponding aldehyde (PhCHO) was released.[9] **VI** is produced via obtaining one electron, then followed by Michael addition to afford intermediate **VII**. The intramolecular Aldol addition of intermediate **VII** yields the product **3-3a**. Notably, the aldehyde generated during the reaction is detected in the form of its corresponding benzyl alcohol at the end of the reaction. The mechanism proposed in scheme 3.7 is also supported by the LC-MS detection.



Scheme 3.7 Proposed reaction pathway

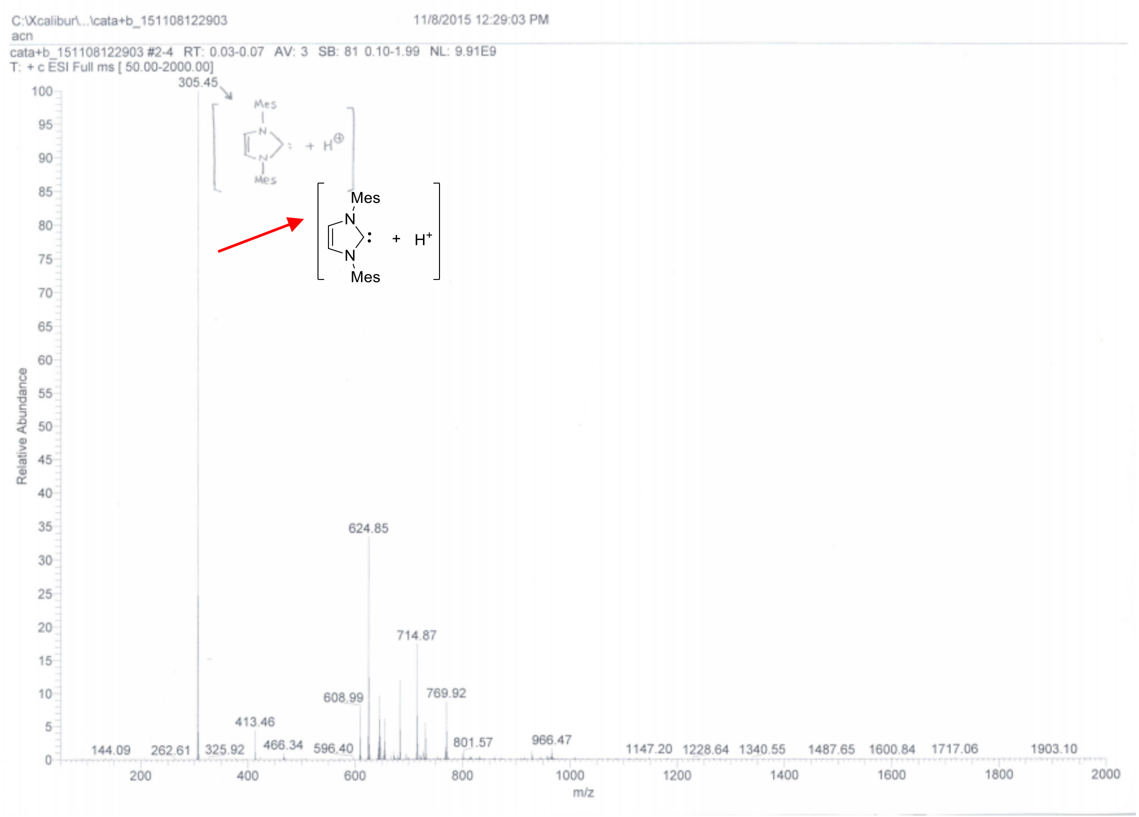


Figure 3.3. 20 mol% NHC and 1.5 equiv. NaO*t*Bu in diethyl ether stirred for 1h

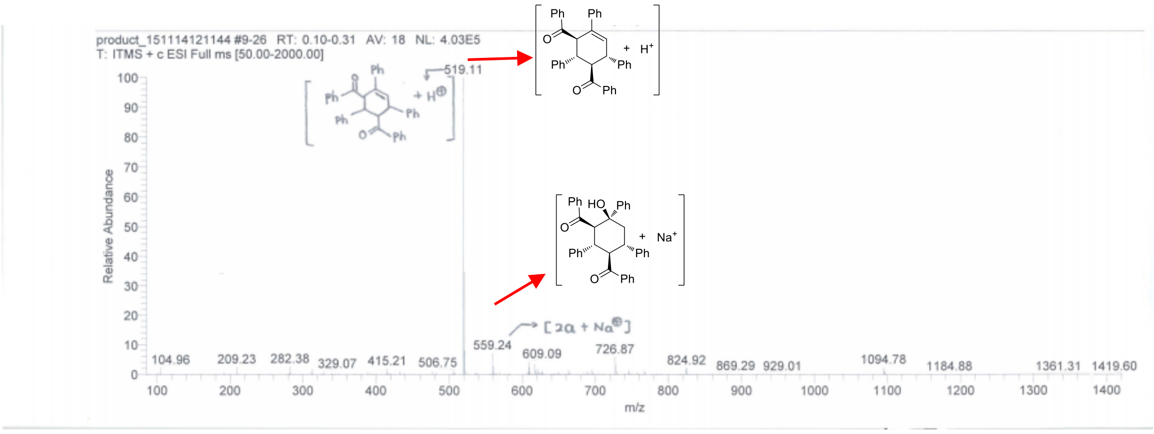


Figure 3.4. Product **3-3a**

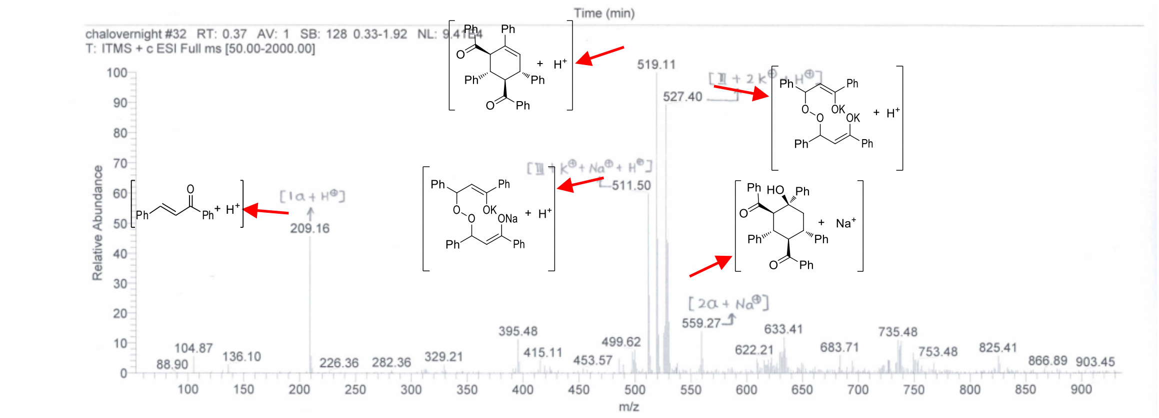


Figure 3.5. Chalcone **3-1a**, 20 mol% NHC and 1.5 equivalents of NaO*t*Bu in diethyl ether stirred for 8 h

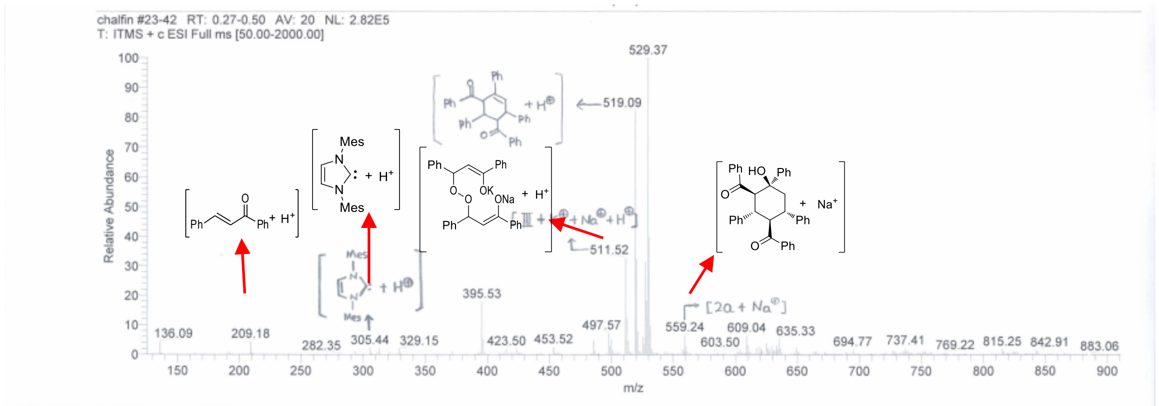
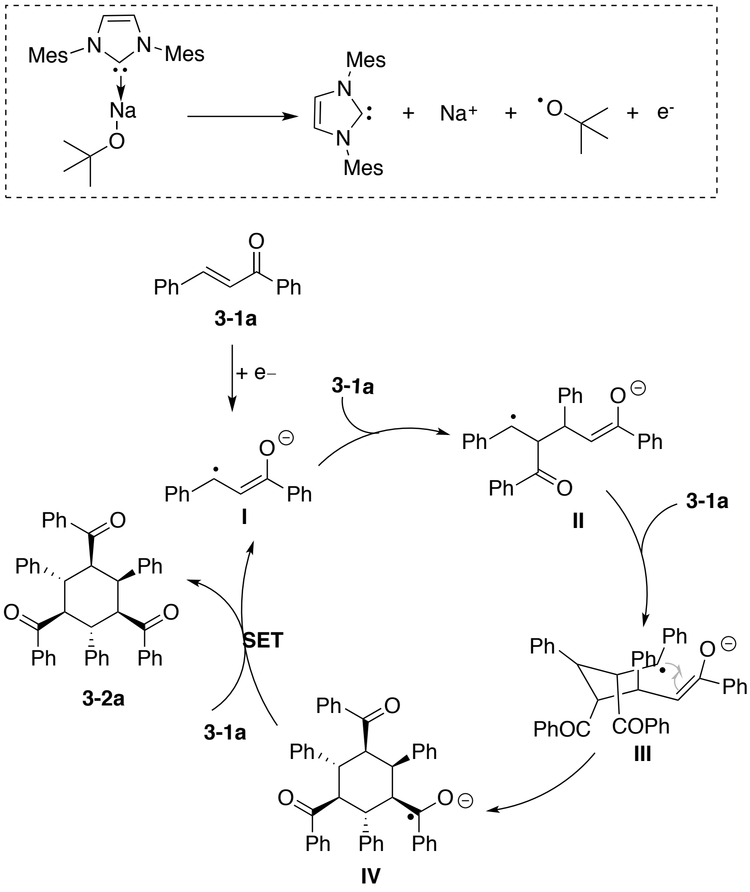


Figure 3.6. Chalcone **3-1a**, 20 mol% NHC and 1.5 equivalents of NaO*t*Bu in diethyl ether stirred for 20 h

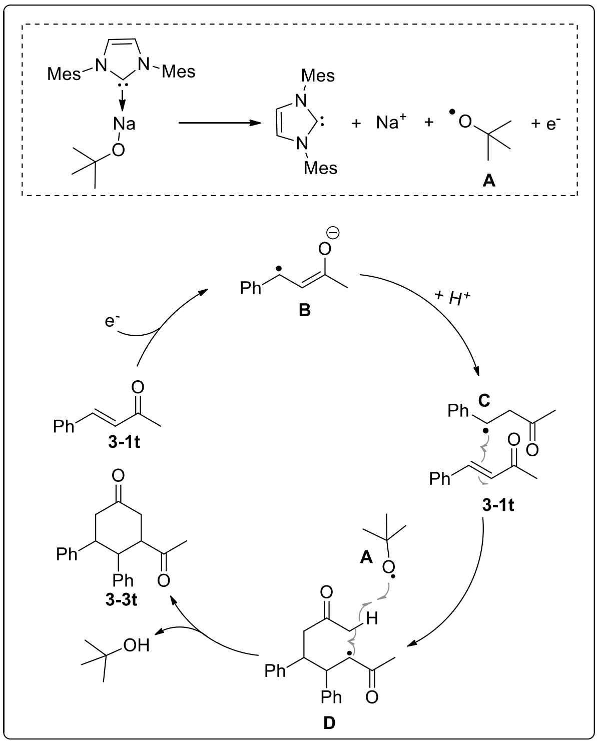
We also proposed the reaction pathways to **3-2a** and **3-3t** based on the experimental results and literature study. The proposed mechanistic pathway of formation of side product **3-2a** is presented in Scheme 3.8.[4] Initially, one electron reduction of chalcone **3-1a** by NHC/NaO*t*Bu gives radical anion **I**, which then adds to another molecule of **3-**

1a to afford radical anion intermediate **II**. Subsequently, intermediate **II** reacts furtherly with the third molecule of **3-1a** to give radical anion **III**, which undergoes 6-exo-trig radical cyclization to generate intermediate **IV**. Finally, a single-electron transfer from **IV** to **3-1a** to produce **3-2a** with the generation of intermediate **I**.



Scheme 3.8 Proposed mechanism for formation of **3-2a**

A detailed description of formation of **3-3t** is summarized in Scheme 3.9.[3b] The reaction starts with **3-1t** receiving one electron from the adduct of NHC and NaO*t*Bu to give radical anion **B**. Intermediate **B** undergoes protonation followed by radical addition to anther molecule of **3-1t** to form radical intermediate **D**. The hydrogen atom transfer (HAT) from the intermediate **D** to *tert*-alkoxyl radical **A**, followed by ring closing to yield product **3-3t** as well as a molecule of *tert*-butanol.



Scheme 3.9 Proposed mechanism for formation of **3-3t**

3.4 Summary

In summary, we have developed the first generation of radical anions from enones triggered by NHC and NaO*t*Bu, which undergoes addition to the molecular oxygen followed by cleavage of the peroxide bond and protonation to generate O-centered radical. Further reactions of this O-centered radical with enone yields 1,2,3,4,5-pentasubstituted cyclohexanols. This approach allows a simple and flexible entry to synthesis of multisubstituted cyclohexanes with five contiguous stereocenters in a one-pot fashion.

3.5 Experimental section

3.5.1 General information

Commercially available materials purchased from Alfa Aesar, Merk or Aldrich were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV400 (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. IR spectra were recorded on a Shimadzu IRPrestige-21 FT-IR spectrometer as neat thinfilms between NaCl plates in case of liquids and as KBr pellets in the case of solids. LC-MS were recorded on ThermoFinnigan LCQ Fleet MS. Melting points were measured on SRS Optimelt Automated Point System SRS. MPA100. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 1443861 (**3-2a**), CCDC 1443862 (**3-3a**).

3.5.3 General procedures

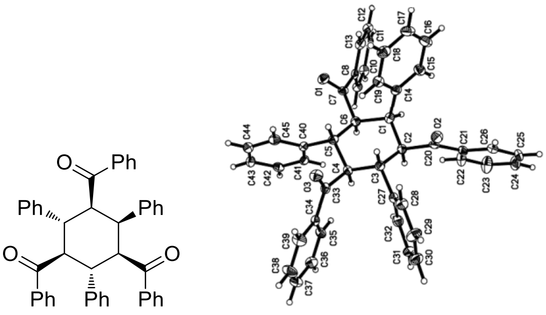
3.5.3.1 General procedures for Table 3.1 (entry 1)

To a 4 mL sample vial equipped with a magnetic stir bar, was added imidazolium-based NHC (**L2**) (6.8 mg, 20 mol %), NaO*t*Bu (15.0 mg, 1.5 equiv) and chalcone **3-1a** (0.1 mmol). The vial was closed with a plastic stopper after addition of 1.5 mL diethyl ether (purchased from Merk for analysis, used without further purification). The resulting mixture was stirred at room temperature. After the consumption of chalcone **3-1a** montiored by TLC, solvent was evaporated and the reaction mixture was then applied to silica gel chromatography (hexane/ethyl acetate = 10:1) to obtain product **3-3a**.

3.5.3.2 General procedures for Table 3.4

To a 8 mL sample vial equipped with a magnetic stir bar, was added imidazolium-based NHC (**L2**) (13.6 mg, 20 mol %), NaO*t*Bu (29.0 mg, 1.5 equiv) and enone **3-1** (0.2 mmol). The vial was closed with a plastic stopper after addition of 3.0 mL diethyl ether (purchased from Merk for analysis, used without further purification). In some cases, 200 μL THF was added in order to increase the solubility of enones. The resulting mixture was stirred at room temperature. After the consumption of enone **3-1** montiored by TLC, solvent was evaporated and the reaction mixture was then applied to silica gel chromatography to obtain product **3-3**.

3.5.4 Characterization of products



3-2a

2,4,6-triphenylcyclohexane-1,3,5-triyl)tris(phenylmethanone)

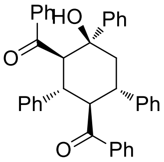
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.65 – 7.62 (m, 4H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.38 – 7.30 (m, 8H), 7.20 – 7.12 (m, 4H), 7.10 – 6.94 (m, 10H), 6.86 (t, *J* = 7.2 Hz, 2H), 4.77 (dd, *J* = 12.0, 5.2 Hz, 2H), 4.45 (t, *J* = 12.0 Hz, 2H), 4.19 (t, *J* = 11.6 Hz, 1H), 3.99 (t, *J* = 5.2 Hz, 1H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 204.90, 197.71, 141.36, 138.78, 137.30, 135.88, 132.68, 131.74, 130.31, 128.59, 128.32, 128.21, 128.10, 127.68, 127.63, 127.43, 127.22, 126.63, 58.20, 53.55, 47.30, 43.37.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{45}H_{37}O_3$, 625.2743 found, 625.2747;

IR (KBr): ν_{max} 3024, 2916, 1681 (C=O), 1667 (C=O), 1589, 1450, 1265, 987, 694 cm^{-1}

mp 302.9-303.4 °C



3-3a

(4-hydroxy-2,4,6-triphenylcyclohexane-1,3-diyl)bis(phenylmethanone)

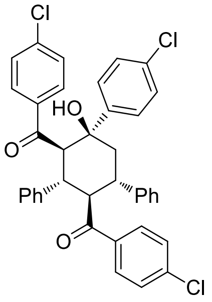
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 2H), 7.29 – 6.95 (m, 20H), 6.83 (t, *J* = 7.6 Hz, 2H), 6.71 (t, *J* = 7.2 Hz, 1H), 5.39 (d, *J* = 2.4 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.26 – 4.14 (m, 2H), 4.10 – 4.02 (m, 1H), 2.56 – 2.48 (m, 1H), 2.26 (dd, *J* = 14.0, 3.6 Hz, 1H);

^{13}C NMR: (100 MHz, $CDCl_3$) δ 207.17, 203.58, 145.88, 142.07, 138.96, 138.61, 138.12, 132.65, 131.76, 128.35, 128.16, 128.06, 127.97, 127.69, 127.66, 127.54, 127.36, 126.98, 126.90, 126.69, 124.80, 75.33, 56.74, 56.72, 48.06, 45.83, 43.34.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{38}H_{32}O_3Na$, 559.2249 found 559.2252;

IR (KBr): ν_{max} 3402 (OH), 1666 (C=O), 1643 (C=O), 1597, 1439, 1257, 1026, 802, 694 cm^{-1}

mp 244.2-244.7 °C



3-3b

(4-(4-chlorophenyl)-4-hydroxy-2,6-diphenylcyclohexane-1,3-diyl)bis((4-chlorophenyl)methanone)

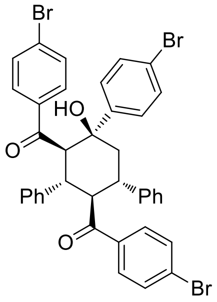
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (d, *J* = 8.8 Hz, 2H), 7.23 (t, *J* = 8.4 Hz, 4H), 7.17 (d, *J* = 8.4 Hz, 4H), 7.11 (t, *J* = 7.6 Hz, 4H), 7.07 – 6.99 (m, 5H), 6.87 (t, *J* = 7.6 Hz, 2H), 6.78 (t, *J* = 7.6 Hz, 1H), 5.36 (d, *J* = 2.4 Hz, 1H), 4.40 – 4.35 (m, 1H), 4.18 – 4.10 (m, 2H), 4.05 – 3.99 (m, 1H), 2.47 – 2.39 (m, 1H), 2.22 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 205.48, 202.13, 144.40, 141.57, 139.68, 138.35, 138.22, 136.98, 135.95, 133.02, 129.07, 128.72, 128.53, 128.41, 128.35, 128.25, 127.95, 127.81, 127.33, 127.02, 126.22, 75.09, 56.51, 56.30, 47.96, 45.65, 43.25.

HRMS: (ESI) [M+Na]$^+$ calcd. for $C_{38}H_{29}O_3NaCl_3$, 661.1080 found, 661.1118;

IR (KBr): v_{max} 3425 (OH), 1672 (C=O), 1651 (C=O), 1589, 1489, 1396, 1087, 833, 702, 532 cm^{-1}

mp 237.9-238.5 ^{o}C



3-3c

(4-(4-bromophenyl)-4-hydroxy-2,6-diphenylcyclohexane-1,3-diyl)bis((4-bromophenyl)methanone)

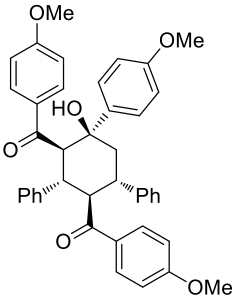
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.24 – 7.21(m, 4H), 7.18 – 7.06 (m, 10H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 2H), 6.79 (t, *J* = 7.6 Hz, 1H), 5.35 (d, *J* = 2.4 Hz, 1H), 4.40 – 4.33 (m, 1H), 4.17 – 4.09 (m, 2H), 4.04 – 3.98 (m, 1H), 2.46 – 2.37 (m, 1H), 2.22 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.70, 202.33, 144.93, 141.53, 138.17, 137.39, 136.36, 131.38, 131.25, 130.93, 129.12, 128.82, 128.55, 128.37, 127.81, 127.36, 127.12, 127.04, 126.57, 121.21, 75.14, 56.53, 56.22, 47.96, 45.61, 43.24.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{38}H_{29}O_3NaBr_3$, 792.9564 found, 792.9537;

IR (KBr): ν_{max} 3441 (OH), 1666 (C=O), 1643 (C=O), 1581, 1489, 1396, 1072, 1002, 833, 702, 532 cm^{-1}

mp 256.8-258.0 °C



3-3d

(4-hydroxy-4-(4-methoxyphenyl)-2,6-diphenylcyclohexane-1,3-diyl)bis((4-methoxyphenyl)methanone)

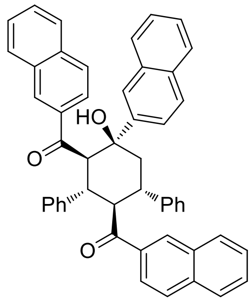
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.35 – 7.31 (m, 4H), 7.26 (d, *J* = 7.2 Hz, 2H), 7.15 – 7.06 (m, 4H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 2H), 6.74 – 6.69 (m, 3H), 6.55 – 6.50 (m, 4H), 5.56 (d, *J* = 2.0 Hz, 1H), 4.44 – 4.36 (m, 1H), 4.19 – 4.12 (m, 2H), 4.07– 4.00 (m, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 2.49 – 2.41 (m, 1H), 2.20 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.97, 201.47, 163.21, 162.43, 158.26, 142.38, 139.02, 138.48, 131.84, 130.96, 130.36, 129.85, 128.26, 127.97, 127.92, 126.72, 126.56, 125.95, 113.40, 112.93, 112.74, 75.00, 55.95, 55.88, 55.26, 55.16, 55.11, 47.99, 46.28, 43.30.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{41}H_{38}O_6Na$, 649.2566 found, 649.2526;

IR (KBr): ν_{max} 3402 (OH), 1658 (C=O), 1597 (C=O), 1512, 1257, 1174, 1026, 833, 702, 540 cm^{-1}

mp 223.2-224.4 °C



3-3e

(4-hydroxy-4-(naphthalen-2-yl)-2,6-diphenylcyclohexane-1,3-diyl)bis(naphthalen-2-ylmethanone)

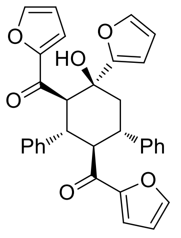
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.78 – 7.56 (m, 10H), 7.49 – 7.27 (m, 14H), 7.08 (t, *J* = 7.6 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.75 (t, *J* = 8.0 Hz, 2H), 6.55 (t, *J* = 7.2 Hz, 1H), 5.69 (d, *J* = 2.4 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.48 (t, *J* = 11.2 Hz, 1H), 4.37 (t, *J* = 11.2 Hz, 1H), 4.25 – 4.18 (m, 1H), 2.77– 2.69 (m, 1H), 2.38 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.92, 203.39, 143.41, 142.17, 138.74, 136.32, 135.36, 135.03, 134.78, 133.10, 132.30, 131.93, 131.66, 129.86, 129.32, 129.30, 128.98, 128.57, 128.41, 128.35, 128.10, 128.00, 127.91, 127.87, 127.57, 127.48, 127.43, 127.26, 126.96, 126.79, 126.39, 126.19, 126.04, 125.73, 124.10, 123.55, 123.17, 123.00, 75.73, 56.88, 56.49, 48.37, 45.96, 43.53.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{50}H_{39}O_3$, 687.2899 found, 687.2899;

IR (KBr): ν_{max} 3410 (OH), 1666 (C=O), 1621 (C=O), 1512, 1357, 1180, 748 cm^{-1}

mp 247.6-248.3 °C



3-3f

(4-(furan-2-yl)-4-hydroxy-2,6-diphenylcyclohexane-1,3-diyl)bis(furan-2-ylmethanone)

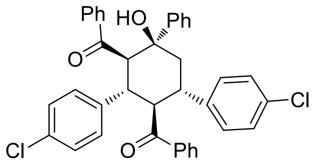
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 – 7.11 (m, 9H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 2H), 6.87– 6.81 (m, 2H), 6.60 (s, 1H), 6.25 (dd, *J* = 3.6, 1.6 Hz, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 6.13 – 6.10 (m, 2H), 5.04 (s, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 4.16 – 3.80 (m, 3H), 2.53 – 2.41 (m, 1H), 2.28 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 192.79, 190.57, 158.27, 153.34, 152.65, 147.08, 145.74, 141.81, 141.31, 138.42, 128.28, 128.02, 127.82, 126.94, 126.69, 118.70, 116.89, 112.21, 111.85, 110.31, 105.49, 72.88, 55.83, 55.00, 45.99, 43.95, 42.10.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{32}H_{27}O_6$, 507.1808 found, 507.1795;

IR (KBr): ν_{max} 3448 (OH), 1658 (C=O), 1646 (C=O), 1465, 1396, 756, 702 cm^{-1}

mp 199.7-202.1 °C



3-3g

(2,6-bis(4-chlorophenyl)-4-hydroxy-4-phenylcyclohexane-1,3-diyl)bis(phenylmethanone)

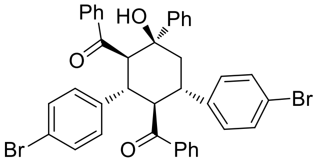
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.29 – 7.15 (m, 10H), 7.12 – 7.02 (m, 9H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.32 (d, *J* = 2.4 Hz, 1H), 4.48 – 4.40 (m, 1H), 4.21 – 4.10 (m, 2H), 4.08 – 3.99 (m, 1H), 2.51 – 2.39 (m, 1H), 2.22 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.68, 202.88, 145.43, 140.40, 138.46, 137.85, 137.11, 133.00, 132.70, 132.43, 132.33, 129.26, 128.51, 128.26, 128.24, 127.87, 127.66, 127.35, 127.18, 124.69, 75.22, 56.51, 56.46, 47.41, 45.69, 42.76.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{38}H_{31}O_3Cl_2$, 605.1650 found, 605.1650;

IR (KBr): ν_{max} 3394 (OH), 1668 (C=O), 1631 (C=O), 1597, 1489, 1096, 1010, 694, 540 cm^{-1}

mp 250.5-252.9 °C



3-3h

(2,6-bis(4-bromophenyl)-4-hydroxy-4-phenylcyclohexane-1,3-diyl)bis(phenylmethanone)

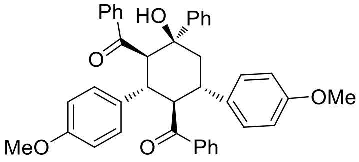
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.31 – 7.16 (m, 10H), 7.15 – 6.92 (m, 11H), 5.31 (d, *J* = 2.4 Hz, 1H), 4.48 – 4.39 (m, 1H), 4.20 – 4.08 (m, 2H), 4.07 – 3.97 (m, 1H), 2.50 – 2.39 (m, 1H), 2.22 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.65, 202.84, 145.39, 140.90, 138.45, 137.85, 137.61, 133.00, 132.34, 131.47, 131.19, 129.63, 128.27, 127.89, 127.87, 127.65, 127.35, 127.19, 124.69, 120.87, 120.54, 75.20, 56.48, 56.34, 47.47, 45.63, 42.82.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{38}H_{30}O_3NaBr_2$, 715.0459 found, 715.0471;

IR (KBr): ν_{max} 3441 (OH), 1666 (C=O), 1631 (C=O), 1597, 1489, 1072, 1010, 694, 540 cm^{-1}

mp 260.4-261.6 °C



3-3i

(4-hydroxy-2,6-bis(4-methoxyphenyl)-4-phenylcyclohexane-1,3-diyl)bis(phenylmethanone)

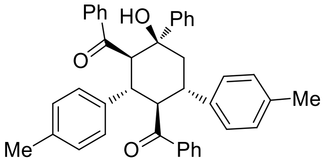
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.6 Hz, 2H), 7.28 – 7.14 (m, 10H), 7.10 – 6.98 (m, 7H), 6.63 (d, *J* = 8.8 Hz, 2H), 6.36 (d, *J* = 8.8 Hz, 2H), 5.35 (d, *J* = 2.4 Hz, 1H), 4.49 – 4.39 (m, 1H), 4.18 – 4.07 (m, 2H), 4.05 – 3.92 (m, 1H), 3.63 (s, 3H), 3.47 (s, 3H), 2.51 – 2.38 (m, 1H), 2.20 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.39, 203.92, 158.16, 145.93, 139.03, 138.17, 134.29, 132.60, 131.72, 130.75, 128.87, 128.13, 127.69, 127.67, 127.59, 127.40, 126.93, 124.78, 113.75, 113.50, 75.39, 57.26, 57.01, 55.11, 54.97, 47.23, 46.10, 42.52.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{40}H_{36}O_5Na$, 619.2460 found, 619.2462;

IR (KBr): v_{max} 3417 (OH), 1666 (C=O), 1643 (C=O), 1512, 1249, 1033, 825, 694, 540 cm^{-1}

mp 199.8-200.1 °C



3-3j

(4-hydroxy-4-phenyl-2,6-di-p-tolylcyclohexane-1,3-diyl)bis(phenylmethanone)

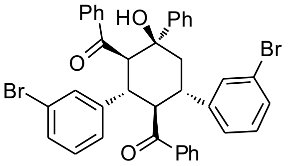
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.28 – 7.12 (m, 10H), 7.10– 6.94 (m, 7H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 2H), 5.34 (d, *J* = 2.0 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.22 – 4.08 (m, 2H), 4.05 – 3.95 (m, 1H), 2.54 – 2.41 (m, 1H), 2.21 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.12 (s, 3H), 1.91 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.34, 203.79, 145.95, 139.09, 138.22, 136.30, 136.06, 135.57, 132.47, 131.54, 128.96, 128.68, 128.10, 127.79, 127.72, 127.59, 127.47, 126.90, 124.81, 75.37, 57.03, 56.98, 47.60, 46.04, 42.93, 20.83, 20.65.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{40}H_{36}O_3Na$, 587.2562 found, 587.2556;

IR (KBr): ν_{max} 3417 (OH), 1666 (C=O), 1643 (C=O), 1597, 1342, 1210, 694, 540 cm^{-1}

mp 270.7-271.9 °C



3-3k

(2,6-bis(3-bromophenyl)-4-hydroxy-4-phenylcyclohexane-1,3-diyl)bis(phenylmethanone)

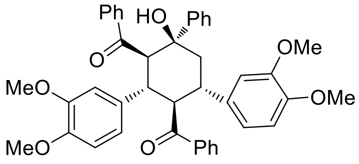
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H), 7.47 (t, *J* = 1.6 Hz, 1H), 7.40 – 6.96 (m, 17H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.86 – 6.80 (m, 1H), 6.69 (t, *J* = 8.0 Hz, 1H), 5.38 (d, *J* = 2.4 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.22 – 4.07 (m, 2H), 4.05 – 3.95 (m, 1H), 2.50 – 2.36 (m, 1H), 2.23 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.54, 202.52, 145.44, 144.21, 140.86, 138.44, 137.80, 133.06, 132.37, 130.64, 130.05, 129.99, 129.87, 129.74, 128.29, 127.85, 127.70, 127.39, 127.19, 127.07, 124.68, 122.43, 122.15, 75.20, 56.15, 55.96, 47.61, 45.82, 43.09.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{38}H_{30}O_3Br_2Na$, 715.0459 found, 715.0447;

IR (KBr): ν_{max} 3402 (OH), 1666 (C=O), 1643 (C=O), 1573, 1188, 1072, 902, 779, 694 cm^{-1}

mp 236.0-237.1 °C



3-3l

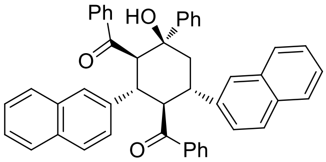
(2,6-bis(3,4-dimethoxyphenyl)-4-hydroxy-4-phenylcyclohexane-1,3-diyl)bis(phenylmethanone)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.33 – 7.16 (m, 8H), 7.13 – 7.01 (m, 4H), 6.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.78 – 6.56 (m, 4H), 6.34 (d, *J* = 8.4 Hz, 2H), 5.40 (d, *J* = 2.0 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.21 – 4.07 (m, 2H), 4.05 – 3.95 (m, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.59 (s, 3H), 3.54 (s, 3H), 2.50 – 2.39 (m, 1H), 2.24 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 207.29, 203.64, 148.59, 148.31, 147.71, 147.62, 145.88, 139.05, 138.19, 134.81, 132.71, 131.92, 131.11, 128.18, 127.69, 127.66, 127.62, 127.34, 127.01, 124.77, 119.71, 111.86, 111.22, 110.90, 75.45, 56.91, 56.87, 55.86, 55.80, 55.78, 55.62, 47.79, 46.26, 43.06.

HRMS: (ESI) [M+Na]$^+$ calcd. for $C_{42}H_{40}O_7Na$, 679.2672 found, 679.2667;

IR (film): ν_{max} 3441 (OH), 3024, 1672 (C=O), 1650 (C=O), 1516, 1257, 1141, 1026, 754cm^{-1}



3-3m

(4-hydroxy-2,6-di(naphthalen-2-yl)-4-phenylcyclohexane-1,3-diyl)bis(phenylmethanone)

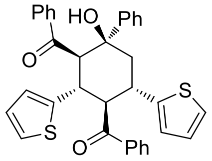
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 – 7.15 (m, 22H), 7.13 – 7.01 (m, 2H), 6.99 – 6.86 (m, 3H), 6.80 (t, *J* = 8.0 Hz, 2H), 5.46 (d, *J* = 2.4 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.54 – 4.37 (m, 2H), 4.35 – 4.25 (m, 1H), 2.75 – 2.55 (m, 1H), 2.35 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 207.13, 203.39, 145.83, 139.55, 138.68, 137.99, 135.99, 133.34, 132.88, 132.56, 132.32, 132.16, 131.66, 128.20, 128.04, 127.88, 127.60, 127.54, 127.38, 127.25, 127.12, 127.04, 126.94, 126.00, 125.78, 125.71, 125.42, 125.33, 124.83, 75.42, 56.79, 56.49, 48.21, 46.17, 43.53.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{46}H_{36}O_3Na$, 659.2562 found, 659.2576;

IR (KBr): v_{max} 3410 (OH), 1668 (C=O), 1643 (C=O), 1597, 1342, 1256, 817, 694, 478 cm^{-1}

mp 283.5-284.1 °C



3-3n

(4-hydroxy-4-phenyl-2,6-di(thiophen-2-yl)cyclohexane-1,3-diyl)bis(phenylmethanone)

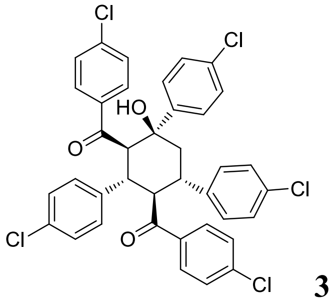
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.31 – 7.24 (m, 2H), 7.20 – 7.01 (m, 7H), 6.93 (d, *J* = 5.2 Hz, 1H), 6.74 (d, *J* = 3.2 Hz, 1H), 6.69 – 6.60 (m, 3H), 6.38 (dd, *J* = 4.8, 3.6 Hz, 1H), 5.28 (d, *J* = 2.4 Hz, 1H), 4.55 (t, *J* = 11.2 Hz, 1H), 4.47 – 4.33 (m, 2H), 4.13 (t, *J* = 11.2 Hz, 1H), 2.53 – 2.43 (m, 1H), 2.39 (dd, *J* = 14.0, 4.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.65, 203.07, 145.46, 145.14, 142.02, 138.59, 137.79, 132.90, 132.14, 128.19, 127.88, 127.72, 127.68, 127.62, 127.11, 126.96, 126.53, 126.23, 125.52, 124.79, 123.88, 123.23, 75.20, 58.89, 57.67, 46.86, 43.30, 39.00.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{34}H_{28}O_3NaS_2$, 571.1378 found, 571.1375;

IR (KBr): v_{max} 3371 (OH), 1666 (C=O), 1635 (C=O), 1589, 1342, 1249, 694, 524 cm^{-1}

mp 260.1-260.4 °C



3-3o

(2,4,6-tris(4-chlorophenyl)-4-hydroxycyclohexane-1,3-diyl)bis((4-chlorophenyl)methanone)

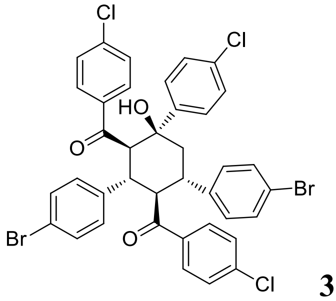
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.8 Hz, 2H), 7.26 – 7.13 (m, 8H), 7.13 – 6.97 (m, 8H), 6.87 (d, J = 8.4 Hz, 2H), 5.26 (d, J = 2.0 Hz, 1H), 4.33 (d, J = 11.2 Hz, 1H), 4.18 – 3.93 (m, 3H), 2.42 – 2.31 (m, 1H), 2.18 (dd, J = 14.0, 3.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.87, 201.34, 143.91, 140.15, 139.91, 139.08, 136.73, 136.46, 135.67, 133.24, 133.20, 132.80, 129.11, 129.03, 128.72, 128.55, 128.50, 128.49, 128.32, 126.13, 74.97, 56.19, 56.06, 47.28, 45.54, 42.67.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{38}H_{27}O_3NaCl_5$, 729.0301 found, 729.0262;

IR (KBr): v_{max} 3487 (OH), 1666 (C=O), 1635 (C=O), 1589, 1489, 1095, 825, 732, 532 cm^{-1}

mp 259.6-261.2 °C



3-3p

(2,6-bis(4-bromophenyl)-4-(4-chlorophenyl)-4-hydroxycyclohexane-1,3-diyl)bis((4-chlorophenyl)methanone)

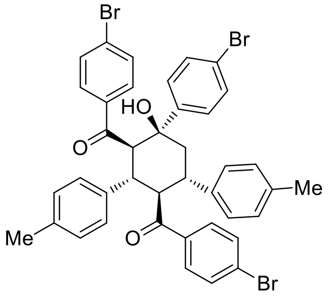
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2H), 7.26 – 7.14 (m, 8H), 7.12 – 7.06 (m, 6H), 7.04 – 6.93 (m, 4H), 5.25 (d, *J* = 2.4 Hz, 1H), 4.32 (d, *J* = 11.2 Hz, 1H), 4.17 – 3.91 (m, 3H), 2.41 – 2.29 (m, 1H), 2.18 (dd, *J* = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.85, 201.30, 143.87, 140.41, 140.15, 139.10, 137.23, 136.44, 135.67, 133.24, 131.66, 131.50, 129.46, 129.03, 128.72, 128.50, 128.48, 128.33, 126.12, 121.32, 120.87, 74.94, 56.06, 56.02, 47.33, 45.47, 42.73.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{38}H_{28}Br_2Cl_3O_3$, 794.9471 found, 794.9457;

IR (KBr): ν_{max} 3441 (OH), 1666 (C=O), 1643 (C=O), 1589, 1489, 1087, 817, 532 cm^{-1}

mp 257.5-259.1 °C



3-3q

(4-(4-bromophenyl)-4-hydroxy-2,6-di-p-tolylcyclohexane-1,3-diyl)bis((4-bromophenyl)methanone)

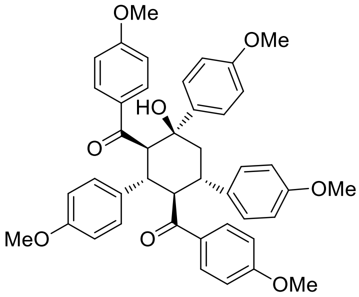
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H)，7.25 – 7.07 (m, 10H), 6.97 (d, *J* = 7.2 Hz, 2H), 6.90 (d, *J* = 7.6 Hz, 2H), 6.67 (d, *J* = 8.0 Hz, 2H), 5.30 (d, *J* = 2.4 Hz, 1H), 4.37 – 4.27 (m, 1H), 4.13 – 4.02 (m, 2H), 3.99 – 3.89 (m, 1H), 2.41 – 2.31 (m, 1H), 2.20 – 2.10 (m, 4H), 1.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.86, 202.49, 145.02, 138.56, 137.52, 136.93, 136.52, 136.48, 135.14, 131.33, 131.18, 130.86, 129.18, 129.16, 128.97, 128.33, 127.64, 126.90, 126.59, 121.12, 75.17, 56.71, 56.50, 47.48, 45.83, 42.84, 20.86, 20.72.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{40}H_{34}Br_3O_3$, 801.0038 found, 801.0092;

IR (KBr): ν_{max} 3448 (OH), 1666 (C=O), 1643 (C=O), 1581, 1396, 1072, 810 cm^{-1}

mp 282.2-282.8 °C



3-3r

(4-hydroxy-2,4,6-tris(4-methoxyphenyl)cyclohexane-1,3-diyl)bis((4-methoxyphenyl)methanone)

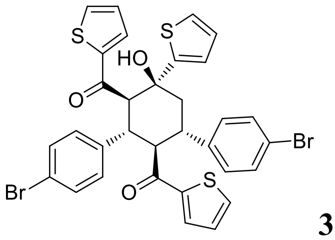
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 9.2 Hz, 4H), 7.17 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 7.2 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 6.54 (d, J = 8.8 Hz, 4H), 6.37 (d, J = 8.8 Hz, 2H), 5.52 (d, J = 2.0 Hz, 1H), 4.40 – 4.30 (m, 1H), 4.18 – 4.03 (m, 2H), 4.03 – 3.90 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 3.62 (s, 3H), 3.47 (s, 3H), 2.46 – 2.33 (m, 1H), 2.16 (dd, J = 14.0, 3.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 205.17, 201.80, 163.19, 162.42, 158.21, 158.01, 157.95, 138.51, 134.61, 131.87, 131.20, 130.97, 130.36, 129.88, 128.80, 125.93, 113.65, 113.36, 112.95, 112.80, 75.06, 56.10, 55.24, 55.16, 55.09, 55.06, 54.91, 47.16, 46.55, 42.48.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{43}H_{42}O_8Na$, 709.2777 found, 709.2783;

IR (KBr): ν_{max} 3387 (OH), 1658 (C=O), 1604 (C=O), 1512, 1257, 1172, 1033, 833, 547 cm^{-1}

mp 247.8-248.8 ^{o}C



3-3s

(2,6-bis(4-bromophenyl)-4-hydroxy-4-(thiophen-2-yl)cyclohexane-1,3-diyl)bis(thiophen-2-ylmethanone)

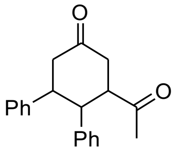
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, *J* = 4.4 Hz, 1H), 7.36 (d, *J* = 4.8 Hz, 1H), 7.31 (d, *J* = 3.3 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.20 – 7.01 (m, 8H), 6.98 – 6.94 (m, 1H), 6.88 – 6.73 (m, 3H), 5.61 (s, 1H), 4.22 – 4.06 (m, 2H), 4.05 – 3.75 (m, 2H), 2.48 – 2.26 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 196.92, 193.60, 151.08, 144.43, 140.48, 137.45, 135.48, 134.03, 133.39, 131.72, 131.52, 131.39, 129.58, 127.77, 127.58, 126.82, 124.05, 122.98, 121.06, 120.70, 74.51, 59.48, 57.95, 47.16, 46.81, 42.44.

HRMS: (ESI) [M+Na]$^+$ calcd. for $C_{32}H_{24}O_3NaS_3Br_2$, 732.9152 found, 732.9152;

IR (KBr): ν_{max} 3433 (OH), 1643 (C=O), 1604 (C=O), 1411, 1257, 1072, 817, 709, 532 cm^{-1}

mp 251.3-252.6 ^{o}C



3-2t

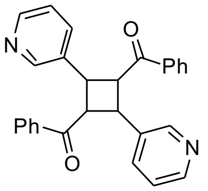
3-acetyl-4,5-diphenylcyclohexanone

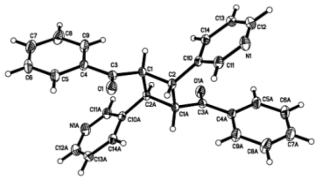
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 8H), 7.04 (d, J = 7.2 Hz, 2H), 3.62 (q, J = 6.4 Hz, 1H), 3.85 – 3.51 (m, 1H), 3.44 (t, J = 6.0 Hz, 1H), 3.20 (dd, J = 15.2, 10.0 Hz, 1H), 3.02 (dd, J = 15.6, 6.0 Hz, 1H), 2.78 – 2.64(m, 2H), 1.63 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.89, 210.68, 143.08, 140.16, 128.98, 128.75, 127.66, 127.36, 127.22, 127.08, 58.74, 44.20, 42.89, 41.13, 40.95, 31.96.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{20}H_{21}O_2$, 293.1542 found, 293.1541;

IR (film): ν_{max} 1707 (C=O), 1454, 700 cm^{-1}





3-3u

(2,4-di(pyridin-3-yl)cyclobutane-1,3-diyl)bis(phenylmethanone)

^{1}H NMR (400 MHz, DMSO) δ 8.49 (s, 1H), 8.22 (s, 1H), 7.85 – 7.72 (m, 3H), 7.51 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.14 (dd, J = 7.6, 4.8 Hz, 1H), 5.07 (dd, J = 10.0, 6.4Hz, 1H), 5.01 – 4.93 (m, 1H).

^{13}C NMR (100 MHz, DMSO) δ 198.52, 150.05, 148.24, 136.31, 135.83, 134.98, 133.74, 128.94, 128.65, 123.37, 49.17, 39.45.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{28}H_{23}N_2O_2$, 419.1760 found, 419.1761;

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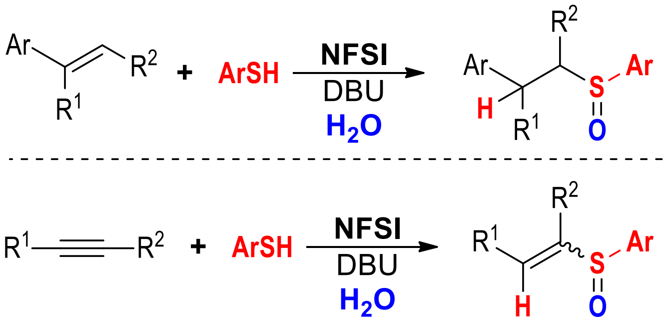
Chapter 4

Sulfoxidation of Alkenes and Alkynes with NFSI as a Radical Initiator and Selective Oxidant

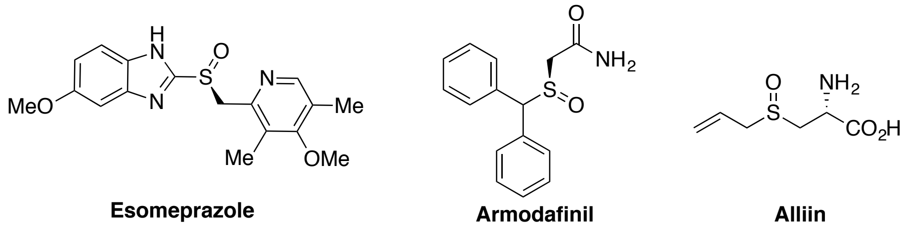


- *radical pathway*
- *metal-free*
- *one-pot reaction*
- *no over-oxidation*

4.1 Introduction

The sulfoxide moiety is an important functional group found in many drugs and natural compounds such as Esomeprazole,[1] Armodafinil,[2] and Alliin (Figure 4.1a).[3] In addition, sulfoxides are also utilized as ligands for catalysis or served as crucial structural motifs for transformations of compounds through reactions such as the Pummerer[4] and Mislow-Evans rearrangements.[5] The most widely used approach to synthesis of sulfoxides is oxidation of sulfides using oxidants such as peroxides[6] and hypervalent iodine compounds,[7] often together with transition metal catalysts (Figure 4.1b).[8] One common concern with the oxidation approach is over-oxidation of sulfides to sulfones, and the development of a regioselective, efficient and one-pot approach to synthesize sulfoxides employing simple and readily available starting materials is still in demand.

(a) Biologically active scaffolds containing sulfoxide



(b) Previous routes for the synthesis of sulfoxides from alkenes/alkynes

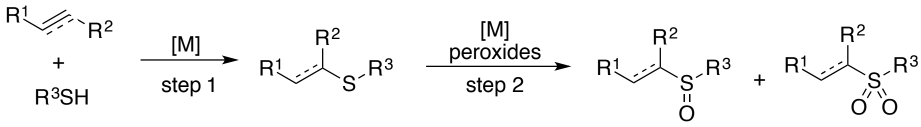
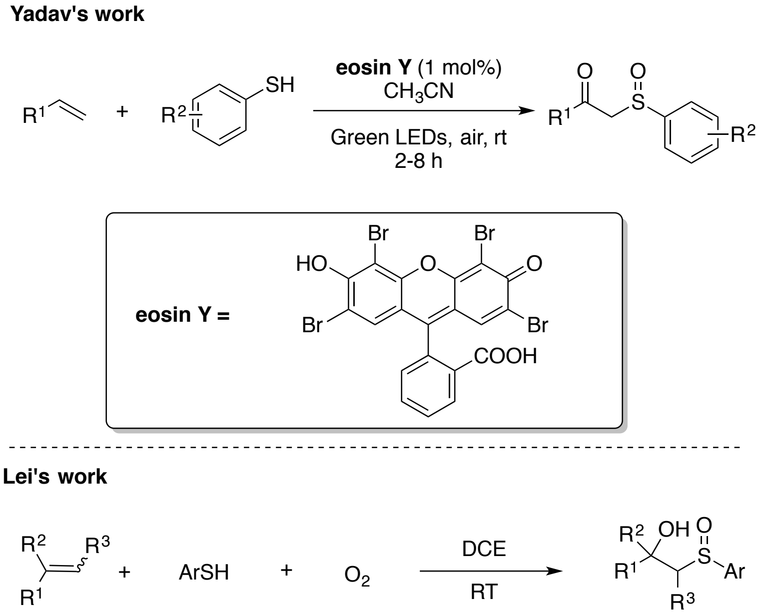
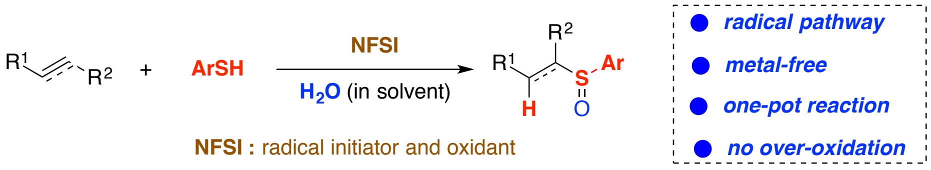


Figure 4.1. (a) Medicinally relevant sulfoxides. (b) Previous two-step pathway to synthesis of sulfoxides from alkenes/alkynes.

Recently, Yadav[9] and Lei[10] independently demonstrated strategies for preparing β-ketosulfoxides and β-Oxy sulfoxides via radical redox reactions of thiols and alkenes in the presence of dioxygen, where dioxygen is not only served as oxidant but also as oxygen source (Scheme 4.1). Herein we report a facile one-pot cascade synthesis of sulfoxides from alkenes and alkynes with thiols. The process is transition metal-free with no over-oxidation occurring. In this work, N-fluorobenzenesulfonimide (NFSI) acts both as radical initiator and oxidant, which is transformed into sodium complex and amine by the end of the reaction (Scheme 4.2). NFSI is an inexpensive shelf-stable reagent,[11] often employed as electrophilic fluorinating agent,[12] aminating reagent,[13] or a combined amino and fluorine source.[14]



Scheme 4.1 Yadav and Lei's work



Scheme 4.2 Our NFSI-enabled selective one-pot access to sulfoxides

Widely used in single-electron transfer (SET) reactions, NFSI has been employed for efficient generation of aminyl radical for Cu-catalyzed radical amination of olefins as reported by Kanai,[15] Zhang[16] and Studer.[17] Zhang and co-workers also developed the radical aminofluorination of styrenes using NFSI.[18] Ritter disclosed Pd-catalyzed direct radical arene amination with NFSI in 2013,[19] while recently, Studer disclosed radical aminooxygenation of alkenes with NFSI in combination with TEMPONa.[20]

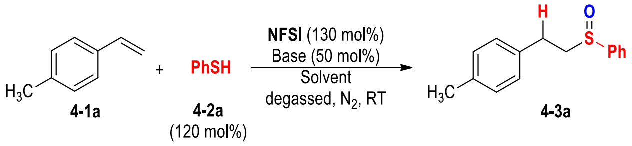
I have focused my PhD research topic on N-heterocyclic carbene-engaged single–electron transfer (SET) reactions. After finishing my previous two parts of work (chapter 2 and chapter 3), I wondered if I can develop more. Hydroamination of alkenes has been an active research area, and the hydroamination of alkene via a radical process has not been well developed. So I hypothesized that the combination of NHC and alkali metal tert-butoxides can initiate the NFSI to produce aminyl radical, which adds to the C-C double bond of alkenes in the presence of hydrogen atom donor to afford the hydroamination products. Then I tried the reaction using 4-methyl styrene and NFSI as starting materials, with thiol as the hydrogen atom donor in the presence of 10 mol% NHC and 50 mol% KO*t*Bu in toluene. Unfortunately, we didn't observe any formation of hydroamination product, instead sulfoxide was isolated in excellent yield (around 90% yield). We then studied the formation of sulfoxide and found that both thiol and NFSI act essential roles in the reaction; the reaction can't proceed without either thiol or NFSI. Further study revealed that the reaction can occur only in the presence of base without NHC. After getting these preliminary results, we turned our attention to the sulfoxidation reactions of alkenes.

4.2 Results and discussion

4.2.1 Condition optimization

The results of condition optimization are summarized in table 4.1. Under an inert atmosphere and in the presence of 50 mol % base K_2CO_3 or K_3PO_4, **4-1a** reacted with thiol **4-2a** in the presence of NFSI to generate the product **4-3a** in low yield (11% yield, entry 1). Strong inorganic bases such as KOMe and NaO*t*Bu gave encouraging yields (23% yield for KOMe and 29% yield for NaO*t*Bu, entries 2,3). After screening a variety of organic bases (entries 4-6), DBU was found to most effectively promote the reaction (72% yield, entry 6). Further investigation revealed that varying the concentration of DBU led to lower yields (entries 7-8). Solvent substitution was then carried out, and compared with other solvents toluene was found most suitable for the reaction (entries 6, 9-12). Subsequently, we discovered that the yield of **4-3a** improved to 87% after increasing the loading of both thiol **4-2a** and NFSI (entry 13).

Table 4.1. Screening of reaction conditions for the reaction of **4-1a** with 4-**2a** in the presence of NFSI[a]



Entry	Base	Solvent	Yield [%][b]
1	K_2CO_3 or K_3PO_4	toluene	11
2	KOMe	toluene	23
3	NaO*t*Bu	toluene	29
4	DIEA	toluene	43
5	DABCO	toluene	66
6	DBU	toluene	72

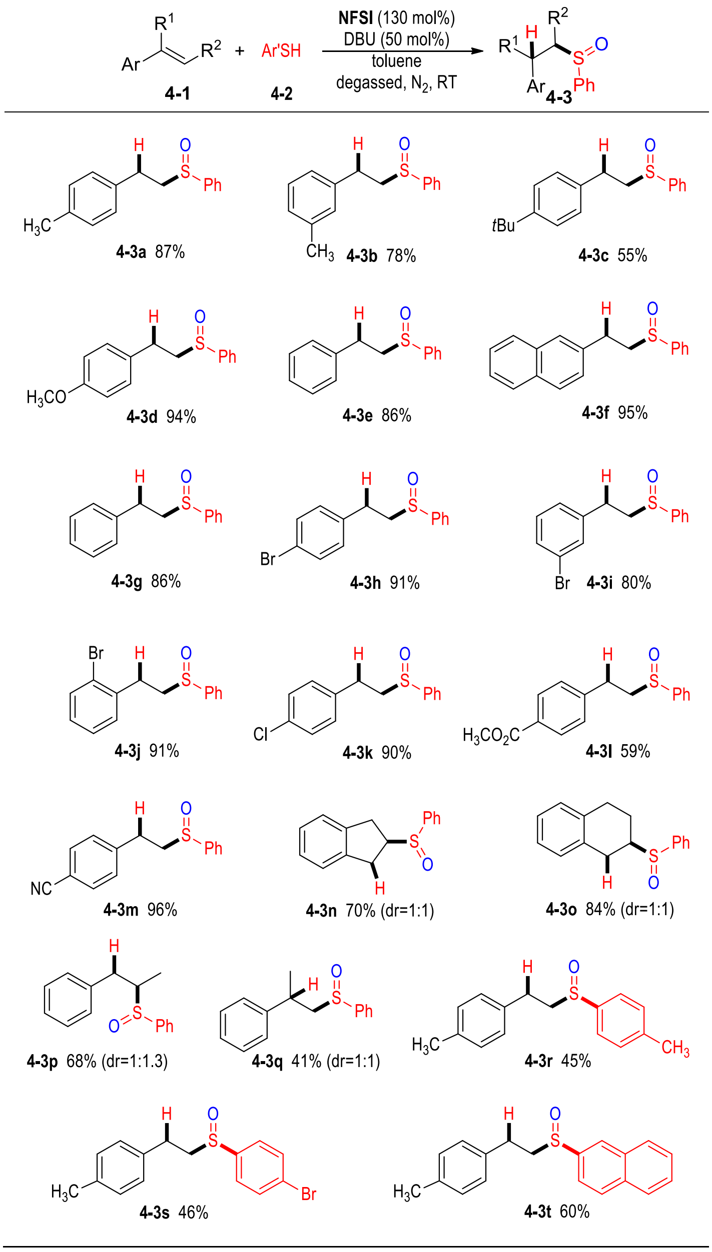
7	DBU (100 mol%)	toluene	35
8	DBU (30 mol%)	toluene	53
9	DBU	THF	52
10	DBU	dioxane	31
11	DBU	CH_3CN	26
12	DBU	EA	48
13[c]	DBU	toluene	87

[a] Conditions: **4-1a** (0.2 mmol, 1.0 equiv.), **4-2a** (0.24 mmol, 1.2 equiv.), NFSI (130 mol%) and base (50 mol%) in 3.0 mL of solvent at rt for 2~5 h; [b] Isolated yield based on **4-1a**. [c] **4-2a** (0.4 mmol, 2.0 equiv.), NFSI (0.36 mmol, 1.8 equiv.).

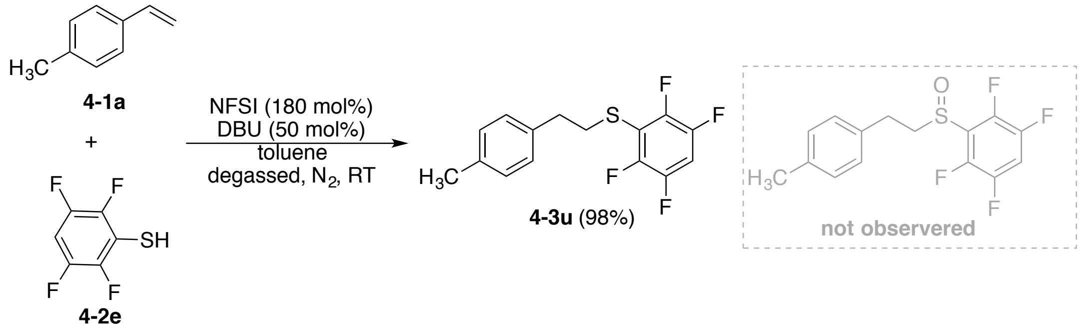
4.2.2 Substrate scope

With optimized reaction conditions in hand we turned to exploring the scope of the reaction, beginning with alkenes (Table 4.2) and thiol **4-2a**. A range of styrenes bearing either electron-donating or electron-withdrawing substituents (**4-1b** to **4-1m**) afforded the desired sulfoxides in moderate to excellent yields, while 2-vinyl naphthalene (**4-1f**) was also converted in high yield. Non-terminal alkenes also reacted well, with the internal alkenes indene (**4-1n**) and 1,2-dihydronaphthalene (**4-1o**) forming the desired products in good yield as did the di-substituted styrenes *trans*-β-methylstyrene (**4-1p**) and α-methylstyrene (**4-1q**). However, for simple aliphatic alkenes, no desired products were formed. In addition, with the use of model substrate **4-1a** the reaction also tolerated the use of other (aromatic) thiols (**4-2r** to **4-2t**), but with decreased yields whether comparatively electron-rich or -poor thiols were utilized. However, when the electron-deficient aryl thiol **4-2e** was used, no desired sulfoxide was isolated, instead sulfide **4-3u** was isolated in 98% yield. This might be due to the electron-deficient sulfide not being easy to oxidize (Scheme 4.3).

Table 4.2. Substrate scope for reactions of alkenes with thiols in the presence of NFSI.[a]

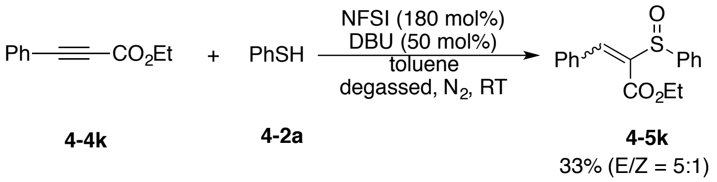


[a] Conditions as in Table 4.1, entry 6; yields (after SiO$_2$ chromatography purification) were based on olefin **4-1**.



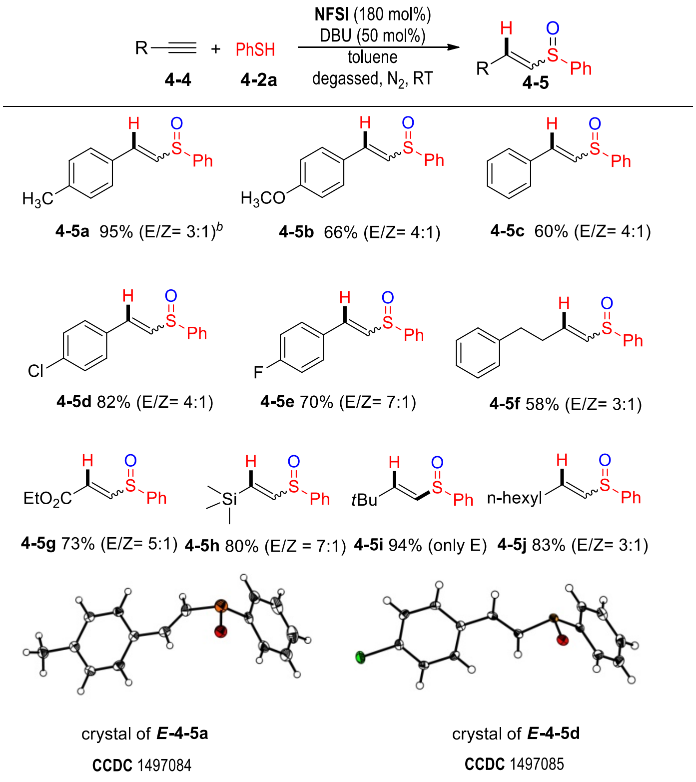
Scheme 4.3 The reaction of electron-deficient aryl thiol **4-2e** with alkene **4-1a**

Subsequently, we examined the use of alkynes as substrates (Table 4.3). These alkynes reacted under the standard conditions with thiol **4-2a** to produce vinyl sulfoxides, with the formation of the *E*-product unsurprisingly dominating. Notably, no products deriving from double thiolation of the alkyne were observed. The reaction proceeded smoothly for aryl alkynes with either electron-withdrawing or electron-donating substituents present on the aromatic ring (**4-4a** to **4-4e**) to afford the desired products in moderate to excellent yields. Other alkynes ranging from alkyl alkynes (**4-4f**, **4-4i** to **4-4j**) to alkynes bearing an ester (**4-4g**) or silyl (**4-4h**) moiety were also converted to give vinylsulfoxides in good yields. The structures of two vinylsulfoxide products (***E*-4-5a**, ***E*-4-5d**) were unambiguously assigned via X-ray crystallography (Table 4.3). Internal alkyne was also tolerated but with low activity, for example, when alkyne **4-4k** was used as the substrate, product **4-5k** was isolated in 33% yield (Scheme 4.4).



Scheme 4.4 The reaction of internal alkyne **4-4k** with **4-2a**

Table 4.3. Substrate scope for reactions of alkynes with thiols in the presence of NFSI[a]



4-5a 95% (E/Z= 3:1)[b]
4-5b 66% (E/Z= 4:1)
4-5c 60% (E/Z= 4:1)
4-5d 82% (E/Z= 4:1)
4-5e 70% (E/Z= 7:1)
4-5f 58% (E/Z= 3:1)
4-5g 73% (E/Z= 5:1)
4-5h 80% (E/Z = 7:1)
4-5i 94% (only E)
4-5j 83% (E/Z= 3:1)

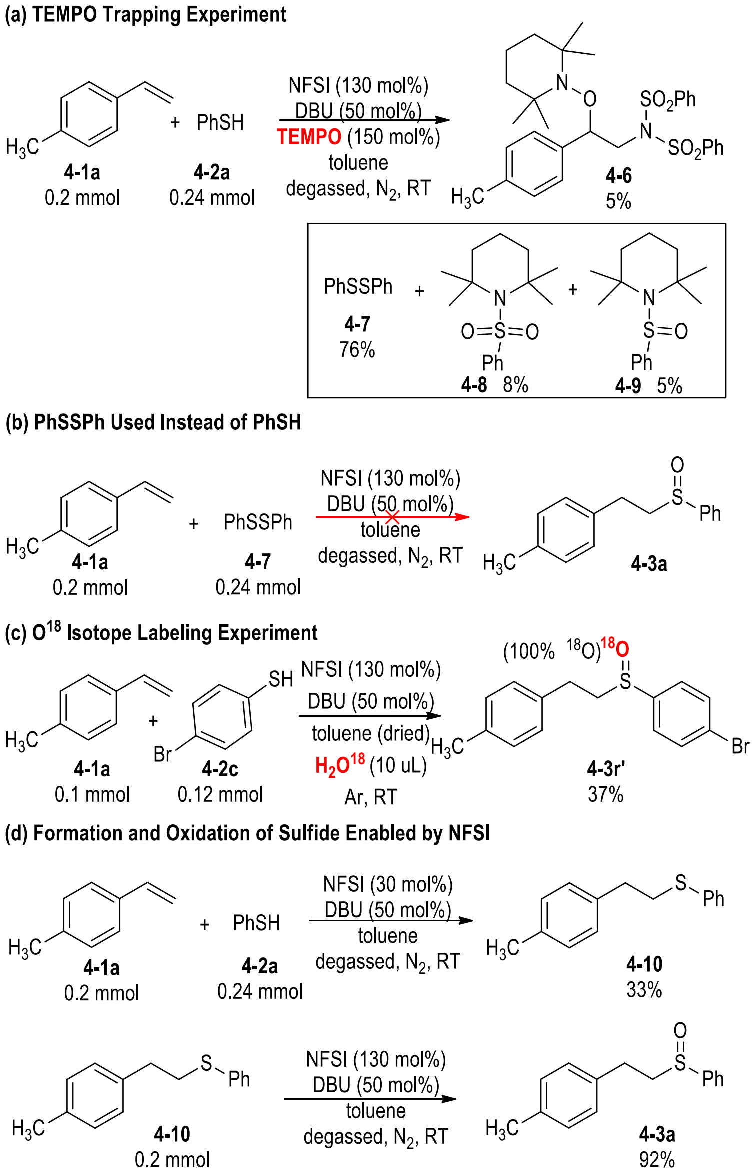
crystal of ***E*-4-5a**
CCDC 1497084

crystal of ***E*-4-5d**
CCDC 1497085

[a] Alkyne (0.2 mmol), **4-2a** (0.4 mmol), NFSI (0.36 mmol) and DBU (50 mol%), in toluene (3 mL) at rt for 16h; yields (after SiO_2 chromatography purification) were based on alkynes; [b] The ratio of E/Z was determined by the weight of isolated E and Z products.

4.3 Mechanistic study

Following this, we performed several studies to gain mechanistic insights into the reaction (Scheme 4.5). 1.5 equivalents of TEMPO were added under standard conditions to trap radical intermediates. However, the reaction was inhibited but none of the desired intermediates were trapped. Instead, other products were obtained (Scheme 4.5a). Product **4-6** had been previously described by Studer in his study on aminooxygenation of alkenes[20] wherein NFSI is reduced to yield an aminyl radical which adds with TEMPO across the alkene. Products **4-7**, **4-8**, and **4-9** (with 89% total yield with respect to the thiol **4-2a**) were previously isolated by Greci and co-workers in a study on the reaction between **4-2a** and TEMPO.[21] The mechanism proposed by Greci for the formation of these products involves TEMPO abstracting a hydrogen radical from thiol **4-2a** to form a thiyl radical, which can dimerize to form disulfide **4-7** or react further with TEMPO to form **4-8** and **4-9**.

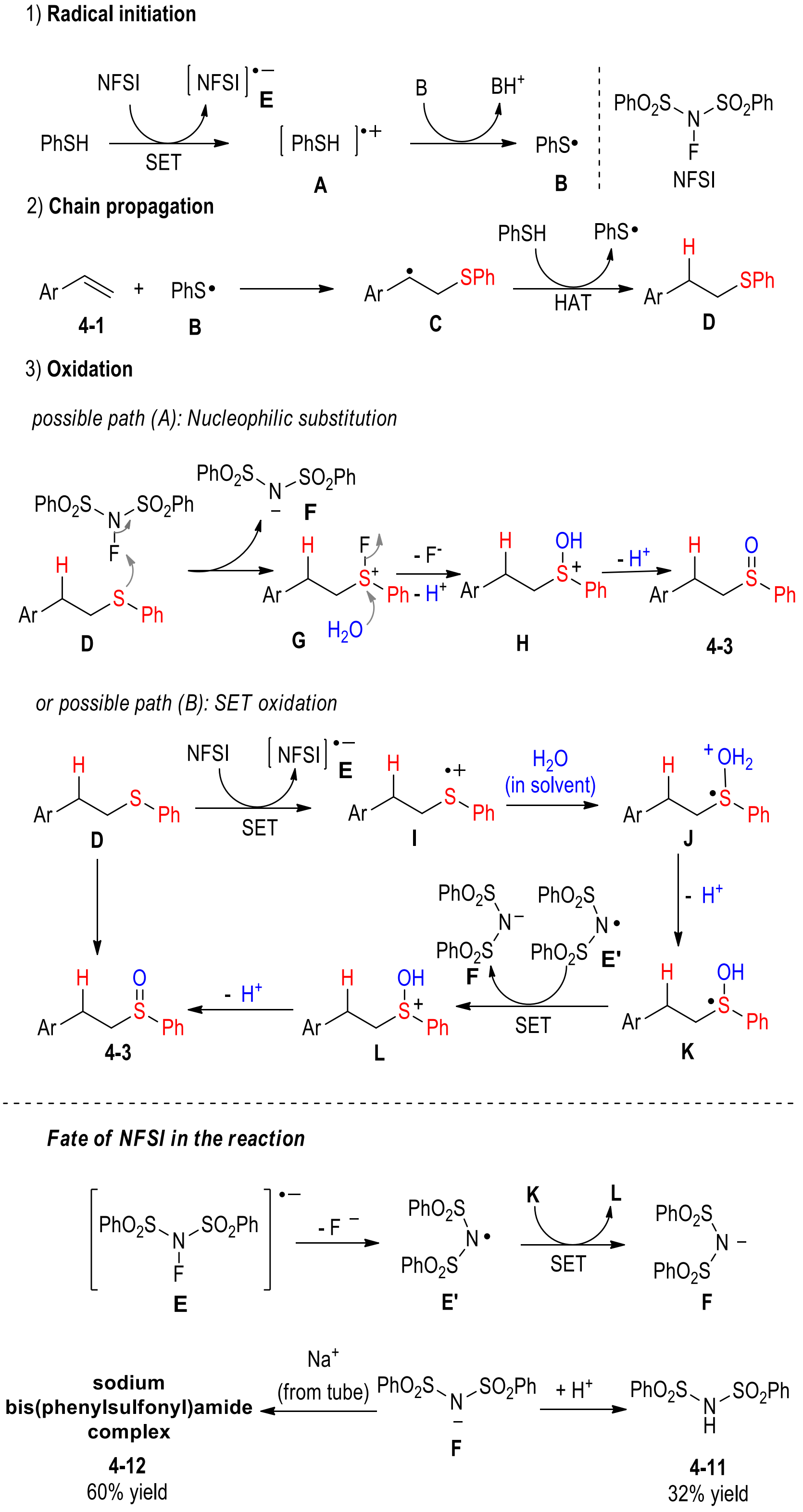


Scheme 4.5 Experiments to probe mechanism.

Another study used diphenyl disulfide in place of thiophenol, but no formation of **4-3a** was detected (Scheme 4.5b). In addition, an ^{18}O isotope labelling experiment was conducted with ^{18}O labelled water (Scheme 4.5c), where ^{18}O labelled sulfoxide was obtained in 37% yield, with no ^{16}O product formation. This establishes that the source of oxygen for sulfoxide formation is trace water in the solvent. Further experiments were conducted to investigate the reaction pathway, varying standard conditions to employ 0.3 equivalents of NFSI resulted in 33% formation of the sulfide **4-10**. Subsequent reaction of **4-10** with 1.3 equivalents of NFSI gave the desired sulfoxide **4-3a** in near quantitative yield (Scheme 4.5d). These experiments form strong evidence for our proposal that NFSI initiates a thiol-ene reaction between styrene **4-1a** and thiol **4-2a**, and that it also efficiently oxidizes the sulfide formed **4-10** to the sulfoxide **4-3a**.

Based on the above mechanistic investigations, we propose the following mechanistic pathway (Scheme 4.6): The reaction is initiated by NFSI, which oxidizes thiol **4-2a** to form radical cation **A**. **A** is then deprotonated by base to provide the thiyl radical **B**.[22] In the chain propagation step, **B** adds to the alkene **4-1** to give carbon-centered radical **C** which abstracts a hydrogen radical from thiol **4-2a** to regenerate another molecule of **B** and afford the sulfide intermediate **D**.[22,23] The NFSI radical anion **E** produced through SET reduction of NFSI expels a fluoride anion to give an aminyl radical **E'**,[20] which is reduced to the sulfonamide anion **F** through a second SET reduction. **F** was isolated as its sodium bis(phenylsulfonyl)amide complex **4-12** and in amine form **4-11** (as determined by X-Ray crystallography, CCDC 1497082 (for **4-12**) and CCDC 1497086 (for 4-**11**)).

Next, sulfide intermediate **D** is oxidized, with two plausible oxidation pathways. Path A is a nucleophilic substitution pathway, an attack by **D** at the electrophilic fluorine of NFSI followed by substitution of the activated sulfide by water to afford intermediate **G**, which was transformed into sulfoxide **4-3** via proton transfer process. Path B is a SET pathway involving a one-electron oxidation of the sulfide **D** by NFSI followed by attack of water at the sulfur radical cation **I** to generate intermediate **J**. Deprotonation of **J** followed by another SET to **E’** yields cation **L**, which forms the desired sulfoxide **4-3** product after deprotonation.



Scheme 4.6 Proposed reaction pathway

In the literature, the mechanism of such reactions involving nucleophiles with electrophilic-fluorine N-F compounds has been debated, with evidence suggesting that either the radical or the substitution pathway is in play depending on the nucleophile and electrophile used.[24] Finding no conclusive evidence in the literature for reactions involving NFSI,[25] we performed cyclic voltammetric experiments to adjudicate between the two possibilities. NFSI has reduction potentials at -0.84, -2.11 V vs. Fc/Fc^+ in CH_3CN (Figure 4.2, and sulfide **4-10** has oxidation potentials at +1.02, +1.44 V vs. Fc/Fc^+ in CH_3CN (Figure 4.3). It indicated that oxidation of sulfide **4-10** to corresponding sulfoxide *via* a SET process by NFSI is possible. However, it must be noted that both pathways of oxidation (path A and path B) may exist in real reactions.

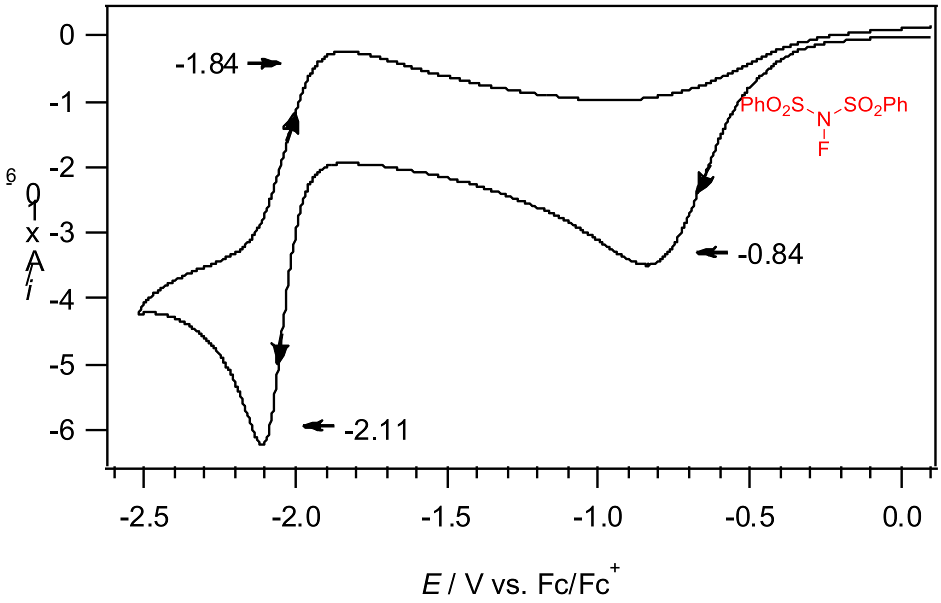


Figure 4.2 Cyclic voltammograms of 2 mM NFSI in CH_3CN containing 0.2 M n-Bu_4NPF_6, recorded using a 1-mm diameter planar GC disk electrode and at a scan rate of 0.1 V/s.

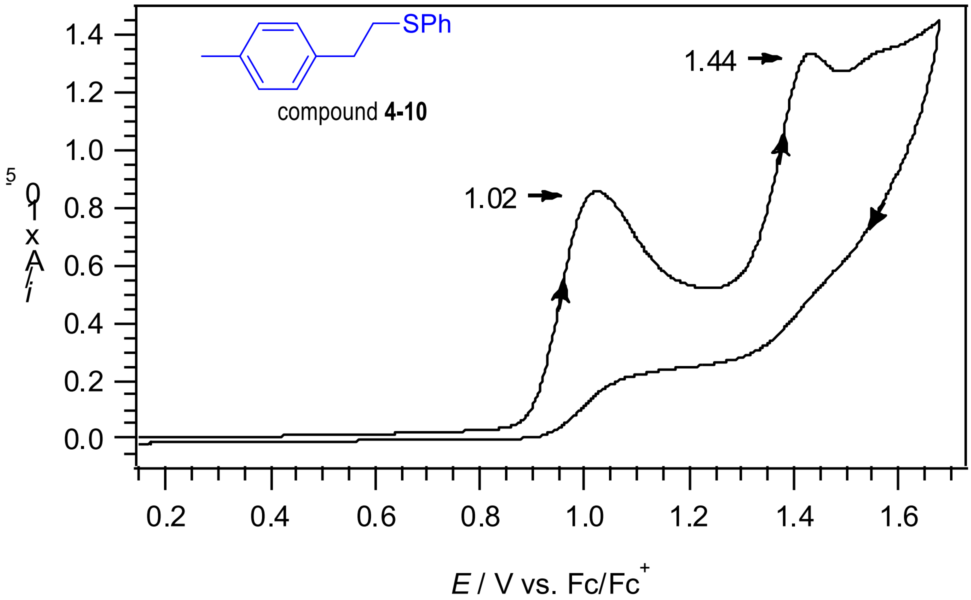


Figure 4.3 Cyclic voltammograms of 2 mM compound **4-10** in CH_3CN containing 0.2 M n-Bu_4NPF_6, recorded using a 1-mm diameter planar GC disk electrode and at a scan rate of 0.1 V/s.

4.4 Summary

In summary, we have developed a facile synthesis of sulfoxides from alkenes and alkynes in the presence of NFSI. Sulfoxides are important structural moieties in natural products and synthetic functional molecules. Our approach provides a metal-free and concise synthesis of this class of molecules without using metal catalysts or reagents. Mechanism studies were conducted, demonstrating that NFSI plays the dual role of initiating the radical thiol-ene/-yne reaction and efficiently oxidizing the sulfides formed *in situ*. The oxygen atom in the sulfoxide products comes from trace water in the reaction mixture; this provides a simple way for the incorporation of ^{18}O isotope. We expect this work to contribute to empirical understanding of radical reactions for further development of useful syntheses.

4.5 Experimental section

4.5.1 General information

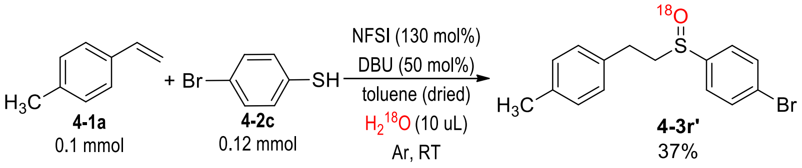
Commercially available materials purchased from Alfa Aesar, Merck or Aldrich were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV400 (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Waters Q-TOF Premier mass spectrometer. IR spectra were recorded on a Shimadzu IRPrestige-21 FT-IR spectrometer as neat thinfilms between NaCl plates in case of liquids and as KBr pellets in the case of solids. LC-MS were recorded on ThermoFinnigan LCQ Fleet MS. Melting points were measured on SRS Optimelt Automated Point System SRS. MPA100. Flash chromatography was performed using Merck silica gel 60 with distilled solvents. Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

4.5.2 General procedures for synthesis of sulfoxides from alkenes/alkynes and thiols in the presence of NFSI

To a dry Schlenk tube equipped with a magnetic stir bar, was added alkene/alkyne (0.2 mmol), NFSI (114 mg, 1.8 equiv.) and DBU (15 uL, 50 mol%). Toluene (3 mL, used without further purification) was then added, the tube was closed after addition of thiol

(0.4 mmol) at the last. The resulting mixture was degassed (three freeze-pump-thaw cycles) and the reaction tube was refilled with N_2 and stirred at room temperature overnight. The solvent was removed under vacuum and then applied to silica gel chromatography (hexane/ ethyl acetate = 5:1 ~ 2:1) to obtain the sulfoxide.

4.5.2 ^{18}O Isotope labelling experiment



Scheme 4.7 ^{18}O isotope labelling experiment

In an argon-filed glove box, NFSI (41 mg) and **4-2c** (23 mg) were added to a 10-mL dry Schlenk tube, followed by addition of **4-1a** (12 mg), DBU (8 mg) and dry toluene (1.5 mL). 10 uL of H_2O^{18} (97 atom % ^{18}O) was added to the mixture through microsyringe, the resulting mixture was vigorously stirred at room temperature for 5h. The percentage of ^{18}O in product was detected by LC-MS using the reaction mixture without purification. According to the results from LC-MS (see below), no ^{16}O product **4-3r** was formed.

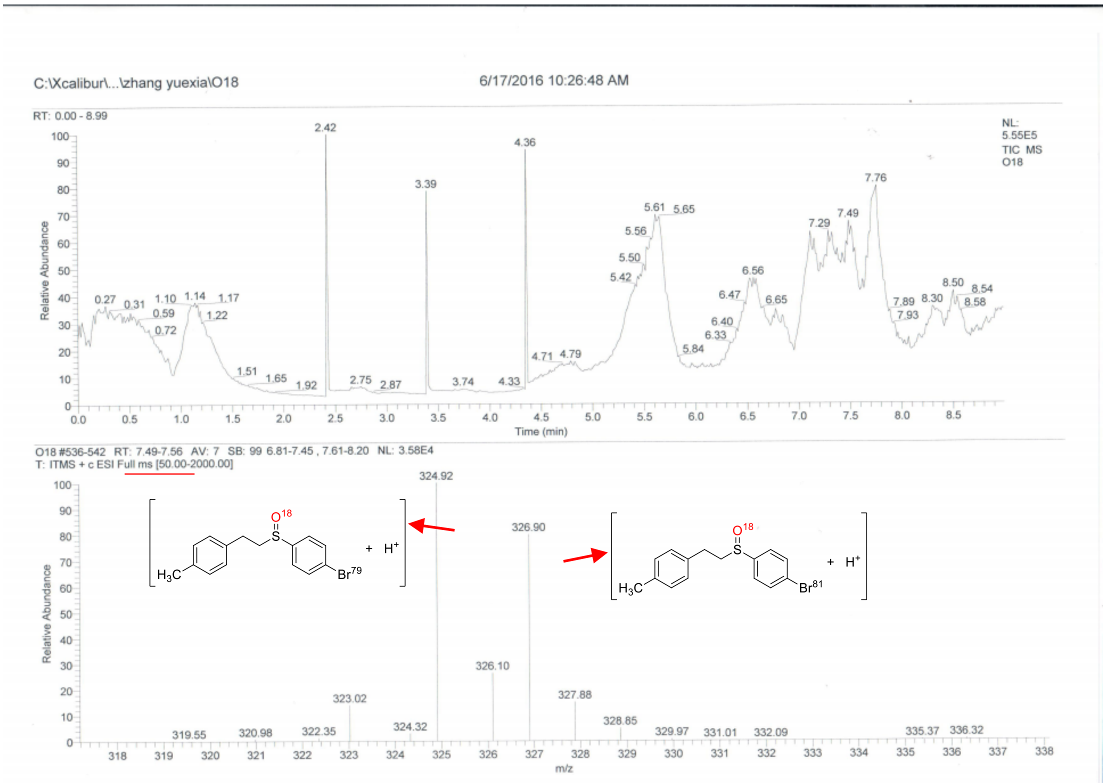


Figure 4.4. LC-MS spectrum of reaction mixture with ^{18}O isotope labelled water.

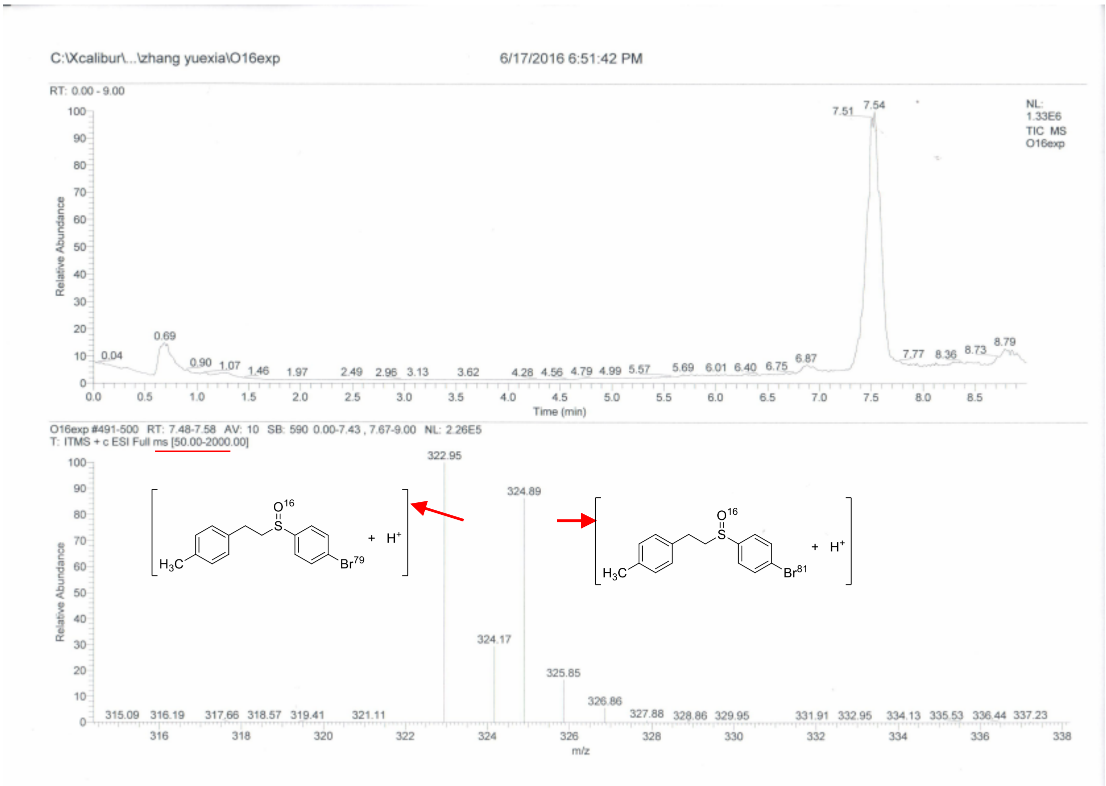
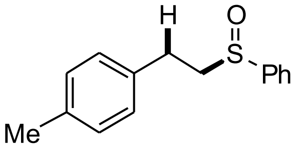


Figure 4.5 LC-MS spectrum of product **4-3r.**

4.5.3 Characterization of products



4-3a

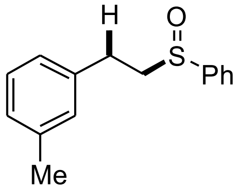
1-methyl-4-(2-(phenylsulfinyl)ethyl)benzene

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 – 7.58 (m, 2H), 7.55 – 7.43 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 3.12 – 2.94 (m, 3H), 2.90 – 2.78 (m, 1H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 143.52, 136.10, 135.47, 130.84, 129.26, 129.11, 128.27, 123.88, 58.31, 27.62, 20.86.

HRMS: (ESI) [M+H]$^+$ calcd. for C$_{15}$H$_{17}$OS, 245.1000 found, 245.1005;

IR (film): $\nu_{\max}$ 3001, 1512, 1442, 1041(S=O), 748, 694 cm^{-1}



4-3b

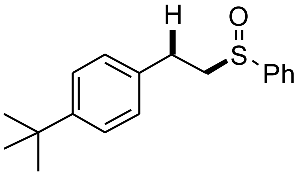
1-methyl-3-(2-(phenylsulfinyl)ethyl)benzene

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70 – 7.59 (m, 2H), 7.58 – 7.45 (m, 3H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 3.14 – 2.96 (m, 3H), 2.93 – 2.78 (m, 1H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 143.71, 138.66, 138.36, 130.95, 129.30, 129.21, 128.59, 127.39, 125.48, 123.99, 58.35, 28.06, 21.30.

HRMS: (ESI) [M+H]$^+$ calcd. for C$_{15}$H$_{17}$OS, 245.1000 found, 245.1001;

IR (film): $\nu_{\max}$ 3055, 1604, 1481, 1087, 1041(S=O), 748, 694, 501 cm^{-1}



4-3c

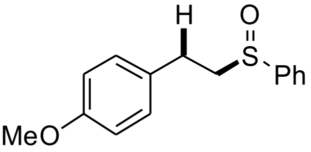
1-(tert-butyl)-4-(2-(phenylsulfinyl)ethyl)benzene

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 2H), 7.57 – 7.43 (m, 3H), 7.35 – 7.27 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 3.12 – 2.96 (m, 3H), 2.94 – 2.80 (m, 1H), 1.29 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.57, 143.73, 135.63, 130.93, 129.20, 128.15, 125.59, 123.98, 58.34, 34.38, 31.29, 27.63.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{18}H_{23}OS$, 287.1470 found, 287.1463;

IR (film): v_{max} 2962, 1512, 1087, 1041(S=O), 748, 694 cm^{-1}



4-3d

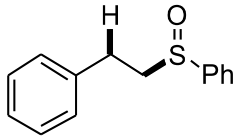
1-methoxy-4-(2-(phenylsulfinyl)ethyl)benzene

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.58 (m, 2H), 7.56 – 7.43 (m, 3H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.88 – 6.77 (m, 2H), 3.77 (s, 3H), 3.11 – 2.94 (m, 3H), 2.92 – 2.76 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.34, 143.71, 130.91, 130.64, 129.48, 129.19, 123.95, 114.10, 58.63, 55.21, 27.33.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{17}O_2S$, 261.0949 found, 261.0950;

IR (film): v_{max} 3001, 1612, 1512, 1442, 1249, 1180, 1041(S=O), 825, 756, 694, 501 cm^{-1}



4-3e

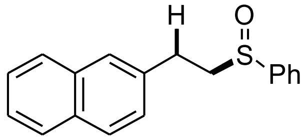
(phenethylsulfinyl)benzene

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 – 7.59 (m, 2H), 7.57 – 7.44 (m, 3H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.24 – 7.12 (m, 3H), 3.16 – 2.97 (m, 3H), 2.96 – 2.80 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 143.58, 138.67, 130.92, 129.18, 128.65, 128.44, 126.60, 123.92, 58.22, 28.09.

HRMS: (ESI) [M+H]$^+$ calcd. for $C_{14}H_{15}OS$, 231.0844 found, 231.0844;

IR (film): ν_{max} 3032, 1496, 1442, 1087, 1041(S=O), 748, 694, 516 cm^{-1}



4-3f

2-(2-(phenylsulfinyl)ethyl)naphthalene

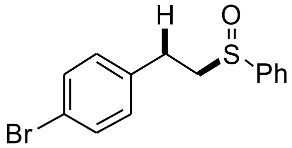
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85 – 7.73 (m, 3H), 7.70 – 7.60 (m, 3H), 7.58 – 7.48 (m, 3H), 7.48 – 7.39 (m, 2H), 7.29 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.33 – 3.21 (m, 1H), 3.21 – 2.98 (m, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 143.58, 136.14, 133.51, 132.22, 131.01, 129.25, 128.42, 127.61, 127.44, 126.96, 126.78, 126.20, 125.64, 124.00, 58.18, 28.27.

HRMS: (ESI) [M+H]$^+$ calcd. for $C_{18}H_{17}OS$, 281.1000 found, 281.1005;

IR (KBr): ν_{max} 3047, 2908, 1435, 1041(S=O), 825, 740, 686, 470 cm^{-1}

mp 66.8-68.2 °C



4-3g

1-bromo-4-(2-(phenylsulfinyl)ethyl)benzene

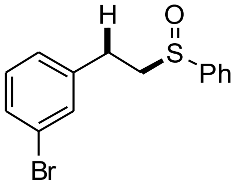
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 2H), 7.57 – 7.47 (m, 3H), 7.45 – 7.36 (m, 2H), 7.12 – 7.00 (m, 2H), 3.16 – 2.93 (m, 3H), 2.92 – 2.75 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.40, 137.68, 131.76, 131.04, 130.24, 129.27, 123.91, 120.51, 57.85, 27.48.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{14}H_{14}OSBr$, 308.9949 found, 308.9954;

IR (KBr): ν_{max} 2916, 1481, 1442, 1041(S=O), 1010, 979, 802, 740, 686, 486 cm^{-1}

mp 63.0-64.7 °C



4-3h

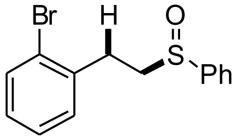
1-bromo-3-(2-(phenylsulfinyl)ethyl)benzene

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 2H), 7.58 – 7.46 (m, 3H), 7.39 – 7.32 (m, 1H), 7.31 (s, 1H), 7.21 – 7.06 (m, 2H), 3.14 – 2.94 (m, 3H), 2.92 – 2.80 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.36, 141.05, 131.53, 131.08, 130.25, 129.82, 129.28, 127.21, 123.94, 122.68, 57.70, 27.63.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{14}H_{14}OSBr$, 308.9949 found, 308.9941;

IR (film): ν_{max} 3055, 3001, 1597, 1566, 1473, 1442, 1087, 1041(S=O), 786, 748, 694, 501 cm^{-1}



4-3i

1-bromo-2-(2-(phenylsulfinyl)ethyl)benzene

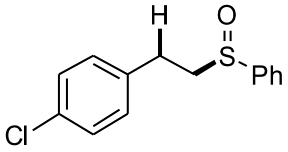
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.61 (m, 2H), 7.58 – 7.46 (m, 4H), 7.27 – 7.20 (m, 2H), 7.12 – 7.03 (m, 1H), 3.24 – 3.07 (m, 2H), 3.05 – 2.94 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.27, 138.06, 132.95, 130.93, 130.79, 129.15, 128.45,

127.74, 124.22, 123.98, 55.76, 28.58.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{14}H_{14}OSBr$, 308.9949 found, 308.9955;

IR (film): v_{max} 3001, 1442, 1219, 1041(S=O), 756, 663 cm^{-1}



4-3j

1-chloro-4-(2-(phenylsulfinyl)ethyl)benzene

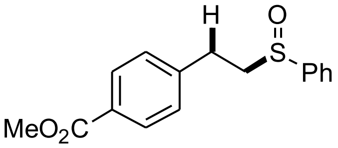
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 2H), 7.56 – 7.47 (m, 3H), 7.27 – 7.22 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 3.14 – 2.94 (m, 3H), 2.91 – 2.80 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.42, 137.16, 132.48, 131.04, 129.86, 129.26, 128.80, 123.91, 57.95, 27.43.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{14}H_{14}OSCl$, 265.0454 found, 265.0455;

IR (KBr): v_{max} 2924, 1489, 1442, 1087, 1041(S=O), 802, 740, 686, 493 cm^{-1}

mp 57.8-59.2 °C



4-3k

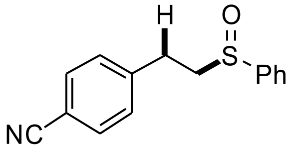
4-(2-(phenylsulfinyl)ethyl)benzoate

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 2H), 7.57 – 7.46 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 3.16 – 2.94 (m, 3H), 2.93 – 2.81 (m, 1H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.44, 149.35, 143.51, 136.27, 131.00, 129.49, 129.25, 123.94, 121.79, 58.06, 27.47, 21.04.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{16}H_{17}O_3S$, 289.0898 found, 289.0894;

IR (film): v_{max} 3001, 1759, 1504, 1365, 1195, 1041(S=O), 910, 748 cm^{-1}



4-3l

4-(2-(phenylsulfinyl)ethyl)benzonitrile

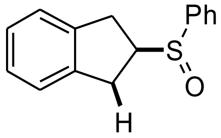
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.49 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 2H), 3.26 – 2.88 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.31, 143.00, 132.42, 131.16, 129.34, 129.31, 123.87, 118.59, 110.61, 57.02, 27.97.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}NOS$, 256.0796 found, 256.0801;

IR (KBr): ν_{max} 3062, 2916, 2222, 1604, 1435, 1172, 1087, 1041(S=O), 987, 817, 748, 686, 547, 486 cm^{-1}

mp 93.0-95.6 °C



4-3m

2-(phenylsulfinyl)-2,3-dihydro-1H-indene

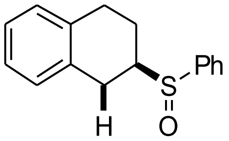
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.65 (m, 2H), 7.58 – 7.45 (m, 3H), 7.22 – 7.08 (m, 4H), 3.72 – 3.61 (m, 1H), 3.54 (dd, *J* = 16.8, 6.8 Hz, 1H), 3.19 (dd, *J* = 16.8, 6.8 Hz, 1H), 3.10 (dd, *J* = 16.8, 8.4 Hz, 1H), 3.01 (dd, *J* = 16.8, 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.10, 140.44, 140.24, 131.22, 129.14, 127.03, 126.87, 124.75, 124.65, 124.32, 63.79, 33.48, 31.80.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{15}OS$, 243.0844 found, 243.0843;

IR (KBr): ν_{max} 3055, 2939, 1481, 1427, 1080, 1033(S=O), 748, 694, 532 cm^{-1}

mp 90.4-92.9 °C



4-3n

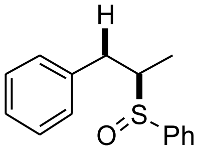
2-(phenylsulfinyl)-1,2,3,4-tetrahydronaphthalene

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 2H), 7.58 – 7.49 (m, 3H), 7.15 – 6.99 (m, 4H), 3.11 (dd, *J* = 16.0, 10.8 Hz, 1H), 3.04 – 2.92 (m, 2H), 2.90 – 2.78 (m, 1H), 2.71 (dd, *J* = 16.0, 4.4 Hz, 1H), 2.28 – 2.17 (m, 1H), 1.91 – 1.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.76, 135.32, 133.97, 131.11, 129.35, 129.07, 128.60, 126.17, 126.12, 124.86, 59.79, 28.63, 26.14, 23.68.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{16}H_{17}OS$, 257.1000 found, 257.0996;

IR (film): ν_{max} 3055, 1489, 1442, 1087, 1041(S=O), 748, 694 cm^{-1}



4-3o

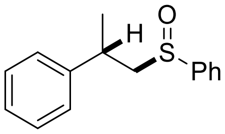
1-phenylpropan-2-yl)sulfinyl)benzene

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.44 (m, 5H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.26 – 7.15 (m, 3H), 3.29 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.95 – 2.82 (m, 1H), 2.60 (dd, *J* = 13.6, 9.2 Hz, 1H), 1.00 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.65, 138.12, 130.77, 129.21, 128.90, 128.64, 126.72, 124.76, 60.90, 36.65, 10.24.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{17}OS$, 245.1000 found, 245.1000;

IR (film): ν_{max} 3055, 1496, 1442, 1087, 1041(S=O), 995, 748, 694, 532, 486 cm^{-1}



4-3p

((2-phenylpropyl)sulfinyl)benzene

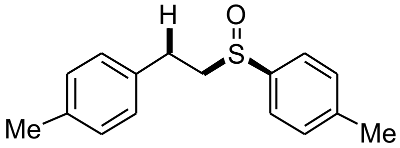
^{1}H NMR (400 MHz, $CDCl_3$) Isomer 1: δ 7.65 – 7.60 (m, 2H), 7.52 – 7.44 (m, 3H), 7.31

– 7.25 (m, 3H), 7.23 – 7.16 (m, 2H), 3.39 – 3.28 (m, 1H), 3.12 (dd, *J* = 12.8, 4.4 Hz, 1H), 2.82 (dd, *J* = 12.8, 10.4 Hz, 1H), 1.54 (d, *J* = 6.8 Hz, 3H); Isomer 2: δ 7.60 – 7.54 (m, 2H), 7.52 – 7.44 (m, 3H), 7.39 – 7.33(m, 2H), 7.31 – 7.25 (m, 1H), 7.23 – 7.16 (m, 2H), 3.48 – 3.39 (m, 1H), 3.07 (dd, *J* = 12.8, 5.6 Hz, 1H), 2.91 (dd, *J* = 12.8, 9.6 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) Isomer 1: δ 144.47, 143.79, 131.03, 129.26, 128.74, 127.17, 126.82, 123.98, 66.64, 34.54, 20.60; Isomer 2: 144.71, 144.24, 130.93, 129.23, 128.85, 127.05, 126.82, 123.83, 67.28, 35.38, 22.24.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{17}OS$, 245.1000 found, 245.1001;

IR (film): v_{max} 2964, 1494, 1442, 1087, 1035(S=O), 748, 700cm^{-1}



4-3q

1-methyl-4-((4-methylphenethyl)sulfinyl)benzene

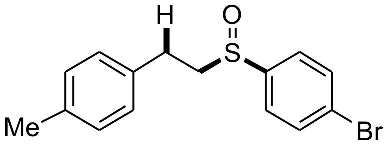
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 3.10 – 2.95 (m, 3H), 2.92 – 2.76 (m, 1H), 2.41 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.42, 140.53, 136.21, 135.75, 129.92, 129.37, 128.38, 124.08, 58.51, 27.77, 21.36, 20.97.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{16}H_{19}OS$, 259.1157 found, 259.1156;

IR (KBr): v_{max} 3016, 2916, 1512, 1450, 1404, 1087, 1041(S=O), 946, 810, 763, 509, 486 cm^{-1}

mp 77.3-78.0 °C



4-3r

1-bromo-4-((4-methylphenethyl)sulfinyl)benzene

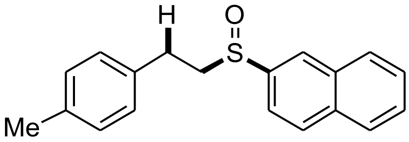
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 2H), 7.52 – 7.47 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 3.12 – 2.94 (m, 3H), 2.91 – 2.76 (m, 1H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.86, 136.38, 135.30, 132.43, 129.42, 128.37, 125.61, 125.38, 58.42, 27.59, 20.98.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{16}BrOS$, 323.0105 found, 323.0101;

IR (KBr): v_{max} 2962, 1512, 1384, 1083, 1045(S=O), 1008, 819, 524, 486 cm^{-1}

mp 67.9 -70.9 °C



4-3s

2-((4-methylphenethyl)sulfinyl)naphthalene

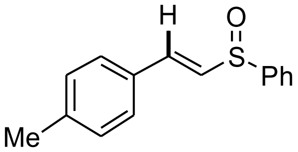
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.99 – 7.86 (m, 3H), 7.61 – 7.54 (m, 3H), 7.11 – 7.02 (m, 4H), 3.21 – 3.02 (m, 3H), 2.93 – 2.79 (m, 1H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.63, 136.21, 135.55, 134.36, 132.83, 129.40, 129.34, 128.43, 128.37, 128.00, 127.69, 127.27, 124.73, 119.76, 58.00, 27.65, 20.94.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{19}H_{19}OS$, 295.1157 found, 295.1156;

IR (KBr): v_{max} 2924, 1512, 1070, 1041(S=O), 908, 815, 742, 528, 472 cm^{-1}

mp 107.8-109.0 °C



***E*-4-5a**

(*E*)-1-methyl-4-(2-(phenylsulfinyl)vinyl)benzene

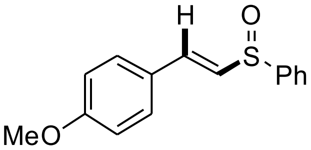
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.63 (m, 2H), 7.57 – 7.43 (m, 3H), 7.40 – 7.30 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 15.6 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.05, 140.19, 136.82, 131.75, 130.97, 130.89, 129.54, 129.33, 127.70, 124.62, 21.30.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{15}OS$, 243.0844 found, 243.0846;

IR (KBr): v_{max} 3016, 2916, 1512, 1442, 1087, 1049(S=O), 972, 794, 740, 686, 501 cm^{-1}

mp 83.8-86.6 °C



***E-4-*5b**

(*E*)-1-methoxy-4-(2-(phenylsulfinyl)vinyl)benzene

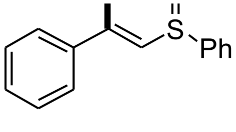
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 2H), 7.58 – 7.45 (m, 3H), 7.44 – 7.36 (m, 2H), 7.32 (d, *J* = 15.6 Hz, 1H), 6.92 – 6.84 (m, 2H), 6.70 (d, *J* = 15.6 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.07, 144.35, 136.95, 130.94, 130.44, 129.38, 129.35, 126.42, 124.65, 114.33, 55.35.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{15}O_2S$, 259.0793 found, 259.0791;

IR (KBr): v_{max} 3001, 2931, 1604, 1512, 1442, 1296, 1257, 1172, 1033(S=O), 964, 802, 748, 686 cm^{-1}

mp 66.3-67.9 °C



***E*-4-5c**

(*E*)-(2-(phenylsulfinyl)vinyl)benzene

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 2H), 7.56 – 7.48 (m, 3H), 7.48 – 7.41 (m, 2H), 7.41 – 7.31 (m, 4H), 6.83 (d, *J* = 15.6 Hz, 1H).

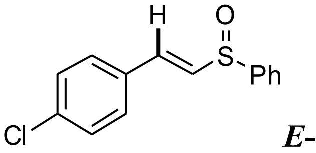
^{13}C NMR (100 MHz, $CDCl_3$) δ 143.90, 136.43, 133.69, 132.93, 131.12, 129.83, 129.42,

128.87, 127.75, 124.69.

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{14}H_{12}OSNa$, 251.0507 found, 251.0508;

IR (KBr): ν_{max} 3016, 1442, 1080, 1041(S=O), 964, 740, 686, 524, 455 cm^{-1}

mp 55.6-57.4 °C



***E*-4-5d**

(*E*)-1-chloro-4-(2-(phenylsulfinyl)vinyl)benzene

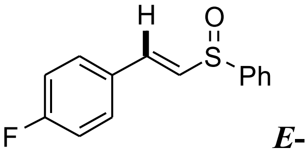
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.62 (m, 2H), 7.58 – 7.46 (m, 3H), 7.42 – 7.28 (m, 5H), 6.82 (d, *J* = 15.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.62, 135.62, 134.61, 133.54, 132.18, 131.22, 129.46, 129.08, 128.89, 124.63.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{14}H_{12}OSCl$, 263.0297 found, 263.0303;

IR (KBr): ν_{max} 3032, 2924, 1489, 1442, 1404, 1087, 1026(S=O), 956, 856, 802, 748, 694, 516 cm^{-1}

mp 95.4-96.6 °C



***E*-4-5e**

(*E*)-1-fluoro-4-(2-(phenylsulfinyl)vinyl)benzene

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 2H), 7.57 – 7.47 (m, 3H), 7.47 – 7.40 (m, 2H), 7.34 (d, *J* = 15.6 Hz, 1H), 7.10 – 7.01 (m, 2H), 6.76 (d, *J* = 15.6 Hz, 1H).

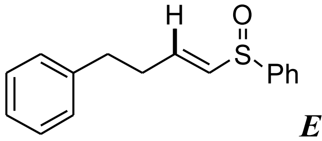
^{13}C NMR (100 MHz, $CDCl_3$) δ 163.56 (d, *J* = 250.9 Hz), 143.87, 135.11, 132.70 (d, *J* = 2.4 Hz), 131.21, 130.00 (d, *J* = 3.4 Hz), 129.62 (d, *J* = 8.5 Hz), 129.49, 124.68, 116.02 (d, *J* = 22.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.20 (d, *J* = 5.3 Hz, 1F).

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{14}H_{12}OSF$, 247.0593 found, 247.0593;

IR (KBr): ν_{max}1597, 1504, 1226, 1157, 1026(S=O), 964, 856, 802, 748, 694, 516, 447 cm^{-1}

mp 53.8-54.3 °C



***E*-4-5f**

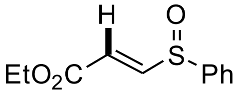
(*E*)-((4-phenylbut-1-en-1-yl)sulfinyl)benzene

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.42 (m, 5H), 7.31 – 7.24 (m, 2H), 7.22 – 7.16 (m, 1H), 7.16 – 7.11 (m, 2H), 6.62 (dt, *J* = 15.2, 6.8 Hz, 1H), 6.21 (dt, *J* = 15.2, 1.2 Hz, 1H), 2.86 – 2.72 (m, 2H), 2.65 – 2.48 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.05, 140.34, 139.79, 135.66, 130.79, 129.23, 128.47, 128.35, 126.19, 124.51, 34.29, 33.54.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{16}H_{17}OS$, 257.1000 found, 257.1001;

IR (film): ν_{max} 3024, 1604, 1496, 1442, 1080, 1041(S=O), 956, 748, 694, 524 cm^{-1}



***E*-4-5g**

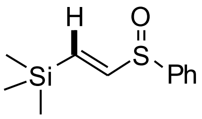
(*E*)-ethyl 3-(phenylsulfinyl)acrylate

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 2H), 7.58 – 7.52 (m, 3H), 7.48 (d, *J* = 14.8 Hz, 1H), 6.73 (d, *J* = 14.8 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.90, 150.97, 141.59, 131.81, 129.78, 124.80, 124.32, 61.39, 14.07.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{11}H_{13}O_3S$, 225.0585 found, 225.0585;

IR (film): ν_{max} 3055, 2985, 1720, 1620, 1288, 1226, 1141, 1049(S=O), 956, 748, 702, 516 cm^{-1}



***E*-4-5h**

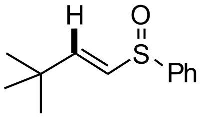
(*E*)-trimethyl(2-(phenylsulfinyl)vinyl)silane

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 2H), 7.54 – 7.45 (m, 3H), 6.97 (d, *J* = 17.6 Hz, 1H), 6.62 (d, *J* = 17.6 Hz, 1H), 0.13 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.84, 143.46, 136.44, 131.02, 129.41, 124.71, -1.66.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{11}H_{17}OSSi$, 225.0769 found, 225.0770;

IR (film): ν_{max} 3055, 1566, 1249, 1149, 1049(S=O), 972, 848, 732, 509 cm^{-1}



***E*-4-5i**

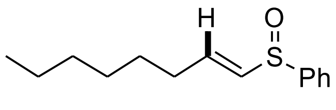
(*E*)-((3,3-dimethylbut-1-en-1-yl)sulfinyl)benzene

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 2H), 7.55 – 7.43 (m, 3H), 6.62 (d, *J* = 15.2 Hz, 1H), 6.14 (d, *J* = 15.2 Hz, 1H), 1.09 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.20, 144.38, 131.02, 130.76, 129.25, 124.49, 34.20, 28.69.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{12}H_{17}OS$, 209.1000 found, 209.1004;

IR (film): ν_{max} 2962, 1473, 1442, 1080, 1041(S=O), 972, 748, 694, 540, 501 cm^{-1}



***E*-4-5j**

(*E*)-(oct-1-en-1-ylsulfinyl)benzene

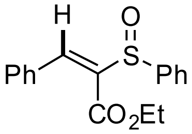
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.57 (m, 2H), 7.55 – 7.43 (m, 3H), 6.62 (dt, *J* = 15.2, 6.8 Hz, 1H), 6.23 (dt, *J* = 15.2, 1.2 Hz, 1H), 2.28 – 2.16 (m, 2H),1.52 – 1.39 (m, 2H), 1.36 – 1.20 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 144.35, 141.48, 134.99, 130.76, 129.24, 124.44, 32.01,

31.47, 28.66, 27.99, 22.47, 13.96.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{14}H_{21}OS$, 237.1313 found, 237.1312;

IR (film): ν_{max} 2924, 2854, 1627, 1442, 1087, 1041(S=O), 956, 748, 694, 501 cm^{-1}



***E*-4-5k**

***(E)*-ethyl 3-phenyl-2-(phenylsulfinyl)acrylate**

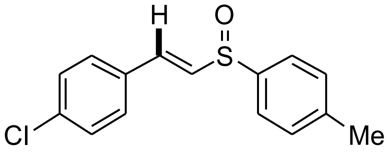
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.78 – 7.73 (m, 2H), 7.60 – 7.56 (m, 2H), 7.52 – 7.45 (m, 6H), 4.17 – 4.00 (m, 2H), 1.03 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.97, 150.80, 143.10, 132.23, 131.16, 131.08, 130.11, 128.84, 128.80, 128.39, 124.32, 61.73, 13.71.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{17}H_{17}O_3S$, 301.0898 found 301.0900;

IR (KBr): ν_{max} 1716, 1600, 1446, 1247, 1209, 1083, 1045(S=O), 767, 754, 692 cm^{-1}

mp 77.9 -79.9 °C



***E*-4-5l**

(*E*)-1-chloro-4-(2-(p-tolylsulfinyl)vinyl)benzene

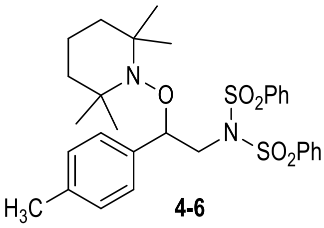
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.27 (m, 7H), 6.79 (d, *J* = 15.6 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.92, 140.53, 135.58, 134.26, 133.81, 132.36, 130.20, 129.12, 128.90, 124.89, 21.39.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{14}OSCl$, 277.0454 found, 277.0453;

IR (KBr): ν_{max} 3008, 1489, 1087, 1049(S=O), 979, 802, 663 cm^{-1}

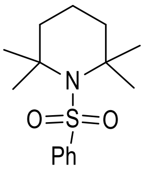
mp 96.1-97.6 °C



4-6

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 – 7.54 (m, 6H), 7.46 – 7.36 (m, 4H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 5.19 (dd, *J* = 10.8, 4.8 Hz, 1H), 4.36 (dd, *J* = 14.8, 10.8 Hz, 1H), 4.02 (dd, *J* = 14.8, 4.8 Hz, 1H), 2.41 (s, 3H), 1.53 – 1.35 (m, 5H), 1.27 – 0.68 (m, 13H).

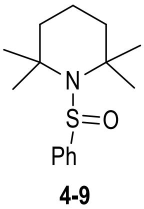
^{13}C NMR (100 MHz, CDCl$_3$) δ 138.71, 137.42, 136.89, 133.54, 129.22, 128.89, 128.83, 128.58, 83.94, 60.01, 50.24, 40.58, 34.49, 21.35, 20.25, 17.19.



4-8

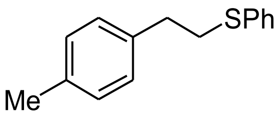
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 – 7.82 (m, 2H), 7.54 – 7.40 (m, 3H), 1.67 (s, 6H), 1.58 (s, 12H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 147.29, 131.20, 128.52, 126.08, 60.82, 43.85, 31.09, 16.74.



4-9

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.73 – 7.64 (m, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 1.90 – 1.30 (m, 15H), 0.91 (s, 3H).



4-10

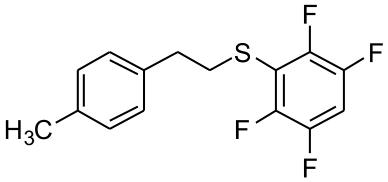
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.21

(t, *J* = 7.6 Hz, 1H), 7.17 – 7.08 (m, 4H), 3.23 – 3.14 (m, 2H), 2.97 – 2.88 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.13, 136.47, 135.94, 129.16, 129.15, 128.87, 128.34, 125.89, 35.19, 35.17, 21.00.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{15}H_{17}S$, 229.1051 found, 229.1054;

IR (film): v_{max} 3055, 1581, 1481, 1435, 810, 740, 686 cm^{-1}



4-3u

(4-methylphenethyl)(2,3,5,6-tetrafluorophenyl)sulfane

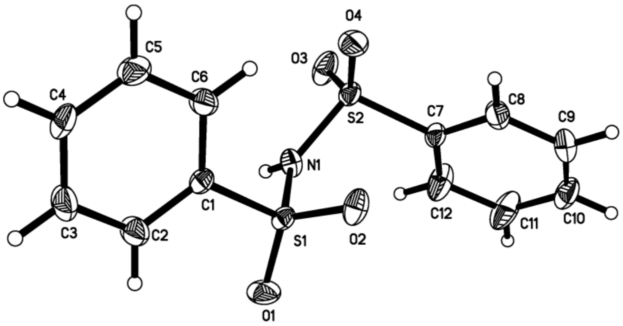
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 7.02 (m, 4H), 7.02 – 6.93 (m, 1H), 3.18 (t, *J* = 8.0 Hz, 2H), 2.85 (t, *J* = 8.0 Hz, 2H), 2.29 (s, 3H).

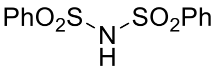
^{13}C NMR (100 MHz, $CDCl_3$) δ 147.41(m), 144.88 (m), 136.21, 136.08, 129.15, 128.37, 115.43 (t, *J* = 19.9 Hz), 105.51 (t, *J* = 22.7 Hz), 36.11, 35.66 (t, *J* = 3.0 Hz), 20.93.

^{19}F NMR (377 MHz, $CDCl_3$) δ -133.72 (m, 2F), -138.48 (m, 2F).

HRMS: (ESI) $[M+Na]^+$ calcd. for $C_{15}H_{12}SNaF_4$, 323.0494 found, 323.0494;

IR (film): v_{max} 2924, 1629, 1490, 1436, 1234, 1172, 914, 891, 713 cm^{-1}





$PhO_2S\text{-}NH\text{-}SO_2Ph$

4-11

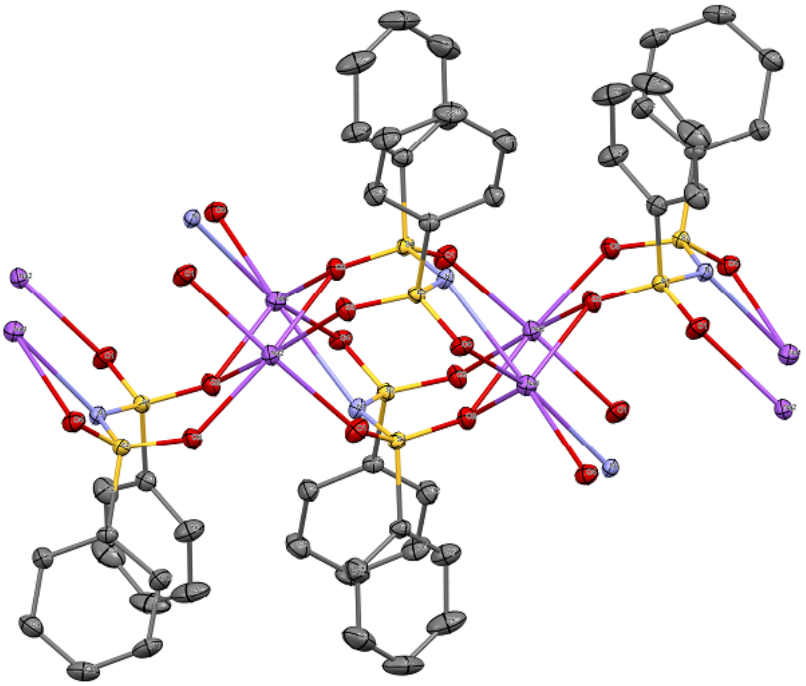
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.56, 134.01, 129.17, 127.81.

HRMS: (ESI) $[M+H]^+$ calcd. for $C_{12}H_{12}NO_4S_2$, 298.0208 found, 298.0208;

IR (KBr): ν_{max} 3124, 1365, 1165, 1087, 871, 756, 686, 578, 547 cm^{-1}

mp 156.1-158.2 °C



Sodium bis(phenylsulfonyl)amide complex **4-12**

^{1}H NMR (400 MHz, CD_3OD) δ 7.71 – 7.64 (m, 2H), 7.42 – 7.35 (m, 1H), 7.32 – 7.25 (m, 2H).

^{13}C NMR (100 MHz, CD_3OD) δ 144.93, 132.13, 129.19, 127.60.

IR (KBr): ν_{max} 1448, 1278, 1261, 1147, 1095, 788, 748, 688, 572, 559 cm^{-1}

mp 326.5-327.5 °C

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