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STUDIES ON COPPER-CATALYZED AEROBIC MOLECULAR TRANSFORMATION WITH HETEROATOM RADICALS

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Studies on Copper-Catalyzed Aerobic Molecular Transformation with Heteroatom Radicals

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With deepest gratitude,

Ya Lin

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List of Abbreviations

δ	chemical shift
Δ	heating
ε	dielectric constant
°C	degree centigrade
Ac	acetyl
aq	aqueous
AIBN	2,2'-azobis(2-methylpropionitrile)
atm	standard atmosphere
BINOL	1,1'-bi-2-napthol
bpy	2,2'-bipyridine
br s	broad singlet
Bu	butyl
cacld	calculated
cm^{-1}	inverse centimetre
d	doublet
dd	doublets of doublet
ddd	doublets of doublets of doublet
dddd	doublets of doublets of doublets of doublet
DBAD	di-*tert*-butyl azodicarboxylate
DFT	density functional theory
DMF	*N*,*N*-dimethylformamide

DMSO	dimethyl sulfoxide
dt	doublets of triplet
EI	electron impact ionization
equiv	equivalent
ESI	electronspray ionization
Et	ethyl
ET	electron transfer
ether	diethyl ether
esp	α,α,α',α'-tetramethyl-1,3-benzenedipropionate
FT-IR	Fourier transform infrared spectroscopy
g	gram
G	Gibbs free energy
h	hour
HRMS	high resolution mass spectroscopy
Hz	Hertz
hν	photoirradiation
i-Bu	isobutyl
i-Pr	isopropyl
IR	infrared
J	coupling constants
K	Kelvin
kcal	kilocalorie

kg	kilogram
LDA	Lithium diisopropylamide
M	concentration (mol/dm^{-3})
M^+	parent ion peak (mass spectrum)
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mmol	millimoles
mol	moles
MS	mass spectrum
Bu	butyl
NHPI	*N*-hydroxyphthalimide
NMI	*N*-methylimidazole
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser enhancement spectroscopy
Nu	nucleophile
OTf	trifluoromethanesulfonate

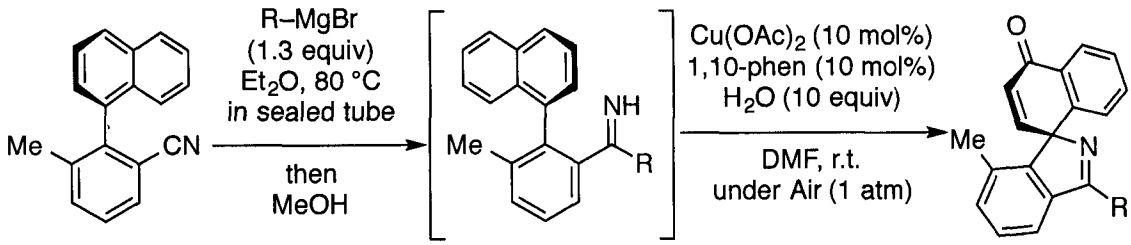
p	page
Pc	phthalocyanine
Ph	phenyl
phen	1,10-phenanthroline
PINO	Phthalimide-*N*-oxy
ppm	parts per million
q	quartet
rt	room temperature
R_f	retention factor
s	singlet
sat.	saturated
t	triplet
t-Bu	tertbutyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
TS	transition state

Abstract

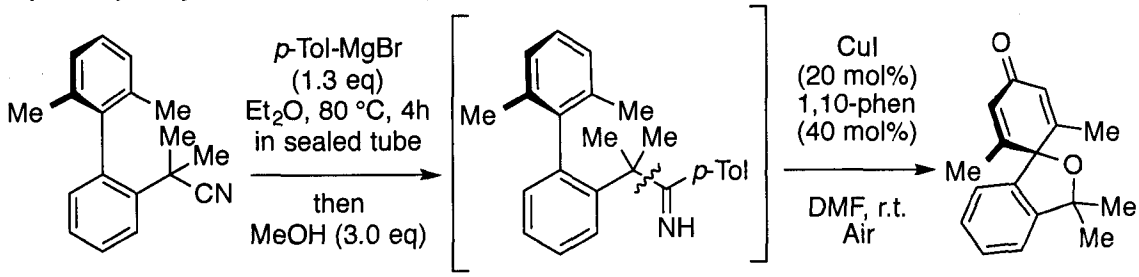
Copper-catalyzed oxidation chemistry using oxygen as the oxidant has been widely studied and employed in various types of powerful molecular transformations. Not only does oxygen maintain catalytic turnover of copper catalyst, but also allow oxygenation of organic substrates. In this thesis, three types of molecular transformations involving heteroatom radicals generated from *N*-H-imines, organohydroperoxides and *N*-hydroxyphthalimide under copper-catalyzed aerobic reaction conditions have been developed.

In the first transformation, azaspirocyclohexadienones were synthesized via intramolecular *ipso*-spirocyclization of iminyl radicals derived from biaryl-*N*-H imines with the benzene rings under copper-catalyzed aerobic reaction conditions (Scheme 1a). Under similar reaction conditions, an unexpected oxospirocyclohexadienone formation from biaryl-2-methane carbonitriles via β-carbon fragmentation of the corresponding iminyl radicals was also discovered (Scheme 1b).

a) Azaspirocyclohexadienone synthesis:

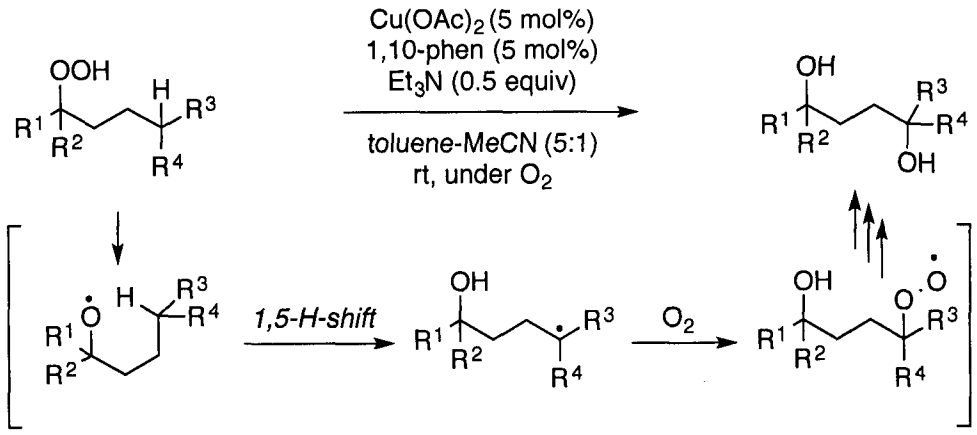


b) Oxospirocyclohexadienone synthesis:



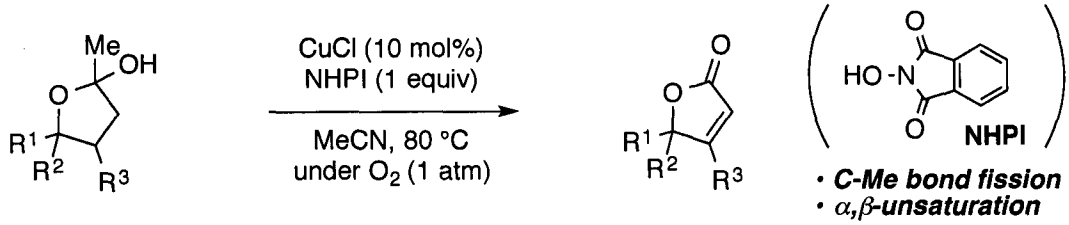
Scheme 1. *Aerobic Cu-catalyzed synthesis of spirocyclohexadienone derivatives via iminyl radicals derived from N-H-imines*

In the second transformation, organohydroperoxides were exploited for the generation of alkoxy-radical species under copper-catalyzed aerobic conditions to perform 1,5-H radical shift on aliphatic C-H bonds. The resulting carbon radical was successfully oxygenated by molecular oxygen, affording 1,4-diols via aliphatic C-H bond oxygenation (Scheme 2). With the utility of *N*-hydroxyphthalimide (NHPI), a similar strategy was applied to the direct 1,4-dioxygenation of alkanes.



Scheme 2. *Cu-catalyzed aerobic oxygenation of aliphatic C-H bonds with hydroperoxides for the synthesis of 1,4-diol.*

The third transformation in this thesis involved the investigation of aerobic copper-catalyzed NHPI-mediated synthesis of lactones from the corresponding lactols through radical-mediated C–C bond cleavage. During this process, NHPI was oxidized to phthalimide *N*-oxy radicals under copper-catalyzed aerobic reaction conditions, which was found to be responsible for the unsaturation and methyl group cleavage.



Scheme 3. *Aerobic Cu-catalyzed NHPI-mediated synthesis of lactones from lactols via radical-mediated C-C bond cleavage.*

Chapter 1: General Introduction

Copper (Cu) catalysts play a significant part in modern synthetic chemistry due to their versatile reactivity. Having multiple oxidation states ranging from Cu(0) to Cu(III), the Cu-metal center can allow both two-electron bond forming pathways and single electron processes, sometimes both in the same catalytic cycle.[1] It is also capable of forming interaction with various types of functional groups via Lewis acid interactions or π-coordination, and is thus able to catalyze a remarkably broad range of molecular transformations.[2]

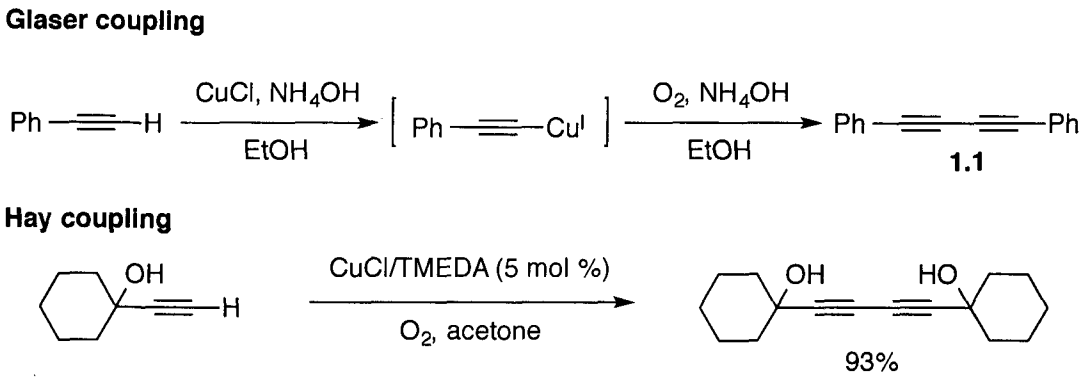
Molecular oxygen (O_2) is a renewable and ecologically benign oxidant. Chemists around the world have been striving to utilize this readily available oxidant for the production of fine chemicals.[3] However, it is forbidden for triplet ground-state O_2 to directly react with singlet ground-state substrates, as that would result in a violation of the conservation of the total angular momentum according to the principle of spin conservation.[4] As a result, this kinetic constraint usually favors the reaction of O_2 with free radical species, where unpaired electrons could combine easily and undergo oxidative transformations. In order to bridge the gap between singlet ground-state substrates and triplet O_2, metal catalysis can be employed to activate O_2 for molecular oxidations.

In biological systems, Cu-metal centers are found in the active site of many metalloenzymes that catalyze oxidation reactions by activation of molecular oxygen.[5] These enzymes are able to activate O_2 for two types of oxidation reactions, namely, "oxygenase", which mediate oxygen-atom transfer for oxygenation of organic substrates and "oxidase", which reduce O_2 to H_2O (sometimes via H_2O_2) while oxidation of organic substrates takes place. These biological reactions triggered an acute interest to study and develop Cu-O_2 complexes for powerful aerobic oxidations of organic substrates outside biological systems.[6] In this chapter, selected reactions involving aerobic Cu-catalyzed

molecular transformations, displaying both oxidase and oxygenase activity will be discussed.

1.1. Oxidative C–C bond Coupling reactions

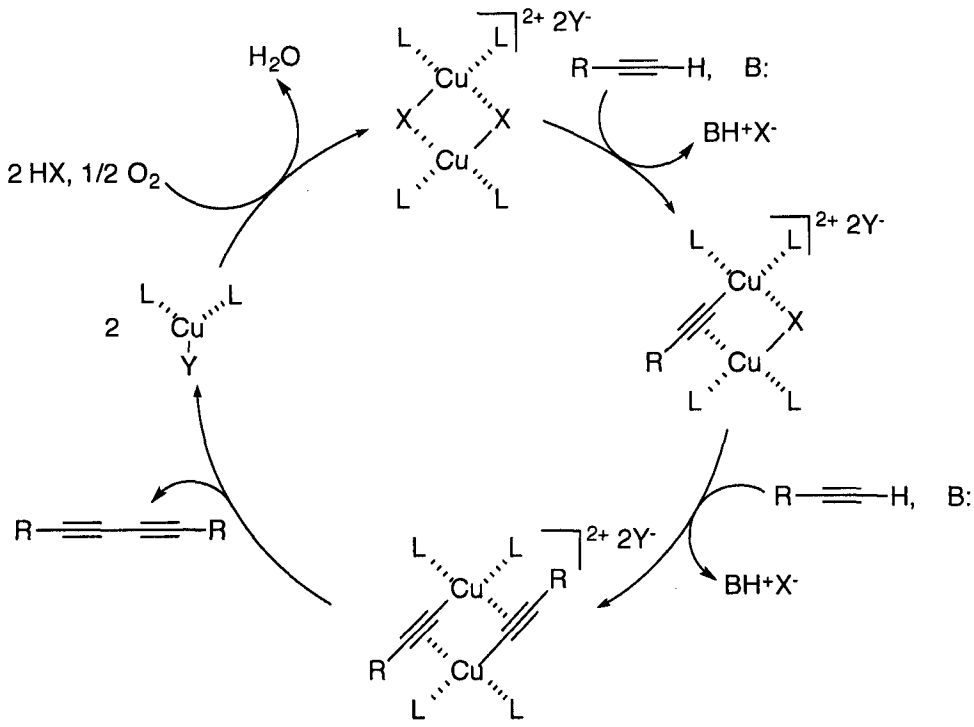
One of the earliest utilities of O_2 as an oxidant in copper chemistry is the oxidative homocoupling of terminal alkynes in the *Glaser–Hay reaction*. In 1869, Carl Glaser treated phenylacetylene with Cu(I)-chloride and aqueous ammonia, forming the Cu(I)-salt of phenylacetylene, which was oxidized upon exposure to air to give homocoupled 1,3-diyne **1.1** (Scheme 1-1).[7] It was not until 1962, that Allan Hay demonstrated the use of catalytic amounts of Cu(I)-TMEDA (*N*,*N*,*N*',*N*'-tetramethylethylenediamine) complex and O_2 as the terminal oxidant for oxidative homocoupling of terminal alkynes (Scheme 1-1).[8]



Scheme 1-1. *Evolution of the Glaser-Hay coupling.*

This C–C bond coupling reaction provided a valuable pathway for the construction of linear π-conjugated acetylenic oligomers, polymers, and the synthesis of natural products.[9] Subsequent effort to improve this reaction includes addition of stoichiometric amount of base, which accelerates the formation of alkynyl cuprate species.[10] Although the detailed mechanism of this coupling reaction is yet to be fully understood, it is proposed by Bolmann that π-coordination of the alkynyl triple bond to Cu(I) species facilitates the activation of the terminal C–H bond by an external base.[11] Since homocoupled products are formed when mixtures of alkynes are used, the

formation of alkynyl radicals is denied, as statistical distributions would be expected. Therefore, it is believed that homocoupling step occurs via reductive elimination as shown in Scheme 1-2.

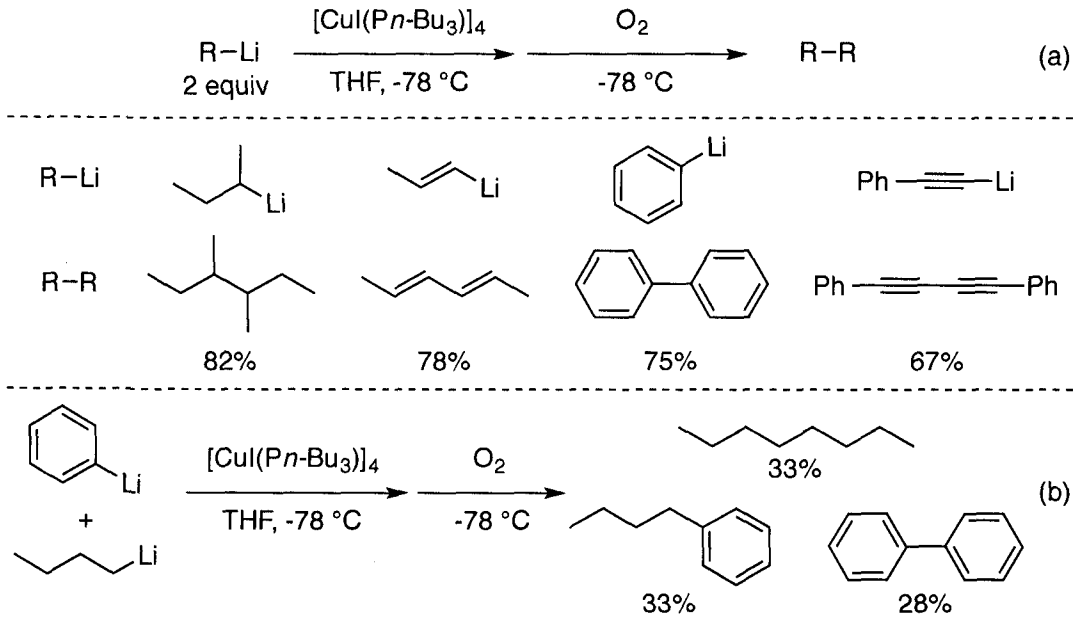


Scheme 1-2. *A proposed mechanism for the Glaser-Hay-coupling.*

This concept triggered the development of various aerobic Cu-catalyzed cross-coupling reactions by using 5-fold excess of coupling partner to obtain unsymmetric cross coupling product. Coupling partners such as alkyl- and aryl-acetylenes,[12] trifluoromethyl anions,[13] and amines or amides[14] were examined. Although DFT studies have been carried out to emulate the role of O_2 in this class of coupling reactions, suggesting participation of Cu_2O_2 species during oxidative coupling process, the outcomes are still non conclusive.[15] Nonetheless, it is noteworthy to see that this class of reactions utilizes O_2 in an oxidase type reaction, whereby O_2 act as an electron sink to maintain the catalytic turnover of a Cu-species, in which O_2 is reduced, giving water as by-product.

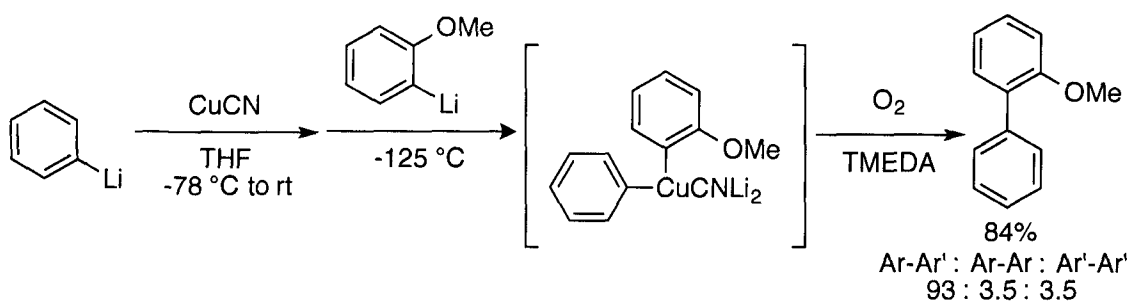
Unlike alkynes, the homocoupling of unactivated hydrocarbons could not be achieved by the *Glaser-Hay* conditions, as direct formation of an organocuprate is required. Fortunately, carbanion species could react with Cu-salts to provide

organocuprate complexes. Whitesides and co-workers first reported that organolithium reagents can react with $[CuI(P^nBu_3)]_4$ to provide copper(I)-ate complex, which undergo dimerization upon exposure with O_2 (Scheme 1-3a).[16] Although mixed organolithium reagents provided a mixture of coupling products (Scheme 1-3b), homocoupling products of primary and secondary alkyl, vinyl, alkynyl, and aryl lithium reagents were obtained efficiently.



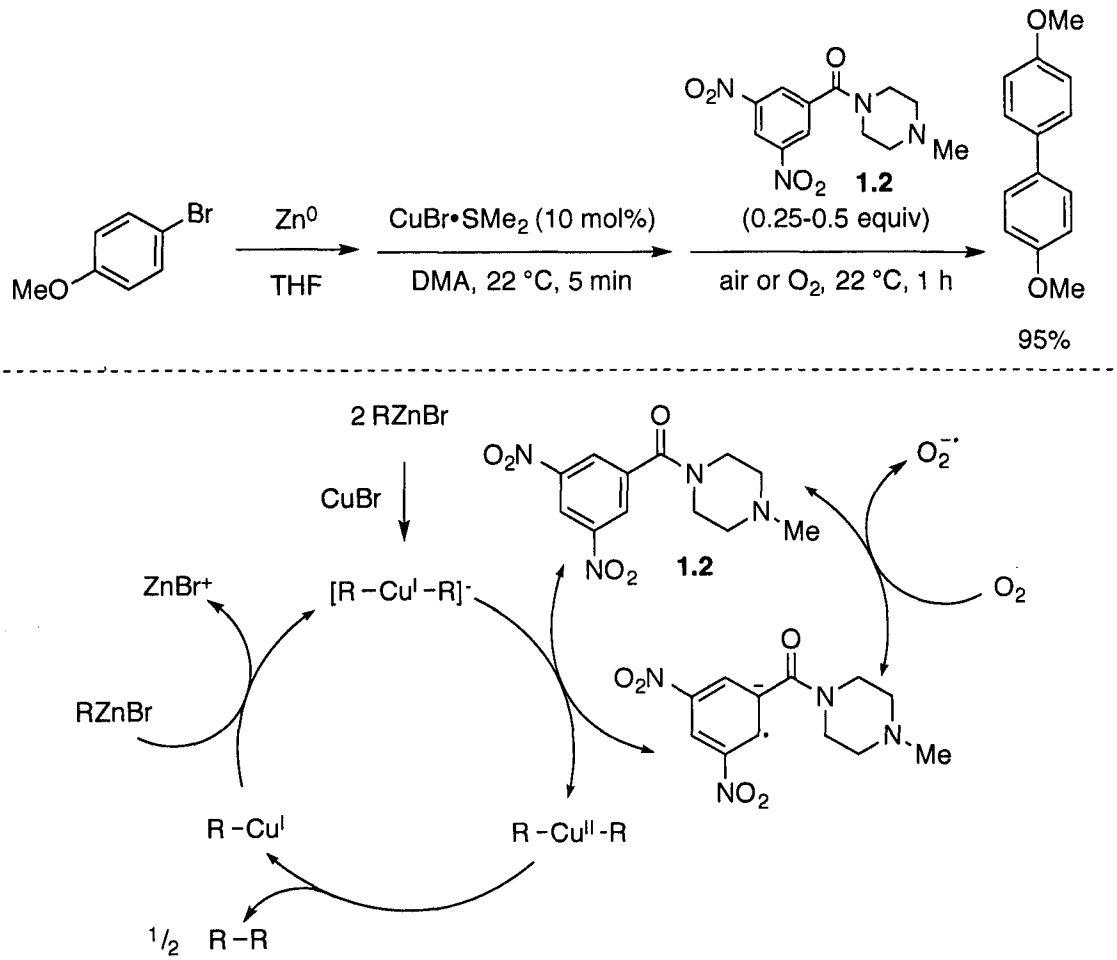
Scheme 1-3. *Cu-mediated homocoupling of organolithium reagents.*

Subsequently, Lipshutz and co-workers achieved heterocoupling by the use of diaryl higher order cuprates.[17] It was discovered that at extreme low temperatures of -125 °C, the formation of diaryl higher order cuprates from two different aryllithiums could be controlled, which produce good yields of unsymmetrical biaryl products upon O_2 oxidation (Scheme 1-4).



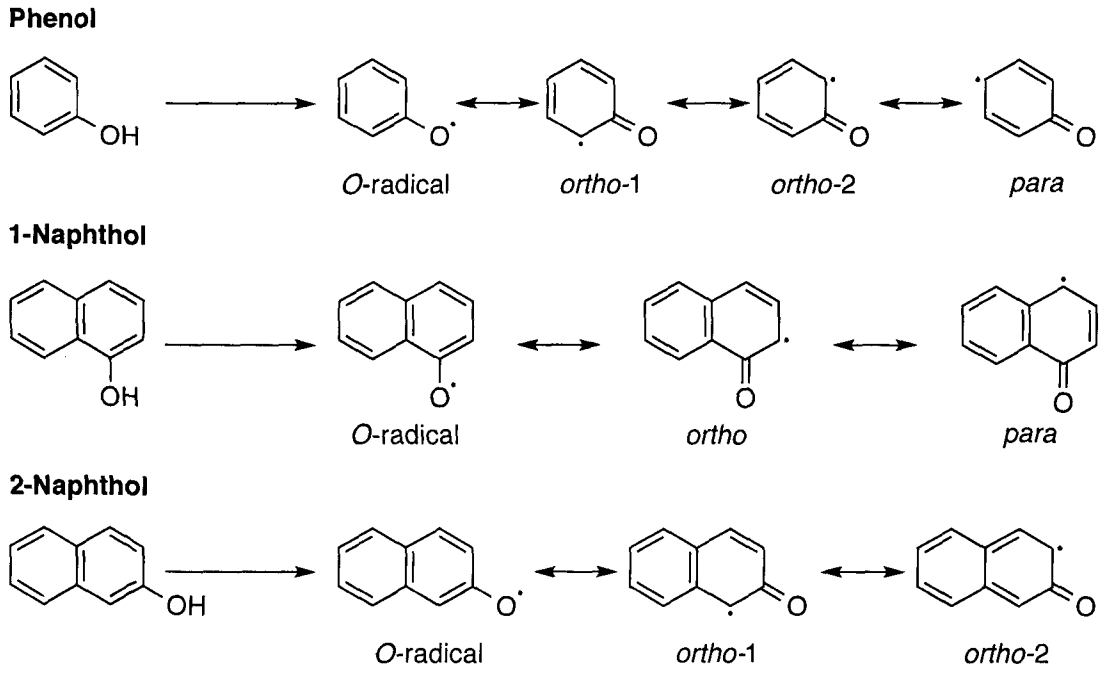
Scheme 1-4. *Cu-mediated heterocoupling of organolithium via diaryl higer order cuprates.*

Catalytic oxidative homocoupling of aryl halides is successively achieved via the use of aryl zinc reagents at ambient temperatures. Aryl zinc reagents generated in situ from aryl halides and zinc, efficiently undergo oxidative homocoupling reaction in the presence of catalytic amounts of CuBr and dinitroarene **1.2** as co-oxidant, under air or O_2 atmosphere (Scheme 1-5).[18] In this reaction, O_2 is the terminal oxidant (oxidase activity) to facilitate substoichiometric use of dinitroarene co-oxidant, which maintains the catalytic turnover of the Cu-catalyst. Whereas, in the absence of co-oxidant, use of O_2 as the sole oxidant results in formation of phenolic products, thus lowering efficiency of this transformation. A proposed mechanism is summarized in Scheme 1-5, in which the dinitroarene co-catalyst **1.2** oxidizes the aryl Cu(I)-complex to a Cu(II)-complex, that undergoes single-electron-transfer and possibly releases aryl radicals. Finally, dimerization of aryl radicals produces the biaryl products.



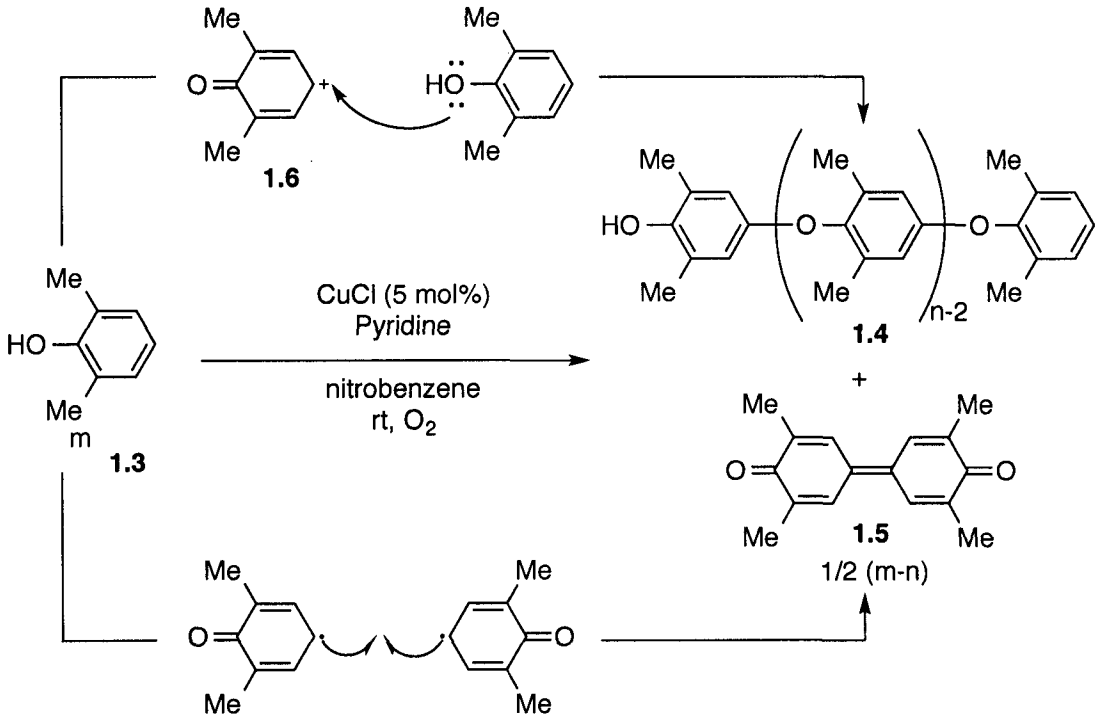
Scheme 1-5. *Cu-catalyzed homocoupling of aryl halides via aryl zinc reagents.*

Apart from biaryl coupling reactions that require prefunctionalization for the formation of reactive site for coupling, phenols and naphthols can be easily oxidized and undergo coupling reactions by forming stabilized radical species as shown in Scheme 1-6.[19] These radical species can be transformed into various coupled products under mild reaction conditions that tolerate many functional groups.



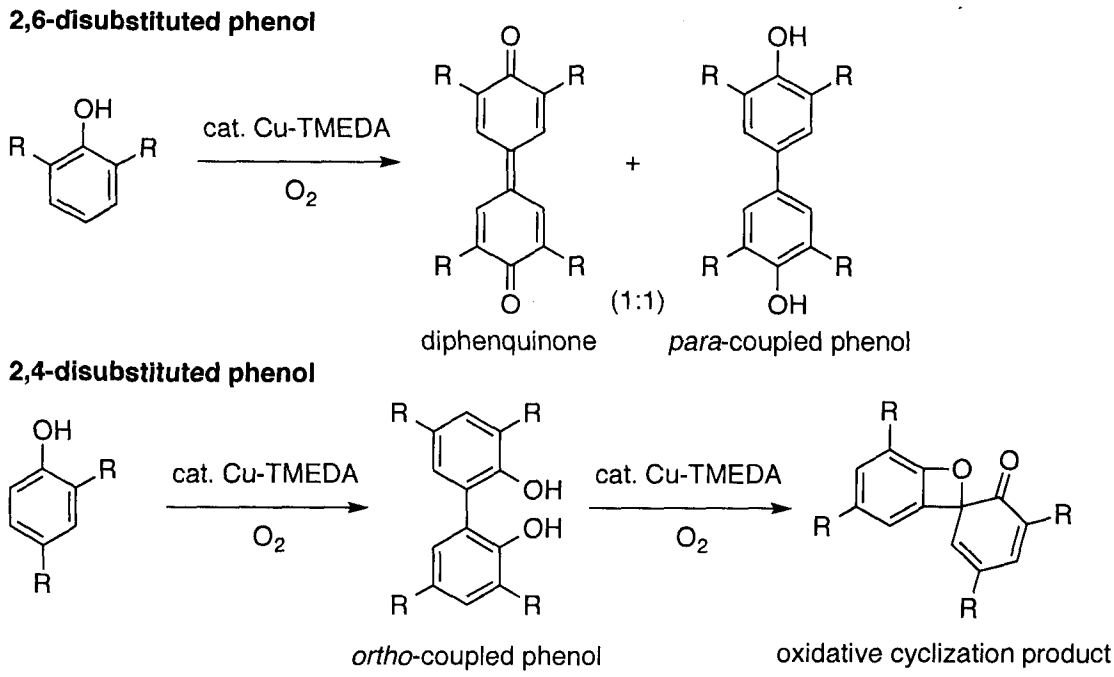
Scheme 1-6. *Radicals arising from phenol, 1-naphthol and 2-naphthol.*

Cu-catalyzed aerobic reaction conditions has been known to be efficient in phenolic radical transformations.[6] One of the earliest studies of oxidative coupling of phenols is the polymerization of 2,6-dimethylphenols (**1.3**), where Hay and co-workers reported the CuCl-pyridine catalyzed carbon-oxygen coupling to provide linear polyphenylene ethers **1.4** together with diphenoquinone **1.5** as by products (Scheme 1-7).[20] Subsequent mechanistic studies suggest that the complicated polymerization process involves a series of transformations involving phenoxium intermediate **1.6**.[21] While the formation of diphenoquinone revealed a reaction pathway for oxidative C–C bond coupling of phenols by minimizing polymerization reaction.



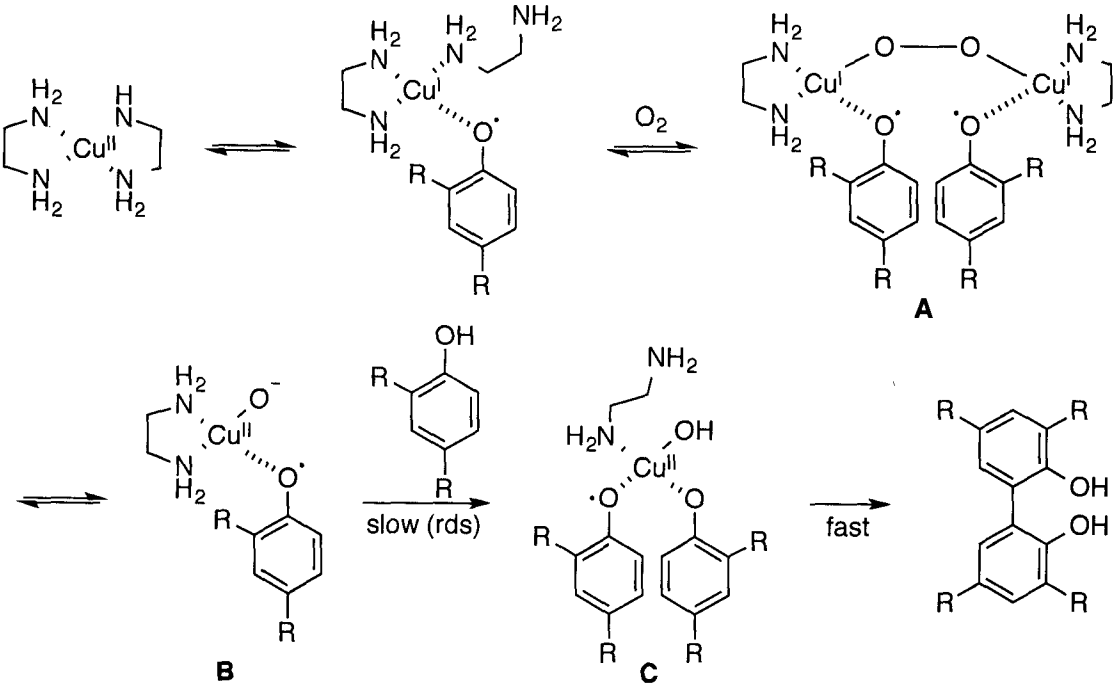
Scheme 1-7. *Oxidative phenol polymerization via C-O coupling.*

One of the challenges in oxidative C–C bond coupling of phenols is regioselectivity control of the resulting coupling products. As both *ortho*- and *para*-positions form relatively stable radicals for coupling according to resonance stabilization of phenol radicals (Scheme 1-6), coupling sites can be predicted and controlled based on substitution patterns on phenols, thus gaining regioselectivity control. For example, when using Cu-TMEDA complex as catalyst, 2,6-di-*tert*-butyl phenols couple at *para*-positions to form diphenoquinones and *para*-coupled phenols,[22] while blocking the *para*-position, such as in 2,4-di-*tert*-butyl phenols, provides *ortho*-coupling products, which can undergo further oxidative cyclization to synthesize polycyclic products (Scheme 1.8).[23]



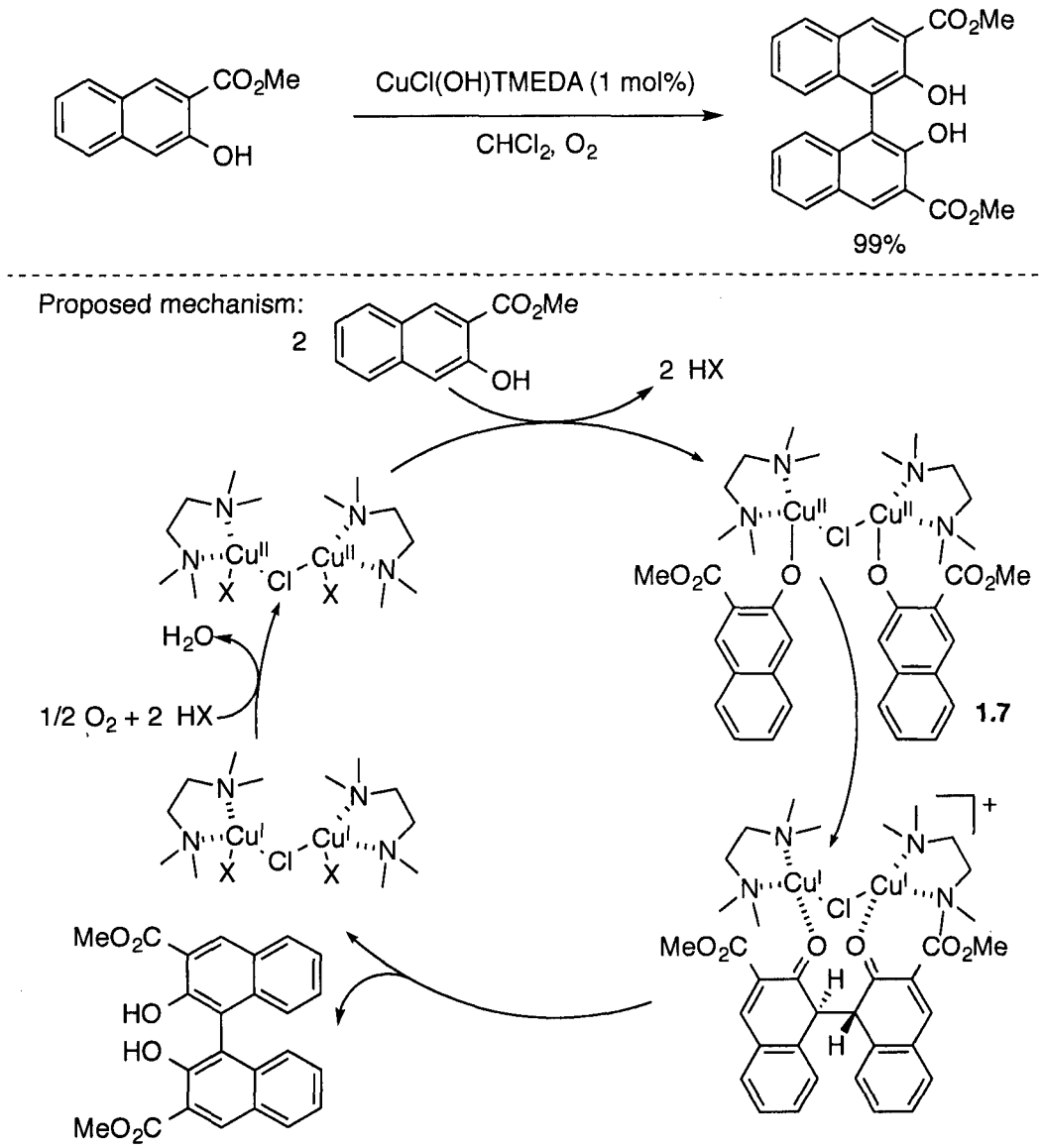
Scheme 1-8. Substituent influenced *oxidative phenol coupling*.

The mechanism of *ortho*−coupling of 2,4-di-*tert*-butylphenol is proposed to proceed via a binuclear diradical mechanism, where Cu(II)-diphenol complex **B** was formed via rapid fragmentation of an unstable peroxide-bridged diradical species **A.** The rate-determining-step is considered to be either the deprotonation[24] or coordination[25] of phenol molecule to form **C** before the coupling step (Scheme 1-9).



Scheme 1-9. *Proposed reaction mechanism to ortho-coupled phenol.*

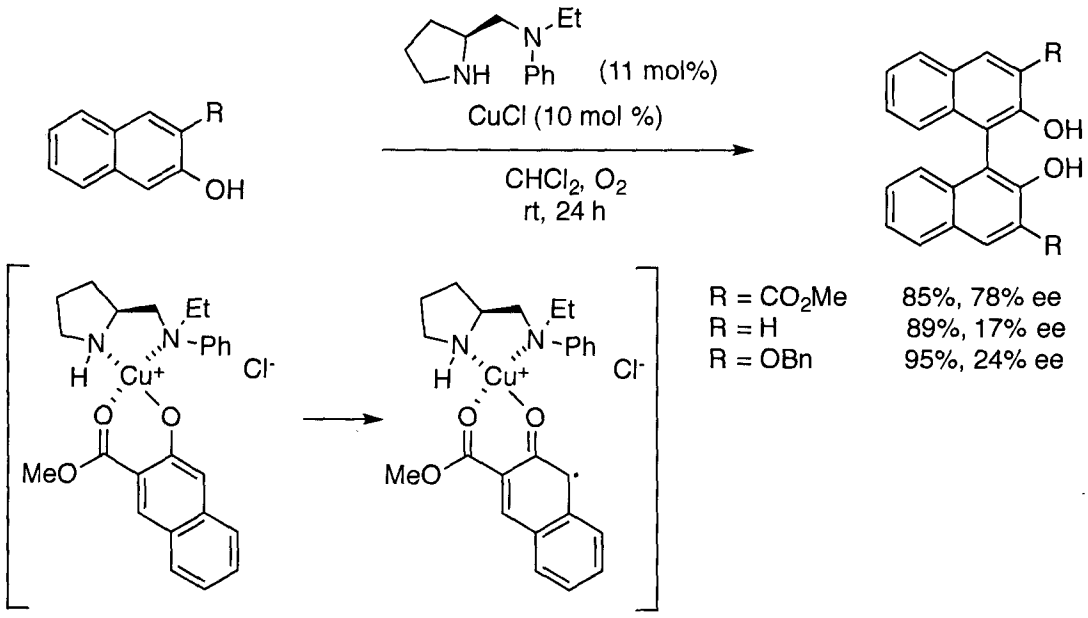
Oxidative homocoupling of 1-naphthols also occurs on both *ortho*- and *para*-positions (Scheme 1-6), as the resonance stabilization of both radicals is similar. Oxidative homocoupling of 2-naphthols selectively occurs at the *ortho*-1-position (Scheme 1-6) due to the higher stability of the naphtholic radical, forming useful BINOL products. Nakajima and co-workers reported an efficient CuCl(OH)-TMEDA catalyzed oxidative coupling of various 2-naphthols for the formation of a broad range of racemic BINOL products using O_2 as the terminal oxidant (Scheme 1-10).[26]



Scheme 1-10. *CuCl(OH)TMEDA catalyzed oxidative coupling of 2-naphthols.*

Roithová and co-workers studied the mechanism in gas phase and found that the CuCl(OH)TMEDA-catalyzed biaryl coupling occurs via copper dimer **1.7** where diamine supports the dimeric clustering of copper which weakens the Cu−OAr naphtholic bond,

thus facilitating the C–C bond formation (Scheme 1-10).[27] As axially chiral compounds have important utilities as ligands and precursors in biomimetic synthesis, this method was further developed for the synthesis of axial chiral BINOL by replacing TMEDA ligand with chiral diamine ligand such as proline[28] or diaza-*cis*-decalin.[29] However, it is required for the ester-coordinating group to be present at 3-position in order to achieve oxidative coupling with good enantioselectivity (Scheme 1-11). Nonetheless, other racemic BINOL products can also be separated via the dynamic thermodynamic resolution method.[30]

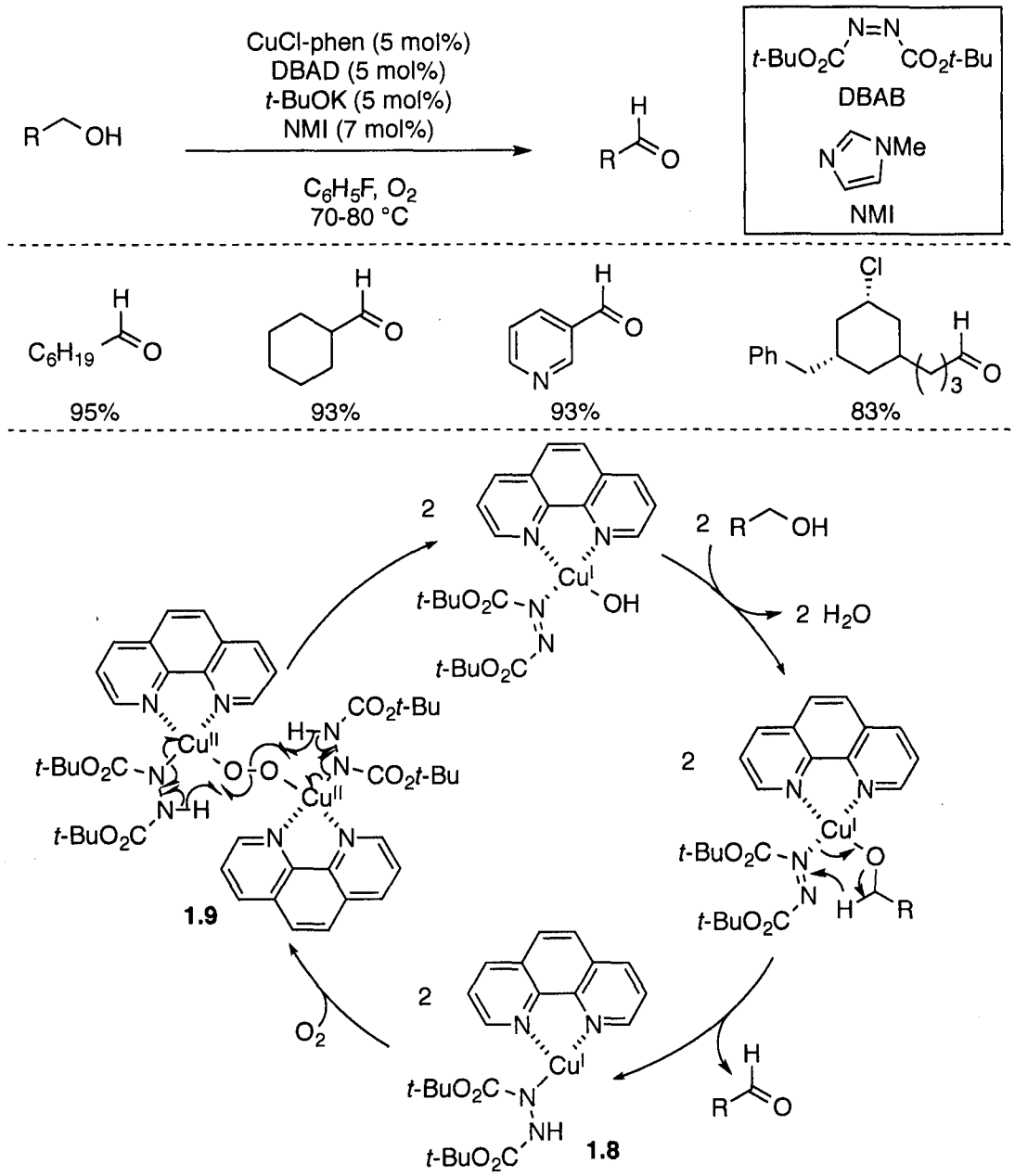


Scheme 1-11. Aerobic *Cu-catalyzed enantioselective naphthol coupling*.

1.2 Alcohol oxidation

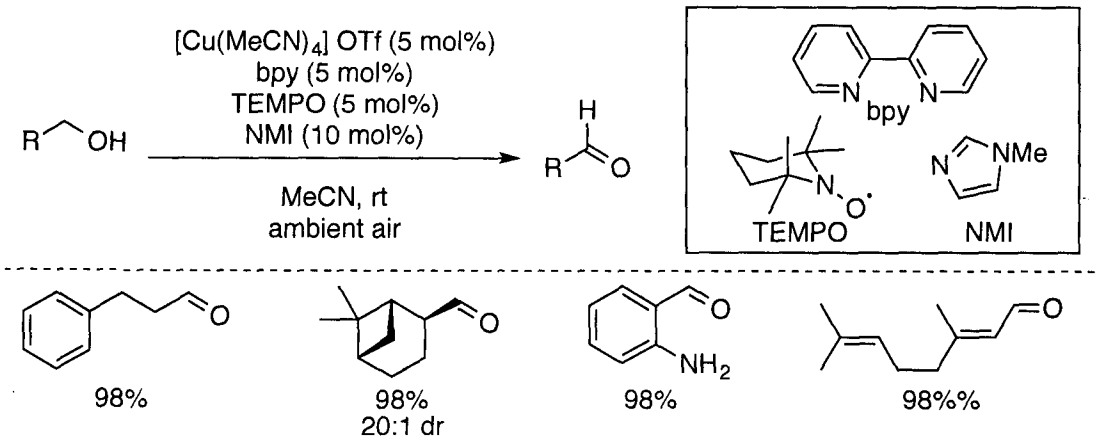
Besides coupling reactions, Cu-O_2 systems are also proficient in dehydrogenative alcohol oxidation for synthesis of carbonyl compounds. There have been studies on the structure and reactivity in biological aerobic oxidation of alcohol to aldehydes by galactose oxidase, which possesses Cu-metal center in its active site.[31] This research motivated the design of various small molecule Cu-catalysts to mimic such aerobic oxidation. One of the most general and efficient methods is the utility of CuCl with 1,10-

phenanthroline (phen) ligand and di-*tert*-butyl azodicarboxylate (DBAD) as co-catalyst in the presence of a catalytic amount of either *t*-BuOK or *N*-methylimidazole (NMI), to oxidize a wide range of alcohols including less reactive aliphatic primary alcohols (Scheme 1-12).[32] The reaction proceeds via Cu(I)/Cu(II) redox cycle whereby DBAD acts as hydride acceptor that oxidizes the alcohol coordinated to the Cu-center. The resulting Cu(I)-complex **1.8** was oxidized by O_2 to Cu(II) peroxo species **1.9**, in which the peroxide bond undergoes homolysis followed by one-electron-reduction of Cu(II) to result in reoxidation of the hydrazine ligand back to azodicarboxylate.



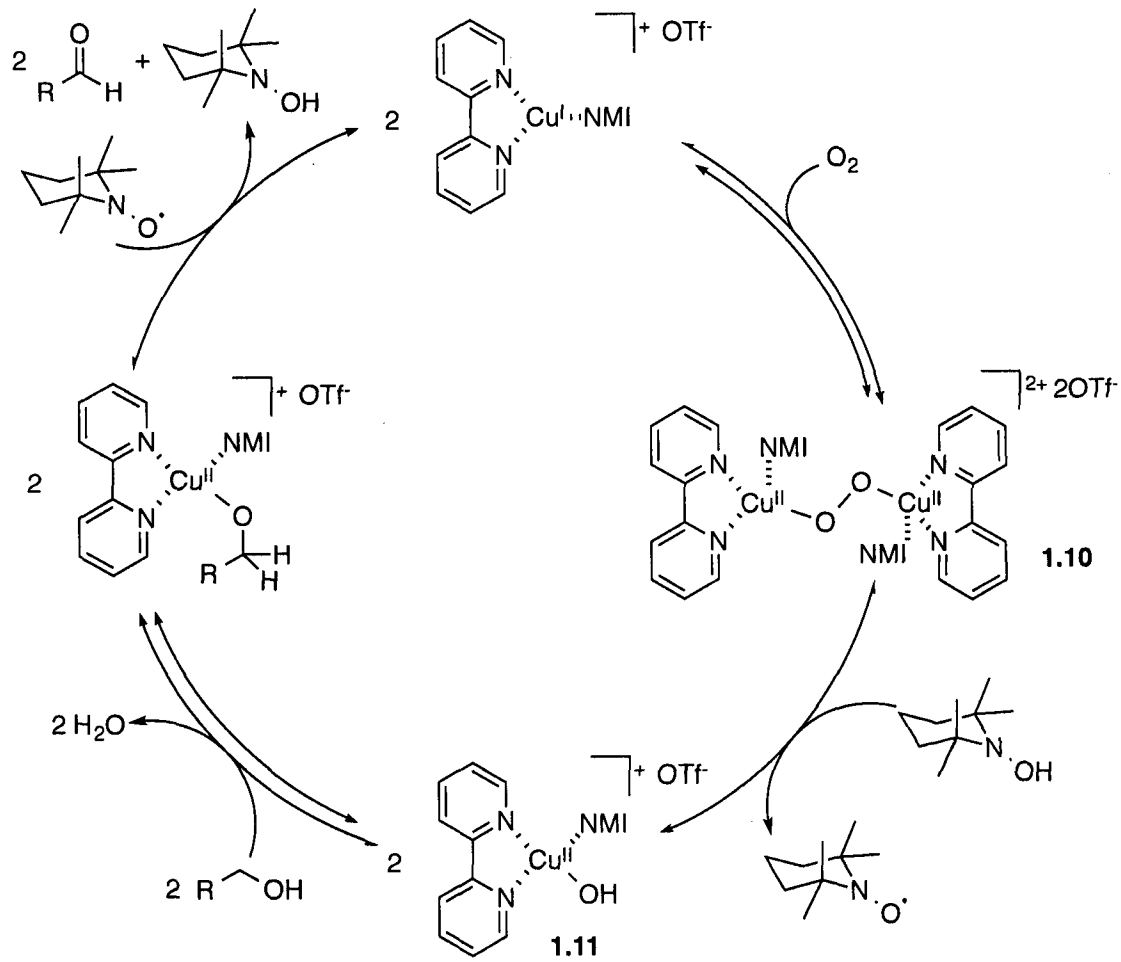
Scheme 1-12. Aerobic *Cu-catalyzed alcohol oxidation using DBAB as a hydride transfer cocatalyst.*

Alongside the use of azodicarboxylate as hyride transfer co-catalyst, nitroxyl radicals, especially TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), are another class of efficient co-catalysts in aerobic copper-catalyzed oxidation of alcohols. Early examples of Cu-TEMPO catalyzed systems are effective in oxidizing primary benzylic and allylic alcohols, but less reactive aliphatic alcohols and sterically hindered secondary alcohols require stronger conditions such as higher catalyst loading or temperatures.[33] Recently, Stahl and co-workers reported the (bpy)Cu(I)/TEMPO catalyzed chemoselective oxidation of primary alcohols with *N*-methylimidazole (NMI) as additive. This system allows the oxidation of a wide range of primary alcohols including allylic, benzylic, and aliphatic primary alcohols with diverse functional groups (Scheme 1-13).[34] This method is subsequently expanded to oxidize secondary alcohols by replacing TEMPO with the less sterically hindered ABNO (9-azabicyclo[3.3.1]nonane *N*-oxyl) as co-catalyst.[35]



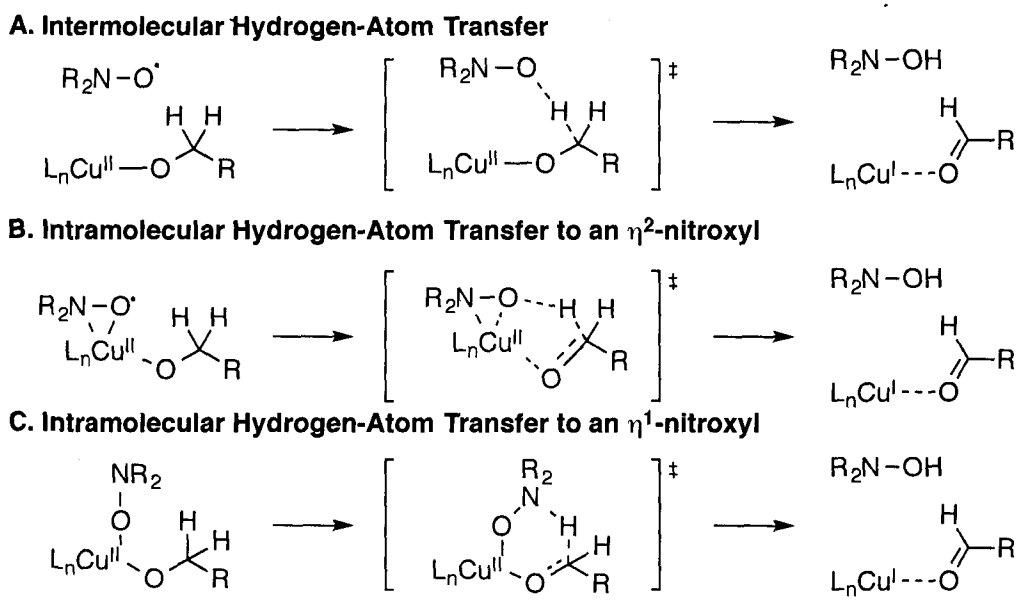
Scheme 1-13. Aerobic (bpy)*Cu-TEMPO catalyzed oxidation of primary alcohols.*

Stahl's group continued to investigate the mechanism via kinetic and spectroscopic methods and found that the transformation proceeds via two-stage catalytic mechanism consisting of a "catalyst oxidation" stage in which Cu(I) and TEMPO–H are oxidized by O_2 via a binuclear Cu_2O_2 species **1.10** to give Cu(II)-alkoxide complex **1.11** and a "substrate oxidation" stage where the nitroxyl radical of TEMPO oxidizes the alcohol via the Cu(II)-alkoxide complex **1.11** to provide aldehyde and TEMPO-H (Scheme 1-14).[36]



Scheme 1-14. Proposed mechanism for the (bpy)*Cu-TEMPO catalyzed aerobic oxidaton of alcohols*.

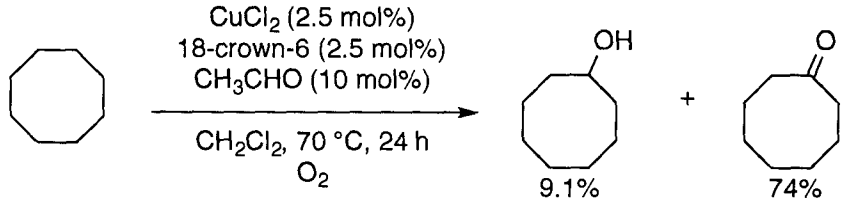
Early mechanistic proposals suggest that TEMPO radical abstracts the α-hydrogen of alcohol during the "substrate oxidation" stage via intermolecular hydrogen abstraction[37] (Scheme 1-15A) or via intramolecular hydrogen-atom transfer where TEMPO is bound to copper in η^2-coordination mode to facilitate the hydrogen transfer[38] (Scheme 1-15B). However, Stahl and co-workers suggest that TEMPO is bound to Cu via η^1-coordination mode where hydrogen-atom or hydride transfer occurs in a concerted manner (Scheme 1-15C).[39] Based on their DFT computational studies and oxidation of radical probe substrates, it is found that the long-lived radical species are not formed during the reaction. Thus, they conclude that the hydrogen transfer should occur via a six-membered transition state analogous to the *Oppenauer* oxidation.



Scheme 1-15. *Mechanistic proposal for"substrate oxidation stage".*

1.3 Oxidation of alkanes

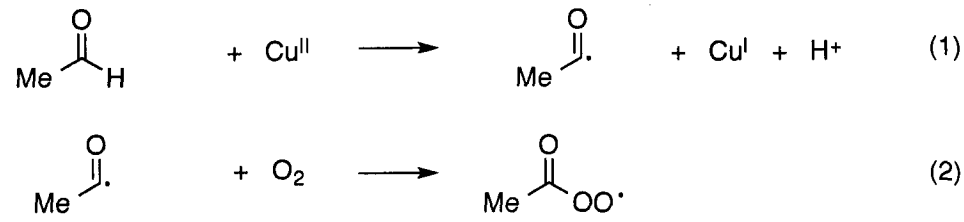
Selective C-H bond oxygenation has been observed in biological oxygenase systems such as monooxygenase tyrosinase and dopamine β-monooxygenase,[40] where the Cu-metalloenzyme center activates O_2 for the hydroxylation of C–H bonds. Direct transformation of alkanes to oxygenated products via oxygenase reactivity of aerobic Cu-catalysis is an attractive transformation of petroleum and natural gas based resources to useful fine chemicals such as alcohols and carbonyl compounds.[41] Therefore, intensive studies have been done to mimic the remarkable selectivity and reactivity of these enzymatic systems with small-molecule Cu-catalysts and O_2 that typically react via radical species. For example, Murahashi and co-workers reported $CuCl_2$-catalyzed aerobic oxidation of alkanes using crown ether, 18-crown-6 (dicyclohexyl-18-crown-6) as ligand, in the presence of acetaldehyde, to give alcohols and ketones (Scheme 1-16).[42]



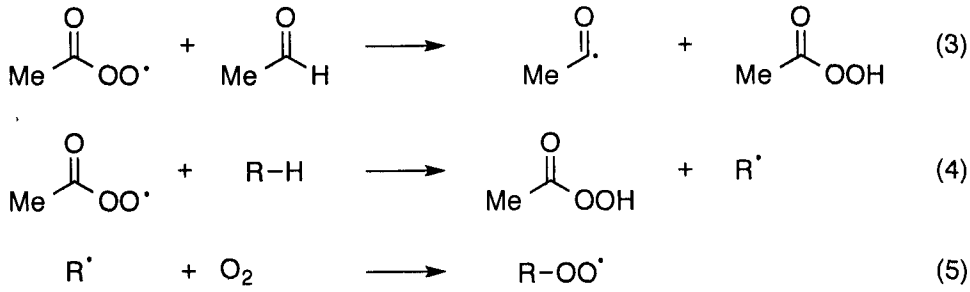
Scheme 1-16. *Cu-crown ether catalyzed aerobic oxidation of alkanes in the presence of acetaldehyde.*

As aliphatic C-H bonds have high bond dissociation enthalpy energies, direct hydrogen abstraction by triplet O_2 is almost impossible. Therefore, it is proposed that the role of acetaldehyde is to react with O_2 in the presence of Cu-crown ether complex to form peracetic acid radicals (Scheme 1-17, eq 1 and 2),[43] which then abstract hydrogen from alkanes to give alkyl radicals (Scheme 1-17, eq 4). Autooxidation of alky radicals with molecular oxygen produce alkylperoxyl radicals (Scheme 1-17, eq 5), which decompose to give ketones and alcohols (Scheme 1-17, eq 6). It is also possible that peracetic acid could be decomposed by Cu-complex to give copper-oxo species, which oxidize the alkane to give alcohol that could be further oxidized to ketone in the same reaction condition (Scheme 1-17, eq 7 and 8).

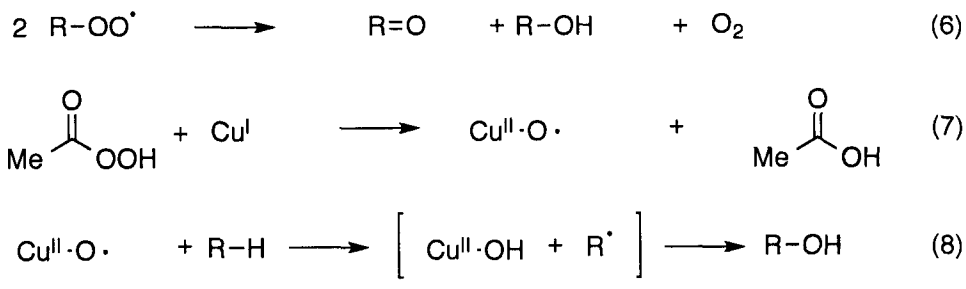
A. Initiation



B. Propagation

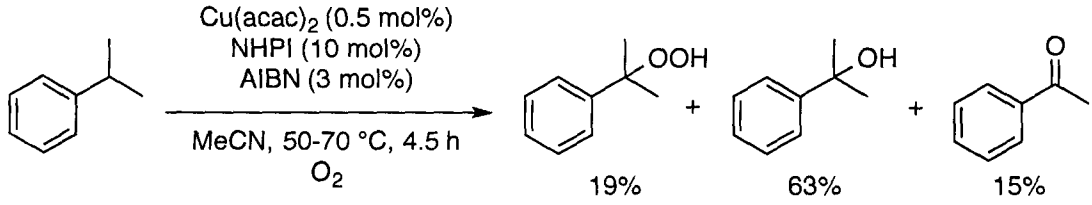


C Termination



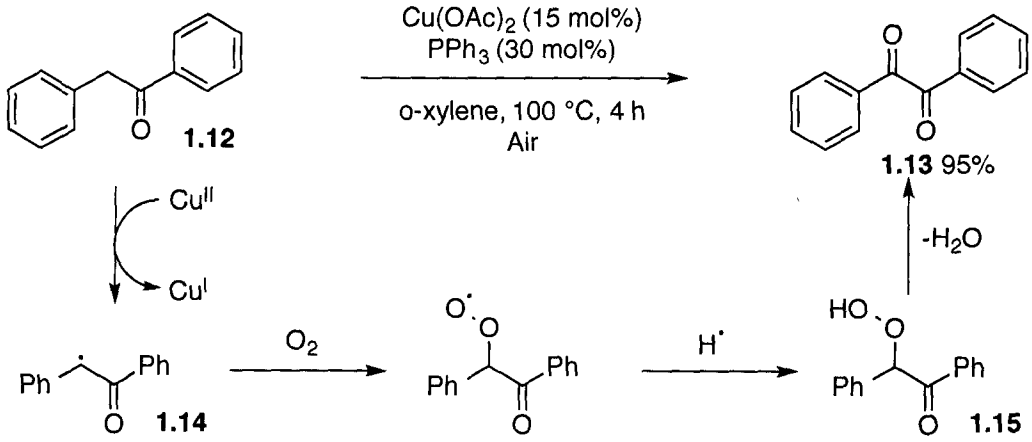
Scheme 1-17. *A proposed mechanism for Cu-crown ether catalyzed aerobic oxidation of alkanes in the presence of acetaldehyde.*

Stabilized N–O radicals are also known to be useful hydrogen abstractors to aid in oxidation of alkanes. For example, Orlinska and co-workers reported the oxidation of cumene to 2-phenyl-2-propanol using NHPI (*N*-Hydroxyphthalimide) and $Cu(acac)_2$ as catalyst, with AIBN as radical initiator (Scheme 1-18).[44] It was presumed that cumene hydroperoxide is first formed via NHPI catalyzed benzylic hydrogen abstraction and autooxidation. Then, Cu-catalyzed decomposition of the initial hydroperoxide adduct could afford 2-phenyl-2-propanol or demethylated acetophenone.



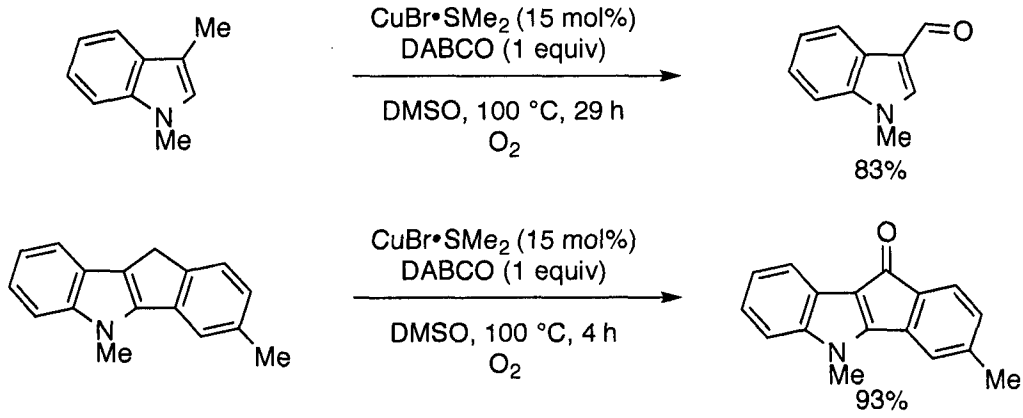
Scheme 1-18. *Cu-NHPI catalyzed aerobic oxidation of cumene.*

In the absence of hydrogen abstraction species, aerobic Cu-catalyzed oxidation of aliphatic C-H bonds could also be achieved on some activated species. For instance, Cacchi and co-workers presented aerobic Cu-catalyzed oxidation of readily available deoxybenzoins (**1.12**) to benzils (**1.13**) under neutral reaction conditions using air as the oxidant (Scheme 1-19).[45] It is proposed that the α-carbonyl-benzylic C–H of **1.12** can be easily oxidized by Cu(II)-catalyst to form the benzylic radical **1.14**, which react with O_2 to afford hydroperoxide intermediate **1.15** followed by elimination of water to give **1.13.**



Scheme 1-19 *Cu-catalyzed aerobic oxidation of deoxybenoins to benzils.*

In view of the applicability of such Cu-catalyzed oxygenation of aliphatic C–H bonds in small molecule synthesis, our laboratory recently developed a useful Cu-catalyzed aerobic methyl or methylene oxygenation of substituted indoles and pyrroles using DABCO (1,4- diazabicyclo[2.2.2]octane) as additive in dimethyl sulfoxide (DMSO) (Scheme 1-20).[46]

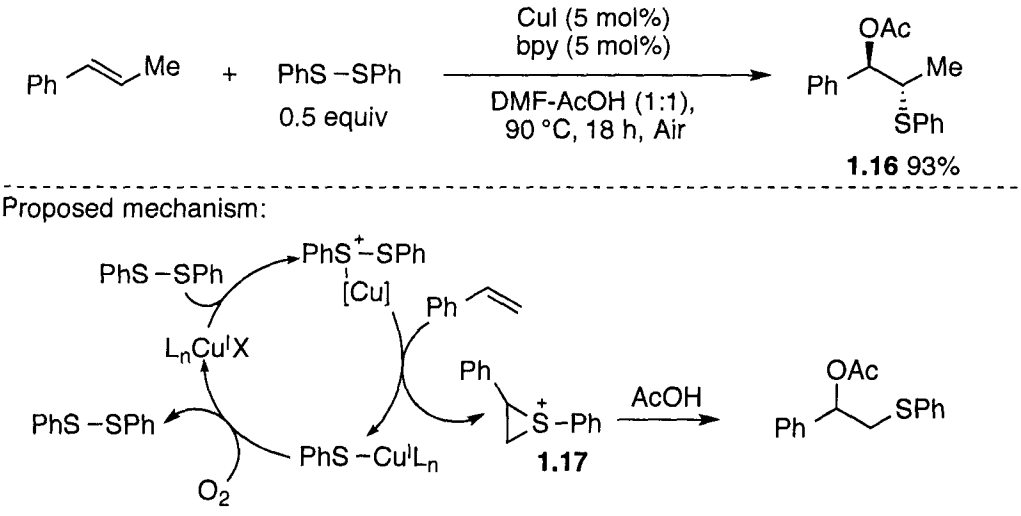


Scheme 1-20. *Cu-catalyzed aerobic methyl/methylene oxygenation of substituted indoles.*

1.4 Oxidative difunctionalization of alkenes

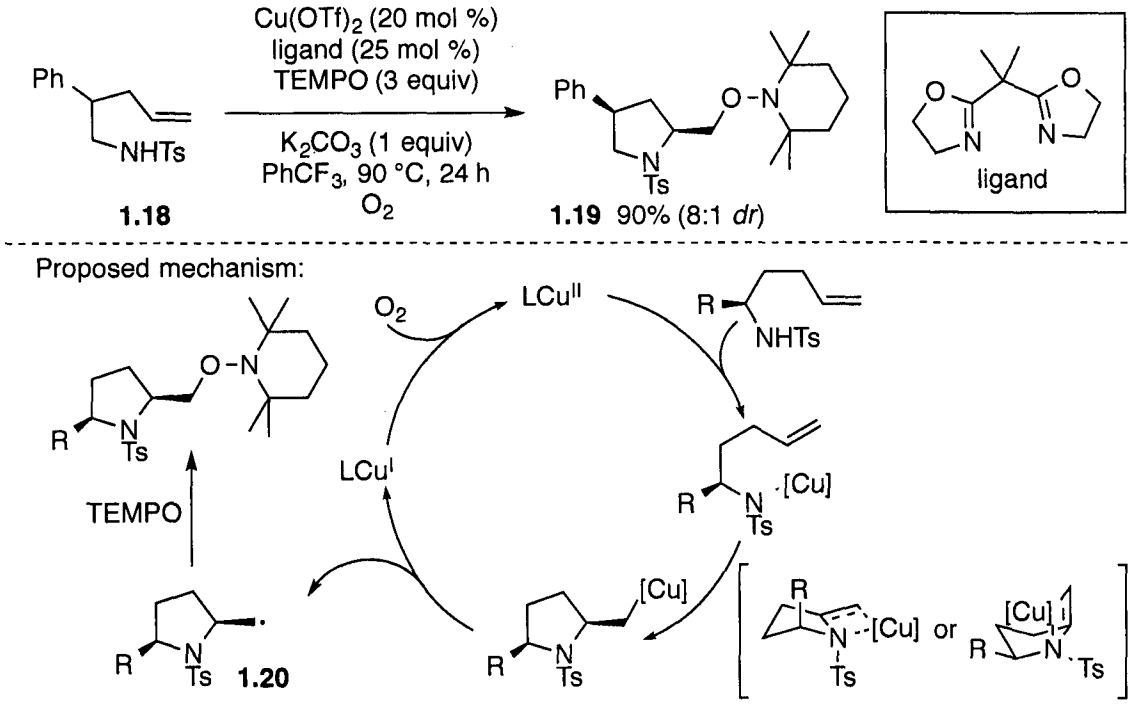
Unlike alkanes, transformations of alkenes are slightly more versatile as the double bond provides π-interaction with Cu-catalysts, which facilitate addition reactions for the functionalization of alkenes. Such addition sometimes results in the formation of alkyl cuprate species that are susceptible to reaction with O_2 to form oxygenation products. Thus both oxygenase and oxidase reactivity can be expected in aerobic Cu-catalyzed transformations of alkenes. Oxidative difunctionalization of alkenes is probably one of the most useful transformations as simple alkenes could be transformed into functionalized compounds, in which, sometimes stereoselective functionalization could be achieved. For example, Taniguchi reported a Cu-catalyzed 1,2-hydroxysulfenylation of alkenes by the use of disulfides and acetic acid in air, which provided a large substrate scope of *anti*-selective 1,2- acetoxysulfenylated product **1.16** in good yield (Scheme 1-21).[47] The mechanism is proposed to proceed via copper coordination to the disulfide,

followed by nucleophilic attack by the alkene to form three-membered sulfonium cation **1.17**, which is then trapped by acetic acid, to provide the anti-selective acetoxysulfenylated product. The resulting PhSCu(I) was oxidized by O_2 to regenerate the Cu(I)-catalyst and disulfide to close the catalytic cycle.



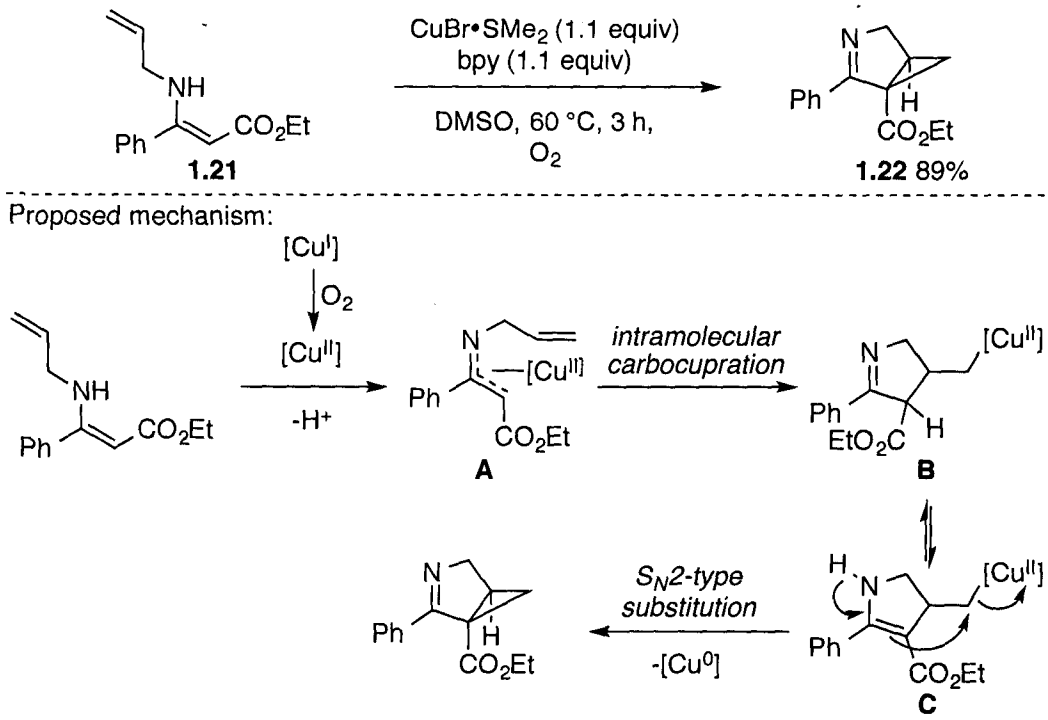
Scheme 1-21. Aerobic *Cu-catalyzed 1,2-hydroxysulfenylation of alkenes by the use of disulfides and acetic acid.*

Chemler and co-workers described diastereoselective copper-catalyzed intramolecular alkene aminooxygenation using TEMPO, which provides methylene-oxy-functionalized disubstituted pyrrolidines **1.19** from the corresponding γ-alkenyl sulfonamides **1.18** (Scheme 1-22).[48] The mechanism is proposed to proceed via initial coordination of the sulfonamide to Cu(II)-catalyst followed by *syn*-aminocupration on the alkene moiety, thus effecting the diastereoselective cyclization. Successive homolytic cleavage of the Cu–C bond affords Cu(I)-species and primary radical **1.20** that is readily trapped by TEMPO. The resulting Cu(I)-species was oxidized by O_2 to regenerate the Cu(II) active catalyst.



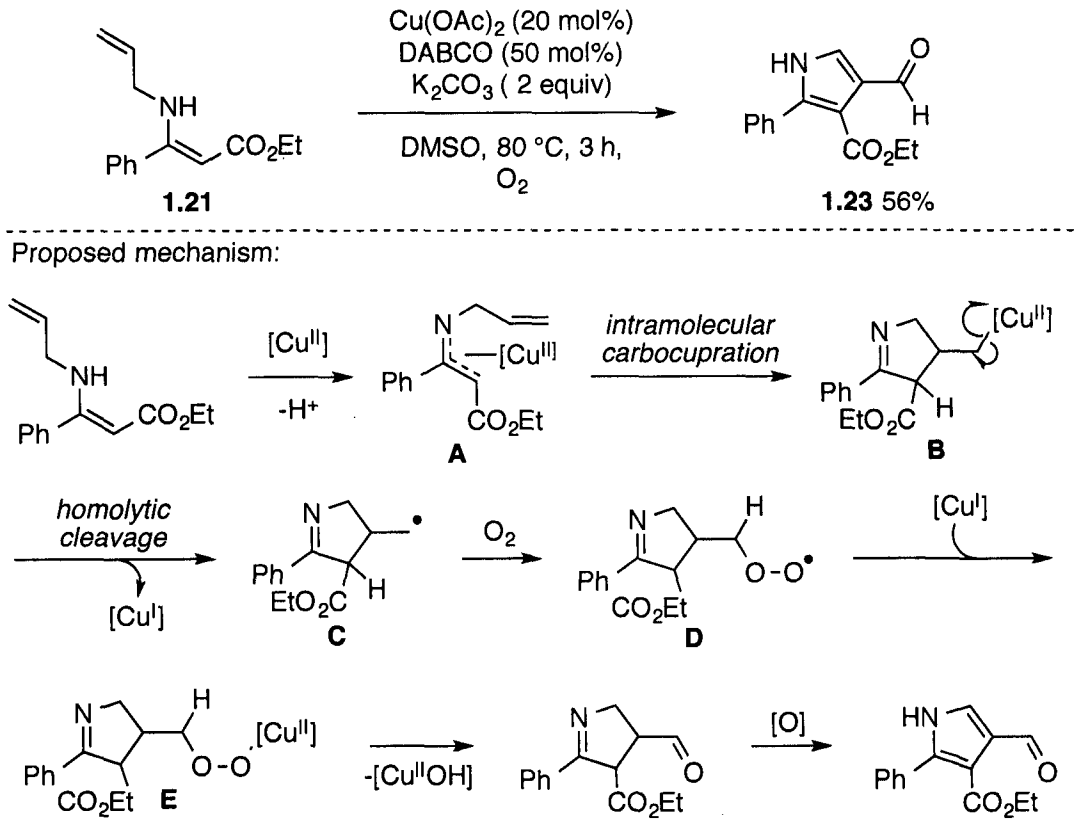
Scheme 1-22. Aerobic *Cu-catalyzed diastereoselective intramolecular amminooxygenation of alkenes.*

Our group recently disclosed an unique intramolecular cyclopropanation of alkenes by treatment of *N*-allylenamine carboxylate **1.21** with stoichiometric amounts of CuBr•SMe_2 and 2,2-bipyridine under an O_2 atmosphere (Scheme 1-23).[49] Bicyclic 3-azabicyclo[3.1.0]hex-2-ene **1.22** is obtained in high yield. It is found that O_2 is indispensable in this transformation. Therefore, it is proposed that Cu(I)Br is oxidized to Cu(II)-species by O_2, that forms copper-azaenolates **A** with the enamine moiety. Cu-azaenolate **A** undergoes C–C bond forming carbocupration with the tethered allyl moiety to give organocopper intermediate **B** of the imine form, which exists as an equilibrium mixture with organocopper intermediate **C** of the enamine form. The second C–C bond formation then occurs via intramolecular S_N2-type cyclization at the organocopper unit to afford the cyclopropane ring.



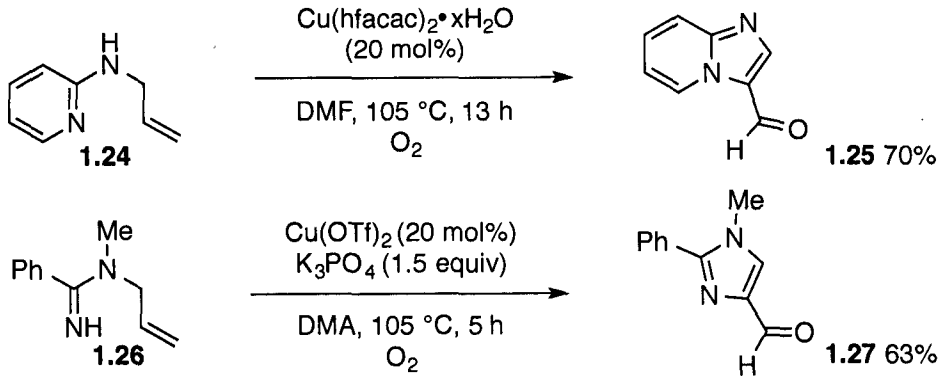
Scheme 1-23. Aerobic *Cu-mediated intramolecular cyclopropanation of alkenes from N-allyl enamine carboxylates.*

On the other hand, addition of K_2CO_3 to Cu–O_2 reaction conditions for the treatment of *N*-allylenamine carboxylate **1.21** provides a distinct pathway toward formation of 4-formylpyrrole **1.23** via carbooxygenation of the alkene (Scheme 1-24). This complementary process only requires a catalytic amount of $Cu(OAc)_2$, to facilitate the process including intramolecular carbocupration of the alkene for formation of organocopper intermediate **B**. In this case, subsequent homolytic cleavage of the carbon–copper bond of **B** results in the release of Cu(I) species and formation of carbon radical **C**, which traps O_2 to give peroxy radical **D**. Reduction of peroxy radical **D** by Cu(I) species produces Cu-peroxide complex **E**, that further undergoes decomposition via elimination of Cu(II)OH as well as oxidative aromatization occurs to afford 4-formylpyrrole **1.23**. The role of K_2CO_3 to enable this distinct pyrrole formation is, however, still unknown.



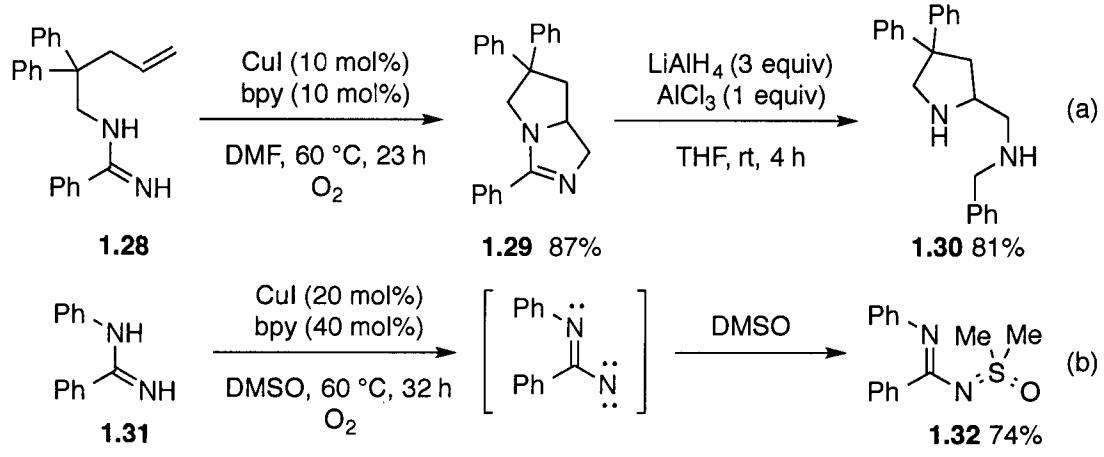
Scheme 1-24. Aerobic *Cu-catalyzed intramolecular carbooxygenation of alkenes from N-allyl enamine carboxylates.*

Analogous to enamine carboxylates, *N*-allyl-2-aminopyridine **1.24** and *N*-allylamidine **1.26** can also undergo intramolecular aminooxygenation via aminocupration-oxygenative carbonylation sequence, under aerobic Cu-catalyzed conditions to provide imidizolyl aldehyde products **1.25** and **1.27,** as reported by Zhu's group (Scheme 1-25).[50]



Scheme 1-25. Aerobic *Cu-catalyzed intramolecular aminooxygenation of alkenes from N-allyl-2-aminopyridines or N-allylamidines.*

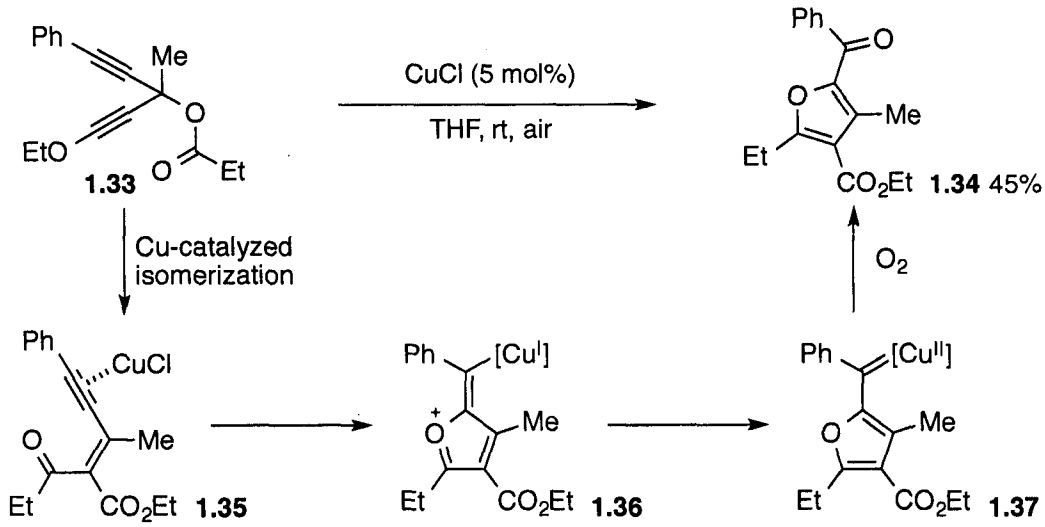
Our laboratory developed Cu-catalyzed aerobic [3+2]-annulation reaction of *N*-alkenyl amidine **1.28**, which provide bicyclic amidine **1.29** that can undergo reductive transformation to useful vicinal diamine **1.30** (Scheme 1-26a).[51] It is found that the amidine moiety is oxidized under the aerobic Cu-catalyzed conditions to nitrene species, which behaves like a 1,3-dipole to facilitate the concerted [3+2]-annulation with alkene. This is supported by isolation of sulfoxyimine **1.32** which suggest the trapping of putative nitrene species generated during the reaction with DMSO, when *N*-phenyl amidine **1.31** was treated with CuI and 2,2′-bipyridine in DMSO under O_2 atmosphere (Scheme 1-26b).



Scheme 1-26. *(a)*Aerobic *Cu-catalyzed [3+2] annulation reaction N-alkenyl amidines to bicyclic amidines and its reduction to vincinal diamines.(b) Trapping of putative nitrene species with DMSO.*

1.5 Oxidative difunctionalization of alkynes

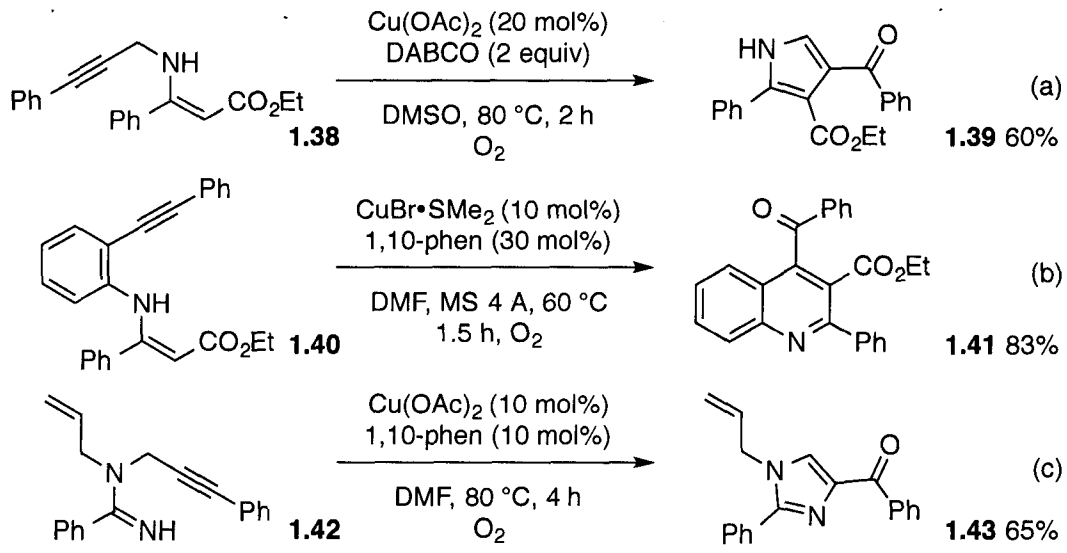
Similar to oxidative difunctionalization of alkenes, alkynes can also be activated via π-interaction with Cu-catalysts and functionalized under aerobic conditions. For example, in an explorative study of Cu-catalyzed cyclization of bispropargylic ester **1.33** for the formation of substituted furans, Barluenga and co-workers found that 2-acylfuran **1.34** could be isolated when the reaction was carried out under ambient air (Scheme 1-27).[52] The reaction is proposed to proceed via the initial Cu-catalyzed isomerization process to afford α,β,γ,δ-unsaturated carbonyl intermediate **1.35** which undergo Cu-mediated 5-exo-dig addition of the carbonyl oxygen to the alkyne. This results in vinyl Cu(I)-species **1.36**, which can isomerize to Cu(II)-carbene **1.37** where upon oxidation by molecular oxygen generates the resultant carbonyl group.



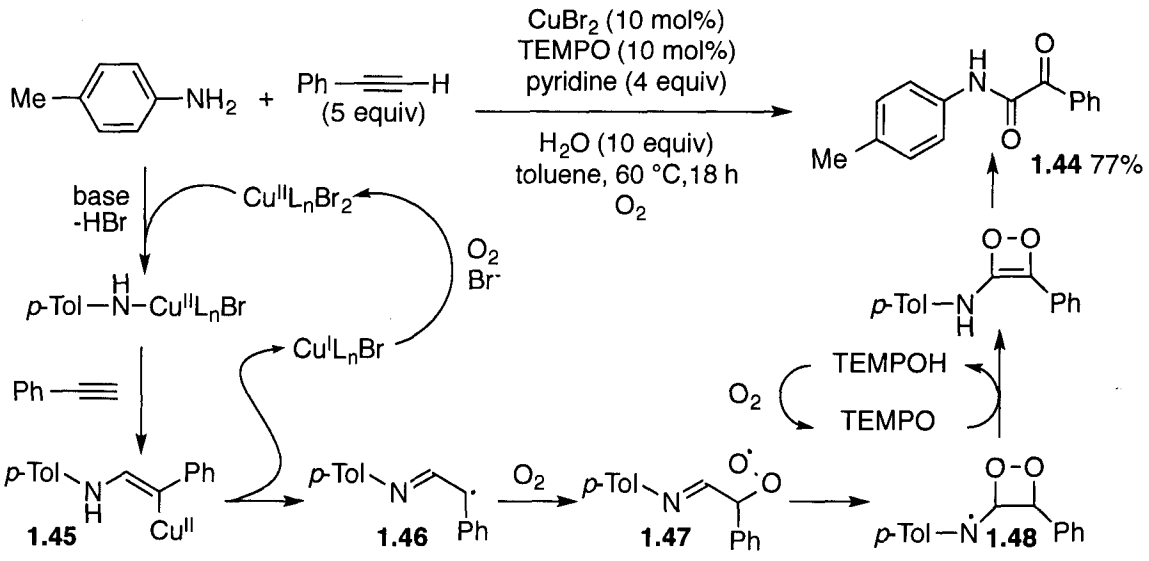
Scheme 1-27. *Aerobic Cu-catalyzed oxidative formation of 2-acylfurans from bispropargylic esters.*

Our group extended the study of intramolecular carbooxygenation of alkenes to that of alkynes using *N*-3-phenylpropargyl enamine **1.38** for the synthesis of 4-benzoylpyrrole **1.39** (Scheme 1-28a).[49] The transformation proceeds via a similar mechanism as the carbooxygenation of *N*-allyl enamine carboxylates involving a sequence of intramolecular carbocupration of alkynes followed by oxygenative carbonylation. This method provides a powerful synthetic pathway for various acylated heterocyclic arenes, which is subsequently exploited in the reaction of *N*-(2-alkynylaryl)enamine carboxylate **1.40** or *N*-alkynylamidine **1.42** for the synthesis of acylated quinolone **1.41** or imidazole **1.43** (Scheme 1-28b and c).[53]

Jiao and co-workers, on the other hand, demonstrated the amidation-diketonization of terminal alkynes for the synthesis of α-ketoamide **1.44** from primary aniline, using catalytic $CuBr_2$ and TEMPO under an O_2 atmosphere (Scheme 1-29).[54] This process is proposed to begin with the initial deprotonative coordination of the aniline to $CuBr_2$, which participates in the aminocupration across terminal alkynes to yield a vinyl Cu(II)-species **1.45**. The vinyl-Cu bond undergoes homolytic cleavage to give stabilized benzylic radical **1.46**, which traps O_2 to give peroxy radical species **1.47** that cyclizes to form 4-membered endoperoxide intermediate **1.48**. Further oxidation by either TEMPO or oxygen, followed by tautomerization results in the ketoamide product **1.44**.



Scheme 1-28. *Aerobic Cu-catalyzed intramolecular carbo- or amino-oxygenation of alkynes for the synthesis of acylated heteroarenes.*

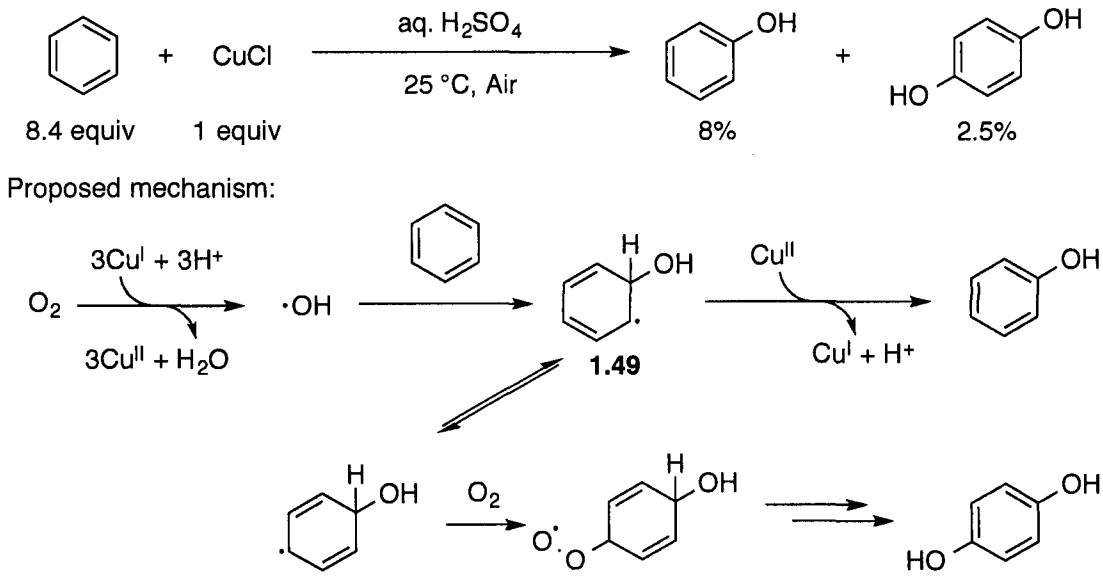


Scheme 1-29. *Aerobic Cu-catalyzed oxidative amidation-diketonization of terminal alkynes with anilines.*

1.6 Transformations of benzene

Unlike the transformation of alkenes and alkynes, transformation of aromatic benzene rings has always been a challenging idea mainly due to its high stability in its aromatic state. However, direct functionalization of simple benzene rings is a highly desirable process in both chemical industry and organic synthesis, bypassing the need of pre-functionalization. For example, Sasaki and co-workers reported direct hydroxylation of benzene using dilute aqueous sulfuric acid, with CuCl as the limiting reagent, under

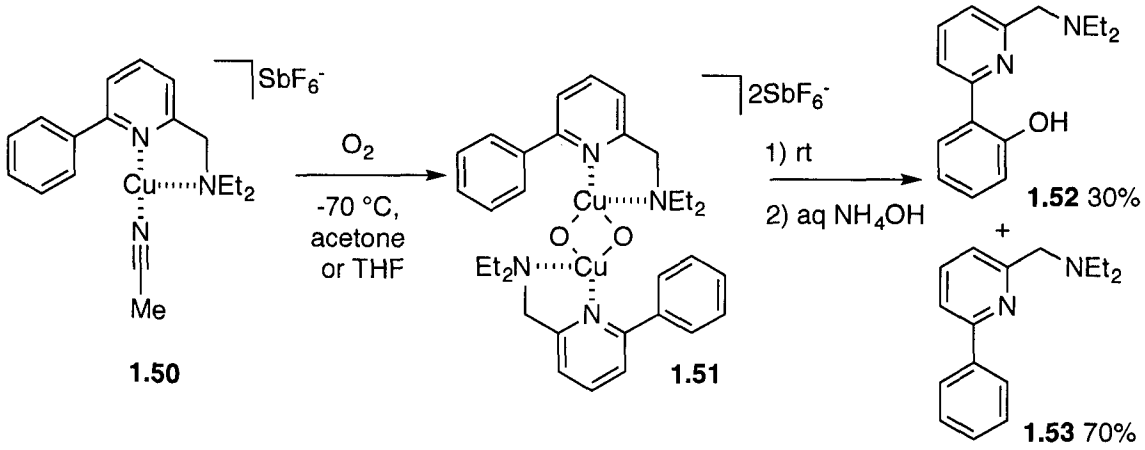
ambient air at room temperature for the synthesis of phenols (Scheme 1-30).[55] Hydroquinone was also isolated as a result of further oxidation with O_2. It is found that Cu(II)-salts are inactive in this process, thus the role of Cu(I)-salt is to serve as the reductant to react with O_2 to form hydroxyl radicals under acidic conditions. The proposed mechanism of this process proceeds via the addition of the *in situ* generated hydroxyl radical to benzene, which result in hydroxycyclohexadienyl radical **1.49** that readily undergo one-electron oxidation and rearomatization to form the phenol product. The hydroquinone byproduct is most likely formed from the reaction of hydroxycyclohexadienyl radical **1.49** with O_2.



Scheme 1-30. *Aerobic Cu-mediated direct hydroxylation of benzene to phenol.*

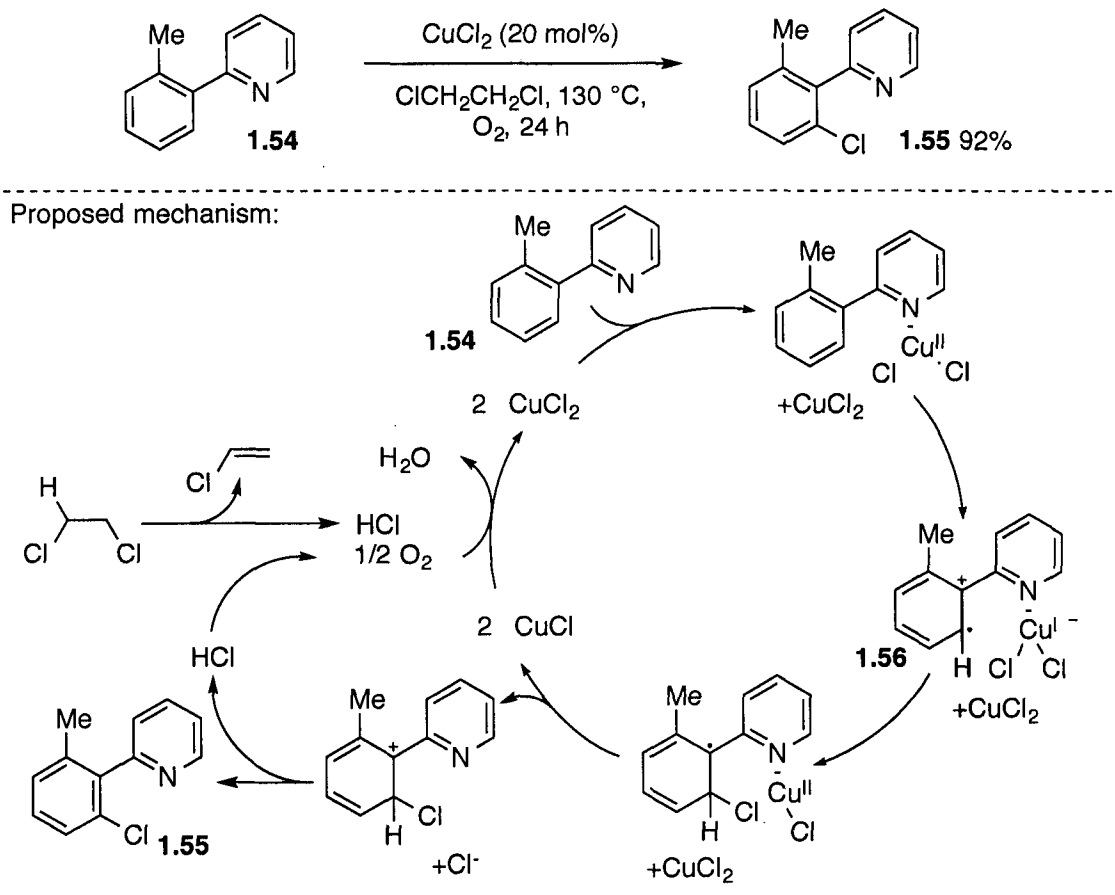
Alternatively, functionalization of benzene rings can also be achieved with the aid of some directing groups, which direct the Cu-catalysts to the desired reaction sites. For example, Tollman and co-workers established the synthesis of copper complex **1.50** with 2-(diethylaminomethyl)-6-phenylpyridine (**1.53**) ligand that forms bis(μ-oxo)dicopper species **1.51** upon exposure to O_2 (Scheme 1-31).[56] When **1.51** is subjected to thermal decomposition and decomplexation, it is found that some of the 2-(diethylaminomethyl)-6-phenylpyridine ligand **1.53** is hydroxylated at the *ortho*-position to give **1.52**.

Therefore, this finding demonstrated the possibility of benzene functionalization with the aid of directing groups.



Scheme 1-31. *Arene hydroxylation of a bis(μ-oxo)dicopper complex.*

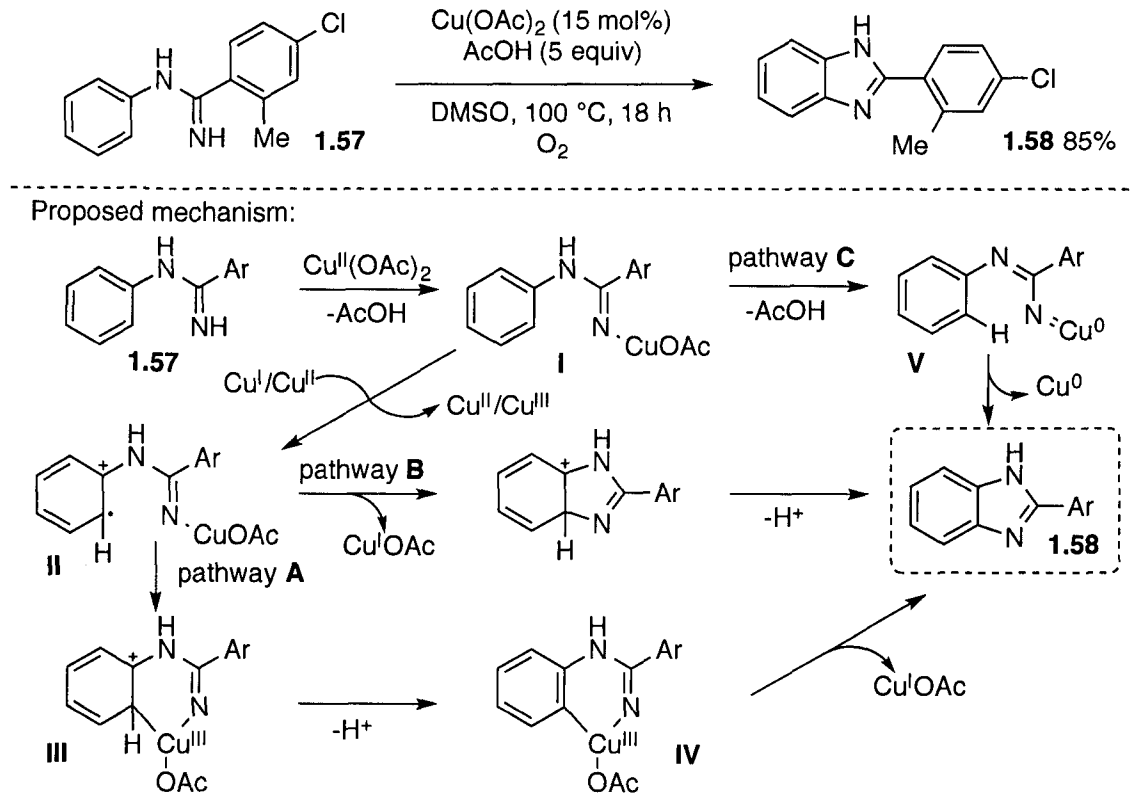
Yu and co-workers reported oxidative chlorination of arene **1.54** with pyridyl directing group, using catalytic $CuCl_2$ in 1,2-dichloroethane under an O_2 atmosphere (Scheme 1-32).[57] The reaction is proposed to proceed via the coordination of $CuCl_2$ to the *ortho*-pyridyl group, which facilitated the formation of radical cation intermediate **1.56** that traps Cl^- from the nearby $CuCl_2$. Subsequent oxidation of the resulting radical intermediate to cation, followed by elimination of proton provides chlorinated product **1.55**. The resulting Cu(I)Cl is reoxidized by O_2 to regenerate the active $Cu(II)Cl_2$ catalyst. As 1,2-dichloroethane can undergo elimination to release HCl, it plays a significant role in the generation of Cl anion. Although bromination, iodination, cyanation, alkoxylation, hydroxylation, thiolation, and amination were also explored, poor to moderate yields of functionalized arenes were obtained, sometimes require stoichiometric amounts of Cu-salts.



Scheme 1-32. *Aerobic Cu-catalyzed oxidative directed chlorination of arenes.*

Buchwald and co-workers, reported intramolecular oxidative cyclization of aryl amidine **1.57** to afford benzimidazole **1.58** using $Cu(OAc)_2$ as catalyst under an O_2 atmosphere (Scheme 1-33).[58] In this case, the amidine moiety with a bulky substituent undergoes oxidative aryl C–N bond formation, which is speculated to proceed via three possible pathways, starting from common copper adduct **I** with concomitant deprotonation. Both pathways A and B proceed via single-electron-oxidation of the aryl ring to form common radical cation **II**. Pathway A proceeds via the radical attack on copper followed by rearomatization to form the metallocyclic Cu(III)-complex **IV**, which undergoes subsequent reductive elimination to afford **1.58**. In pathway B, the radical cation **II** is proposed to react directly with the amidine nitrogen and release Cu(I)OAc, that is followed by rearomatization to give **1.58**. Alternatively, pathway C is also suggested for the formation of copper nitrene intermediate **V**, that may proceed either via

direct insertion into the arene C−H bond or via electrocyclic ring-closure followed by [1,3]-H-shift to afford **1.58**.



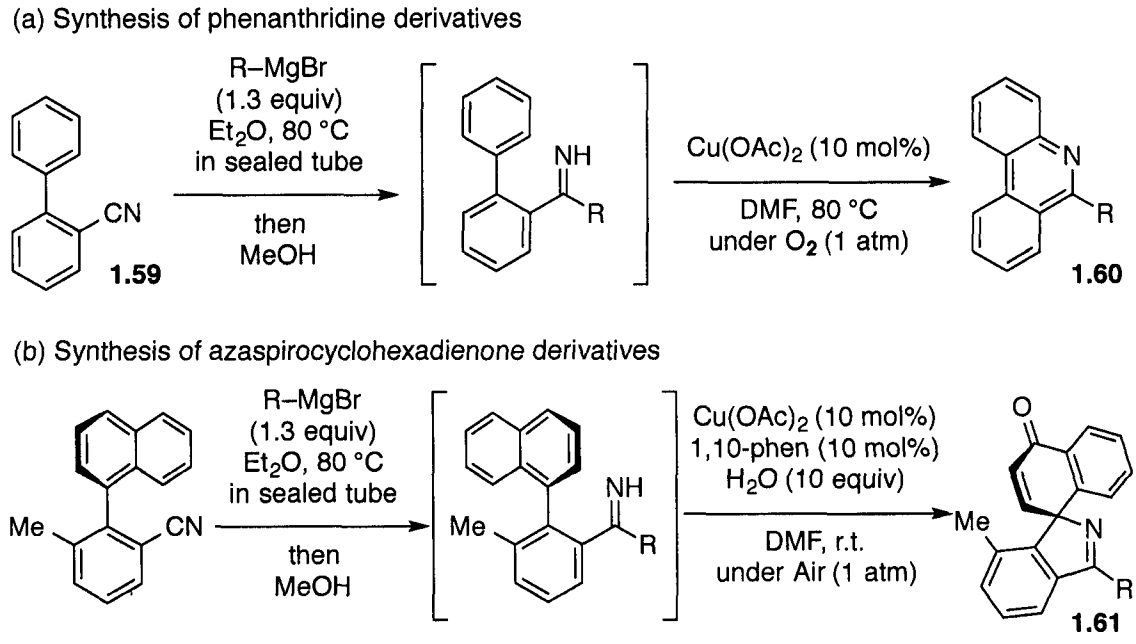
Scheme 1-33. *Aerobic Cu-catalyzed amidine-directed oxidative intramolecular C-H insertion into arenes.*

1.7 Perspective for the thesis

Intrigued by the wide applications of the Cu–O_2 system in various classes of molecular transformations, the author strives to explore the utility of Cu-catalyzed aerobic reaction conditions in molecular transformations involving heteroatom radicals. As higher-valent Cu(II)-species are effective to induce one-electron-oxidation, radical transformation via single-electron-transfer from appropriate electron-rich organic molecules could be readily initiated.[59] Thus, the combination of Cu-complexes with O_2 surfaced as a facile process allowing catalytic turnover in net oxidative processes,[60] while performing potentially useful radical transformations with heteroatoms.

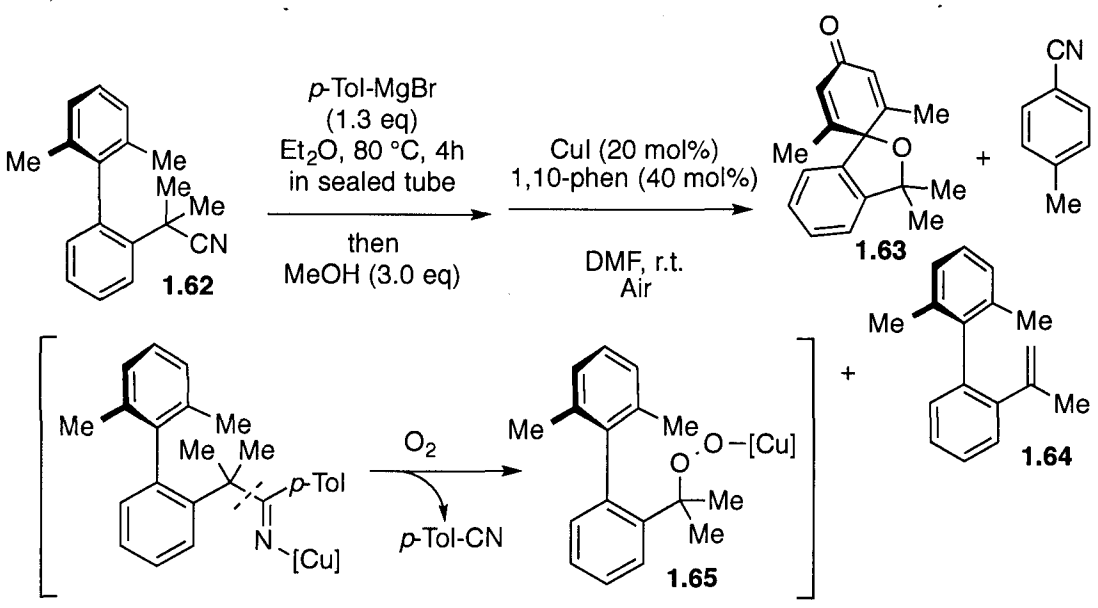
In this thesis, the study of Cu-catalyzed aerobic molecular transformations involving nitrogen- and oxygen-centered radicals generated from *N*-H-imines, organohydroperoxides and *N*-hydroxyphthalimide will be presented. The initial interest

sparked from the study of Cu–catalyzed aerobic C–N bond formation on an intramolecular aryl C–H bond using the biaryl-*N*-H imines generated from biaryl-2-carbonitrile **1.59** to afford phenanthridine derivative **1.60** (Scheme 1-34a).[61] By installing *ortho*-substituents on the biaryl-2-carbonitriles, a helical effect was created as rotation about the biaryl axis is hindered. Thus, an orthogonal reactivity was observed using similar reaction conditions, affording azaspirocyclohexadienone **1.61** (Scheme 1-34b). The copper catalyzed aerobic spirocyclization of biaryl *N*-H imines via 1,4-aminooxygenation of benzene rings from readily available biaryl-2-carbonitriles and Grignard reagents in a one-pot manner is studied and presented in Chapter 2.[62]



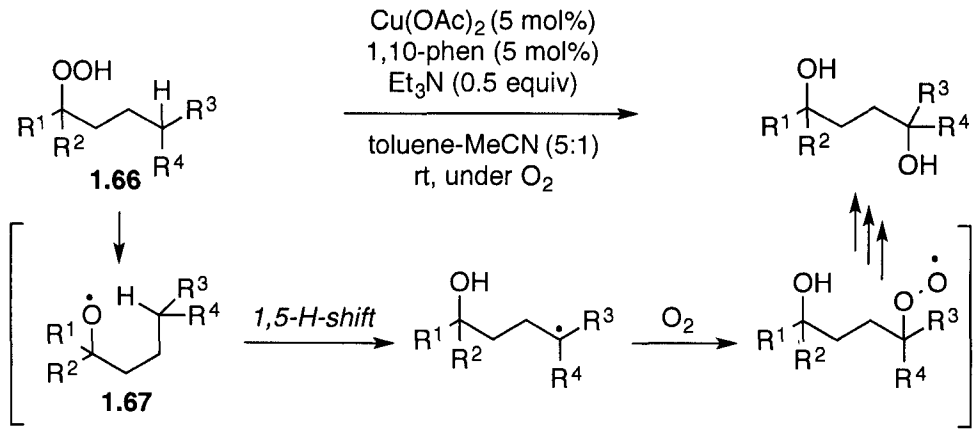
Scheme 1-34. *Aerobic Cu-catalyzed synthesis of phenanthridine derivatives and azaspirocyclohexadienone derivatives starting from biaryl-2-carbonitriles and Grinard reagents.*

When biaryl-2-methane carbonitrile **1.62** is treated under similar reaction conditions, oxospirocyclohexadienone **1.63** is isolated together with germinal alkene **1.64** and *p*-tolylcarbonitrile (Scheme 1-35). It is postulated that the *N*-H imine undergoes a C–C bond cleavage to give *p*-tolylnitrile and copper-peroxy intermediate **1.65**, which could generate hydroxyl radical for spirocyclization with the benzene ring to afford the oxospirocyclohexadienone **1.63**.



Scheme 1-35. Aerobic *Cu-catalyzed synthesis of oxopirocyclohexadienone starting from biaryl-2-methane carbonitrile and Grinard reagents.*

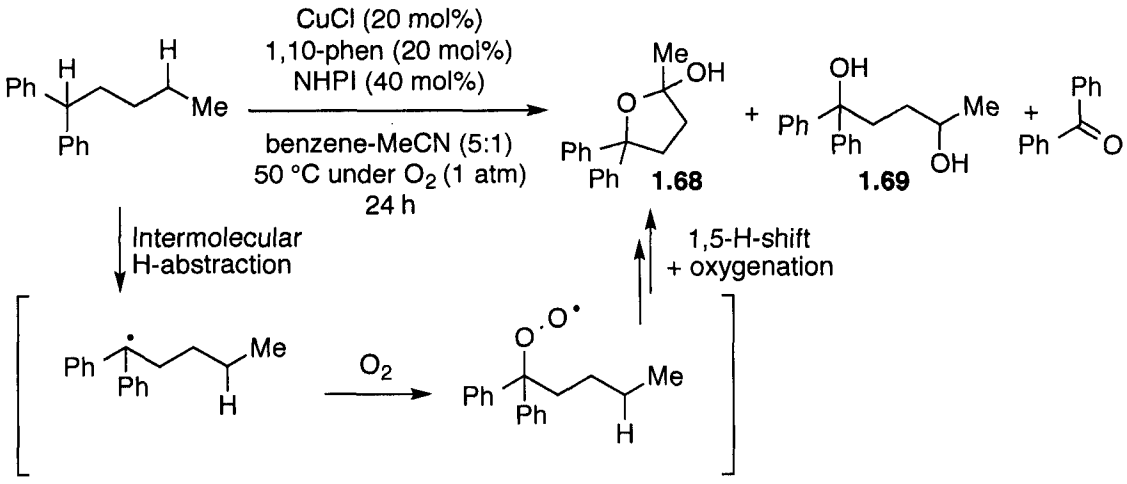
Inspired by the above oxospirocyclohexadienone synthesis, it was hypothesized that organohydroperoxide **1.66** could generate alkoxy-radical species **1.67** under Cu-catalyzed aerobic conditions to perform 1,5-H radical shift on aliphatic C-H bonds. The resulting carbon radical could be oxygenated by O_2. Thus, Cu-catalyzed aerobic oxygenation of aliphatic C-H bonds with hydroperoxides for the synthesis of 1,4-diols is explored and the results and findings are described in Chapter 3 (Scheme 1-36).[63]



Scheme 1-36. *Cu-catalyzed aerobic oxygenation of aliphatic C-H bonds with hydroperoxides for the synthesis of 1,4-diol.*

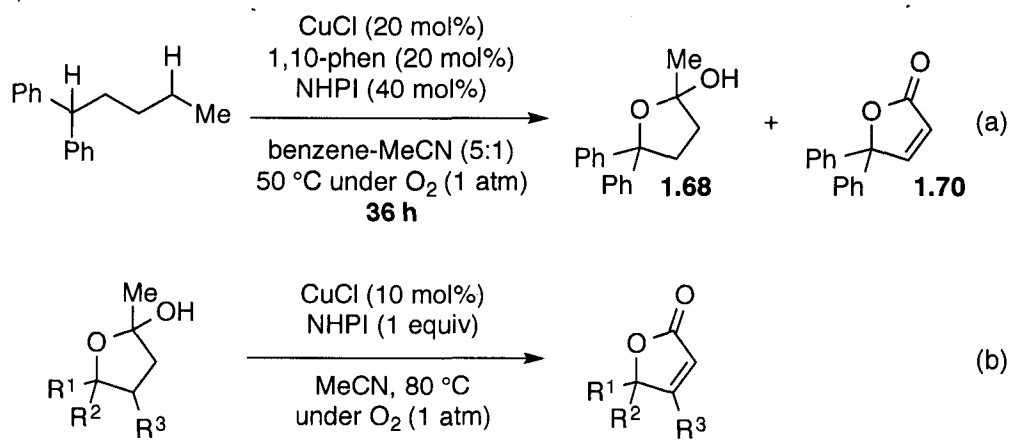
This methodology is further applied in the direct aerobic polyoxygenation of alkanes. With the use of *N*-hydroxyphthalimide (NHPI) under Cu-catalyzed aerobic reaction conditions, phthalimide *N*-oxyl radical can be generated for intermolecular

hydrogen abstraction of alkanes. The resulting carbon-radicals could be trapped with molecular oxygen to form hydroperoxides, which proceeds with further 1,5-hydrogen abstraction, resulting in direct formation of 1,4-dioxygenated compounds including lactol **1.68** and 1,4-diol **1.69** from non-oxygenated alkanes (Scheme 1-37).



Scheme 1-37. *Aerobic Cu-NHPI catalyzed direct polyoxygenation of alkanes.*

During the study of direct aerobic polyoxygenation of alkanes, α,β-unsaturated lactone **1.70** is also isolated after prolonging the reaction time from 24 to 36 hours, while the yield of lactol **1.68** decreased (Scheme 1-38a). It is found that α,β-unsaturated lactone **1.70** was formed from lactol **1.68** via elimination of the methyl group as well as α,β-unsaturation under the Cu-catalyzed aerobic reaction conditions (Scheme 1-38b). The investigation of this unprecedented aerobic Cu-catalyzed NHPI-mediated synthesis of α,β-unsaturated lactones from the corresponding lactols via radical C-C bond cleavage is discussed in Chapter 4.[64]



Scheme 1-38. *Aerobic Cu-catalyzed NHPI-mediated synthesis of α,β-unsaturated lactones from the corresponding hemiacetals via radical C-C bond cleavage.*

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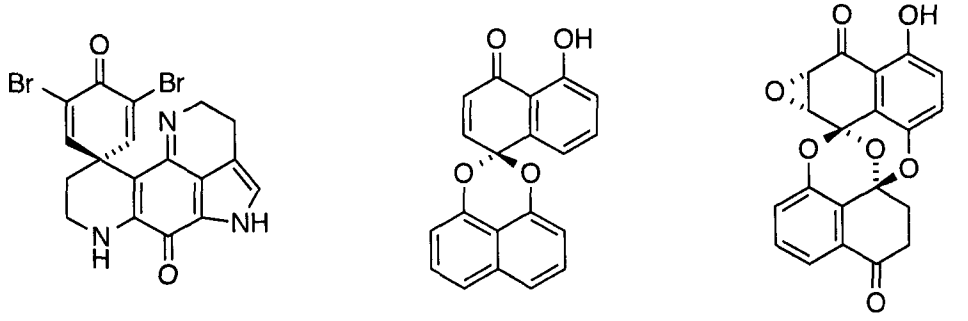
Chapter 2: Copper-Catalyzed Aerobic Spirocyclization of Biaryl-*N*-H-imines via 1,4-Aminooxygenation of Benzene Rings

2.1 Introduction

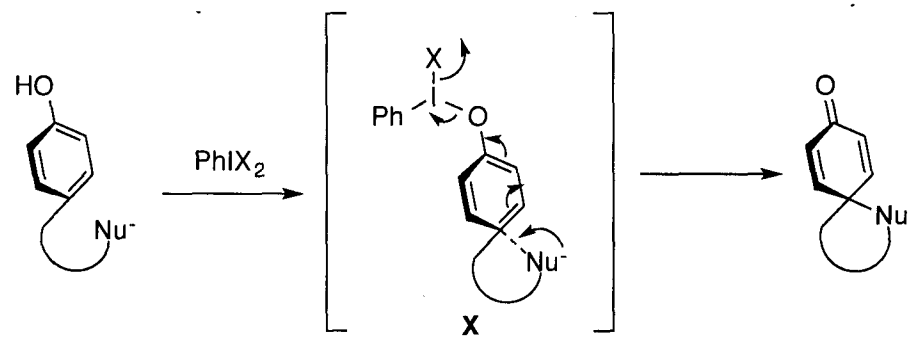
Spirocyclohexadienone structures are found in several biologically active natural products.[1] For instance, discorhabdin C, a member of the discorhabdin alkaloids isolated from marine sponges, is a potential anti-tumor agent, exhibiting extreme toxicity toward P388 tumor cells and L1210 leukemia cells (Figure 2-1a).[2] Fungi metabolites, such as palmarumycin CP_1 and preussomerin G, which possess both antifungal and antibacterial activities, are also built around spirocyclohexadienone core structures (Figure 2-1b and c).[3] Hence, the construction of the spirocyclohexadienone scaffolds is an important process toward the synthesis of these important compounds.



(a) *Discorhabdin C* (b) *Palmarumycin CP_1* (c) *Preussomerin G*

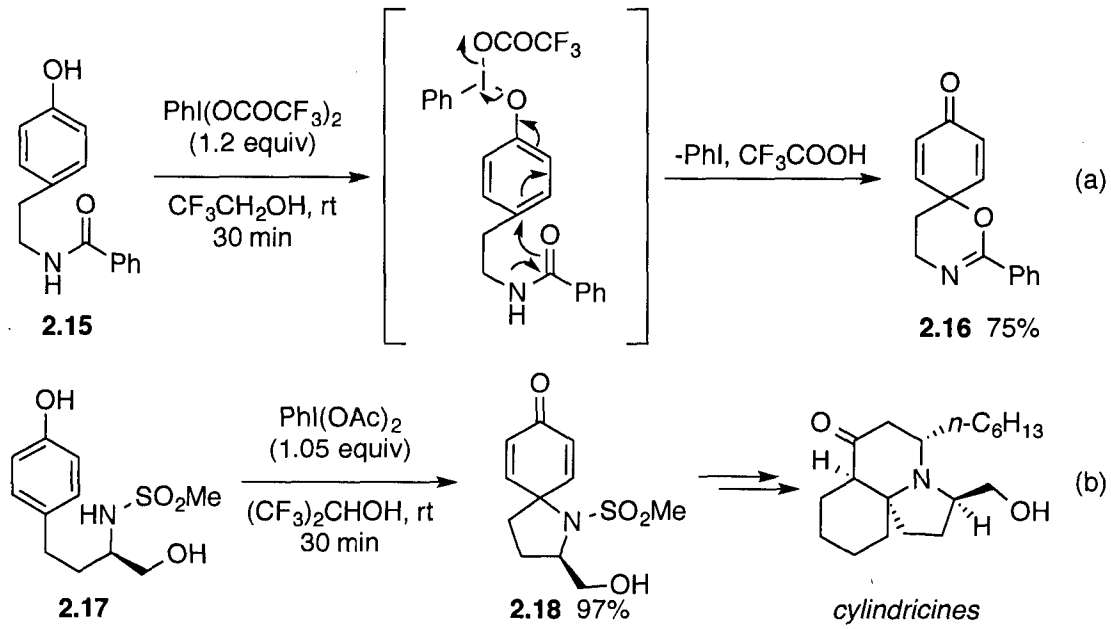
Figure 2-1. *Spirocyclohexadienones core structures in biologically active natural products*

One of the most established methods to construct such spirocyclic cores is oxidative intramolecular spirocyclization of phenol derivatives, using a stoichiometric amount of hypervalent iodine reagents.[4] In this process, the phenolic hydroxyl group is oxidized by hypervalent iodine reagent ($PhIX_2$) to form aryloxyiodonium(III) intermediate **X**, which activates the phenol ring for intramolecular spirocyclization at the *ipso*-position with internal nucleophile (Nu^-) to afford spirocyclohexadienone product (Scheme 2-1).



Scheme 2-1. *Organohypervalent iodine reagent mediated intramolecular ipso-spirocyclization of phenols.*

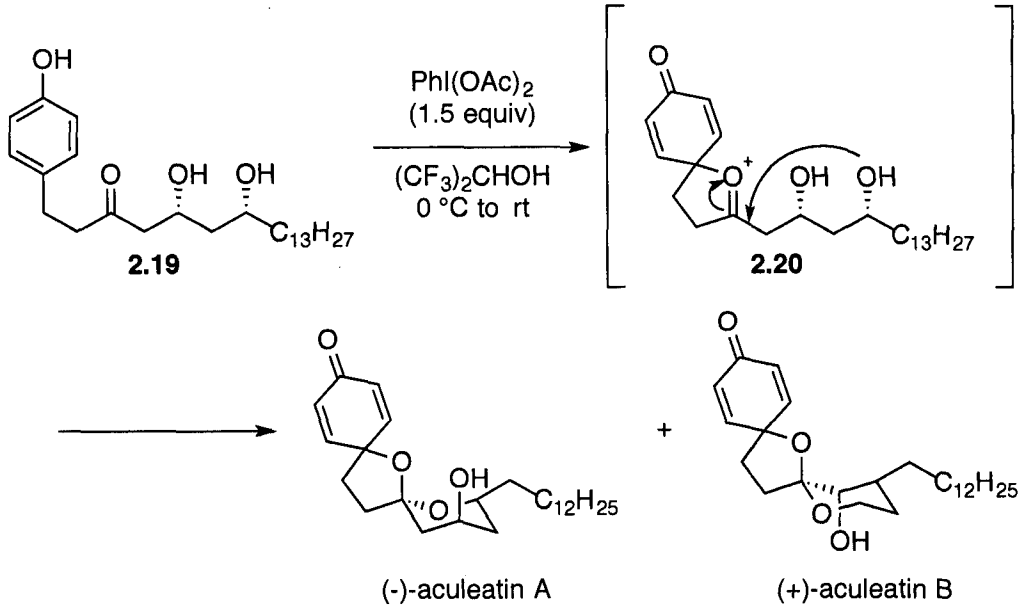
For example, Kita and co-workers developed hypervalent iodine-mediated spirocyclization of *N*-acyltyramine **2.15** to oxospirocyclohexadienone **2.16**, utilizing the amido group as the internal nucleophile (Scheme 2-2a).[5] This strategy was later applied in the total synthesis of discorhabdin C.[6] On the other hand, Ciufolini and co-workers also reported spirocyclization of phenolic primary amine **2.17** using a slight excess amount of iodosobenzene diacetate to azaspirocyclohexadienone **2.18**, which was utilized in the synthesis of cytotoxic active compounds, the cylindricines (Scheme 2-2b).[7]



Scheme 2-2. *Hypervalent iodine mediated spirocyclization phenolic derivatives for the synthesis of spirocyclohexadienones scaffold.*

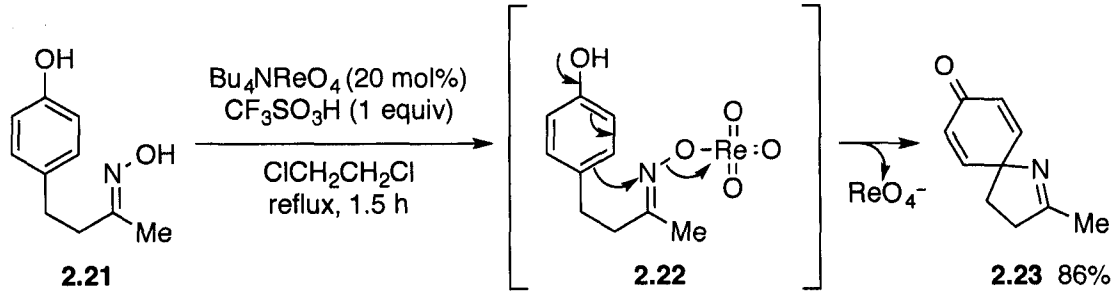
In addition, Wong and co-workers utilized the oxidation of 2-(4-hydroxyphenyl) ethyl ketone derivative **2.19** with stoichiometric amounts of iodosobenzene diacetate to access spirocyclohexadienone-oxocarbenium ion **2.20**, which allows cascade

intramolecular cyclization with a hydroxyl group to achieve both aculeatin A and B in one step (Scheme 2-3).[8]



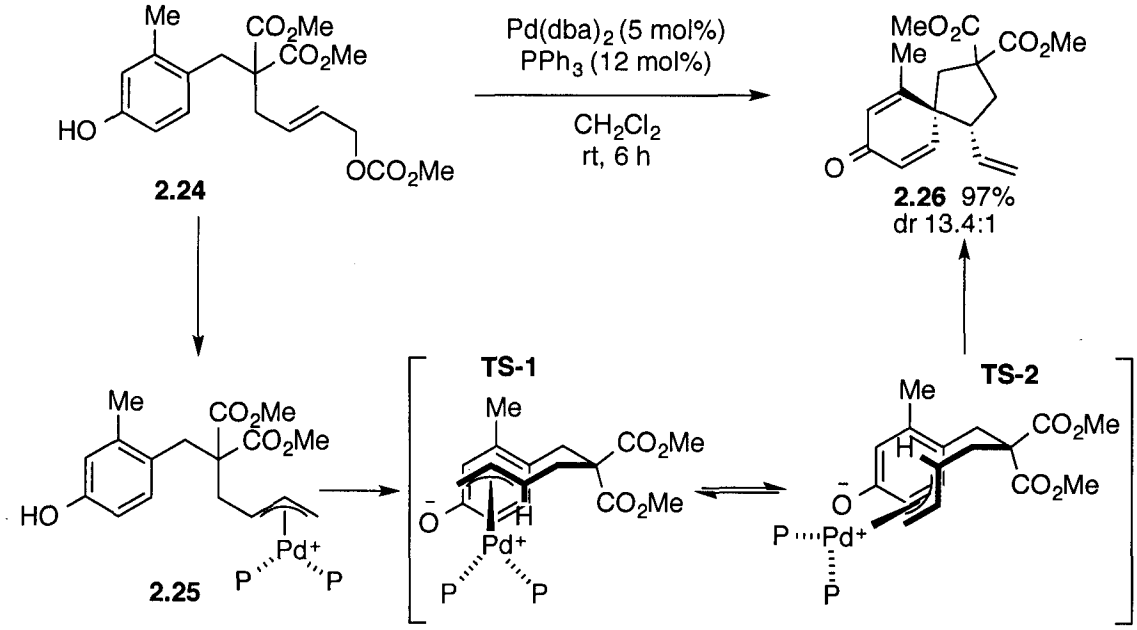
Scheme 2-3. *Hypervalent iodine mediated oxidation of 2-(4-hydroxyphenyl)ethyl ketone derivatives for the synthesis of aculeatin analogs.*

Besides the use of hypervalent iodine reagents for intramolecular nucleophilic spirocyclization of phenols, transition-metal catalyzed spirocyclization of phenols has also been developed for the synthesis of spirocyclohexadienone scaffolds. Narasaka and co-workers discovered the tetrabutylammonium perrhenate catalyzed spirocyclization of *p*-hydroxphenethyl ketone oxime **2.21** to azaspirocyclochexadienone **2.23** (Scheme 2-4).[9] In this case, the oxime **2.21** formed *O*-trioxorhenio oxime **2.22**, which allows intramolecular nucleophilic substitution at the oxime sp^2 nitrogen with the *ipso*-carbon of phenol moiety to afford **2.23**, and regenerate the rhenium catalyst.



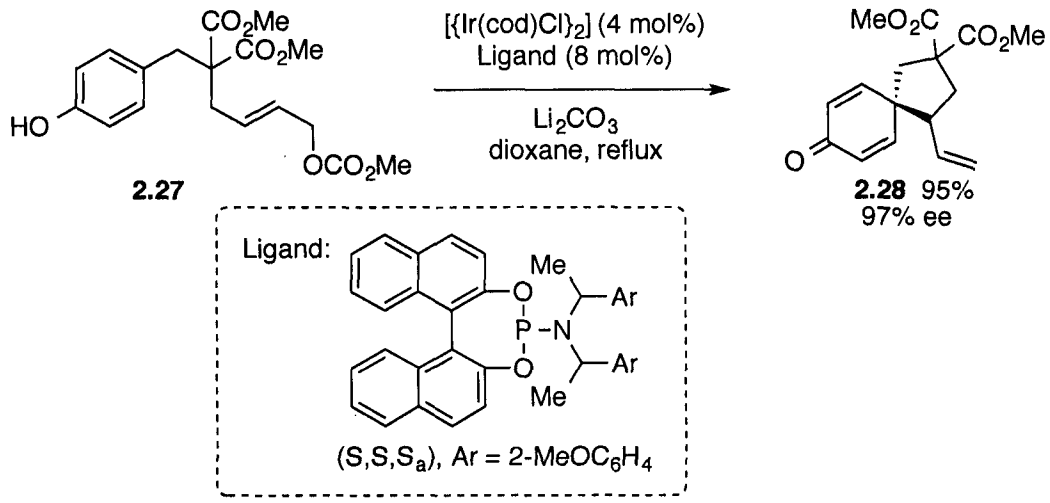
Scheme 2-4. *Rhenium catalyzed of spirocyclization of p-hydroxyphenethyl ketone oxime derivatives.*

Recently, Hamada and co-workers reported palladium-catalyzed intramolecular spirocyclization via *ipso*-Friedel-Crafts allylic alkylation of phenols tethered with allylic carbonate (**2.24**) to deliver spiro[4.5]cyclohexadienone (**2.26**) (Scheme 2-5).[10] It is postulated that oxidative addition of allylic carbonate to the Pd(0)-catalyst first occurs to form π-allylpalladium species **2.25**. Next, deprotonation of the phenol by the endogenous methoxide anion proceeds to facilitate the nucleophillic attack of the *ipso*-carbon of phenol. Carbon-carbon bond formation occurs via transition states **TS-1** or **TS-2**, where the proximal arrangement of both reactive centers is facilitated by the chair-like transition state structure. The use of chiral diphosphine ligands in this method can also provide enantioselective spirocyclization to construct all-carbon quaternary spirocenters.



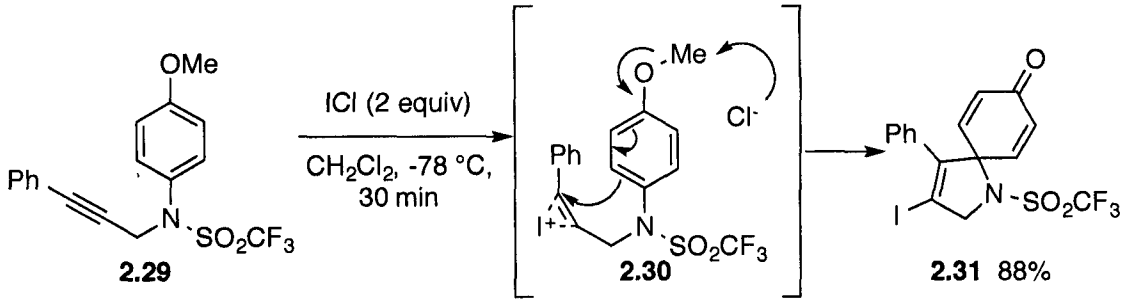
Scheme 2-5. *Palladium-catalyzed intramolecular spirocyclization via ipso-Friedel-Crafts allylic alkylation of phenols to spiro[4.5]cyclohexadienones.*

You and co-workers reported their work on iridium-catalyzed asymmetric allylic spirocyclization of 4-hydroxyphenyl-tethered allylic carbonates using chiral binaphthol phosphoramidite ligand **2-27**, leading to substituted spirocyclohexadienone **2.28** with up to 97 % enantiomeric excess (Scheme 2-6).[11]



Scheme 2-6. *Iridium-catalyzed asymmetric intramolecular spirocyclization of 4-hydroxylphenyl-tethered allylic carbonates with chiral binaphtol phosphoramidite ligand.*

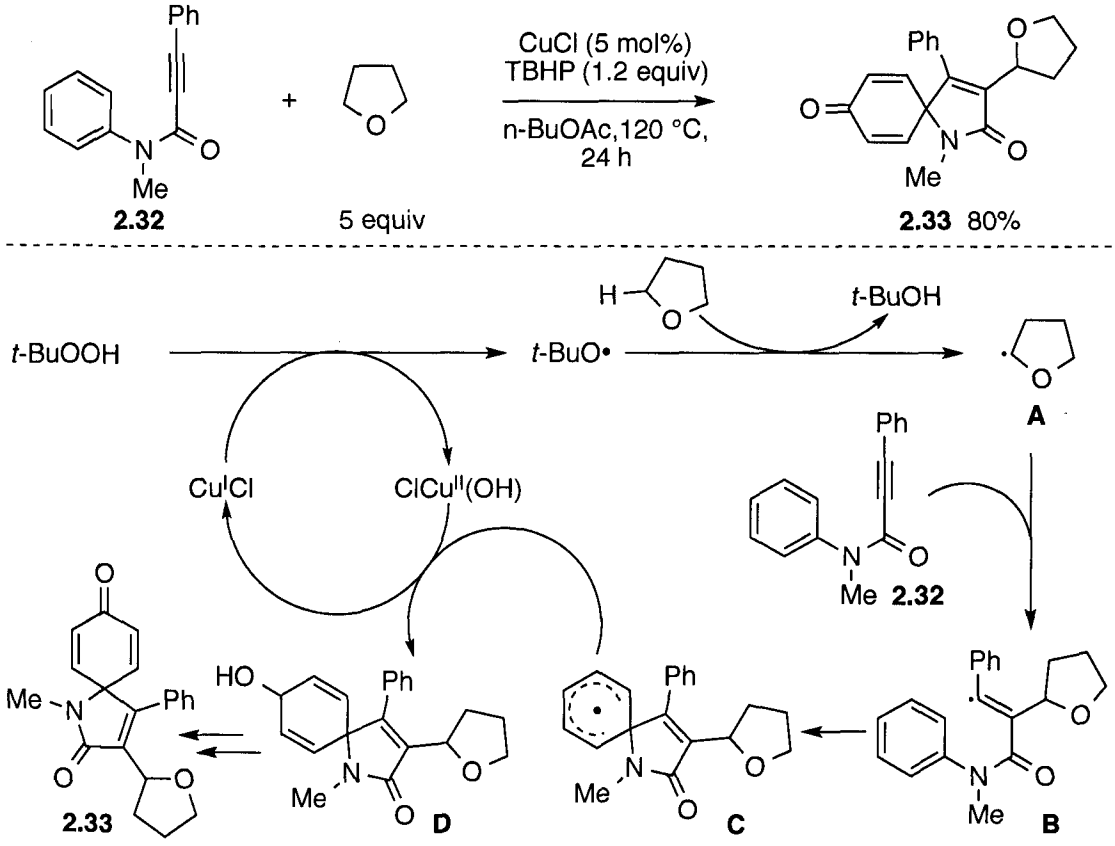
Alternatively, halogenated spirocyclodienone derivatives **2.31** can also be constructed via electrophilic *ipso*-carbocyclization of methoxy-substituted 4-aryl-1-alkynes **2.29** with halogen electrophiles as reported by Larock's group (Scheme 2-7).[12] This reaction is driven by the formation of iodonium cation **2.30** that induces intramolecular *ipso*-carbocyclization to achieve the resultant halogenated spirocyclodienone product.



Scheme 2-7. *Intramolecular electrophilic ipso-halocyclization of methoxy-substituted 4-aryl-1-alkynes with halogen electrophiles.*

Although the utility of phenolic derivatives to construct spirocyclohexadienone backbone has been established, oxidative intramolecular *ipso*-cyclization with dearomatization of simple benzene rings are also attractive strategies toward the construction of spirocyclohexadienone scaffolds. For example, Li and co-workers disclosed an example of Cu-catalyzed synthesis of 3-etherified azaspiro[4.5]trienone **2.33** from *N*-arylpropiolamide **2.32** and ethers using *tert*-butylhydroperoxide (TBHP) as

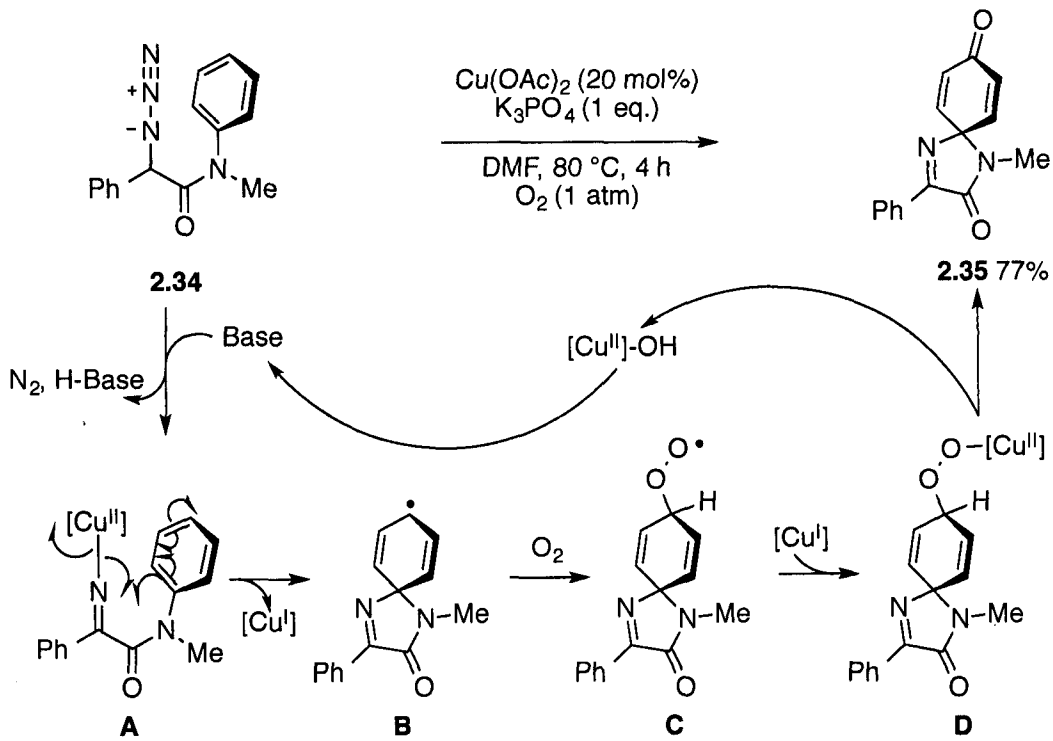
oxidant (Scheme 2-8).[13] It is proposed that the transformation proceeds through sequential oxidative C(sp3)–H functionalization, *ipso*-carbocyclization, and oxidative dearomatization. Firstly, Cu(I)-catalyzed reduction of TBHP to produce Cu(II)-OH species and *tert*-butyl alkoxide radical, which abstracts hydrogen radical from THF to generate alkyl radical **A**. Subsequently, alkylation of alkyne **2.32** via addition of alkyl radical **A** affords vinyl radical **B**, which undergo intramolecular *ipso*-carbocyclization to give radical **C**. The Cu(II)-OH species then oxidizes radical **C** to regenerate the active Cu(I) species together with corresponding dienol-intermediate **D**, that undergoes further oxidation to afford the desired azaspiro[4,5]-trienone **2.33**.



Scheme 2-8. *Copper-catalyzed synthesis of etherified azaspiro[4.5]trienones from N-arylpropiolamides and ethers.*

Recently, our group has been studying the copper-mediated oxidative functionalization of C–C unsaturated bond using enamine carboxylates,[14] amidines,[15] and *N*–H imines,[16] under aerobic reaction conditions to synthesize azaheterocycles. In these systems, molecular oxygen not only acts as the terminal oxidant to maintain the catalytic

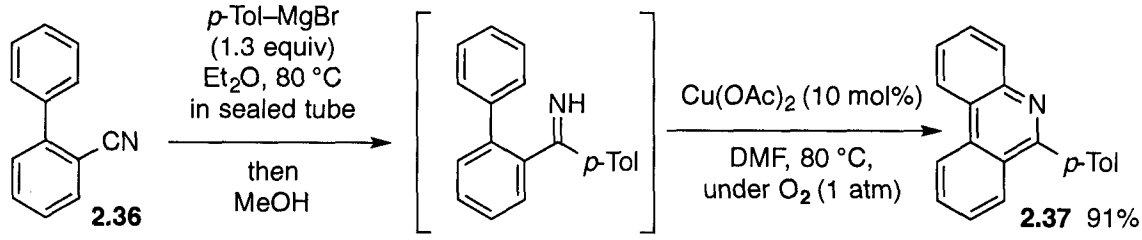
cycle, but also provides a source of the oxygen atom for formation of carbonyl bonds in some cases.[17] During these studies, copper-catalyzed aerobic synthesis of azaspirocyclohexadienone **2.35** from α-azido-*N*-arylamide **2.34** was discovered (Scheme 2-9).[18] It is proposed that the reaction proceeds through denitrogenative formation of iminyl copper species **A** from α-azido-*N*-arylamides **2.34**, followed by the oxidative formation of iminyl radical and its *ipso*-cyclization to the intramolecular benzene ring on the amido-nitrogen to generate cyclohexadienyl radical **B**. Trapping of molecular oxygen with cyclohexadienyl radical **B** results in formation of peroxy radical **C**. Single-electron-reduction of peroxy radical **C** by Cu(I) species forms Cu(II)-peroxy species **D**, which undergoes decomposition to release Cu(II)-OH species and azaspirocyclohexadienone **2.35**.



Scheme 2-9. *Copper-catalyzed aerobic synthesis of azaspirocyclohexadienones from α-azido-N-arylamides.*

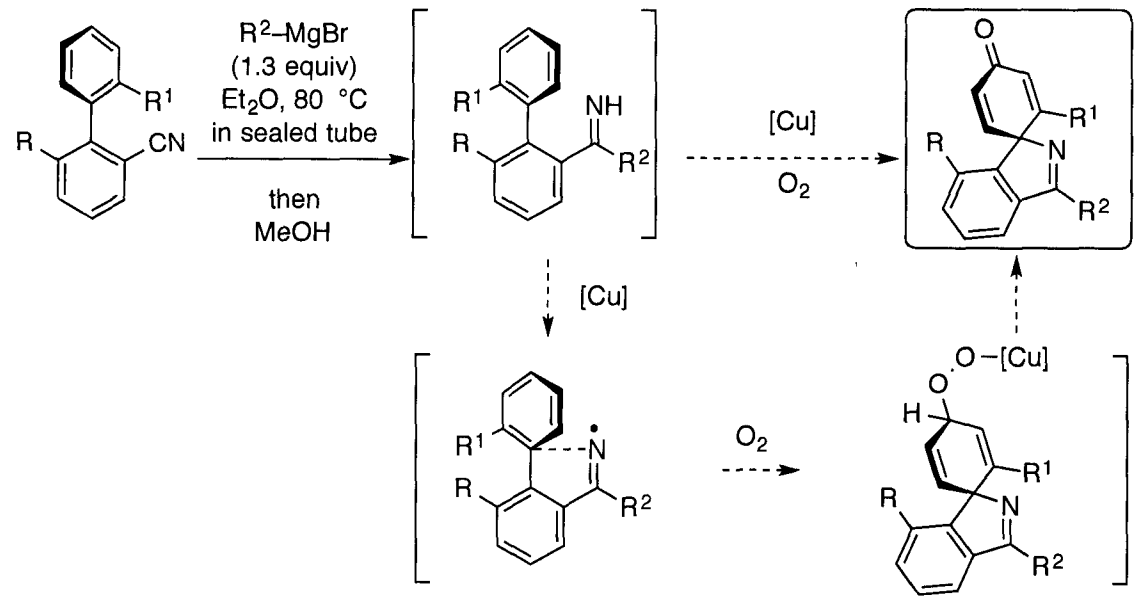
WIth this unprecedented oxygenative dearomatization of benzene rings under copper-catalyzed aerobic conditions with *N*-H-imines for the construction of spirocyclohexadienone scaffolds, the author explored the utility of this concept in

transforming other readily available building blocks toward azaspirocyclohexadienones. One of the alternative ways to access *N*–H imines is to utilized carbonitriles as a precursor by the reaction with Grignard reagents followed by protonation.[19] Using this pathway, our group previously reported synthesis of phenanthridine derivative **2.37** via Cu–catalyzed aerobic aromatic C–H bond amination through radical cyclization of the putative iminyl radicals presumably formed via single-electron-oxidation of the *N*-H imine intermediate (Scheme 2-10).[20]



Scheme 2-10. *Aerobic Cu-catalyzed synthesis of phenanthridine derivatives starting from biaryl-2-carbonitriles and Grinard reagents.*

On the other hand, it is hypothesized that the *ortho*-substituents effect should prevent the aromatic C–H amination, while maintaining a helical sense on the biaryl-2-*N*-H-imine by hindering rotation about the biaryl axis (Scheme 2-11). This will allow the putative iminyl radical species to interact with the π-face of the benzene ring rather than benzene sp^2 carbon, thus allowing the analogous spirocyclization.



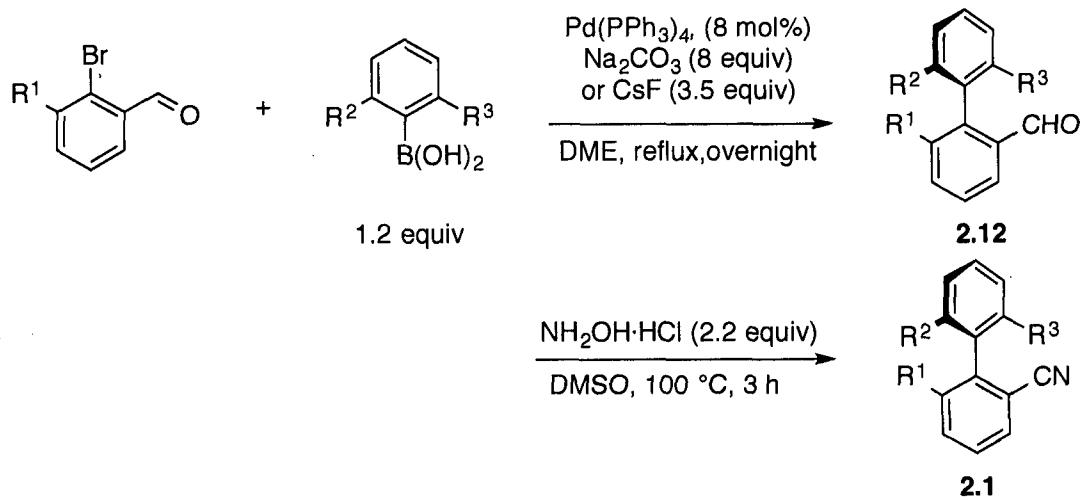
Scheme 2-11. *Working hypothesis of an aerobic Cu-catalyzed spirocyclization of biaryl-2-N-H imines with ortho-substituents.*

In this chapter, the author describes the synthesis of spirocyclohexadienones via Cu-catalyzed aerobic spirocyclization of benzene rings, exploiting the use of biaryl *N*–H imines, which can be prepared from readily available biaryl-2-carbonitriles and Grignard reagents in one-pot manner. During the course of substrate scope screening for synthesis of azaspirocyclohexadienones, the author also found unexpected oxospirocyclohexadienone formation from biaryl-2-methane carbonitriles under similar reaction conditions.

2.2 Results and Discussion

2.2.1 Preparation of biaryl carbonitriles

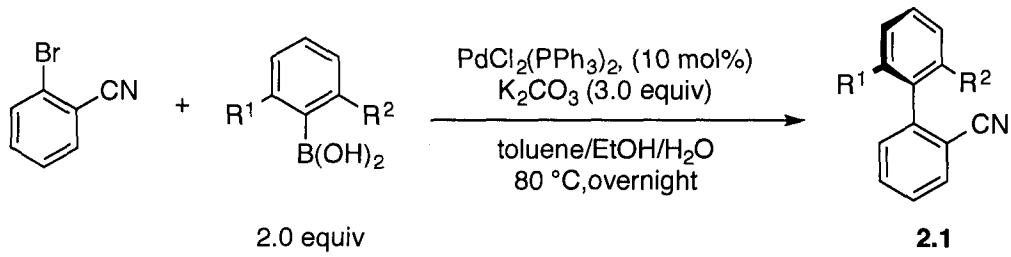
Biaryl-2-carbonitriles **2.1** are synthesized via two methods. **Method A** utilized Pd(0)-catalyzed Suzuki–Miyaura cross coupling reaction of 2-bromoaryl aldehydes and aryl boronic acids[21] followed by treatment of biaryl-2-carbaldehydes **2.12** with hydroxylamine[22] as shown in Scheme 2-12. Biaryl-2-carbonitriles **2.1a-2.1h** and **2.1p-2.1s** are synthesized by this method. Details of procedures and yields can be found in Chapter 5, Section 5.2.1.1.



Scheme 2-12. *Preparation of biaryl-2-carbonitriles Method A.*

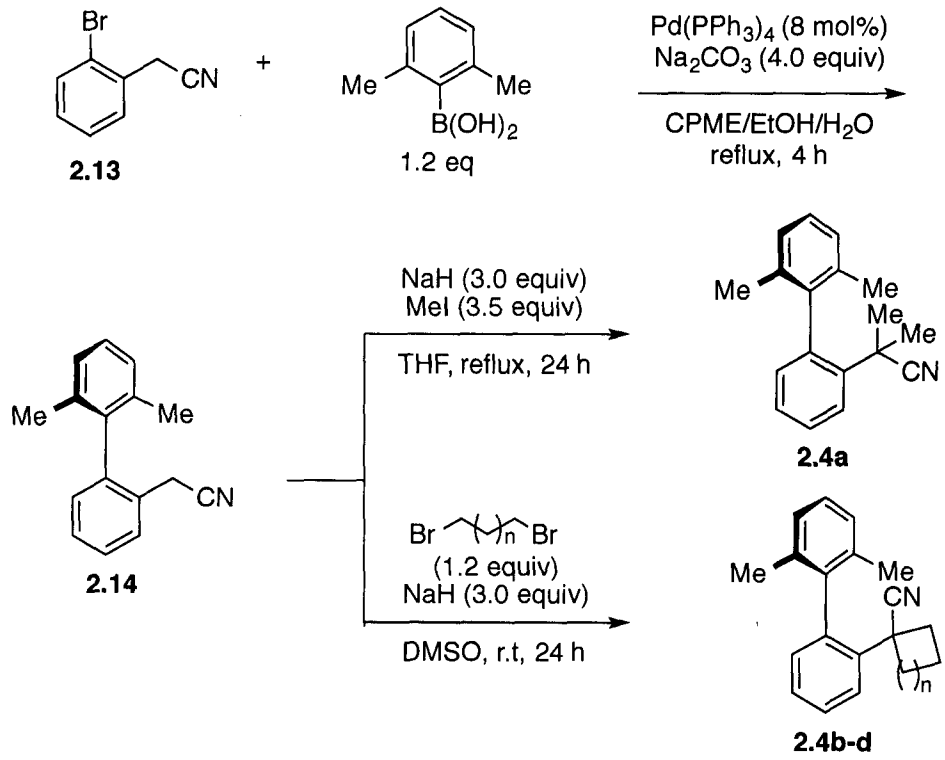
Method B utilized Pd(II)-catalyzed Suzuki–Miyaura cross coupling reaction of 2-bromobenzonitriles and aryl boronic acids as shown in Scheme 2-13. Biaryl-2-

carbonitriles **2.1i-o** are synthesized by this method. Details of procedures and yields can be found in Chapter 5, Section 5.2.1.2.



Scheme 2-13. *Preparation of biaryl-2-carbonitriles Method B.*

As shown in Scheme 2-14, biaryl-2-methane carbonitriles **2.4** are prepared by Pd(0)-catalyzed Suzuki–Miyaura cross coupling reaction of 2'-bromobenzylcyanide **2.13** with aryl boronic acids, followed by dialkylation of biaryl-2-acetonitrile **2.14** with methyl iodide or dibromoalkanes using sodium hydride as base. Details of procedures and yields can be found in Chapter 5, Section 5.2.1.3.



Scheme 2-14. *Preparation of biaryl-2-methane carbonitriles.*

2.2.2 Synthesis of azaspirocyclohexadienones via 1,4-aminooxygenation of benzene rings

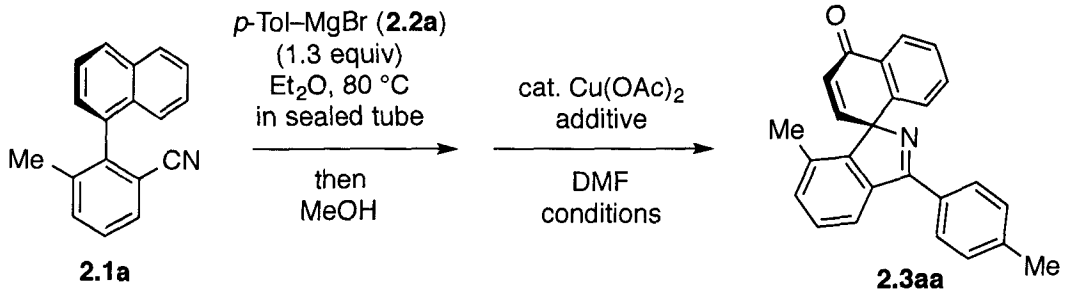
2.2.2.1 Optimization of reaction condition

As mentioned in section 2.1, it was hypothesized that biaryl-2-carbonitriles with *ortho*-substituents may provide azaspirocyclohexadienones using similar conditions from the synthesis of phenanthridine derivatives. Hence, the investigation was initiated by subjecting 3-methyl-2-(1-naphthyl)benzonitrile (**2.1a**) and *p*-tolylmagnesium bromide (**2.2a**) as the typical substrates, with the modification of reaction conditions from phenanthridine synthesis (Table 2-1). The reaction of Grignard reagent **2.2a** to benzonitrile **2.1a** proceeded smoothly in Et_2O at 80 °C in a sealed tube. After protonation with MeOH, $Cu(OAc)_2$ (20 mol%) and DMF (diluted to 0.1 M) were subsequently added before heating the reaction mixture to 80 °C under an O_2 atmosphere (1 atm). After stirring for 20 h, the *N*-H-ketimine was consumed and the reaction was quenched with aqueous 1 M HCl, affording the expected azaspirocyclohexadienone **2.3aa** in 34% yield, without any other isolable products (entry 1). The structure of **2.3aa** was confirmed by X-ray crystallographic analysis and this result prompted the further optimization of the reaction conditions to improve the yields.

Addition of nitrogen ligands such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 2,2'-bipyridine or (bpy), 1,10-phenanthroline (1,10-phen) improved the yield of **2.3aa** to 52-61% (entries 2-4). With 1,10-phenanthroline as a ligand, both CuBr and $CuBr_2$ showed similar catalytic activity with $Cu(OAc)_2$ (entries 5 and 6). Interestingly, the reaction with $Cu(OAc)_2$ and 1,10-phenanthroline (20 mol%) also proceeded at room temperature (entry 7), and the yield of **2.3aa** improved dramatically to 81% when H_2O (10 equiv) was added (entry 8). Furthermore, reduction of the oxygen partial pressure using air (0.21 atm of O_2) accelerated the reaction (entry 9). Reduction of catalyst loading to 10 mol% did not affect the chemical yield (entry 10), while 5 mol% of the catalysts

results in slower reaction rates (entry 11). When the reaction was carried out under an inert atmosphere (argon), the reaction did not proceed at all, recovering only the corresponding hydrolyzed ketone, even though a stoichiometric amount of $Cu(OAc)_2$-phen was used (entry 12).

Table 2-1. Optimization of reaction conditions for azaspirocyclohexadienone synthesis.



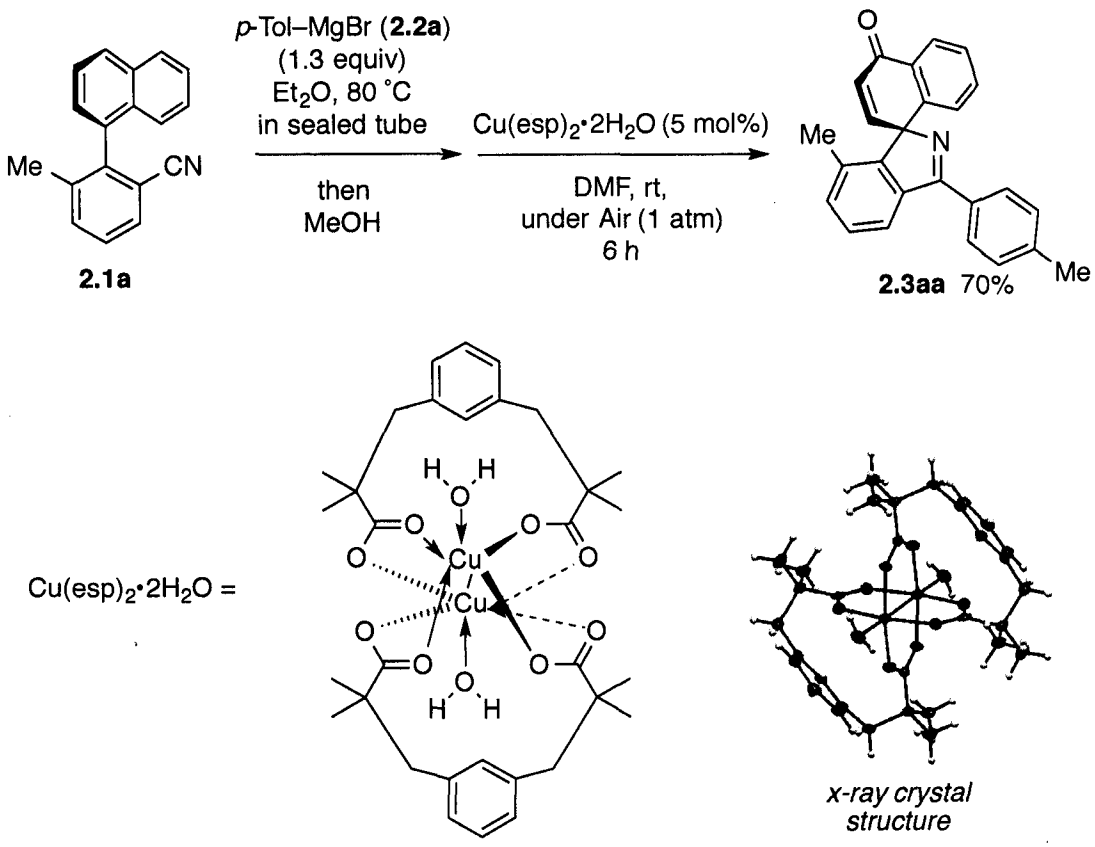
2.1a **2.3aa**

entry[a]	catalyst [mol%]	additive-1 [mol%]	additive-2 [equiv]	atmosphere [1 atm]	Temp [°C]	time [h]	yield[b] [%]
1	$Cu(OAc)_2$ (20)	—	—	O_2	80	20	34
2	$Cu(OAc)_2$ (20)	DABCO (20)	—	O_2	80	3	59
3	$Cu(OAc)_2$ (20)	bpy (20)	—	O_2	80	5	52
4	$Cu(OAc)_2$ (20)	1,10-phen (20)	—	O_2	80	3	61
5	$CuBr{\cdot}SMe_2)$(20)	1,10-phen (20)	—	O_2	80	4	61
6	$CuBr_2$ (20)	1,10-phen (20)	—	O_2	80	5	50
7	$Cu(OAc)_2$ (20)	1,10-phen (20)	—	O_2	rt	3	55
8	$Cu(OAc)_2$ (20)	1,10-phen (20)	H_2O (10)	O_2	rt	4	81
9	$Cu(OAc)_2$ (20)	1,10-phen (20)	H_2O (10)	Air	rt	2	82
10	**$Cu(OAc)_2$ (10)**	**1,10-phen (10)**	**H_2O (10)**	**Air**	**rt**	**3**	**80**
11	$Cu(OAc)_2$ (0.05)	1,10-phen (5)	H_2O (10)	Air	rt	17	76
12	$Cu(OAc)_2$ (100)	1,10-phen (100)	H_2O (10)	Argon	rt	48	0

[a] All reactions were carried out using 0.5 mmol of carbonitrile **2.1a** with 1.3 equiv of Grignard reagents **2.2a** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 2 h followd by addition of MeOH (60 mL), DMF (4 mL), Cu-catalysts and additives. [b] Isolated yields. DABCO = 1,4-diazabicyclo[2.2.2]octane; bpy = 2,2'-bipyridine; 1,10-phen = 1,10-phenanthroline.

It is known that the structure of copper(II) acetate is binuclear with four carboxylate bridges.[23] Thus, the effect of a bimetallic structure of Cu species in the present spirodienone formation was also investigated. Bimetallic $Cu^{II}_2(esp)_2{\cdot}2H_2O$ was prepared (see Chapter 5, section 5.2.2. for preparation procedure) according to the

modified Du Bois' procedure[24] for the present aerobic spirocyclization. Interestingly, the reaction with 5 mol% of $Cu^{II}_2(esp)_2 \cdot 2H_2O$ proceeded smoothly without the aid of any additive such as 1,10-phen and H_2O, providing **2.3aa** in 70% yield under air (Scheme 2-15). In consideration that the use of hydrate complex $Cu^{II}_2(esp)_2 \cdot 2H_2O$ alone could already achieve spirodienone formation with smiliar effectiveness as the present best reaction condition [Table 2-1, entry 10], which require the combination of $Cu(OAc)_2$, 1,10-phen, and H_2O; it is deduced that H_2O is likely required for the formation of a $Cu(OAc)_2$-phen hydrate complex.



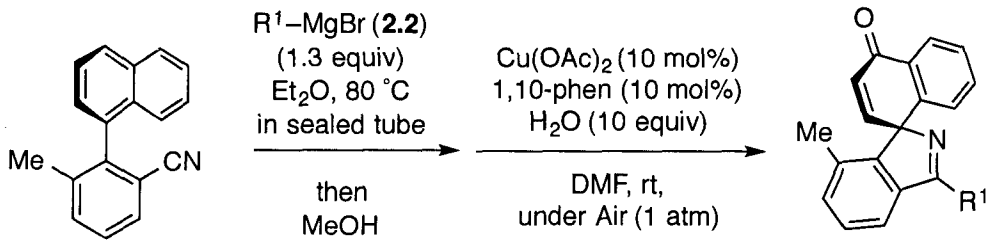
Scheme 2-15. *The reaction of **2.1a** carried out with $Cu(esp)_2 \cdot 2H_2O$ as the catalyst.*

2.2.2.2 Scope and limitation

With the optimized reaction conditions in hand [Table 2-1, entry 10, $Cu(OAc)_2$ (10 mol%), 1,10-phen (10 mol%), H_2O (10 equiv), under air at rt], the scope of Grignard reagents **2.2** for synthesis of azaspirocyclohexadienone derivatives **2.3** from carbonitrile

2.2a was first investigated (Table 2-2). Aryl Grignard reagents bearing both electron-donating (entries 1-3) and -withdrawing groups (entry 4) as well as C-Cl bond (entries 5 and 6) could be utilized to give the corresponding azaspirocyclohexadienones **2.3** in good yields. It is also feasible to install bulky substituents such as 1-naphthyl and mesityl groups on R^1 (entries 7 and 8). The reaction of alkylketimine generated from primary alkyl Grignard reagent **2.2j** proceeded smoothly, while that of secondary **2.2k** was sluggish (entries 9 and 10).

Table 2-2. Scope of Grignard reagents.



2.1a **2.3**

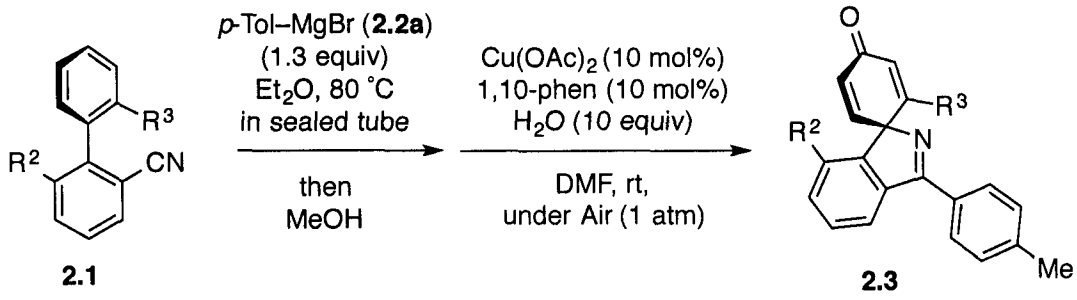
entry[a]	R^1–MgBr (**2.2**)	Time [h]	Yield [%][b]
1	**2.2b**: 4-MeO-C_6H_4-MgBr	20	**2.3ab**: 80
2	**2.2c**: 2-MeO-C_6H_4-MgBr	20	**2.3ac**: 72
3	**2.2d**: 4-PhO-C_6H_4-MgBr	72	**2.3ad**: 76
4	**2.2e**: 4-CF_3-C_6H_4-MgBr	19	**2.3ae**: 80
5	**2.2f**: 4-Cl-C_6H_4-MgBr	48	**2.3af**: 70
6	**2.2g**: 3-Cl-C_6H_4-MgBr	5	**2.3ag**: 70
7	**2.2h**: 1-naphthyl-C_6H_4-MgBr	4	**2.3ah**: 85
8	**2.2i**: 2,4,6-$(Me)_3$-C_6H_4-MgBr	3.5	**2.3ai**: 65
9[c]	**2.2j**: *n*-C_8H_{17}-MgBr	3	**2.3aj**: 70
10[c]	**2.2k**: *i*-C_3H_7-MgBr	3	**2.3ak**: 29

[a]All reactions were carried out using 0.5 mmol of carbonitrile **2.1a** with 1.3 equiv of Grignard reagents **2.2** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (4 mL), $Cu(OAc)_2$ (10 mol%), 1,10-phen (10 mol%), H_2O (10 equiv) and stirring at rt under an Air atmosphere (1atm). [b] Isolated yields. [c] The reactions with Grignard reagents **2.2j** and **2.2k** were stirred for 24 h.

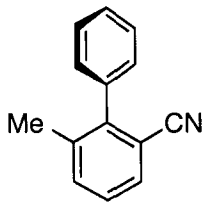
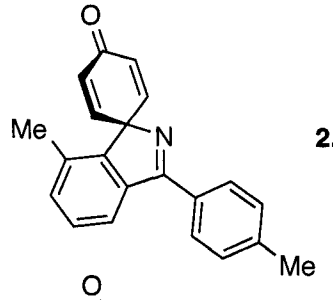
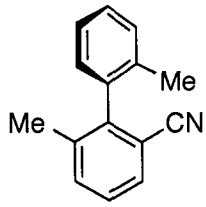
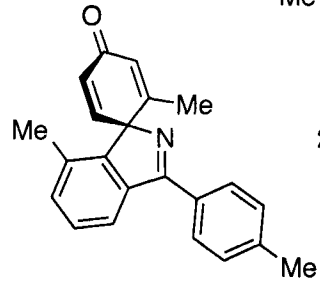
Next, various biaryl-2-carbonitriles **2.1** with different substituents were treated with the optimized standard conditions using *p*-tolyl Grignard reagent **2.2a** (Table 2-3).

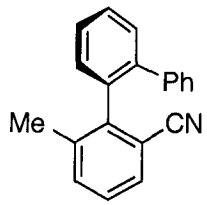
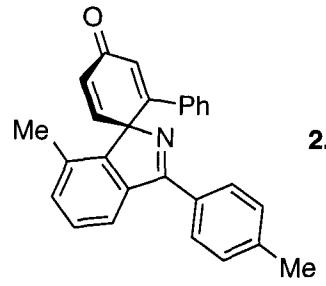
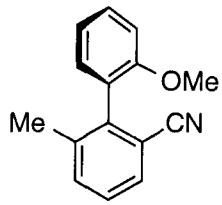
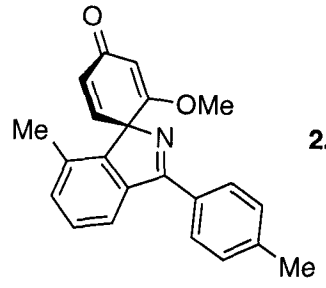
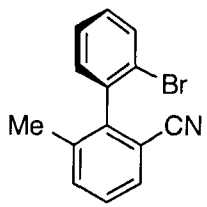
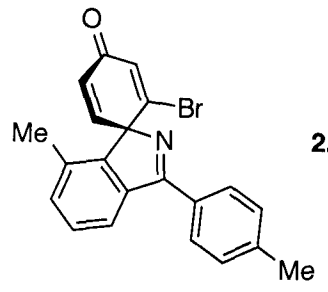
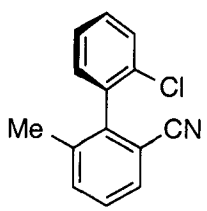
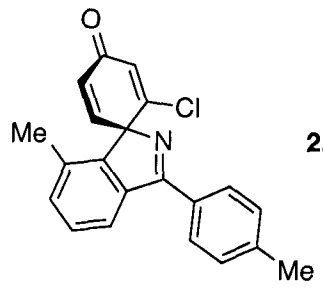
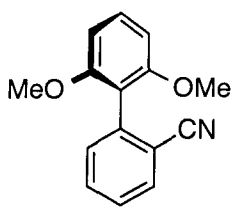
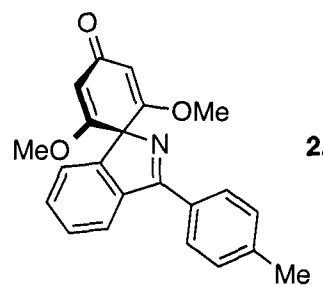
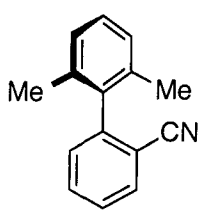
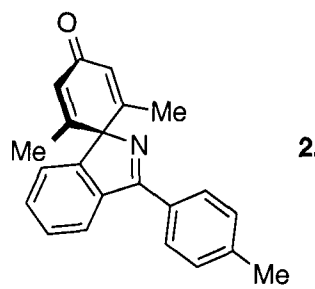
In general, as the configurational (rotational) stability of the biaryl motifs become more rigid by installing more than two substituents in R^2 and R^3, the oxygenative spirocyclization proceeded smoothly, affording the corresponding azaspirocyclohexadienones **2.3ca-2.3ja**, **2.3pa** in good yields (entry 2-9 and 15, 60%-82%). The reactions of the substrates bearing only one substituent in either R^2 or R^3, however, became sluggish to give azaspirocyclohexadienones **2.3ba**, **2.3ka-2.3oa** in moderate yields (entry 1 and 10 to 14, 32%-44%). The reactions of [1,1'-binaphthalene]-2-carbonitrile (**2.1q**) and 2-(anthracen-9-yl)benzonitrile (**2.1r**) proceeded smoothly to give **2.3qa** and **2.3ra** in 87% and 80% yield, respectively. While the reaction of 2-(dibenzofuran-4-yl)benzonitrile (**2.1s**) was carried out at 60 °C to give **2.3sa** in 77% yield.

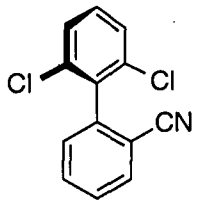
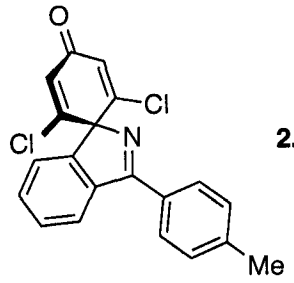
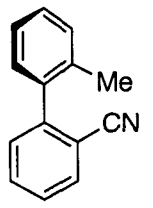
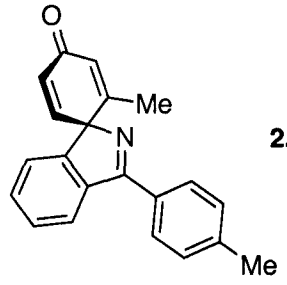
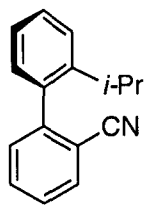
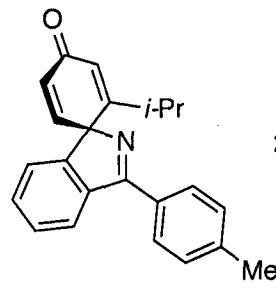
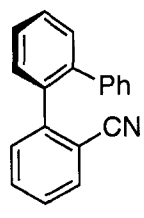
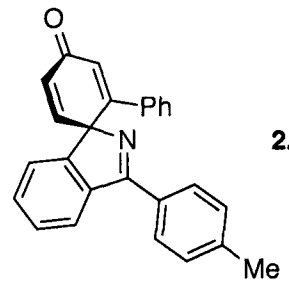
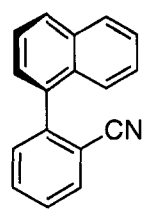
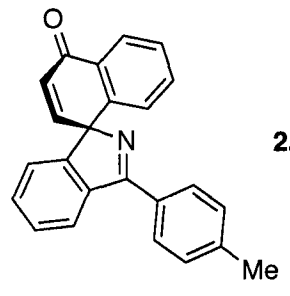
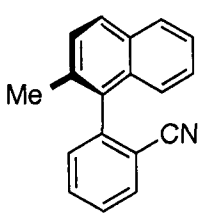
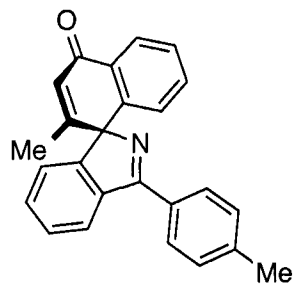
Table 2-3. Scope of biaryl-2-carbonitriles.

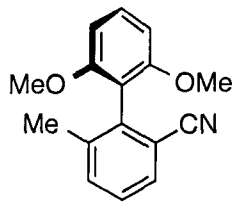
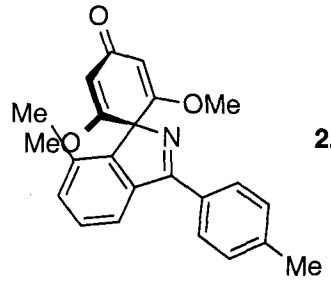
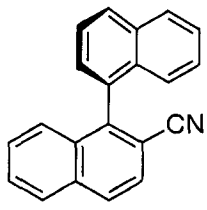
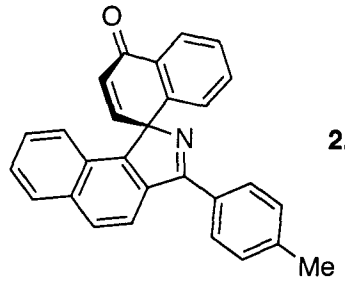
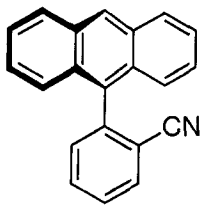
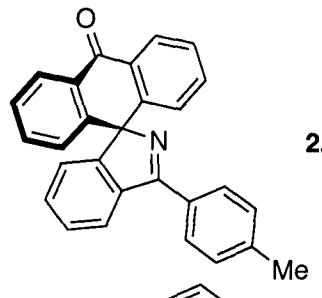
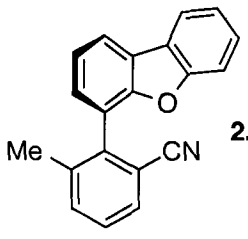
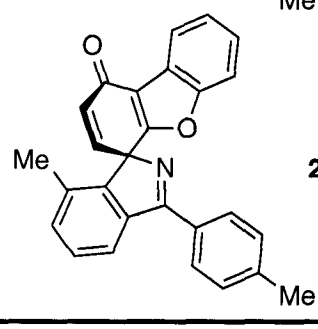


2.1 **2.3**

entry[a]	Substrate		Product		Yield [%][b]
1[c]		**2.1b**		**2.3ba**	37
2		**2.1c**		**2.3ca**	78

entry[a]	Substrate		Product		Yield [%][b]
3		**2.1d**		**2.3da**	82
4		**2.1e**		**2.3ea**	60
5		**2.1f**		**2.3fa**	81
6		**2.1g**		**2.3ga**	74
7		**2.1h**		**2.3ha**	48
8		**2.1i**		**2.3ia**	68

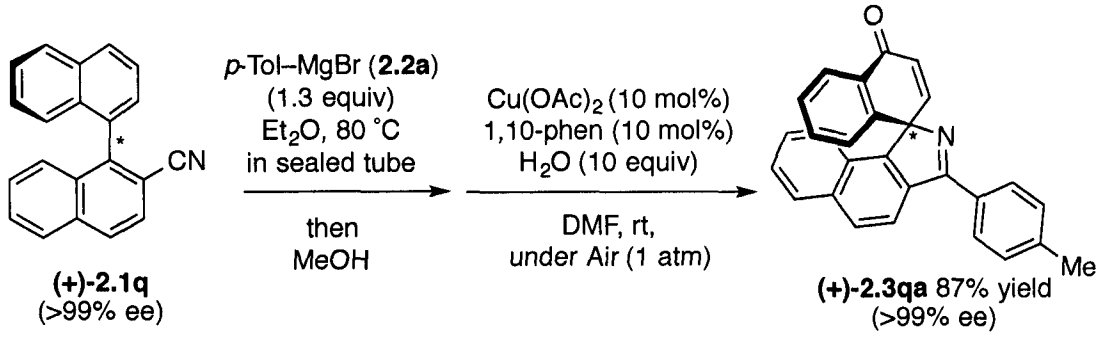
entry[a]	Substrate		Product		Yield [%][b]
9		**2.1j**		**2.3ja**	69
10		**2.1k**		**2.3ka**	49
11		**2.1l**		**2.3la**	42
12		**2.1m**		**2.3ma**	36
13		**2.1n**		**2.3na**	41
14		**2.1o**		**2.3oa**	32

entry[a]	Substrate		Product		Yield [%][b]
15		**2.1p**		**2.3pa**	61
16		**2.1q**		**2.3qa**	87
17		**2.1r**		**2.3ra**	80
18[d]		**2.1s**		**2.3sa**	77

[a]Unless otherwise noted, all reactions were carried out using 0.5 mmol of carbonitrile **2.1** with 1.3 equiv of *p*-tolyl Grignard reagents **2.2a** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (4 mL), $Cu(OAc)_2$ (10 mol%), 1,10-phen (10 mol%), H_2O (10 equiv) and stirring at rt under an Air atmosphere (1atm). [b]Isolated yields were recorded and are shown. [c] The reactions was conducted without the addition of H_2O. [d] The reactions was conducted at 60 °C.

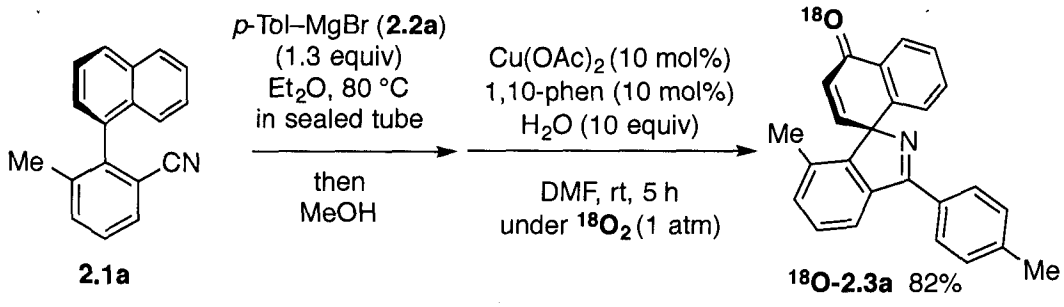
In consideration to synthesize optically active azaspirocyclohexadienones using the present developed Cu-catalyzed aerobic spirocyclization protocol, it was envisioned that transmission of the axial chirality of the biaryl carbonitriles **2.1**[25] to the spiro-central chirality of **2.3** could be achieved.[26] Therefore, the optically active [1,1'-binaphthalene]-2-carbonitrile (+)-**2.1q** was prepared (>99% enantiomeric excess based on HPLC analysis

with reference to racemic **2.1q**. See Chapter 5, Section 5.2.5. for spectra information) and treated with the standard reaction conditions. Delightfully, azaspirodienone (+)-**2.3qa** was isolated as an enantiomerically pure form (>99% enantiomeric excess based on HPLC analysis with reference to racemic **2.3qa**. See Chapter 5, Section 5.2.5. for spectra information), which suggested that the present process is able to transmit axial chirality to spiro-center chirality to synthesize optically active azaspirodienones (Scheme 2-16). As (+)-**2.1q** was prepared from enantiomerically pure (*R*)-[1,10-binaphthalene]-2-carbaldehyde, the absolute configuration of (+)-**2.1q** is presumed to be (*R*). Therefore, based on the assumption that transmission of axial chirality to spiro-central chirality was successful, the absolute configuration of (+)-**2.3qa** is also presumed to be (*R*). The structures of both (+)-**2.1q** and (+)-**2.3qa** were secured by X-ray crystallographic analysis; however, the absolute configuration of (+)-**2.3qa** is yet to be fully determined.



Scheme 2-16. *Transmission of axial chirality to spiro-center chirality.*

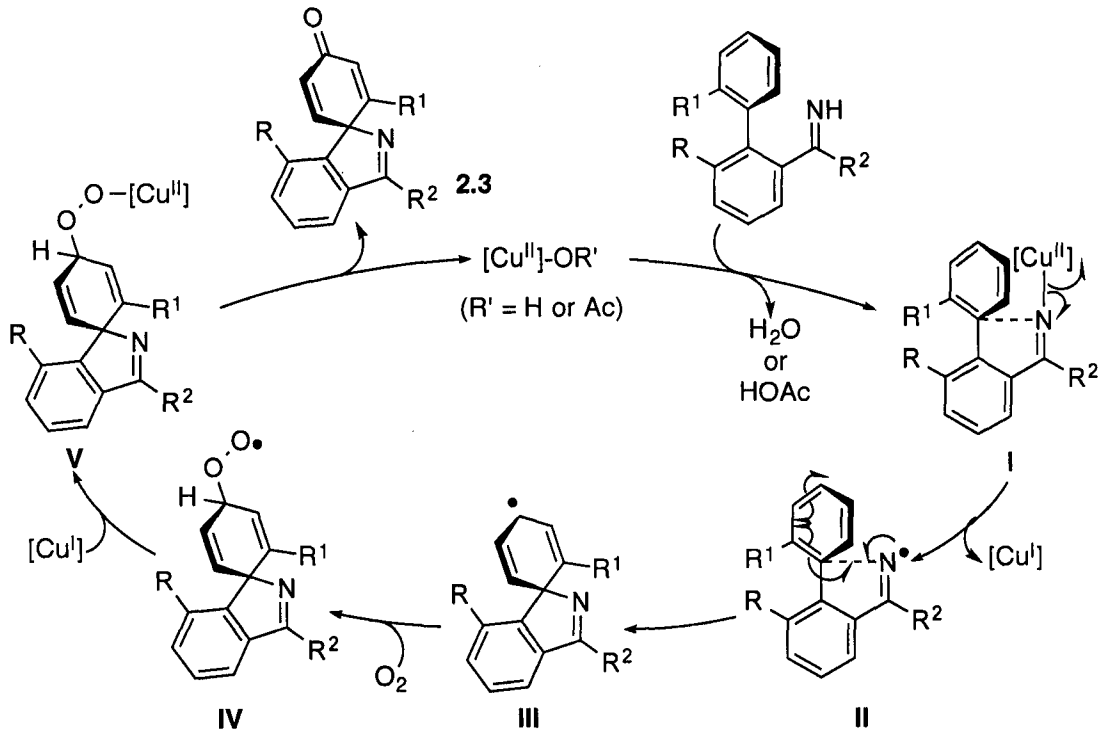
An isotope labeling experiment by the utilization of $^{18}O_2$ in the reaction of biaryl-2-carbonitrile **2.1a** provided azaspirocyclohexadienone **^{18}O-2.3a** smoothly in 82% yield (Scheme 2-17). The incorporation of ^{18}O on the carbonyl group of azaspirocyclohexadienone **^{18}O-2.3a** was confirmed by mass spectroscopy, where ^{18}O was observed in the elemental composition, as well as IR spectroscopy, where a rightward shift of the C=O bond stretching in contrast to **^{16}O-2.3a** could be observed (see Chapter 5 section 5.2.4 for spectra information).



Scheme 2-17. *Isotope labelling experiment using $^{18}O_2$ showing incorporation of atmospheric oxygen atom on carbonyl group of azaspirocyclohexadienone **2.3a**.*

2.2.2.3 Mechanism discussion

With reference to our previous report on Cu-catalyzed aerobic synthesis of azaspirocyclohexadienones from α-azido-*N*-arylamides (Scheme 2-9),[18] the spirocyclization of biaryl-*N*-H-imines should undergo a analogous mechanism involving the iminyl radical species and its *ipso*-spirocyclization with the benzene ring. Therefore, a proposed mechanistic pathway for the azaspirocyclohexadienone **2.3** is outlined in Scheme 2-18. It is proposed that the reaction is initiated by oxidative generation of iminyl radical from biaryl-*N*-H-imine with $Cu(OAc)_2$ along with the release of Cu(I) species. The effect of *ortho*-substituents on biaryl-*N*-H-imines induced the formation of rigid helical structure, which facilitates *ipso*-spirocyclization of iminyl radical **II** to the intramolecular benzene ring to generate cyclohexadienyl radical **III**. Trapping of molecular oxygen with cyclohexadienyl radical **III** results in formation of peroxy radical **IV**, which undergoes single-electron-reduction by Cu(I) species to generate Cu(II)-peroxy species **V**. Decomposition of Cu(II)-peroxy species **V** via *Fenton*-type homolytic cleavage[28] of the O–O bond followed by elimination of Cu(II)-OH species to deliver azaspirodienones **2.3**.

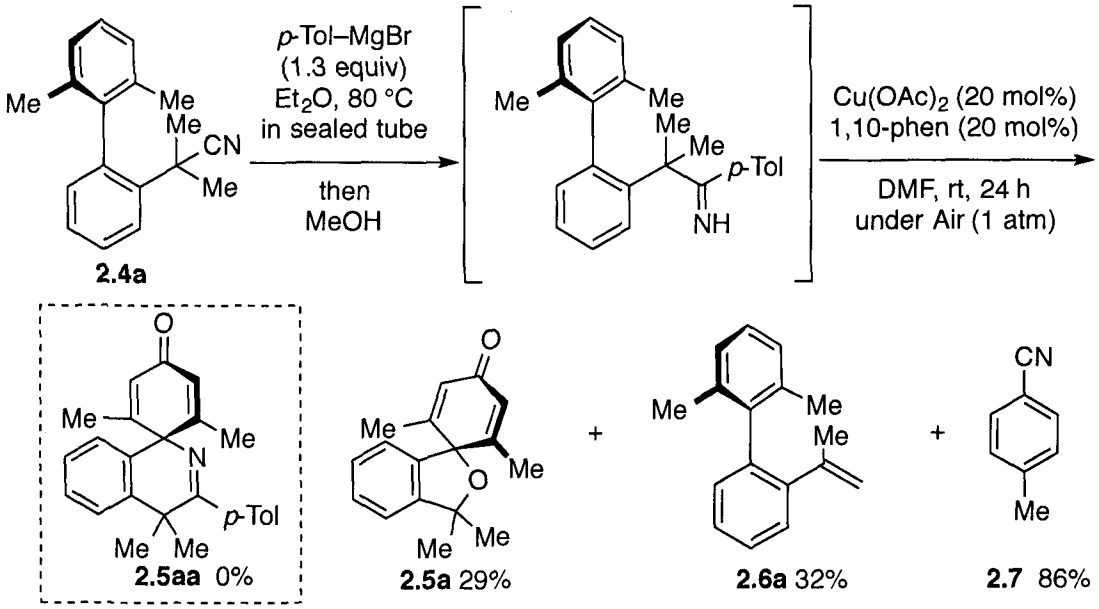


Scheme 2-18 *A proposed mechanism for the copper-catalyzed aerobic synthesis of azaspirocyclohexadienones from biaryl-N-H-imines.*

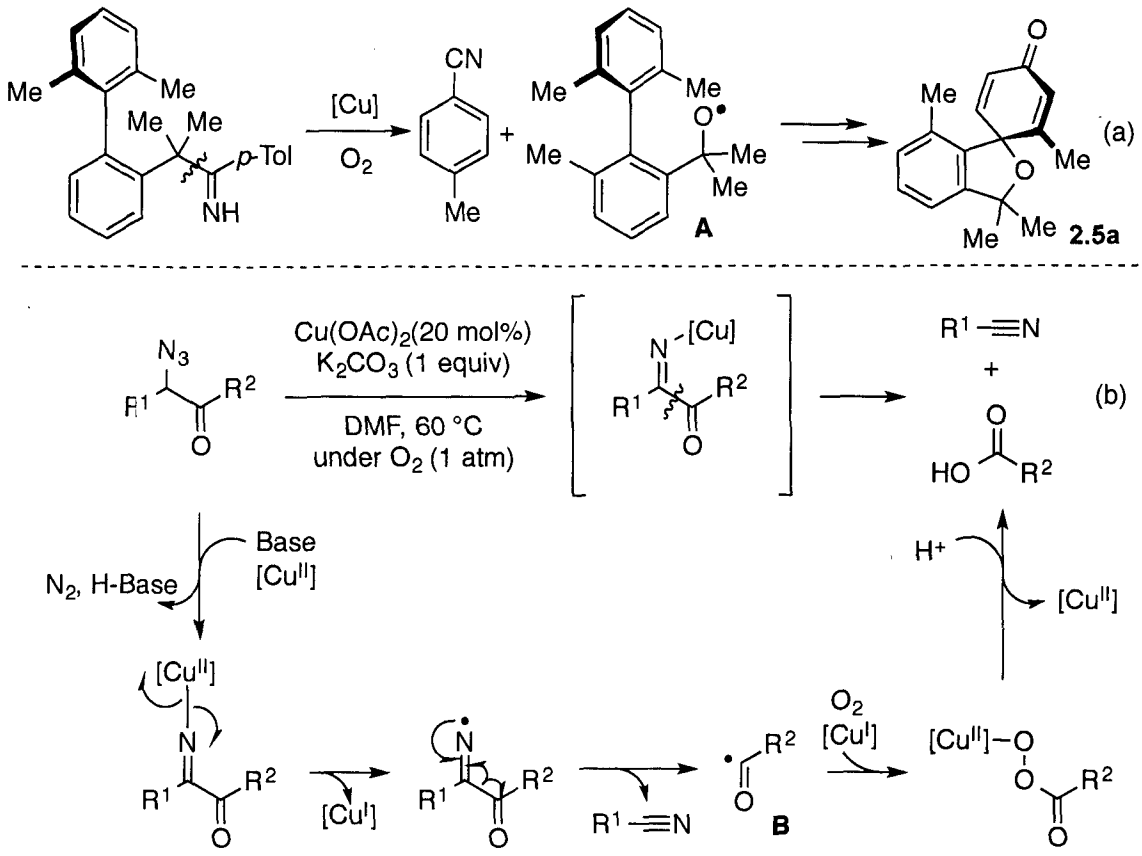
2.2.3. Synthesis of oxospirocyclohexadienones via 1,4-dioxygenation of benzene rings

To investigate the possibilities of synthesizing six-membered ring spirocycles using the above presented spirocyclization protocol, biaryl-2-methane carbonitrile **2.4a** was prepared aiming at synthesizing six-membered ring azaspirocyclohexadienone **2.5aa**. However, when carbonitrile **2.4a** was treated with the standard reaction conditions, unexpected oxospirocyclohexadienone **2.5a** was isolated in 31% yields, together with alkene **2.6a** and *p*-tolylcarbonitrile (**2.7**) in 24% and 68% yields, respectively (Scheme 2-19). This finding suggested that the putative iminyl radical intermediate undergoes C–C bond cleavage to give *p*-tolylnitrile (**2.7**) and alkoxy radical **A** that might undergo spirocyclization under the aerobic Cu-catalyzed condition to afford oxospirocyclohexadienone **2.5a** (Scheme 2-20a). Our group previously observed similar the C–C bond cleavage of iminyl copper species generated from α-azido carbonyl compounds to provide nitriles and carboxylic acid under Cu-catalyzed aerobic conditions (Scheme 2-20b).[27] It was found that upon C–C bond cleavage, the β-fragment (acyl

radical) traps molecular O_2 to give acylperoxy copper species **B**, which decomposes to form carboxylic acids. Thus, this unprecedented formation of oxospirocyclohexadienone from biaryl-2-methane carbonitriles **2.4a** using the aerobic copper catalyzed spirocyclization strategy was investigated.



Scheme 2-19. *Unexpected oxospirocyclohxadienone formation from biaryl-2-methane carbonitrile.*

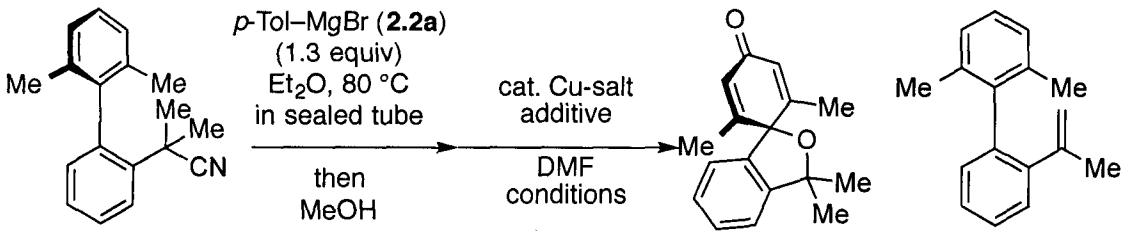


Scheme 2-20. *(a)Possible C-C bond cleavage of biaryl-2-methane N-H-imine for oxospirocyclohxadienone formation. (b) C-C bond cleavage of iminyl copper species to nitriles and carboxylic acids.*

2.2.3.1 Optimization of reaction condition

To begin with the investigation, 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)-2-methylpropanenitrile (**2.4a**) and *p*-tolylmagnesium bromide (**2.2a**) were selected as the typical substrates for the optimization of reaction conditions (Table 2-4). The addition of Grignard reagent **2.2a** to carbonitrile **2.4a** proceeded smoothly in Et_2O at 80 °C in a sealed tube. After protonation with MeOH, $Cu(OAc)_2$ (20 mol%), 1,10-phen (20 mol%) and DMF (diluted to 0.1 M) were added and stirred at room temperature under ambient air (1 atm). The reaction was completed after 5 h, affording the oxospirocyclohexadienone **2.5a** and alkene **2.6a** in 29% and 32% yield, respectively (entry 1). Increasing the loading of 1,10-phen to 40 mol % improved the yields slightly, giving **2.5a** as the major product (entry 2). Screening of bidentate and monodentate nitrogen ligands such as 2,2'-bipyridine (bpy) and 1,4-diazabicyclo[2.2.2]octane (DABCO) showed that bidentate ligands are essential in this reaction (entries 3 and 4). With 1,10-phenanthroline as the best ligand, screening of various Cu(II) and Cu(I) salts was conducted and CuI showed the best selectivity, providing **2.5a** in 46% yield (entries 5-8). However, increasing the oxygen content by conducting the reaction under O_2 atmostphere could not further increase the yield of **2.5a** (entry 9). Moreover, reduction of catalyst loading to 10 mol% lowered the total chemical yield (entry 10), while stoichiometric amounts of the Cu-catalysts did not further improve the yields or selectivity (entry 11).

Table 2-4. Optimization of reaction conditions for azaspirocyclohexadienone synthesis.



2.4a **2.5a** **2.6a**

entry[a]	Cu-salt [mol%]	additive [mol%]	Atmos-phere	time [h]	Yield[b] [%] **2.5a**	**2.6a**	*p*-Tol-CN (**2.7**)
1	$Cu(OAc)_2$ [20]	1,10-phen [20]	Air	5	29	32	86
2	$Cu(OAc)_2$ [20]	1,10-phen [40]	Air	4	(40)	(31)	86
3	$Cu(OAc)_2$ [20]	2,2-Bipyr [40]	Air	4	32	36	80
4	$Cu(OAc)_2$ [20]	DABCO [40]	Air	4	10	21	87
5	$CuCl_2$ [20]	1,10-phen [40]	Air	4	27	22	78
6	CuCl [20]	1,10-phen [40]	Air	4	37	28	96
7	CuBr [20]	1,10-phen [40]	Air	4	(40)	(27)	(95)
8	CuI [20]	1,10-phen [40]	Air	4	(46)	(28)	(78)
9	CuI [20]	1,10-phen [40]	O_2	4	43	37	99
10	CuI [10]	1,10-phen [20]	Air	4	37	34	95
11	CuI [100]	1,10-phen [100]	Air	4	46	30	93

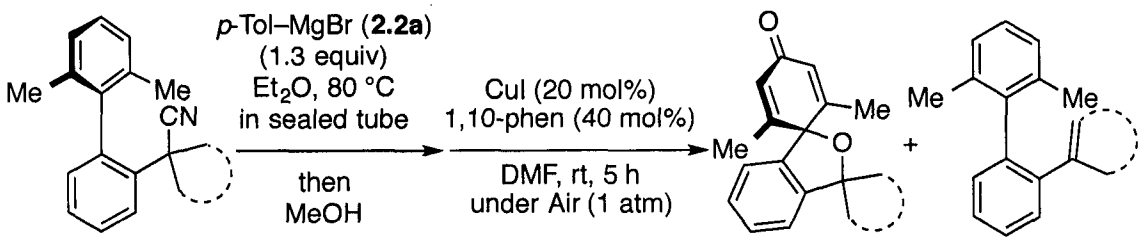
[a] All reactions were carried out using 0.5 mmol of carbonitrile **2.4a** with 1.3 equiv of Grignard reagents **2.2a** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 4 h followed by addition of MeOH (60 mL), DMF (4 mL), Cu-catalysts and additives. [b] ^1H NMR crude yields based on 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields in parenthese. 1,10-phen = 1,10-phenanthroline; bpy = 2,2'-bipyridine; DABCO = 1,4-diazabicyclo[2.2.2]octane.

2.2.3.2 Scope and limitation

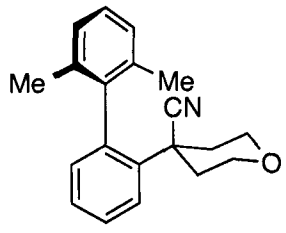
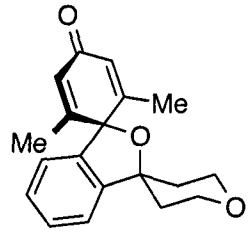
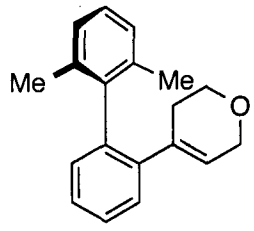
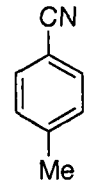
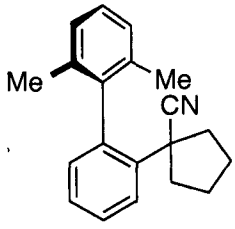
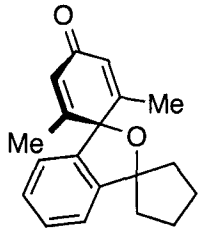
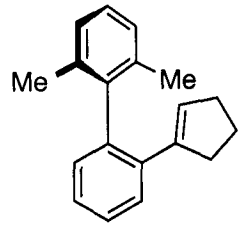
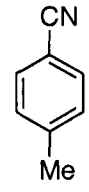
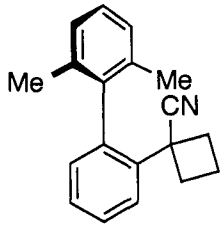
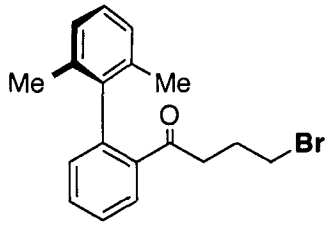
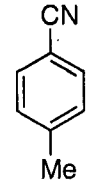
Although the formation of alkene **2.6** could not be avoided at this point, it is still interesting to probe the potential utility and mechanism of this transformation toward oxospirocyclohexadienone **2.5**. In view of synthesizing polyspirocyclic compounds, biaryl-2-methane carbonitriles **2.4** with cyclic hydrocarbons of various ring size was treated the current best reaction condition (Table 2-4, entry 8, CuI (20 mol%, 1,10-phen (40 mol%) under air at rt) using *p*-tolyl Grignard reagent **2.2a** (Table 2-5). It was found that carbonitriles **2.4b** and **2.4c** with 5- or 6-membered rings undergo the oxospirocyclization successfully, giving the tricyclic oxospirocyclohexadienones **2.5b**

and **2.5c** in 42% and 36% yields, respectively. It is worthy to note that cyclic alkenes **2.6b** and **2.6c** were also formed in 40% and 27% yields, respectively. On the other hand, in the case of carbonitrile **2.4d** having strained cyclobutane ring, the desired oxospirocyclohexadienone was not obtained at all. Instead, γ-bromoketone **2.7** was isolated in 44% yield via cleavage of the cyclobutane ring.

Table 2-5. Scope of biaryl-2-methane carbonitriles.



2.4 **2.5** **2.6**

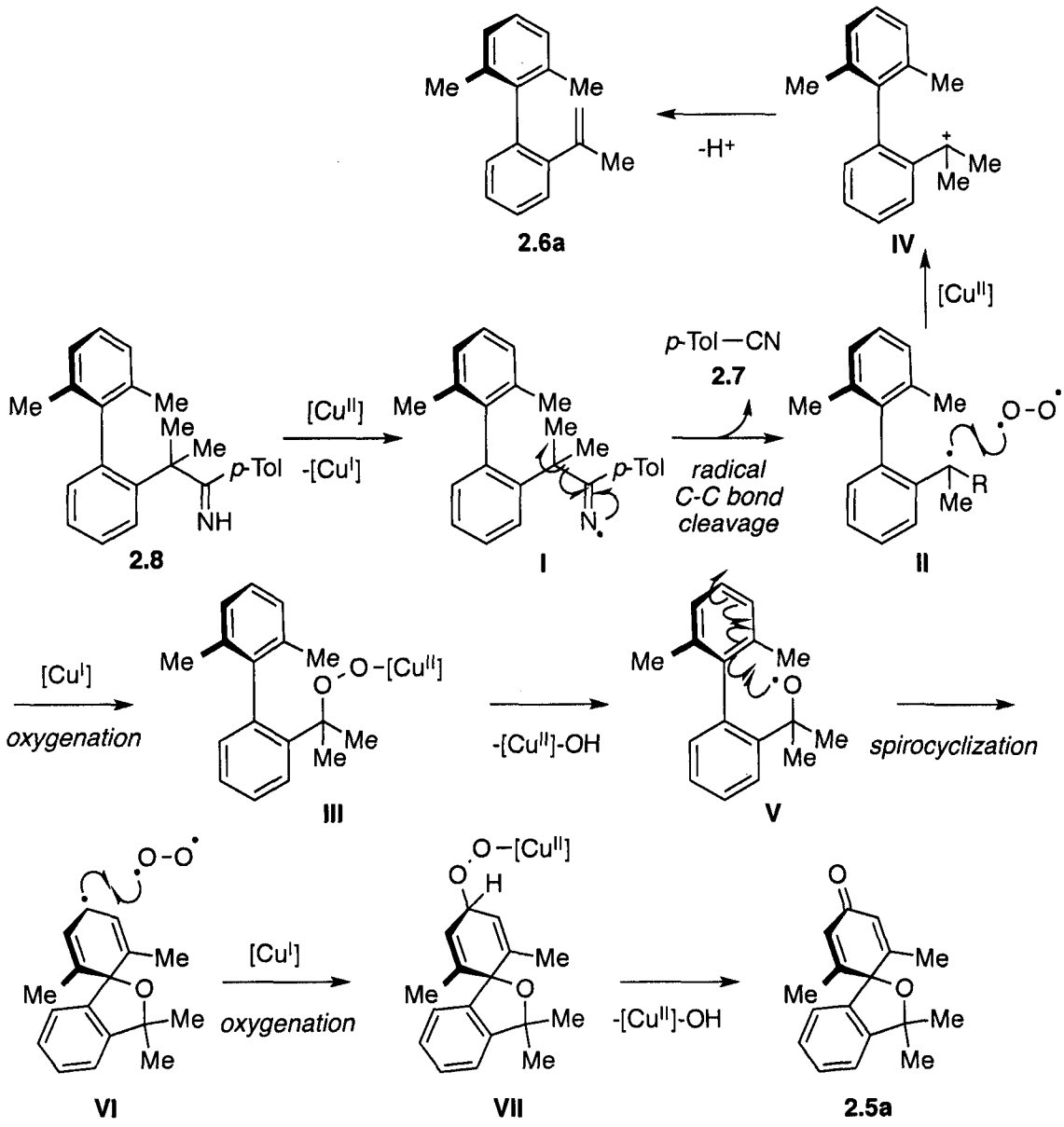
entry[a]	Substrate	Products[b]		
1				
	2.4b	**2.5b** 48%	**2.6b** 40%	90%[c]
2				
	2.4c	**2.5c** 36%	**2.6c** 27%	76%[c]
3				
	2.4d	**2.7** 44%		80%[c]

[a] All reactions were carried out using 0.5 mmol of carbonitriles **2.4** with 1.3 equiv of Grignard reagents **2.2a** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 4 h followed by addition of MeOH (60 mL), DMF (4 mL), CuI (20 mol%) and 1,10-phen (40 mol%). [b] Isolated yields. [c] ^1H NMR yields based on 1,1,2,2-tetrachloroethane as an internal standard. 1,10-phen = 1,10-phenanthroline

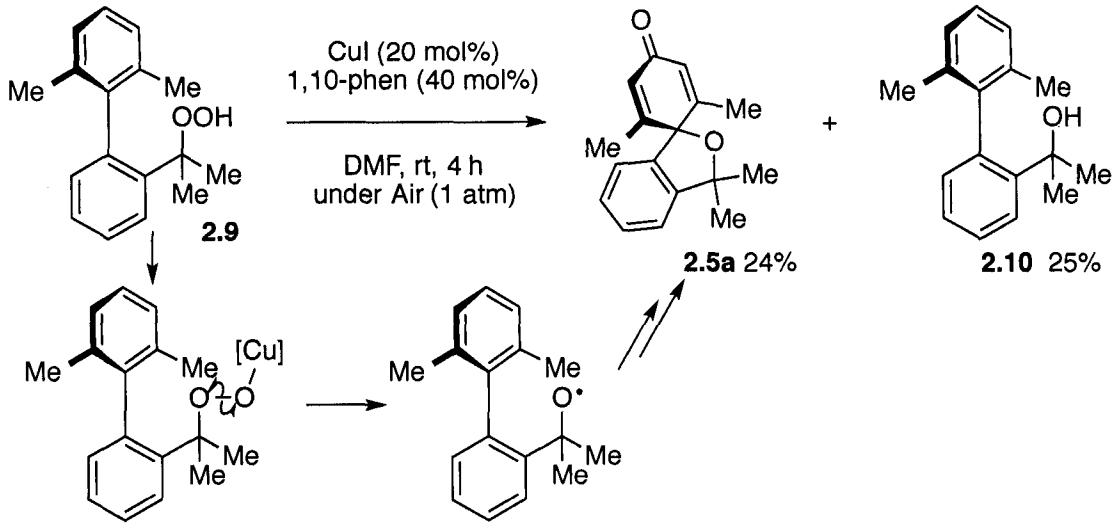
2.2.3.3 Mechanism discussion

With reference to our previous report on Cu-catalyzed aerobic C–C bond cleavage of iminyl copper species (Scheme 2-20b), it is presumed that *N*–H imine **2.8a** from biaryl-2-methane **2.4a** first react with $Cu(OAc)_2$ to form iminyl radical species **I**, which undergoes β-carbon elimination to give *p*-tolylcarbonitrile and biaryl-2-isopropyl radical **II** (Scheme 2-21). The resulting tertiary radical **II** can either trap molecular oxygen to give alkylperoxo copper(II) complex **III** or be further oxidized to carbocation **IV** to form alkene **2.6a**. Alkylperoxo copper **III** then undergoes *Fenton*-type homolytic cleavage[28] of the O–O bond to give alkoxy radical **V** that cyclizes to afford cyclohexadienyl radical **VI**. Subsequent oxygenation and C=O bond formation provides oxospirocyclohexadiene product **2.5a**.

To support the above proposed mechanism, biaryl hydroperoxide **2.9** was prepared (see Chapter 5 section 5.2.7 for preparation method) and treated with CuI (20 mol%) and 1,10-phenanthroline (40 mol%) under ambient air (Scheme 2-22). As expected, oxospirocyclohexadienone **2.5a** was formed in 24% yield along with biaryl alcohol **2.10** in 25% yields. These results are in agreement with the proposed reaction mechanism involving alkyl peroxo-copper **III** and alkoxy radical **V**, as reaction intermediates for formation of oxospirodienone, despite low yields. In addition, alkene formation is not observed in the reaction of biaryl hydroperoxide **2.9**, hence the formation of carbocation **IV** is most likely the result of oxidation of tertiary carbon radical **II** by Cu(II)-species, prior to oxygenation.

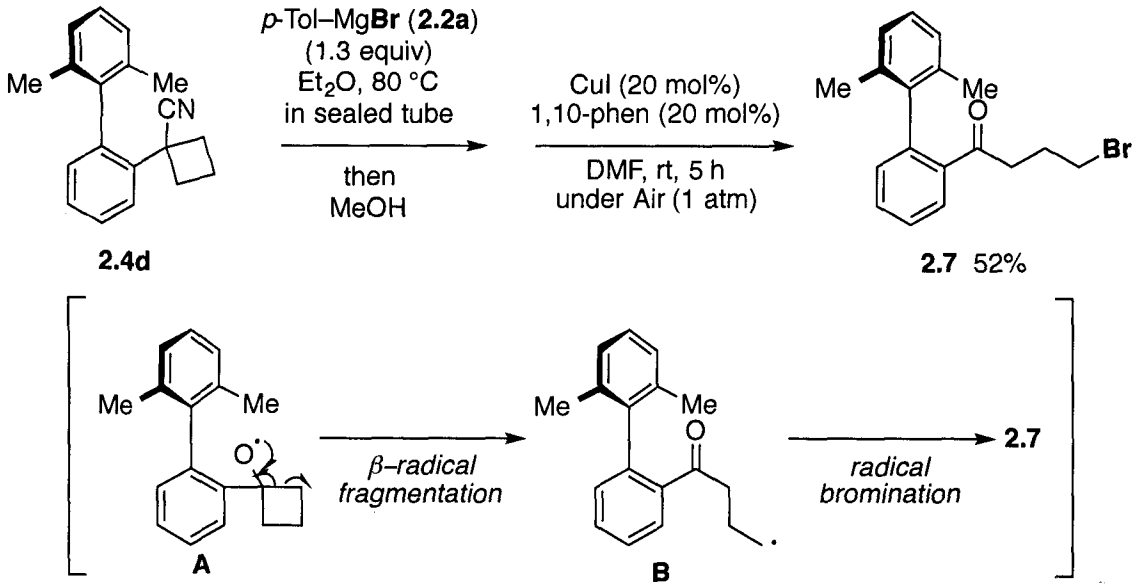


Scheme 2-21. *A proposed mechanism for the copper-catalyzed aerobic synthesis of oxospirocyclohexadienones from biaryl-N-H-imines.*



Scheme 2-22 *Formation of oxospirocyclohexadienone **2.5a** from biaryl hydroperoxide **2.9** under aerobic Cu-catalyzed conditions.*

Moreover, the outcome of the reaction of carbonitrile **2.4d** having a strained cyclobutyl moiety also supports the presence of alkoxy radical intermediate like **V** (Scheme 2-21). The cleavage of the cyclobutane ring is most likely caused by the presence of the cyclobutoxy-radical **A**, which undergoes strain-releasing ring-cleavage to give γ-keto radical **B.** Subsequent radical bromination of γ-keto radical **B** delivers γ-bromoketone **2.7**, where $MgBr_2$ of Grignard reagent **2.2a** provides the initial bromine source under aerobic copper reaction conditions (Scheme 2-23).[29]



Scheme 2-23. *Evidence of the presence of O-radical formation.*

2.3 Conclusions

In summary, Cu-catalyzed aerobic spirocyclization of biaryl *N*-H imines has been developed for the construction of the spirodienone framework. Molecular oxygen (O_2) is essential for achieving the present catalytic spirocyclization, where one of the oxygen atoms of O_2 is regioselectively incorporated into the benzene ring with dearomatization. Both azaspirocyclohexadienones and oxospirocyclohexadienones have been successfully synthesized using the present reaction conditions from biaryl-2-carbonitriles and biaryl-2-methane carbonitriles, respectively. Moreover, it was found that biaryl-hydroperoxide could also undergo spirocyclization for the formation of oxospirocyclohexadienones via

alkoxy radicals under Cu-catalyzed aerobic reaction conditions, that inspired the exploration of utilizing organohydroperoxides in radical transformation. This is discussed in Chapter 3.

2.4 References

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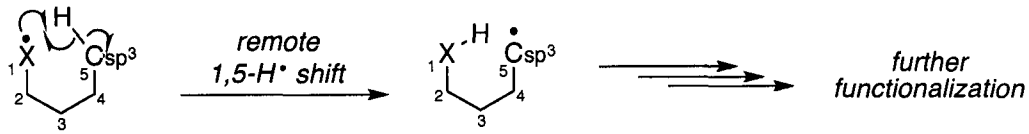
Chapter 3: Cu-Catalyzed Aerobic Aliphatic C-H Oxygenation with Hydroperoxides

3.1 Overview

Aliphatic sp^3 C–H bonds are commonly found in organic molecules. However, in the absence of adjacent activating groups such as carbonyl groups, these aliphatic C-H bonds are basically unreactive under most reaction conditions. In addition, it is challenging to perform site selective sp^3 C–H functionalization of organic molecules with diverse types of aliphatic C-H bonds.[1] Nonetheless, recent achievements in using transition-metal catalysts via directed C–H metallation and concerted C–H oxidation with metal–carbene or nitrene (singlet) species have shown new perspectives in developing synthetic methods to directly functionalize these inert bonds, enabling sp^3 C–H oxidation in chemo-, regio-, and stereoselective manner.[2] Alternatively, the utility of radical species to perform remote H-radical (typically, 1,5-H) shift to generate sp^3 carbon-radicals, has been widely used to achieve oxidative functionalization of sp^3 C-H bonds in chemo- and regioselective fashion (Scheme 3-1).[3]

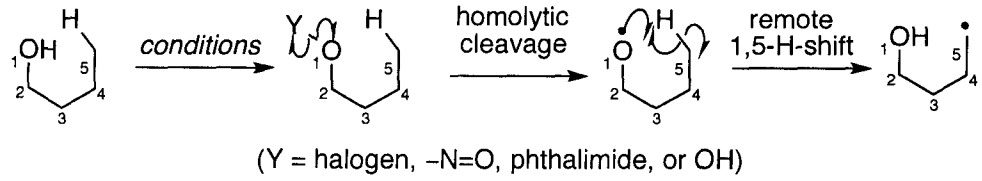


(X = O, N or C)

Scheme 3-1. *sp^3 C-H functionalization by remote 1,5 H-radical abstraction by radical species.*

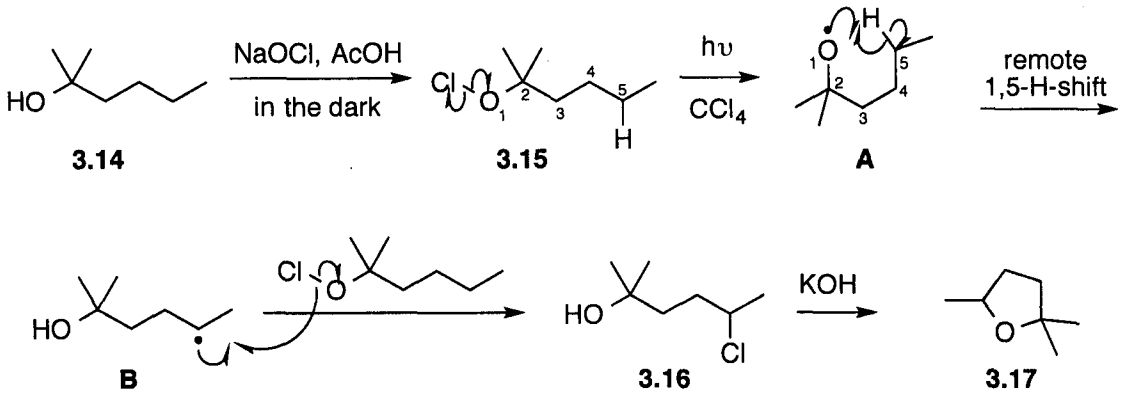
Among radical species, alkoxy radicals are more reactive than alkyl or aminyl radicals in 1,5-H-radical abstractions, due to the higher bond dissociation energies[4] of the resulting O-H bond (435 kJ/mol) of aliphatic alcohols. However, the high bond dissociation energy of O-H bonds of aliphatic alcohols also results in high difficulties in oxidizing the O-H bond to O-radicals. Thus, various reactive precursors have been designed for generation of alkoxy radicals in remote 1,5-H-shift and the functionalization

of the resulting carbon-radicals.[5] Generally, alkoxy radicals can be generated from precursors containing a weak oxygen-heteroatom bond (RO-Y, <292 kJ/mol) (Scheme 3-2).[6] This weak oxygen-heteroatom bond (O-Y bond) could either be installed on the precursor or generated from its alcohol analog in *situ*. Upon homolysis of this bond via irradiation or thermally, the alkoxy radical can be generated.



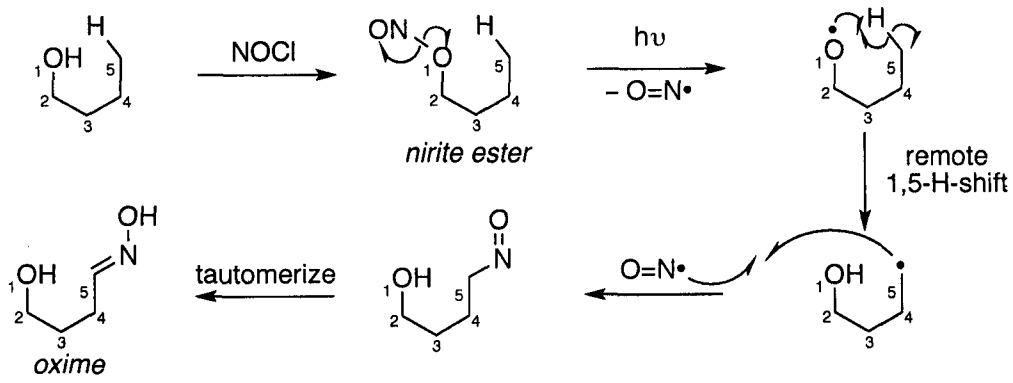
Scheme 3-2. *Generation of alkoxy radicals and their 1,5-H radical shift.*

For instance, by treatment of aliphatic alcohol **3.14** with sodium hypochlorite and acetic acid in the dark, alkyl hypochlorite **3.15** is prepared, which is then subjected to photolysis for generation of alkoxy radical **A** (Scheme 3-3).[7] The alkoxy radical **A** proceeds to abstract H-radical from the available δ-carbon to generate the carbon radical **B**. The subsequent abstraction of a chlorine radical from another hypochlorite molecule, affording 1,4-chlorohydrin **3.16**. Under basic reaction conditions, 1,4-chlorohydrin **3.16** can cyclize smoothly to produce tetrahydrofuran derivative **3.17**. In contrast to hypochlorites that are preformed before subjecting to photolysis, alkyl hypoiodites are generated in *situ* by treating the corresponding alcohol with iodine and a stoichiometric amount of oxidant such as iodosobenzene diacetate,[8] mercury oxide[9] and lead(IV)acetate,[10] to enable similar transformation.

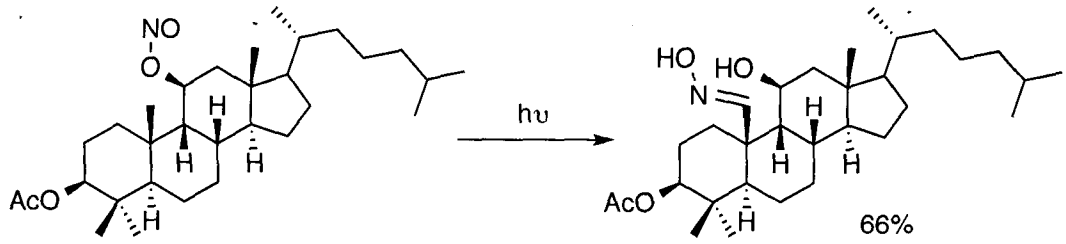


Scheme 3-3. *Aliphatic C-H functionalization by remote 1,5-H-shift using alkoxy radical generated from alkyl hypochloride.*

Barton and co-workers reported the photolysis of nitrite esters (preformed from aliphatic alcohols and nitrosyl chlorides) as an alternative method to generate alkoxy radicals (Scheme 3-4).[11] It was discovered that after the photolysis of nitrite ester, alkoxy radical was generated along with the release of nitric oxide. The alkoxy radical continues to abstract a hydrogen atom from the δ-carbon, in which the resulting carbon-radical subsequently captures the nitric oxide liberated upon the original homolysis. The resulting nitroso group readily tautomerizes to form an oxime. This type of reaction is commonly known as the Barton reaction. This remote functionalization strategy was applied in the introduction of nitrogen functional groups on to steroids, having four fused rings containing many unactivated aliphatic C-H bonds (Scheme 3-5).[12]

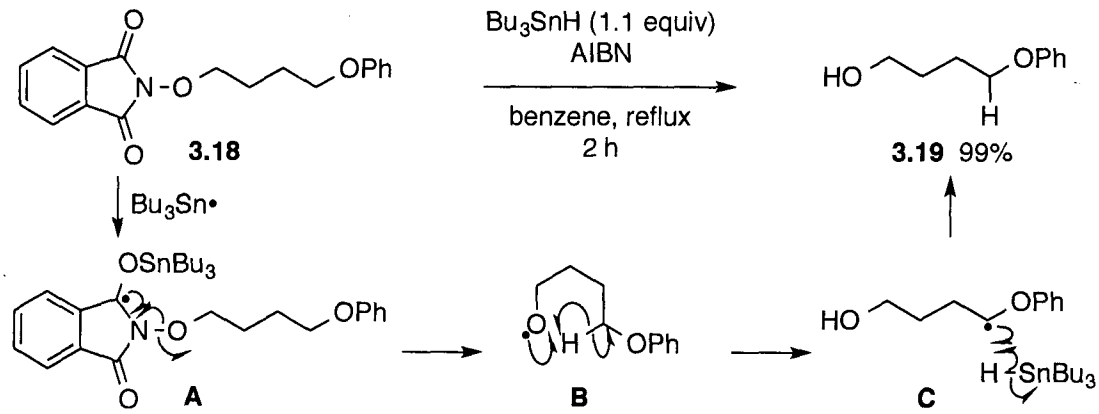


Scheme 3-4. *Generation of alkoxy radicals via nitrite ester and their 1,5-H radical shift.*

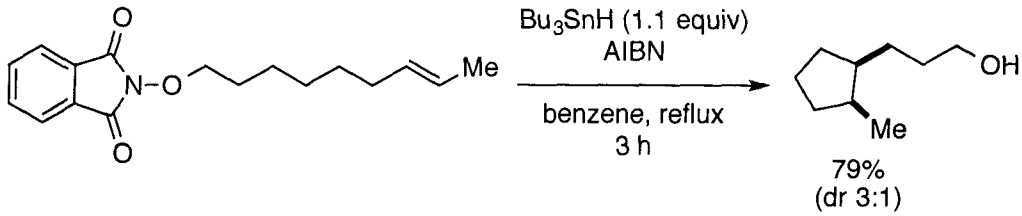


Scheme 3-5. *Installation of nitrogen functional group on aliphatic C-H bonds on steriod frameworks using nitrite ester.*

In addition, Kim and co-workers demonstrated a facile generation of alkoxyl radical by treating *N*-alkoxyphthalimide **3.18** with a stoichiometric amount of tributyltin hydride and AIBN (2,2'-azobisisobutyronitrile) as radical initiator (Scheme 3-6).[13] It was supposed that the addition of tributyltin radical on the amide carbonyl group of *N*-alkoxyphthalimide **3.18** provides a radical intermediate **A**, which results in the homolytic cleavage of the weak N-O bond. Thus, the generated alkoxy radical **B** results in 1,5-H-radical shift. Sammis and coworkers later utilized this strategy to generate alkoxy radicals for a radical relay cyclization process to construct carbocycles (Scheme 3-7).[14]

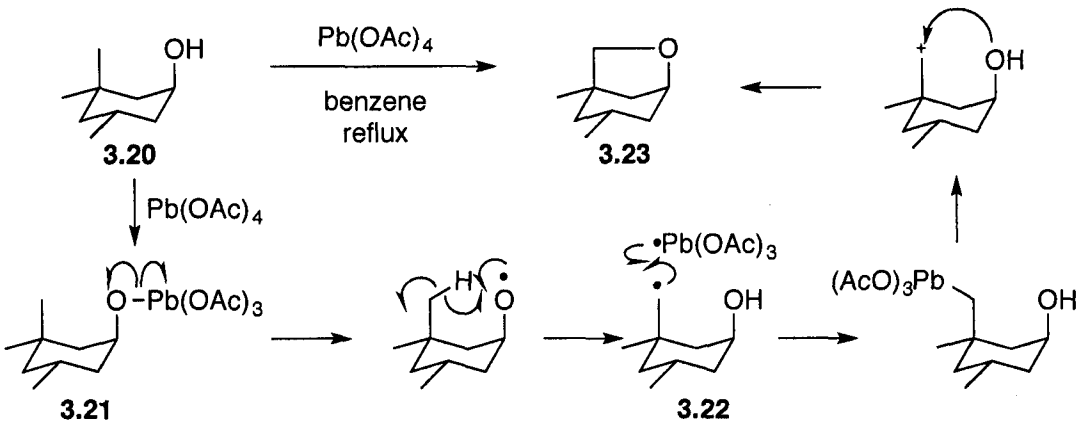


Scheme 3-6. *Generation of alkoxy radical from N-alkoxyphthalimides with Bu_3SnH.*



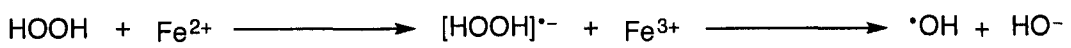
Scheme 3-7. *Radical relay carbocyclization from N-alkoxyphthalimide.*

In-*situ* generation of alkoxy radicals for 1,5-hydrogen-shift can be done by direct oxidation of the corresponding aliphatic alcohols using lead(IV) acetate. For example, treatment of aliphatic alcohol **3.20** with $Pb(OAc)_4$ results in the formation of tetrahydrofuran derivative **3.23** (Scheme 3-8).[15] Under thermal reaction conditions, homolytic cleavage of lead(IV) alkoxide **3.21** results in the formation of an alkoxyl radical which abstracts H-radical from the δ-carbon to give carbon radical **3.22**. With appropriate conformation, the carbon radical **3.22** could recombine with the $\bullet Pb(OAc)_3$ radical counterpart and cyclize to afford the resultant tetrahydrofuran product **3.23**.



Scheme 3-8. *$Pb(OAc)_4$ mediated oxidative formation of tetrahydrofuran derivatives.*

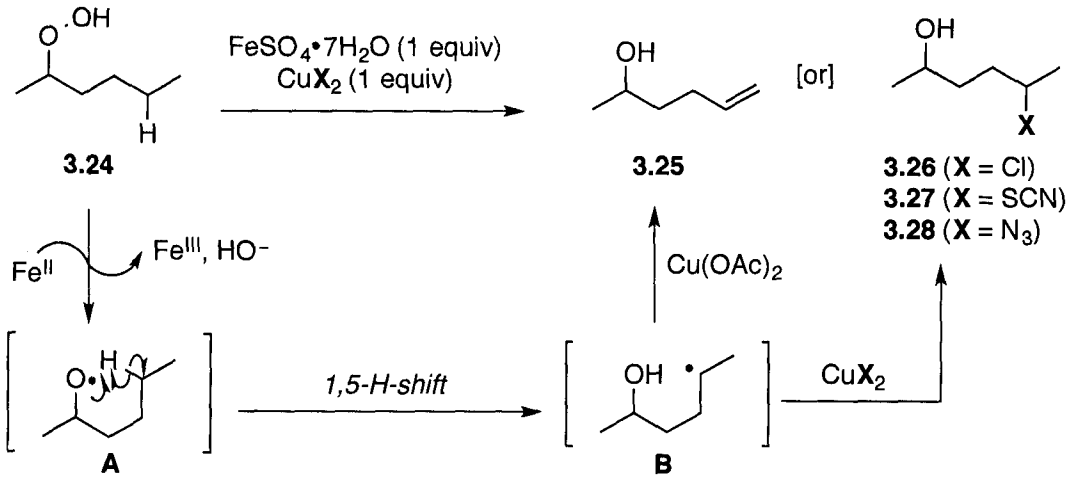
Hydroperoxides, on the other hand, can be reduced with lower valent metal salts to produce alkoxy radicals, along with the elimination of hydroxyl ions. Such phenomenon has been observed in hydrogen peroxide decomposition via Fenton's reaction where by the O–O bond undergoes one-electron reductive decomposition with lower valent ferrous ions to generate hydroxy radicals (Scheme 3-9).[16]



Scheme 3-9. *Hydrogen peroxide decomposition by Fenton's reaction.*

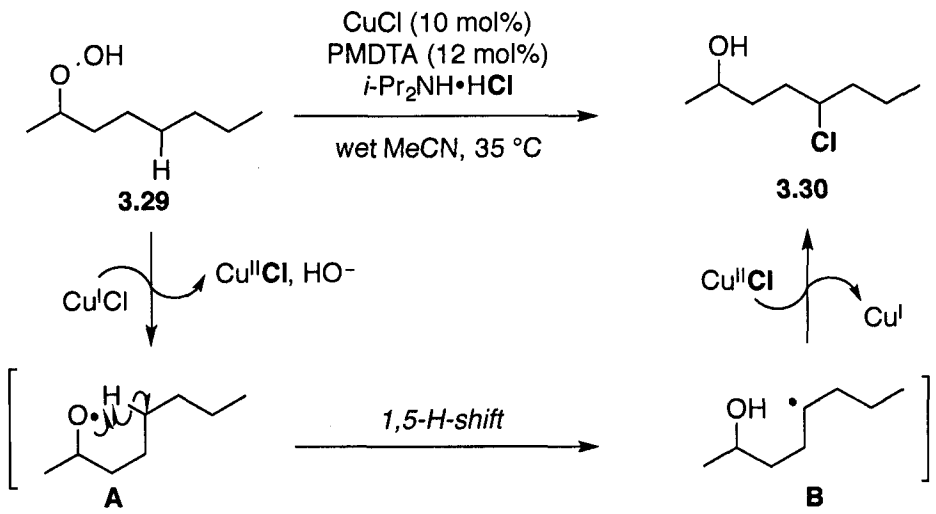
Čeković pioneered the studies of remote functionalization of sp^3 C-H bonds of alkyl hydroperoxide **3.24** with Fe(II)-Cu(II) bimetallic system (Schem 3-10).[17] The

process is proposed to begin with single-electron-reduction of hydroperoxide **3.24** by Fe(II) species to generate the alkoxy radical **A**, which performs 1,5-H radical shift to generate the corresponding carbon-radical **B**. The resulting carbon-radical **B** is further oxidized by Cu(II) salts to achieve: (1) remote desaturation product **3.25** (using $Cu(OAc)_2$) or (2) functionalized products such as alkyl chloride **3.26**, thiocyanate **3.27**, and azide **3.28**, depending on the counter ions of the Cu(II) salts.



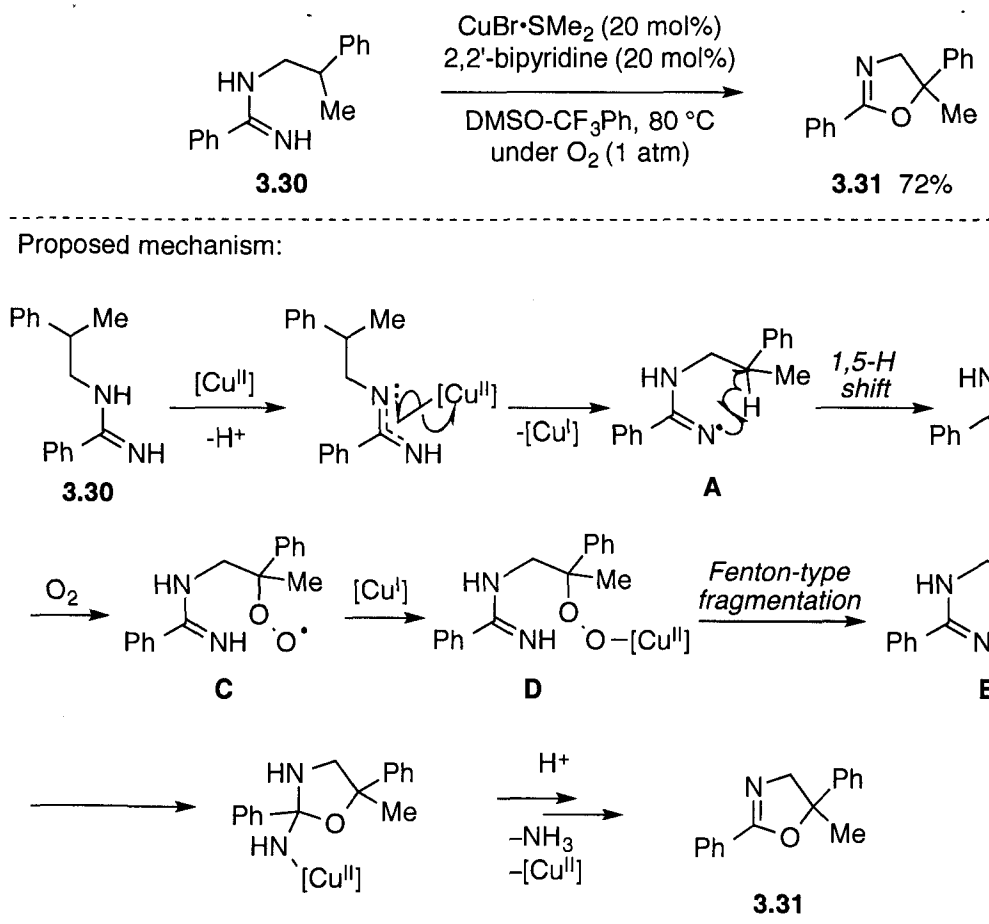
Scheme 3-10. *Remote functionalization of sp^3 C-H bonds on alky peroxides by Fe(II)-Cu(II) bimetallic system.*

Subsequently, Ball and co-workers developed Cu-catalyzed aliphatic C–H chlorination of alkyl hydroperoxide **3.29** using CuCl as the sole catalyst together with *N,N,N',N'',N''*-pentamethyldiethylenetriamine (PMDTA) as a ligand and ammonium chloride salt as the chlorine atom source (Scheme 3-11).[18] The reaction is proposed to proceed with the reduction of hydroperoxide **3.29** by the starting Cu(I) species to generate alkoxy radical **A**, followed by 1,5-H-radical shift to afford carbon radical **B**. Oxidative chlorine-atom transfer functionalization of the resulting carbon-radical **B** by Cu(II)–Cl species enabled the redox-neutral catalytic turnover with the single metallic system.



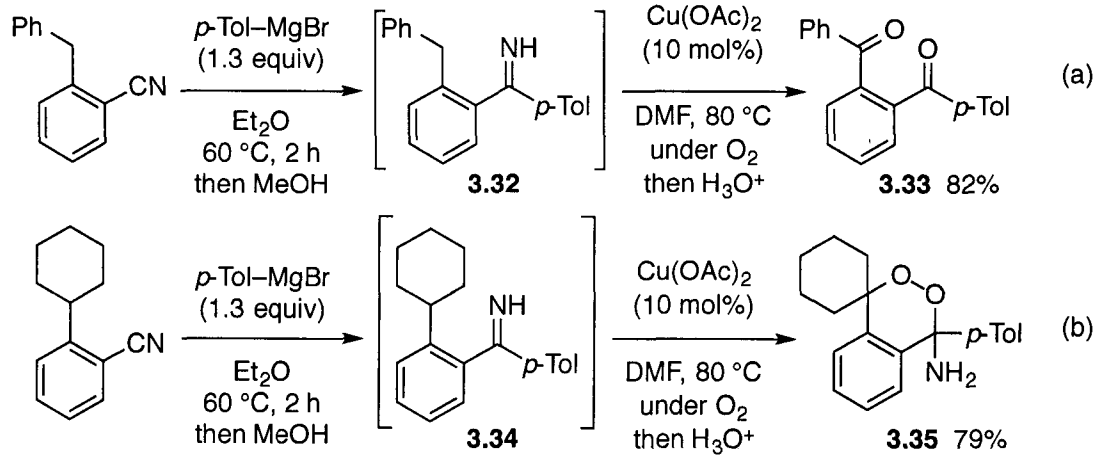
Scheme 3-11. *Cu-catalyzed remote sp^3 C-H chlorination of alky peroxides.*

Recently, our group has studied 1,5-H-radical shift with nitrogen radicals such as amidinyl or iminyl radical generated under Cu-catalyzed aerobic reaction conditions, in which the resulting carbon radical could be oxygenated by trapping molecular oxygen to form a new C–O bond. For example, single-electron-oxidation of *N*-alkylamidine **3.30** under Cu-catalyzed aerobic reaction conditions afforded amidinyl radical **A**, which undergoes 1,5-H-radical shift to generate the corresponding carbon radical **B** (Scheme 3-12).[19] The successive trapping of the resulting carbon-radical **B** with molecular oxygen affords peroxy radical **C**, which undergoes single-electron-reduction to form peroxy copper **D**. Subsequent *Fenton*-type fragmentation of peroxy-copper species **D** results in alkoxide **E**, cyclization of which with the amidine moiety delivers dihydrooxazole **3.31** along with ammonia liberation.



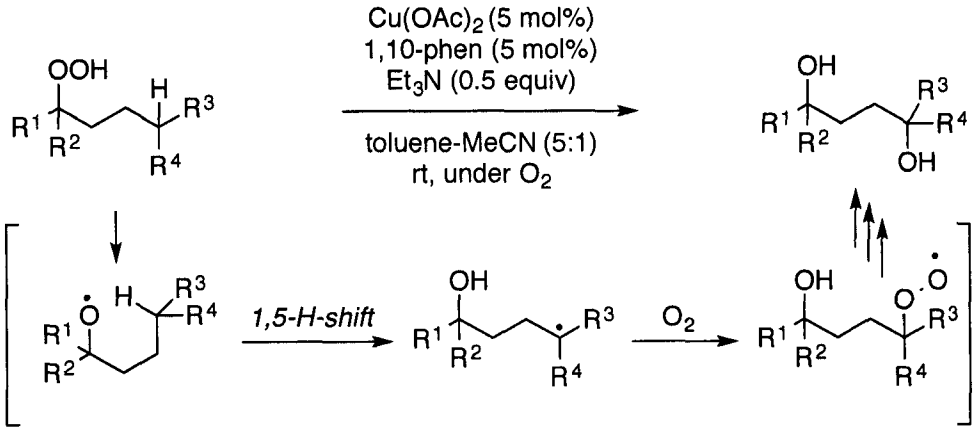
Scheme 3-12. *Cu-catalyzed aerobic sp^3 C-H oxygenation of N-alkylamidines.*

Similarly, Cu-catalyzed aerobic reactions of *N*–H ketimine **3.32** provided iminyl radical, which achieved directed sp^3 C–H oxygenation of secondary benzylic C–H bond to provide 1,2-diacylbenzene **3.33** (Scheme 3-13a).[20] Moreover, *N*–H ketimine **3.34** tethered with tertiary benzylic C–H bond also undergoes directed C–H oxygenation to afford amino endoperoxide **3.35** (Scheme 3.13b).[21]



Scheme 3-13. *Cu-catalyzed aerobic sp^3 C-H oxygenation of N-H-ketimines.*

In this context, it was considered that hydroperoxide can be exploited as a precursor for the corresponding alkoxy radical under Cu-catalyzed aerobic reaction conditions to achieve sp^3 C–H oxygenation via remote 1,5-H-shift. Unlike nitrogen-centered radicals derived from amidines or *N*–H ketimines that could be generated under oxidative reaction conditions, previous reports by Čeković or Ball showed that generation of oxygen-centered radicals from hydroperoxides required reductive reaction conditions with lower valent iron or copper species. If reductive generation of the alkoxy-radical from hydroperoxide could be achieved under an O_2 atmosphere (oxidative conditions), the resultant carbon-radical generated by 1,5-H radical shift could be trapped with O_2 to form the new C–O bond (Scheme 3-14). Herein, the realization of the above concept for aerobic synthesis of 1,4-diols from hydroperoxides is described, that is catalyzed by the $Cu(OAc)_2$-1,10-phenanthroline system in the presence of Et_3N as a terminal reductant.

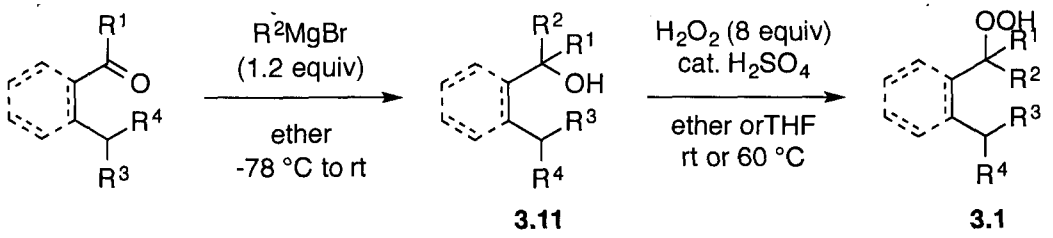


Scheme 3-14. *An initial concept for Cu-catalyzed aerobic sp^3 C-H oxygenation of alkyl hydroperoxides.*

3.2 Results and Discussion

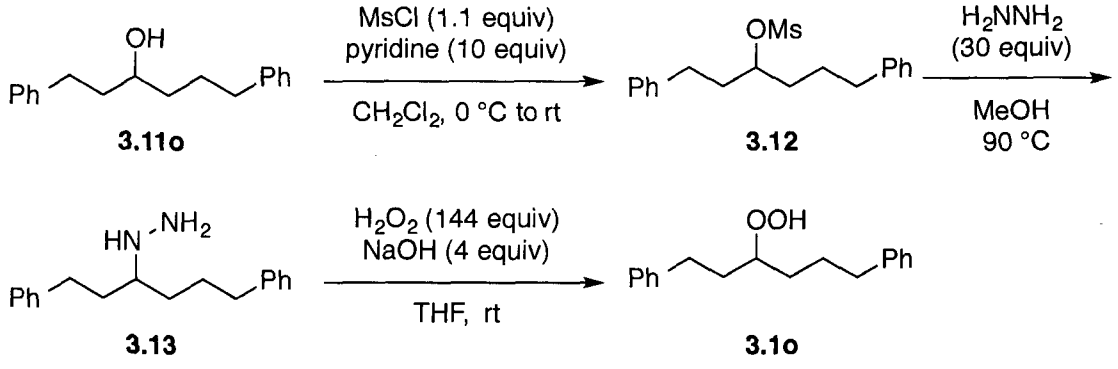
3.2.1 Preparation of hydroperoxides 3.1

As shown in Scheme 3-15, tertiary hydroperoxide **3.1** is generally synthesized from ketone with Grignard reagent for the formation of various tertiary alcohols **3.11**, which undergo S_N1 substitution with H_2O_2 catalyzed by a small amount of sulfuric acid. All hydroperoxides **3.1,** execpt **3.1o**, are synthesized by this synthetic route. Details of experimental procedure and yields can be found in Chapter 5, Section 5.3.1.1



Scheme 3-15. *A general scheme for the preparation of tertiary hyroperoxides* ***3.1.***

Secondary peroxide **3.1o** was prepared by sequence of reactions based on previously reported procedure from literature[18] as shown in Scheme 3-16. These steps involved: 1) the conversion of secondary alcohol **3.11o** to its corresponding methanesulfonate **3.12** for a substitution reaction to synthesize hydrazine **3.13** and 2) treatment of the hydrazine **3.13** with an alkaline solution of H_2O_2 to give secondary hydroperoxide **3.1o**. Details of experimental procedure and yields can be found in Chapter 5, Section 5.3.1.4.



Scheme 3-16. *A general scheme for the preparation of secondary hyroperoxide* ***3.1o.***

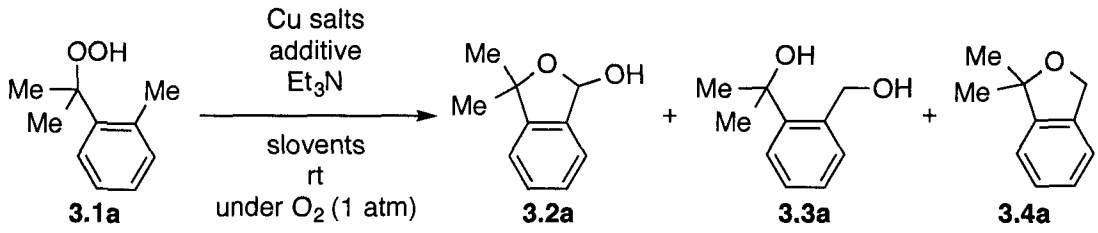
3.2.2 Synthesis of 1,4-diols from hydroperoxides

3.2.2.1 Optimization of reaction condition

To maintain lower valent Cu(I) species under oxidative reaction conditions in conducting reactions under an O_2 atmosphere, proper terminal reductants should be identified. It is known that tertiary amines are readily oxidized by higher-valent transition-metals [such as Fe(III) or Cu(II)] to iminium ions via single-electron-transfer (SET) processes, which in turn generate lower valent transition-metal species during the

process.[22] Hence, the investigation began with the Cu-catalyzed aerobic reactions of 1-(2-hydroperoxypropan-2-yl)-2-methylbenzene (**3.1a**) in the presence of Et_3N as a terminal reductant to maintain lower valent Cu(I) species in the reaction mixture (Table 3-1). Hydroperoxide **3.1a** was first treated with $Cu(OAc)_2$ (20 mol%) and Et_3N (2 equiv) in DMF at room temperature under an O_2 atmosphere. Delightfully, after stirring for 17 h, the expected C–H oxygenated products, cyclic hemiacetal **3.2a** and 1,4-diol **3.3a** were isolated in 49% and 8% yields, respectively (entry 1). When nitrogen ligands such as 2,2'-bipyridine (bpy) and 1,10-phenanthroline (1,10-phen) was added, the reaction completed in shorter reaction times (entries 2 and 3). The reactions with $CuCl_2$ as well as CuCl resulted in comparable yields with that of $Cu(OAc)_2$ (entries 4 and 5). Initial screening of solvents revealed that the use of non-polar solvents such as benzene and toluene result in dramatic increase of the overall yield (entries 6–8). This is likely due to the effect of higher solubility of atmospheric O_2 in non-polar solvents,[23] which in turn results in a higher concentration of O_2 in the reaction mixture available for the oxygenation process. Further optimization of the solvent screening found that the co-solvent system (benzene/MeCN or toluene/MeCN) performed more effeciently to give the highest yield (83–87% combined yields of **3.2a** and **3.3a**, entries 9–11), in which the amount of Et_3N could be reduced to 0.5 equiv (entries 10 and 11). It is noteworthy that the catalytic loading of $Cu(OAc)_2$–1,10-phen could be lowered to 5 mol % while maintaining good combined yields of **3.2a** and **3.3a** (89%, entry 13).

Table 3-1. Optimization of the reaction conditions.



3.1a **3.2a** **3.3a** **3.4a**

entry[a]	Cu-salts [mol%]	Additive [mol%]	Et_2N [equiv]	Solvent [0.1 M]	time [h]	Yield [%][b] **3.2a**	**3.3a**	**3.4a**
1	$Cu(OAc)_2$ [20]	—	2.0	DMF	17	49	8	0
2	$Cu(OAc)_2$ [20]	bpy [20]	2.0	DMF	3	49	9	0
3	$Cu(OAc)_2$ [20]	1,10-phen [20]	2.0	DMF	3	53	12	0
4	$CuCl_2$ [20]	1,10-phen [20]	2.0	DMF	6	52	10	0
5	CuCl [20]	1,10-phen [20]	2.0	DMF	3	52	10	0
6	$Cu(OAc)_2$ [20]	1,10-phen [20]	2.0	MeCN	2	55	20	0
7	$Cu(OAc)_2$ [20]	1,10-phen [20]	2.0	benzene	5	71	13	0
8	$Cu(OAc)_2$ [20]	1,10-phen [20]	2.0	toluene	9	70	14	0
9	$Cu(OAc)_2$ [20]	1,10-phen [20]	2.0	benzene/MeCN (5:1)	2	76	11	0
10	$Cu(OAc)_2$ [20]	1,10-phen [20]	0.5	benzene/MeCN (5:1)	3	74	9	0
11	$Cu(OAc)_2$ [20]	1,10-phen [20]	0.5	toluene/MeCN (5:1)	3	74	10	0
12	$Cu(OAc)_2$ [10]	1,10-phen [10]	0.5	toluene/MeCN (5:1)	3	75	16	0
13	$Cu(OAc)_2$ [5]	1,10-phen [5]	0.5	toluene/MeCN (5:1)	3	75	14	0
14[c]	$Cu(OAc)_2$ [5]	1,10-phen [5]	0.5	toluene/MeCN (5:1)	3	—	90	0
15[d]	$Cu(OAc)_2$ [5]	1,10-phen [5]	0.5	toluene/MeCN (5:1)	1	0	0	47

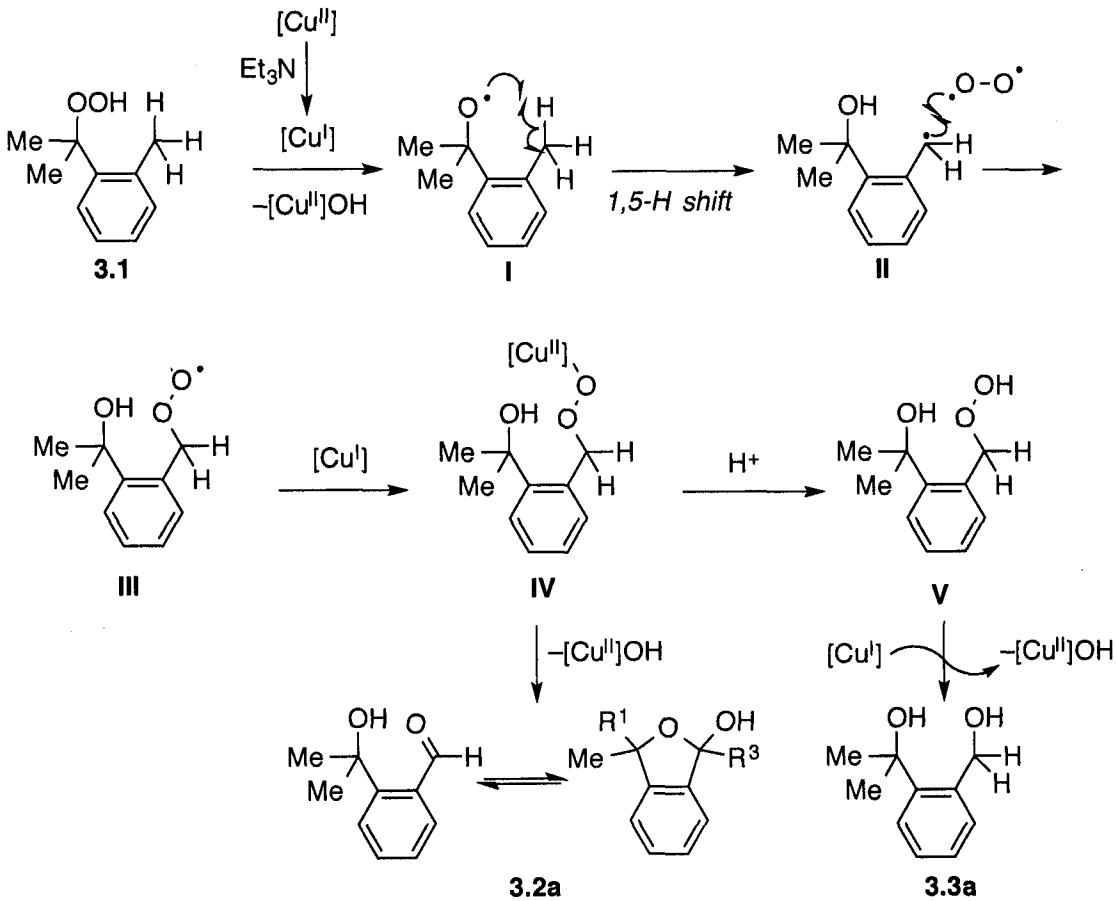
[a]Reactions were carried out using 0.3 mmol of hydroperoxide **3.1a** in solvents (3 mL, 0.1 M) at room temperature under an O_2 atmosphere. [b]Isolated yields are recorded. [c]After stirring 3 h, the volatile materials were removed in vacuo, and the resulting crude materials were further treated with $LiAlH_4$ (1.2 equiv) in THF for 1 h. [d] The reaction was conducted under a N_2 atmosphere.

Upon completion of the C–H oxygenation under the reaction conditions in entry 13, the resulting crude residue after removal of the solvents was treated with $LiAlH_4$ in THF, affording 1,4-diol **3.3a** as the sole product in 90% yield (entry 14). The Cu-

catalyzed reaction of **3.1a** under an inert (N_2) atmosphere gave an intramolecular C–H oxygenation product, dihydroisobenzofuran **3.4a** in 47% yield (entry 15).

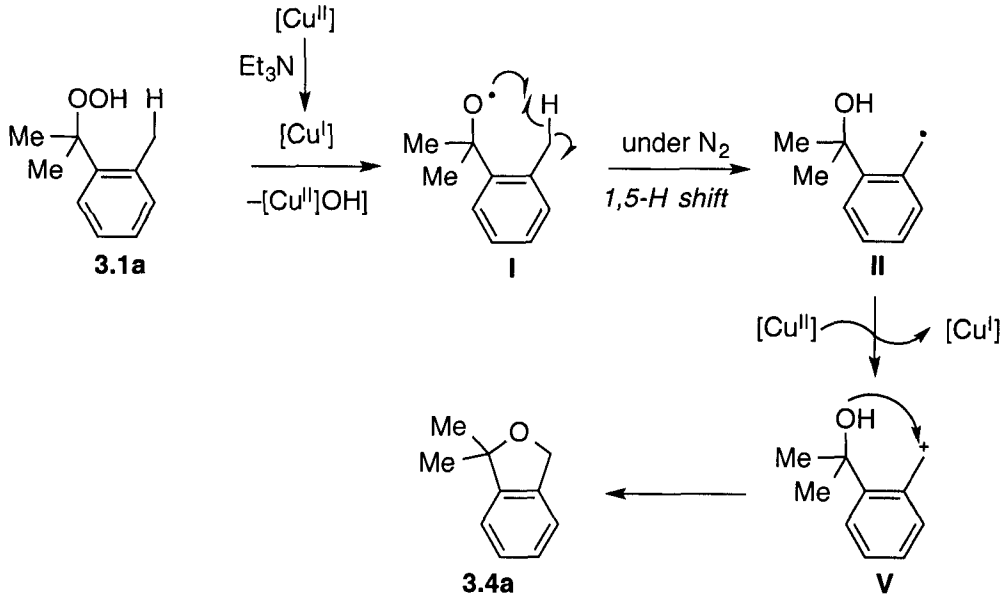
3.2.2.2 Mechanism discussion

The proposed reaction pathways for the formation of **3.2a** and **3.3a** are described in Scheme 3-17. Firstly, single-electron-reduction of the starting $Cu(OAc)_2$ by Et_3N forms the Cu(I) species, which reduces hydroperoxide **3.1a** to generate alkoxy-radical **I** with the release of Cu(II) species. 1,5-H-Radical shift of alkoxy-radical **I** generates carbon-radical **II**, which is trapped by molecular O_2 to give peroxy radical **III**. Probably further reaction of **III** with Cu(I) species gives Cu(II)-peroxide **IV**, which undergoes fragmentation to give aldehyde that cyclizes to afford hemiacetal **3.2a**. Protonation of Cu(II)-peroxide **IV** results in formation of hydroperoxide **V**, while further reduction of the resulting hydroperoxide delivers 1,4-diol **3.3a**.



Scheme 3-17. *The proposed reaction mechanism for formation of 3.2a and 3.3a*

In the case of the reaction of **3.1a** conducted in the absence of molecular O_2 (under a N_2 atmosphere, Table 1, entry 15), the resulting carbon-radical **I** is oxidized by the Cu(II) species to give carbocation **V**,[24] which is trapped by the intramolecular hydroxy group to give ether **3.4a** (Scheme 3-18).

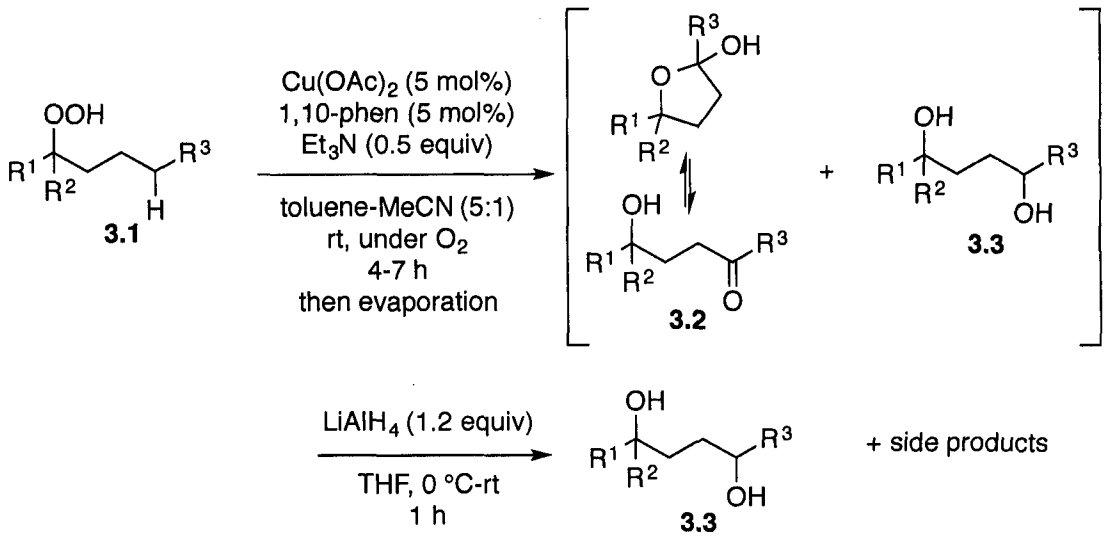


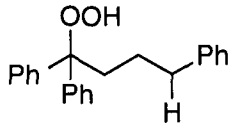
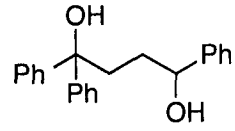
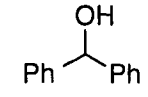
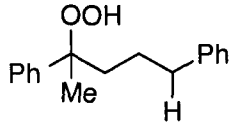
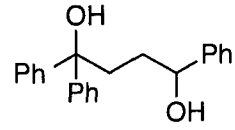
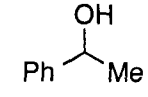
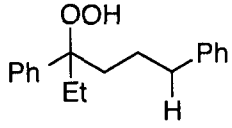
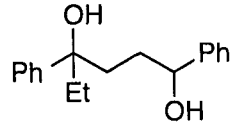
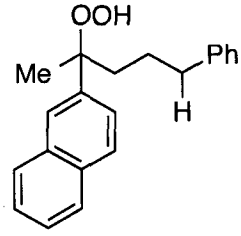
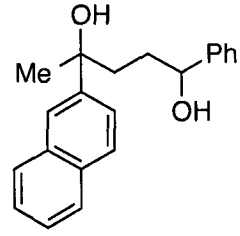
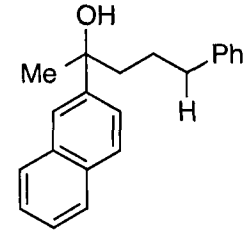
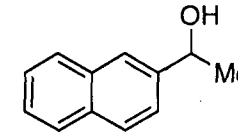
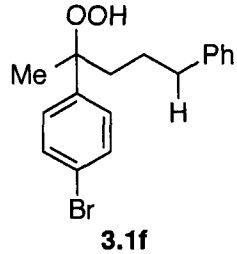
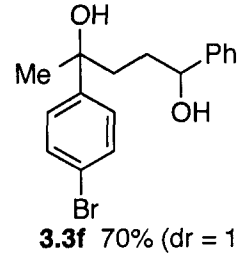
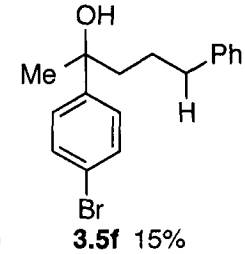
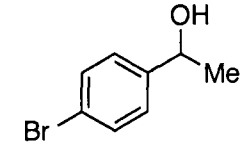
Scheme 3-18. *The proposed reaction mechanism for formation of **3.4a** from **3.1a**.*

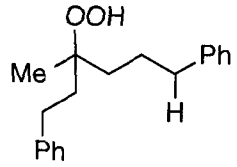
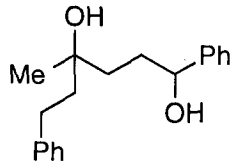
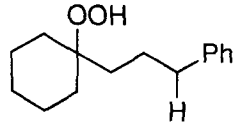
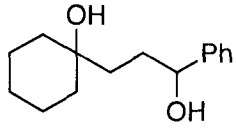
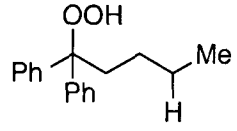
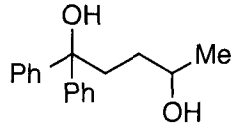
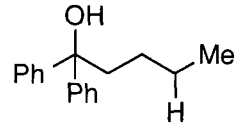
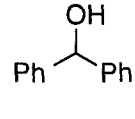
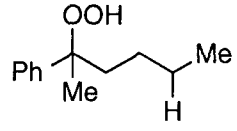
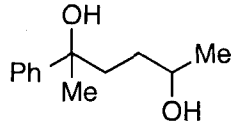
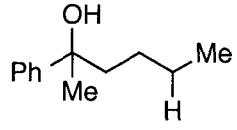
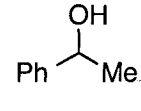
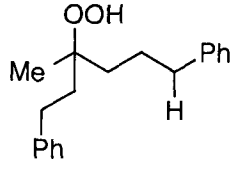
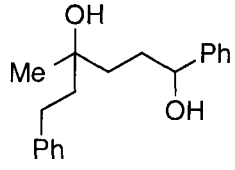
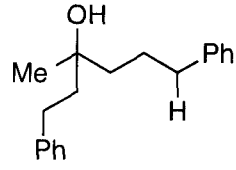
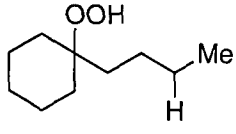
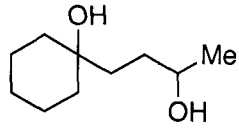
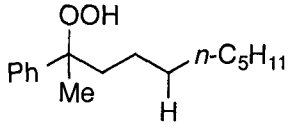
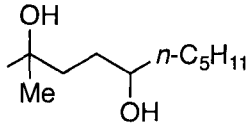
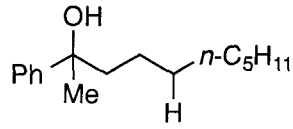
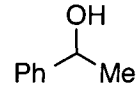
3.2.2.3 Scope and limitation

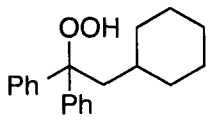
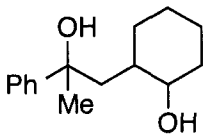
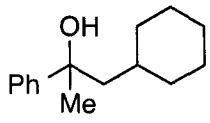
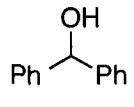
With the optimized protocol in hand, the substrate scope for the synthesis of 1,4-diols by targeting methylene C–H oxygenation with various tertiary hydroperoxides **3.1** was examined (Table 3-2). Generally, oxygenation of benzylic methylene C–H bonds proceeded smoothly to give the corresponding 1,4-diols **3.3** in good to moderate yields (77–51% yields, entries 1–7). Additionally, the present method also allowed oxygenation of non-benzylic methylene C–H bonds, although yields of obtained 1,4-diols **3.3** were relatively low (65–40% yields, entries 8–13).

Table 3-2. Scope of oxygenation of secondary C-H bonds.



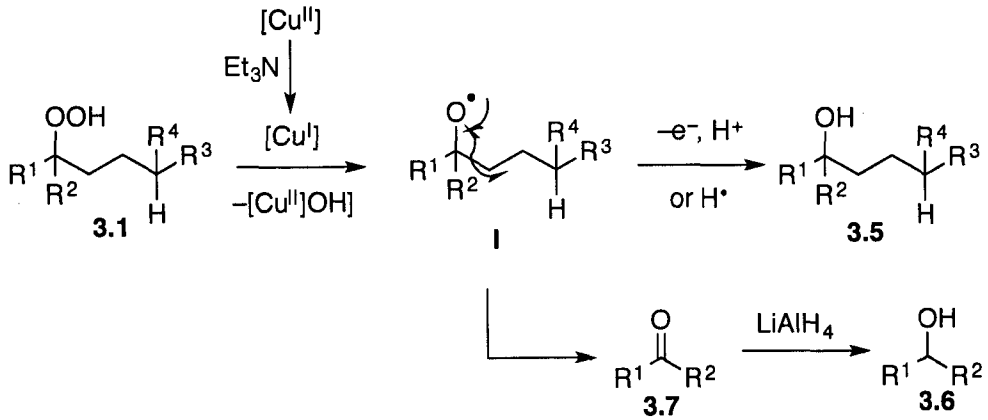
entry[a]	Hydroperoxide **3.1**	1,4-Diols **3.3**	side products: alcohol **3.5**	side products: alcohol **3.6**
1	 **3.1b**	 **3.3b** 77%	—	 **3.6b** 8%[b]
2	 **3.1c**	 **3.3c** 72% (dr = 1:1)	—	 **3.6c** 8%[b]
3	 **3.1d**	 **3.3d** 51% (dr = 1:1)	—	—
4	 **3.1e**	 **3.3e** 62% (dr = 1:1)	 **3.5e** 9%	 **3.6e** 17%[b]
5	 **3.1f**	 **3.3f** 70% (dr = 1:1)	 **3.5f** 15%	 **3.6f** 15%[b]

entry[a]	Hydroperoxide **3.1**	1,4-Diols **3.3**	side products	
			alcohol **3.5**	alcohol **3.6**
6	 **3.1g**	 **3.3g** 51% (dr = 1:1)	—	—
7	 **3.1h**	 **3.3h** 56%	—	—
8	 **3.1i**	 **3.3i** 65%	 **3.5i** 18%	 **3.6b** 14%[b]
9	 **3.1j**	 **3.3j** 62% (dr = 1.27:1)	 **3.5j** 23%	 **3.6c** 20%[b]
10	 **3.1k**	 **3.3k** 40% (dr = 1:1)	 **3.5k** 16%	—
11	 **3.1l**	 **3.3l** 48%	—	—
12	 **3.1m**	 **3.3m** 45% (dr = 1.27:1)	 **3.5m** 18%	 **3.6c** 20%[b]

entry[a]	Hydroperoxide **3.1**	1,4-Diols **3.3**	side products	
			alcohol **3.5**	alcohol **3.6**
13	 **3.1n**	 **3.3n** 51% (*trans/cis* = 1.37:1)	 **3.5n** 13%	 **3.6b** 23%[b]

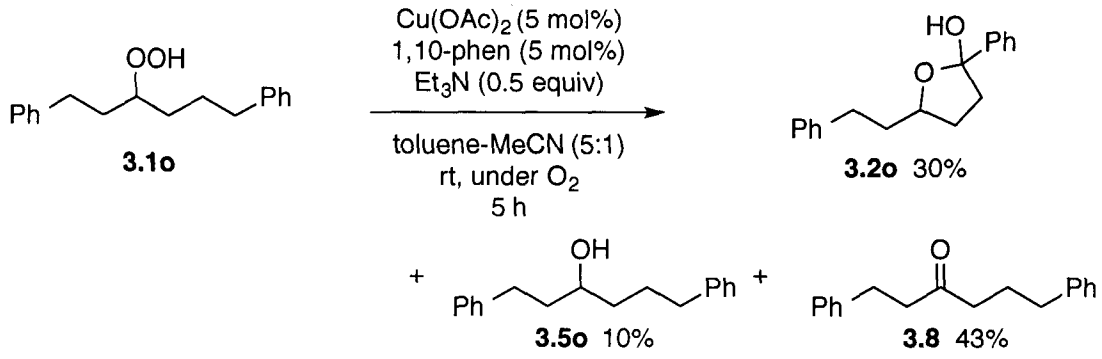
[a]Reactions were carried out using 0.5 mmol of hydroperoxide **1** with $Cu(OAc)_2$ (5 mol %) and Et_3N (0.5 equiv) in toluene/MeCN (5:1, 0.1 M) at room temperature under an O_2 atmosphere. After stirring 4-7 h, the volatile materials were removed in vacuo, and the resulting crude materials were further treated with $LiAlH_4$ (1.2 equiv) in THF for 1 h. [b]Isolated yields are recorded.

Besides the targeted 1,4-diols **3.3**, either reduced alcohols **3.5** (up to 23% yield) or fragmented alcohols **3.6** (up to 23% yield), or both were also observed as minor products in most of the reactions (except for cases in entries 3, 6, 7 and 11). This is because alkoxy-radical **I** generated from the reduction of hydroperoxide **3.1** also induces side reactions, which result in the formation of **3.5** and **3.6** or **3.7**, as summarized in Scheme 3-19. The formation of alcohol **3.5** occurs when alkoxy-radical **I** either undergoes one-electron-reduction followed by protonation or external H-radical abstraction, prior to the 1,5-H radical shift. On the other hand, in the case when β-fragmentation from alkoxy-radical **I** takes place before the 1,5-H radical shift, ketone **3.7** is formed, which is further reduced to alcohol **3.6** by $LiAlH_4$ in the subsequent step.



Scheme 3-19. *The reaction mechanism for formation of 3.5, 3.6, and 3,7.*

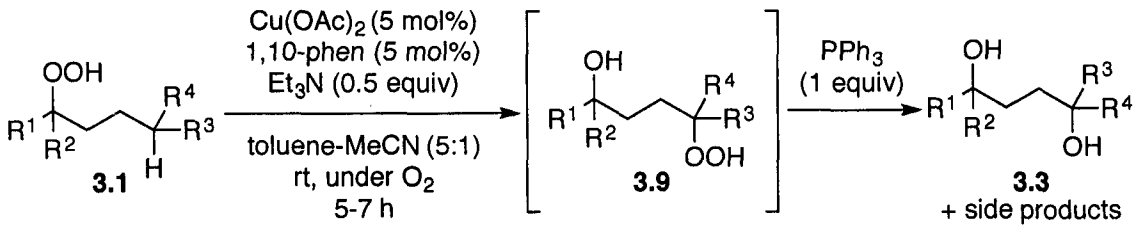
When secondary hydroperoxide **3.1o** was treated with the Cu-catalyzed aerobic condition, the in *situ* formed secondary alkoxy-radical quickly transformed to ketone **3.8o** in 43% yield, while C–H oxygenation product **3.2o** (as a keto form) was isolated in only 30% yield along with corresponding reduced alcohol **3.5o** in 10% yield. (Scheme 3-19).

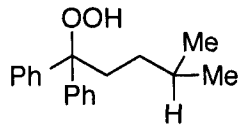
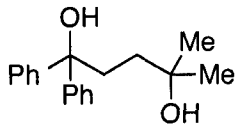
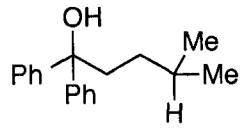
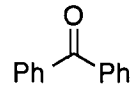
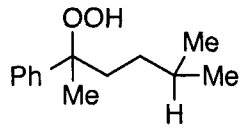
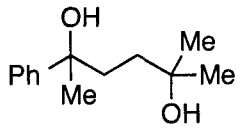
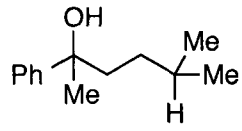
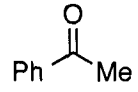
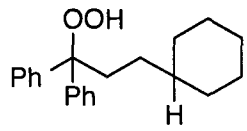
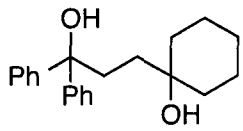
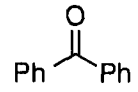
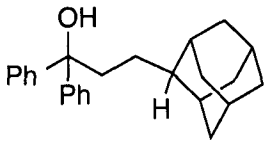
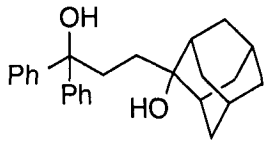
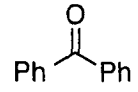


Scheme 3-20. *The reaction of secondary hydroperoxide 3.1o.*

Next, oxygenation of tertiary C–H bonds was also examined under the present Cu-catalyzed aerobic conditions with tertiary hydroperoxide **3.1** (Table 3-3). In these cases, hydroperoxide **3.9** were formed as initial aerobic C–H oxygenation product from the Cu-catalyzed aerobic reactions after stirring for 5–7 h. To obtain the desired 1,4-diol **3.3**, hydroperoxide **3.9** were reduced by PPh_3 (1 equiv), which was successively added to the reaction mixtures after the consumption of starting materials. Although the desired 1,4-diol **3.3** were obtained with this one-pot procedure, the isolated yields of **3.3p–3.3r** were moderate (45–52% yields, entries 1–3). The oxygenation of the adamantyl C–H bond was particularly sluggish, affording the desired 1,4-diol **3.3s** in only 23% yield (entry 4). Similarly, the formation of reduced alcohols **3.5** (entries 1 and 2) and fragmented ketones **3.7** (entries 1–4) were observed as minor products in these cases.

Table 3-3. Sope of oxygenation of tertiary C-H bonds.



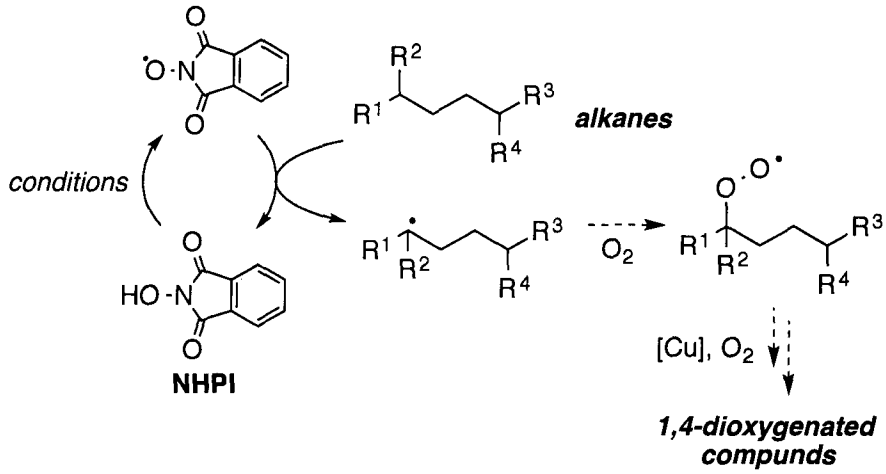
entry[a]	Hydroperoxide **3.1**	1,4-Diols **3.3**	side products: alcohols **3.5**	side products: ketones **3.7**
1	 **3.1p**	 **3.3p** 52%	 **3.5p** 16%	 **3.6b** 28%[b]
2	 **3.1q**	 **3.3q** 45%	 **3.5q** 23%	 **3.6c** 24%[b]
3	 **3.1r**	 **3.3r** 47%	—	 **3.6b** 12%[b]
4	 **3s** 23%	 **3s** 23%	—	 **3.6b** 12%[b]

[a]Reactions were carried out using 0.5 mmol of hydroperoxide **1** with $Cu(OAc)_2$ (5 mol %) and Et_3N (0.5 equiv) in toluene/MeCN (5:1, 0.1 M) at room temperature under an O_2 atmosphere. After stirring 5-7 h, the reaction mixture was further treated with PPh_3 (1 equiv) at rt. Isolated yields are recorded. [b] ^1H NMR yields with 1,1,2,2-tetrachloroethane as an internal standard.

3.2.3 Direct 1,4-dioxygenation of alkanes via aerobic oxygenation using Cu-NHPI system

Next, the direct aerobic dioxygenation of alkanes using the present radical strategy was challenged. It is hypothesized that alkanes with C–H bonds bearing relatively weak bond-dissociation enthalpies (i.e., tertiary alkyl C–H bonds, benzylic C–H bonds, etc.) can undergo selective intermolecular H-abstraction in the presence of a suitable radical

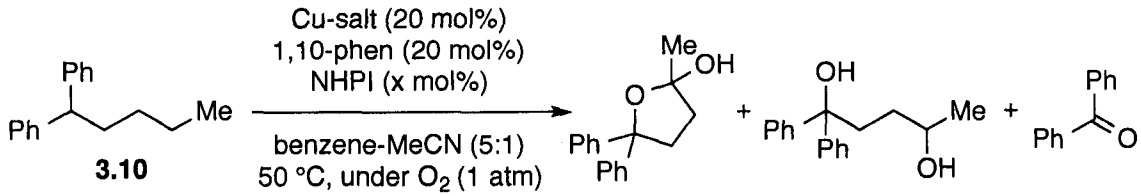
species, for the generation of carbon-radicals. Trapping of molecular oxygen with the generated carbon radicals thus produces hydroperoxides directly. Once the *in situ* formation of hyroperoxides is established, the present remote C–H oxygenation with hydroperoxides should proceed for the direct formation of 1,4-dioxygenated compounds from nonoxygenated alkanes (Scheme 3-21). It is known that phthalimide *N*-oxyl (PINO) radicals are effective in intermolecular H-abstraction of various types of sp^3 C-H bonds, which can be generated oxidatively from *N*-hydroxyphthalimides (NHPI) under aerobic reaction conditions in the presence of transition metal catalysts (such as Co or Cu-salts).[25] Hence, the introduction of NHPI to the present reaction conditions was done with the aim to achieve direct aerobic 1,4-dioxygenation of alkanes.



Scheme 3-20. *A working hypothesis for the synthesis of 1,4-dioxygenated products from alkanes.*

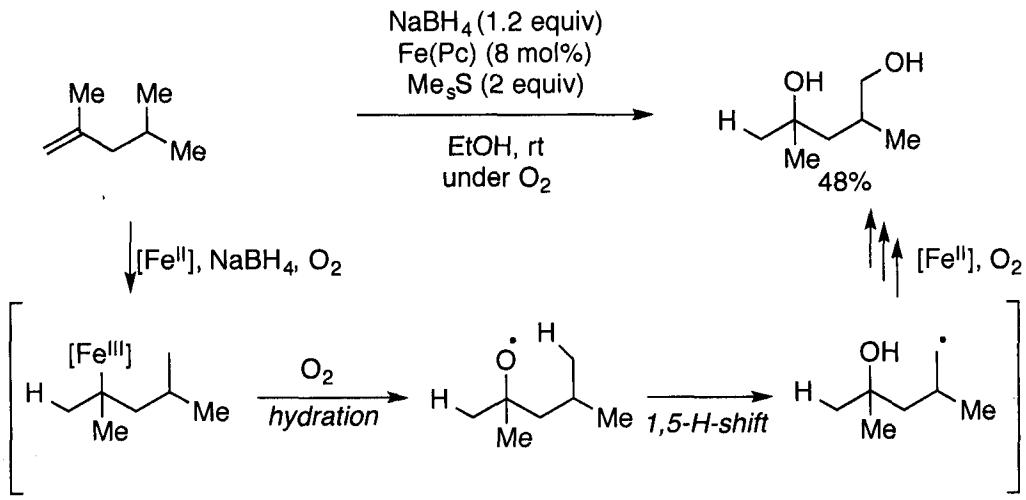
In this context, 1,1-diphenyl pentane (**3.10**) bearing a dibenzylic tertiary C–H bond was treated with the catalytic system of $Cu(OAc)_2$-1,10-phen (20 mol%) with NHPI (20 mol%) in benzene/ MeCN solvent under an O_2 atmosphere (1 atm) (Scheme 3-22). However, the reaction did not proceed even after heating the reaction at 50 °C and the starting alkane **3.10** was recovered completely. Fortunately, by changing the catalyst from $Cu(OAc)_2$ to CuCl, the reaction proceeded to afford a mixture of lactone **3.2i** and 1,4-diol **3.3i** in 29% and 3% yields, respectively, via the desired 1,4-dioxygenation, while benzophenone (**3.7b**) was also formed in 30% yield through fragmentation of the

transient alkoxy radical. With the use of 40 mol% of NHPI, slightly improved yields of 1,4-dioxygenation products **3.2i** and **3.3i** (40% and 4% yields, respectively) was observed. Complementary to the present method, Taniguchi and co-worker recently reported the synthesis of 1,4-diols from alkenes via iron-catalyzed aerobic hydration using iron phthalocyanine (Pc) complex, sodium borohydride, and molecular oxygen (Scheme 3-23).[26] The second hydroxy group is installed by directed sp^3 C–H oxygenation, which is based on a 1,5-H-shift process of a transient alkoxy radical that is formed by formal hydration of the olefin.



Cu-Salt	NHPI	3.2i	3.3i	3.7b
$Cu(OAc)_2$	20 mol%	-	-	-
CuCl	20 mol%	29%	3%	30%
CuCl	40 mol%	40%	4%	23%

Scheme 3-22. *Aerobic 1,4-dioxygenation of alkanes in the CuCl-NHPI catalytic system.*



Scheme 3-23. *Fe-catalzyed synthesis of 1,4-diols via hydration, 1,5-H-shift sequence under an O_2 atmosphere.*

3.3 Conclusions

In conclusion, the Cu-catalyzed aerobic oxygenation of aliphatic C–H bonds by 1,5-H radical shift of putative alkoxy radicals derived from hydroperoxides **3.1** followed

by trapping of the resulting carbon-radicals with molecular oxygen has been realized. Preliminary result involving the direct 1,4-dioxygenation of alkane **3.10** was demonstrated by using the present method.

3.4 References

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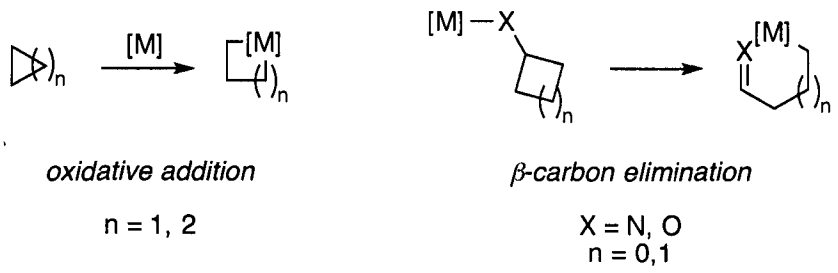
Chapter 4: Synthesis of Lactones from Hemiacetals by Cu-Catalyzed Aerobic C–C Bond Cleavage with *N*-Hydroxy Phthalimide

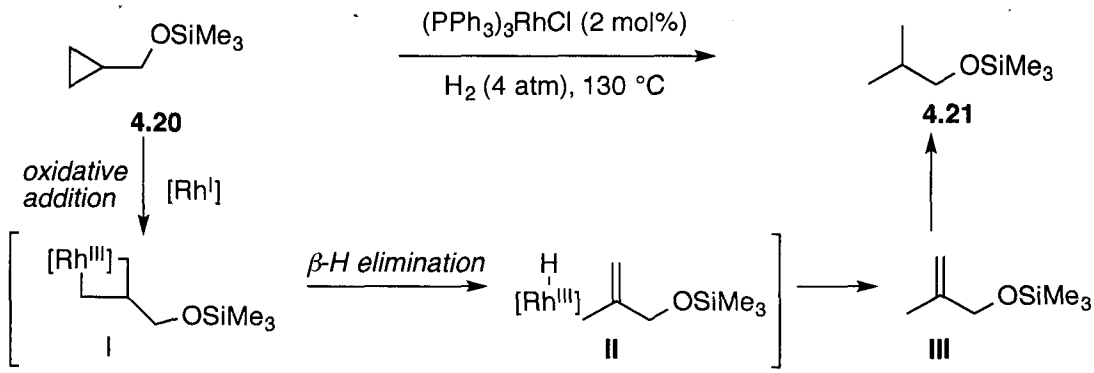
4.1 Overview

The study of molecular transformations involving C–C bond fission provides new perspectives to exploit inert C–C bonds as possible syntons for chemical functionalization. In the recent years, developments in selective C-C bond cleavage and functionalization via catalytic processes using transition-metals [M] have attained significant success.[1] These methods are commonly driven by release of ring strain or generation of a relatively stable C–[M] bond as the driving force of the inert C–C bond cleavage. For example, three- and four-membered cycloalkanes readily undergo C–C bond cleavage processes, either by direct insertion of transition-metal complexes into the C–C bond of the ring or through β-carbon elimination of heteroatom-metal species, resulting in useful intermediates for further functionalization (Scheme 4-1).



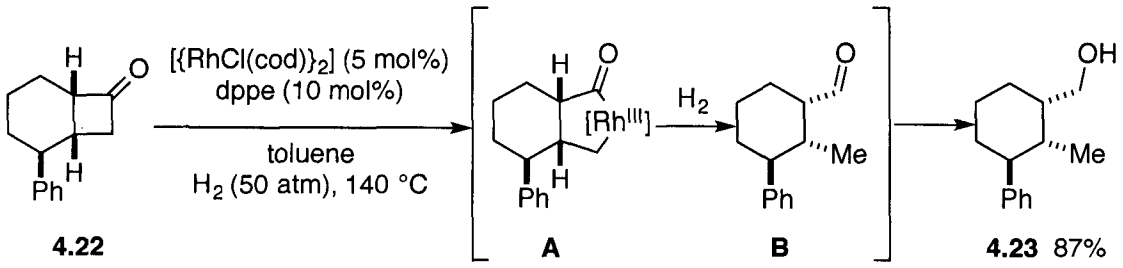
Scheme 4-1. *Transition-metal-catalyzed C-C bond activation.*

Chirik and co-workers demonstrated the selective activation of C–C bonds in substituted cyclopropane derivatives using $(PPh_3)_3RhCl$ as the catalyst (Scheme 4-2).[2] The reaction proceeds with oxidative addition of the non-sterically hindered C–C bond of cyclopropane **4.20** to the Rh(I) complex to result in Rh(III) metallocycle **I**. Subsequent β-hydride elimination occurs, which releases the ring strain in **I** to afford branched alkene **III**, followed by catalytic hydrogenation affords isobutoxytrimethylsilane **4.21**.

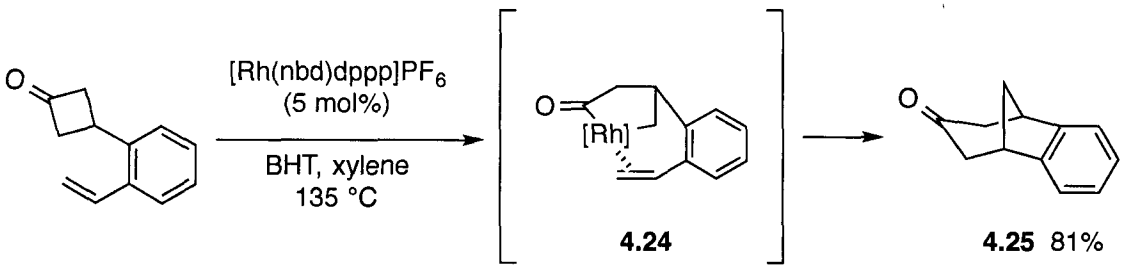


Scheme 4-2. *Rh(I)-catalyzed C-C bond activation of cyclopropane.*

Ito and co-workers studied the Rh(I)-catalyzed C−C bond cleavage of cyclobutanone **4.22** for the synthesis of primary alcohol **4.23** (Scheme 4-3).[3] It was found that the Rh(I) complex inserts into the acyl–carbon bond to form rhodacycle **A**, which undergoes reductive ring cleavage under a hydrogen atmosphere to result in the formation of aldehyde **B**. Further catalytic hydrogenation of **B** delivers alcohol **4.23** as the final product. In the absence of hydrogen atmostphere, insertion of Rh(I) catalysts to cyclobutanones proceeds to afford rhodacycle **4.24** (Scheme 4-4) that is used for various functionalization such as interception of an intramolecular alkenyl group to afford bridged tricyclic ketone **4.25** (Scheme 4-4).[4]

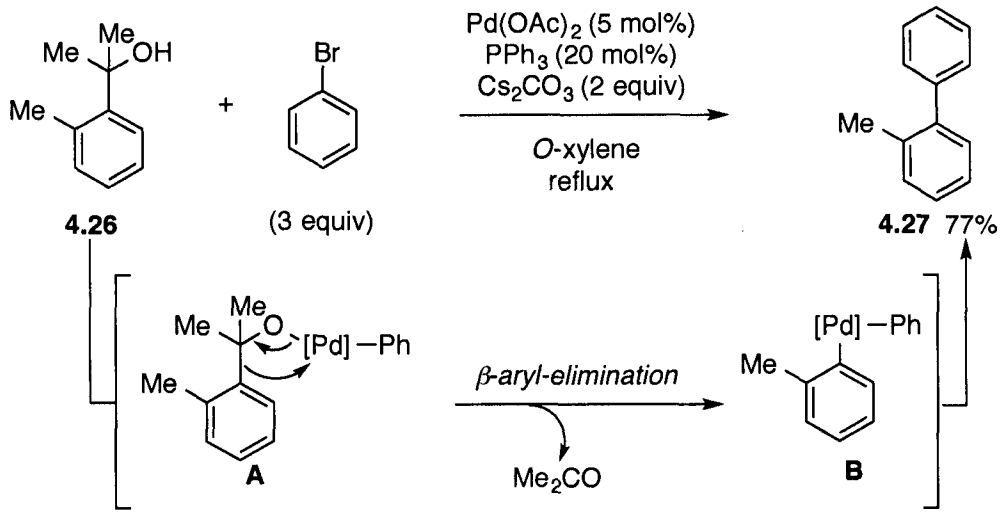


Scheme 4-3. *Rh(I)-catalyzed C-C bond activation of cyclobutanone.*



Scheme 4-4. *Interception of rhodacycle **4.24** by intramolecular alkene moiety.*

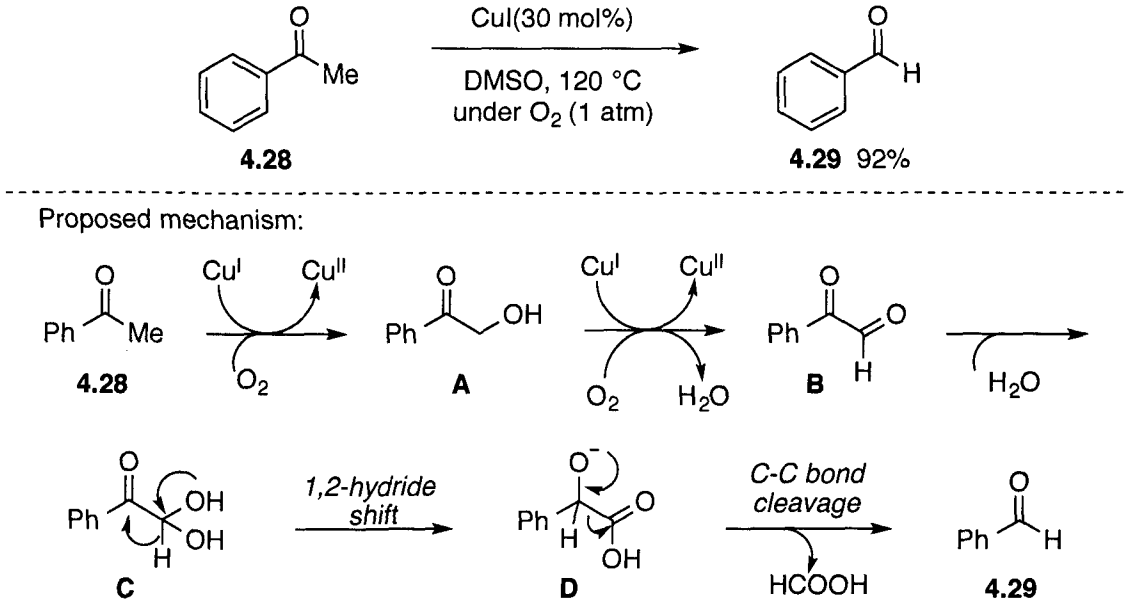
On the other hand, unstrained molecules are also able to undergo selective C–C bond cleavage through β-carbon elimination of heteroatom-metal species, driven by the formation of the relatively stable C–[M] bond.[5] For example, Miura and co-workers reported that the reaction of tertiary alcohol **4.26** and bromobenzene with Pd(II) catalyst produced coupling product, 2-methylphenylbiphenyl (**4.27**) (Scheme 4-5).[6] In this case, β-aryl elimination of alkoxy Pd(II) complex **A** is driven by elimination of acetone along with formation of new aryl C_{sp}^2–Pd bond in diaryl-Pd-complex **B**. Subsequent C–C bond reductive elimination from diaryl-Pd-complex **B** affords biaryl product **4.27**.



Scheme 4-5. *Pd(II)-catalyzed C-C-bond cleavage of tertiary alcohol toward biaryl synthesis.*

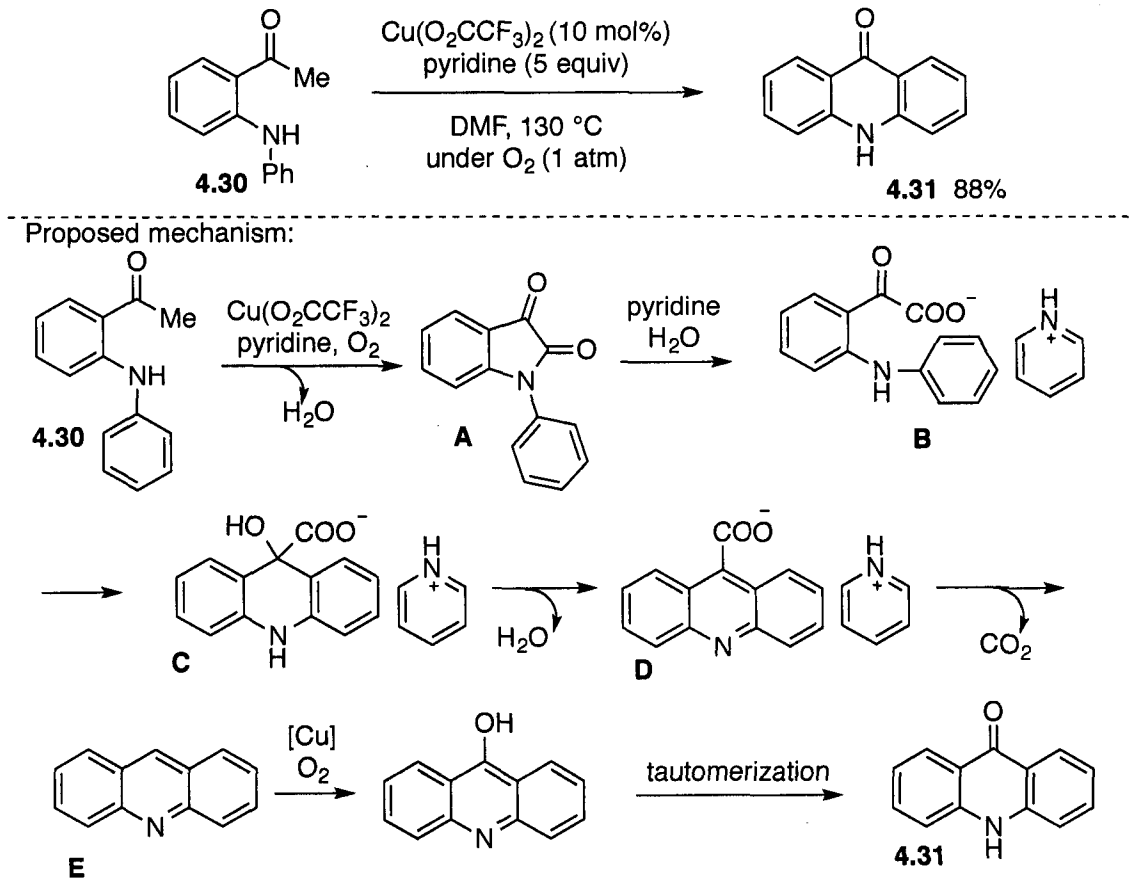
Apart from the utility of noble transition metals for C–C bond activation driven by oxidative addition or β-carbon elimination, recent examples of oxidative C–C bond cleavage under Cu-catalyzed aerobic conditions involving oxygenation of compounds, have also surfaced, that is mainly enabled by radical processes. For example, Bi, Liu, and co-workers presented chemoselective oxidative cleavage of the C(CO)–CH_3 bond of acetophenone (**4.28**), catalyzed by CuI under an oxygen atmosphere to afford benzadehyde (**4.29**) (Scheme 4-6).[7] This oxidative cleavage process could be selectively terminated at the aldehyde without its over-oxidation into carboxylic acids. It is proposed that the process involves a sequence of reactions starting from α-oxygenation of acetophenone (**4.28**) under the Cu-O_2 system to generate α-mono(hydroxyl)-

acetophenone **A**, which is further oxidized to phenylglyoxal intermediate **B**. Consecutive hydration of **B**, followed by 1,2-hydride shift, where the methyl hydrogen of α-dihydroxylated-acetophenone **C** is transferred to the carbonyl carbon in the *Cannizzaro* type reaction[8] to afford alkoxide **D**. Finally, C–C bond cleavage occurs with release of formic acid to afford benzaldehyde.



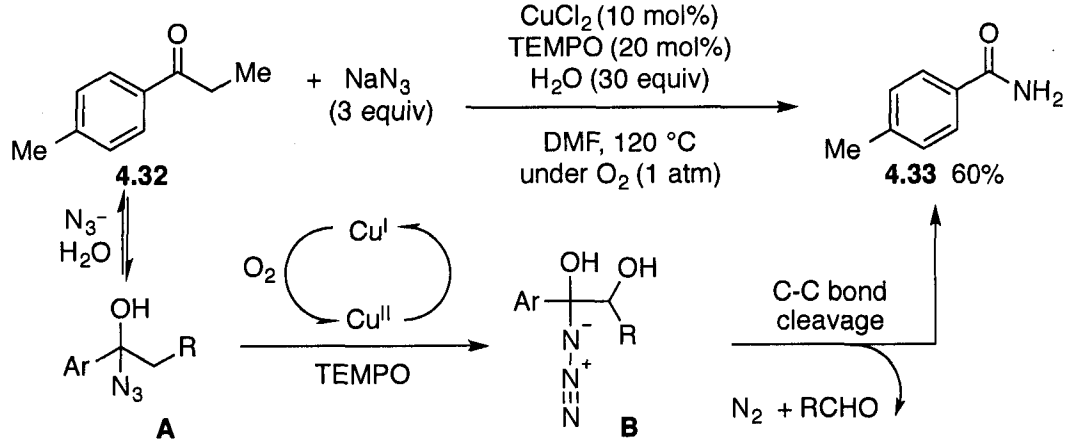
Scheme 4-6. *Cu(I)-catalyzed oxidative C(O)-C-bond cleavage of acetophenone to benzalddehyde under an O_2 atmosphere.*

Fu and co-workers demonstrated the synthesis of acridone derivative **4.31** via oxidative C(CO)–CH_3 bond cleavage of 1-[2-(arylamino)aryl]ethanone **4.30** catalyzed by $Cu(O_2CCF_3)_2$ under an O_2 atmosphere (Scheme 4-7).[9] They proposed a mechanism via the presence of 1-arylindoline-2,3-dione **A** formed by oxidation of **4.30** under the Cu-O_2 system. 1-Arylindoline-2,3-dione **A** is hydrolyzed with pyridine and H_2O to pyridinium carboxylate complex **B** under heating conditions, that is followed by Friedel–Crafts type cyclization to give hydroxyl-dihydroacridine-carboxylate **C**. Dehydration of **C** results in construction of acridine skeleton **D**, which undergoes decarboxylation to generate acridine **E**. Finally, Cu-catalyzed aerobic reaction of acridine **E** and sebsequent tautomerization affords **4.31**.



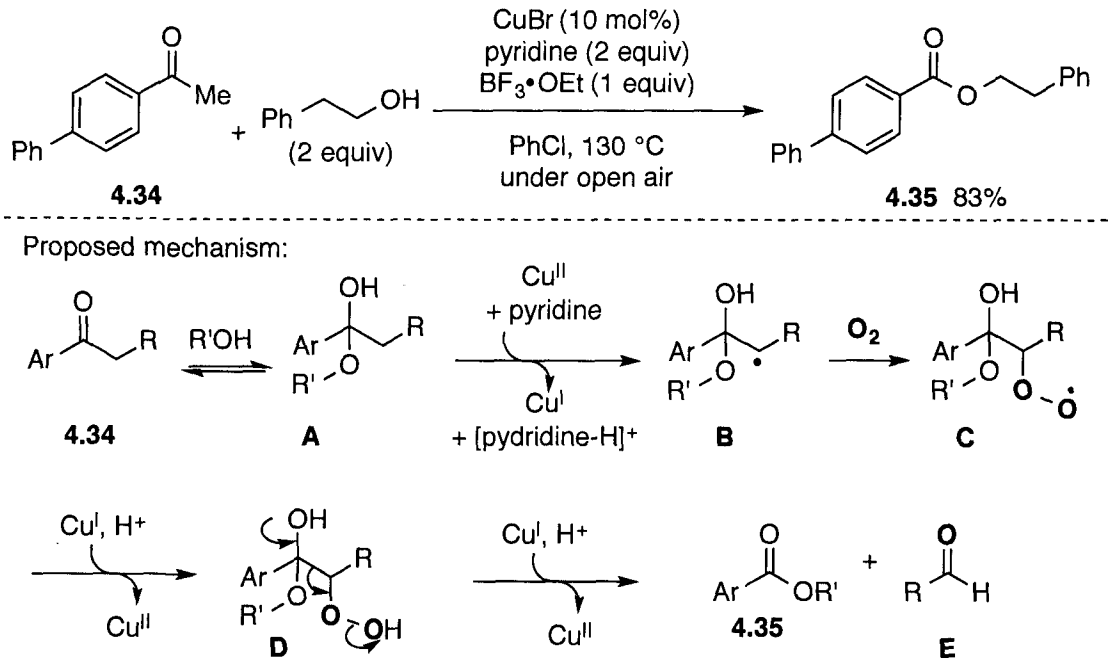
Scheme 4-7. *Cu-catalyzed aerobic synthesis of acridones.*

Jiao and co-workers reported Cu-catalyzed aerobic oxidative C(O)–C(alkyl) bond cleavage of aryl alkyl ketones for formation of benzamides in the presence of sodium azide (Scheme 4-8).[10] It is suggested in the proposed mechanism that aryl alkyl ketone **4.32** is initially attacked by the azide nucleophile to form azidohydrin **A**. Cu-O_2 oxidation of azidohydrin **A** generates α-hydroxylated intermediate **B**, which undergoes C–C bond cleavage to afford amide **4.33** with release of molecular N_2 and aldehyde.



Scheme 4-8. *Cu-catalyzed aerobic oxidative C(O)-C(alkyl) bond cleavage of ketone* ***4.32*** *forthe synthesis of bezaimides* ***4.33****.*

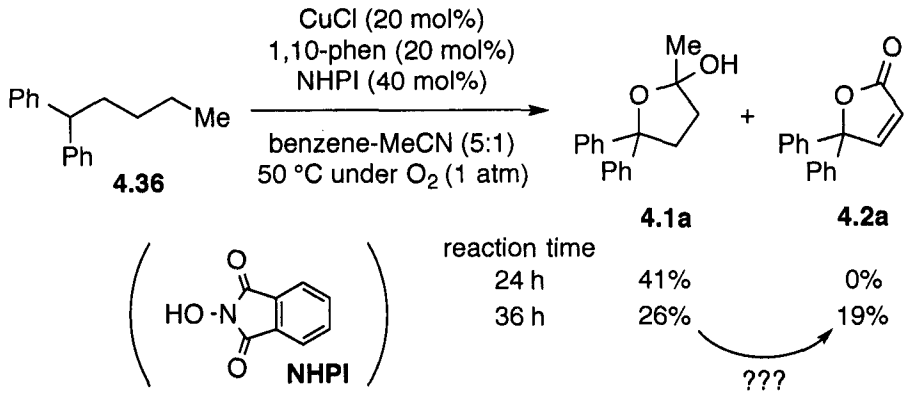
Subsequently, Jiao's group reported the Cu-catalyzed aerobic oxidative esterification of various ketones such as **4.34** via C(CO)−C(alkyl) bond cleavage with a variety of alcohols under an air atmosphere (Scheme 4-9).[11] It is proposed that the reaction proceeds via formation of hemiacetal **A** by nucleophilic addition of ketone with alcohol in a reversible manner. Hemiacetal **A** is oxidized by Cu(II) via single-electron-transfer to generate C-radical intermediate **B**, with the release of Cu(I) species. Then, the C-radical **B** is trapped with O_2 to generate peroxy radical **C**. Reduction of peroxy radical **C** by Cu(I) species, followed by protonation affords hydroperoxide **D**. Finally, fragmentation of hydroperoxide **D** leads to C−C bond cleavage, affording ester **4.35** along with formation of aldehyde **E**.



Scheme 4-9. *Cu-catalyzed aerobic oxidative C(O)-C(alkyl) bond cleavage of ketone **4.34** for the synthesis of esther **4.35**.*

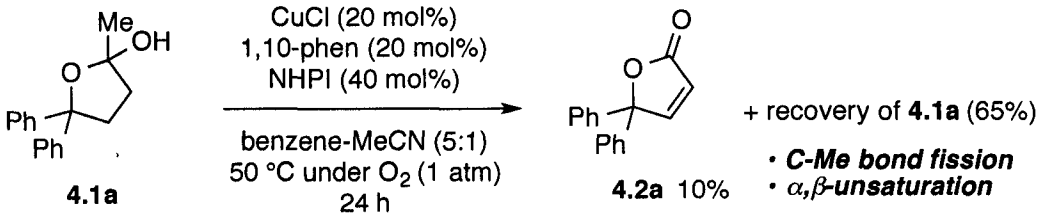
Our group has developed methods involving aliphatic C-H oxidation using hetero-atom radicals generated under Cu-catalyzed aerobic reaction conditions.[12] During our studies of Cu-catalyzed aerobic oxygenation of aliphatic C-H bonds via 1,5-hydrogen radical transfer of the alkoxy radical generated from peroxy derivatives, the direct oxygenation of alkanes were also investigated, as presented in Chapter 3, section 3.2.3 of

this thesis.[13] It was found that in the presence of *N*-hydroxyphthalimide (NHPI), alkane **4.36** can be oxygenated to lactol **4.1a** in 41% yield after 24 h under Cu-catalyzed aerobic conditions (Scheme 4-11). When the reaction time is prolonged to 36 h, α,β-unsaturated lactone **4.2a** was isolated in 19% yield along with lactol **4.1a** in 26% yield.



Scheme 4-10. *First encounter of α,β-unsaturated lactone **4.2a** by prolonging reaction time in 1,4 dioxygenation of alkane **4.36**.*

It was suspected that α,β-unsaturated lactone **4.2a** was derived from lactol **4.1a** through elimination of the methyl group as well as desaturation under the Cu-NHPI-O_2 conditions. Thus, lactol **4.1a** was treated under the same reaction conditions and indeed lactone **4.2a** was obtained in 10%, with the recovery of **4.1a** in 65% yield (Scheme 4-12).



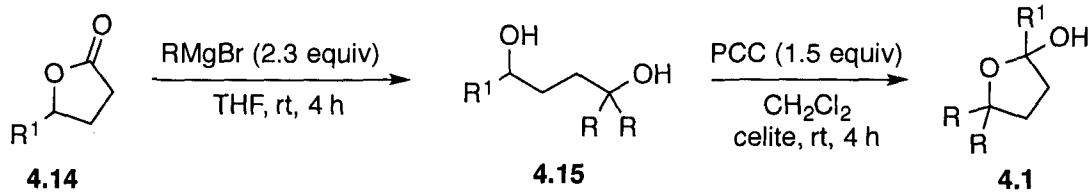
Scheme 4-11. *Confirmation of α,β-unsaturated lactone **4.2a** formation from lactol **4.1a**.*

In conjunction with the recent developments in Cu-catalyzed aerobic reactions involving C-C bond cleavages, this unprecedented molecular transformation of lactols was investigated, with the aim at developing new approaches toward synthesis of unsaturated lactones via the C-C bond fission. The results and findings of this investigation will be presented in this chapter.

4.2 Results and Discussion

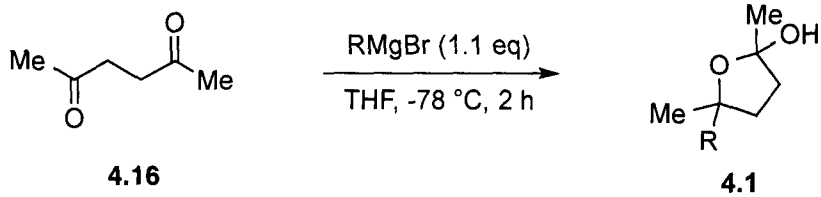
4.2.1 Preparation of lactols

Generally, lactols presented in this chapter are prepared using three main methods. **Method A** utilizes a sequence of double addition of Grignard reagents (R–MgBr) to γ-substituted-γ-butyrolactone **4.14** to afford diol **4.15**, followed by pyridinium chlorochromate (PCC) oxidation to lactol **4.1** (Scheme 4-13). Lactols **4.1a**, **4.1j**, **4.1l**, and **4.1ad-4.1af** were synthesized by this method. Details of procedures and yields can be found in Chapter 5, Section 5.4.1.1.



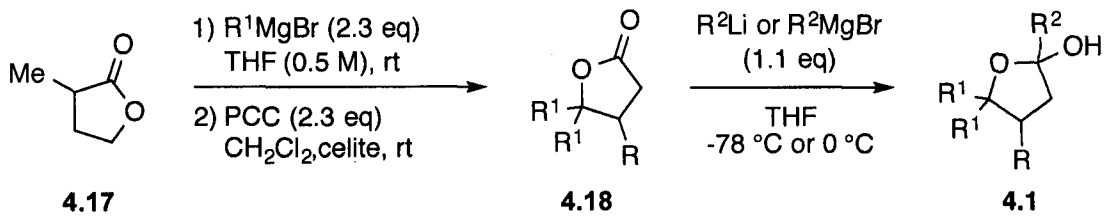
Scheme 4-12. *Preparation of lactols **4.1** using Method A.*

Method B is via the single addition of Grignard reagents (R–MgBr) to hexane-2,5-dione (**4.16**) at low temperature (-78 °C) (Scheme 4-14). Lactols **4.1b-4.1i** were synthesized by this method. Details of procedures and yields can be found in Chapter 5, Section 5.4.1.2.



Scheme 4-13. *Preparation of lactols **4.1** using Method B.*

In **Method C**, lactols **4.1** were prepared by first treating γ-butyrolactones **4.17** with Grignard reagents, followed by PCC oxidation to afford γ,γ-disubstituted-γ-butyrolactones **4.18**. Then, lactones **4.18** are treated with methyl lithium or Grignard reagents to afford lactols **4.1** (Scheme 4-15). Lactols **4.1k, 4.1n, 4.1aa-ac** and **4.6** were synthesized by this method. Details of procedures and yields can be found in Chapter 5, Section 5.4.1.3.



4.17 **4.18** **4.1**

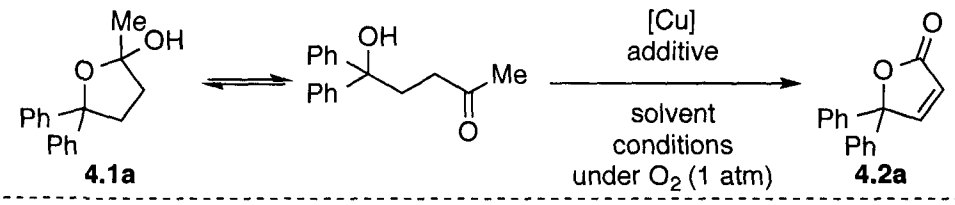
Scheme 4-14. *Preparation of lactols **4.1** using Method C.*

4.2.2 Synthesis of lactones via Aerobic C-C bond cleavage of hemiacetals

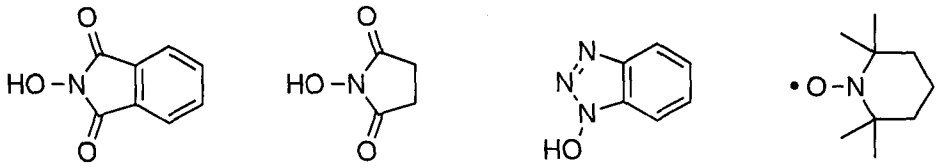
4.2.2.1 Optimization of reaction condition

The investigation began with the use of lactol **4.1a** (which exist as an equilibrium mixture with the corresponding acylic form and γ-hydroxy ketone) to optimize the reaction conditions for synthesis of lactone **4.2a** (Table 4-1). Treatment of lactol **4.1a** with CuCl (20 mol%) and NHPI (**A**) (0.4 equiv) in benzene-MeCN solvent system under an O_2 atmosphere at 50 °C provided α,β-unsaturated lactone **2a** in only 24% yield after 11 h along with recovery of lactol **4.1a** (entry 1). Increasing the amounts of NHPI to 1 equiv allowed the consumption of lactol **4.1a**, giving lactone **4.2a** in slightly higher yields (39%, entry 2). Employing MeCN as the sole solvent further increased the yield of **4.2a** to 49% yield (entry 3). Furthermore, raising the reaction temperature to 80 °C improved the yield of **4.2a** to 71% yield (entry 4). Screening of various Cu-salts and solvents showed that the reaction performs best with CuCl in MeCN (entries 5-9). The catalyst loading of CuCl could be reduced to 5 mol% with maintaining the yield of **4.2a**, while the reaction rate became much slower (entries 10 and 11). In the reaction using 10 mol% CuCl and 1 equiv of NHPI (entry 10), phthalimide (**4.3**) was observed in 20% yield. **4.3** was observed in all the reactions with NHPI. However, due to the low solubility of **4.3**, it was easily lost during the work-up process. Thus, the yield of **4.3** in other cases was not pursued. The use of *N*-hydroxysuccinimide (**B**) or *N*-hydroxybenzotriazole (**C**) instead of NHPI (**A**) was not ideal for the present transformation (entries 12 and 13). No formation of lactone **2a** was observed in reaction with TEMPO (**D**) (entry 14).

Table 4-1. Optimization of reaction conditions.



additives

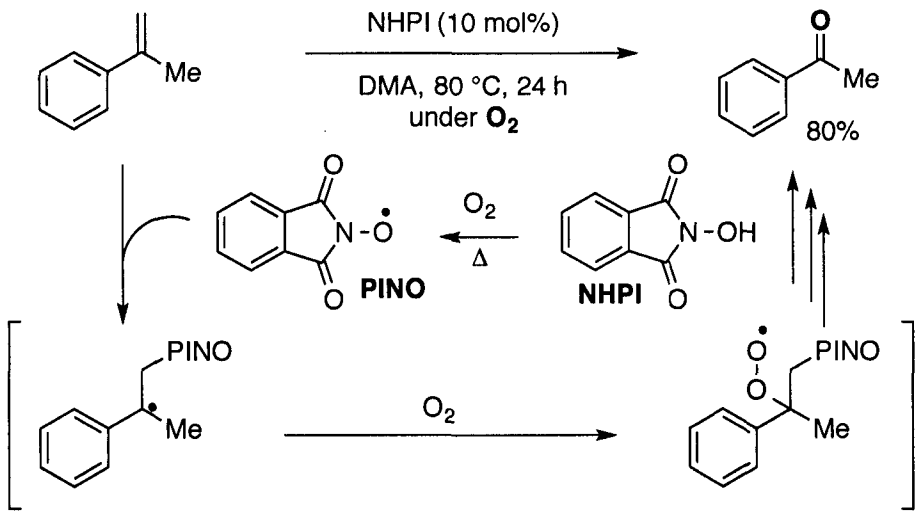


Entry[a]	Cu-salt [mol%]	Additive [equiv]	Solvent [0.1M]	Temp [°C]	time [h]	Yield[b] [%]
1	CuCl [20]	**A** [0.4]	benzene-MeCN (5:1)	50	11	24
2	CuCl [20]	**A** [1]	benzene-MeCN (5:1)	50	11	39
3	CuCl [20]	**A** [1]	MeCN	50	7	49
4	CuCl [20]	**A** [1]	MeCN	80	6	71
5	CuBrI [20]	**A** [1]	MeCN	80	19	50
6	CuI [20]	**A** [1]	MeCN	80	19	11
7	$Cu(OAc)_2$ [20]	**A** [1]	MeCN	80	19	11
8	CuCl [20]	**A** [1]	EtOAc	80	20	55
9	CuCl [20]	**A** [1]	DMSO	80	24	64
10	**CuCl [10]**	**A [1]**	**MeCN**	**80**	**12**	**72**
11	CuCl [5]	**A** [1]	MeCN	80	24	72
12	CuCl [20]	**B** [1]	MeCN	80	48	45
13	CuCl [20]	**C** [1]	MeCN	80	48	13
14	CuCl [20]	**D** [1]	MeCN	80	24	0
15[c]	CuCl [20]	**A** [1]	MeCN	80	24	6
16	—	**A** [1]	MeCN	80	72	20

[a] The reactions were carried out using 0.5 mmol of **4.1a** in 5 mL of solvent (0.1 M) under an O_2 atmosphere (1 atm). [b] Phthalimide (**4.3**) was isolated in 20% yield. [c] Reaction was conducted under Argon atmosphere.

When the reaction was carried out under an argon atmosphere instead of O_2, only 6% of **4.2a** was obtained, suggesting O_2 is indispensible in the present transformation (entry 15). It is worthy to note that the reaction also proceeded in the absence of CuCl, giving **4.2a** in 20% yield after stirring for 3 days (entry 16). This suggests that NHPI plays a crucial role in the current C–C bond fission, but CuCl is indispensable to facilitate the present transformation. Jiao and co-workers recently reported metal-free oxidative C–

C double bond cleavage of substituted styrene to ketone, catalyzed by NHPI under an oxygen atmosphere (Scheme 4-15).[14] It is supposed that phthalimide *N*-oxy (PINO) radical generated from thermal homolysis of NHPI, initiated the C–C double bond cleavage under an O_2 atmosphere.

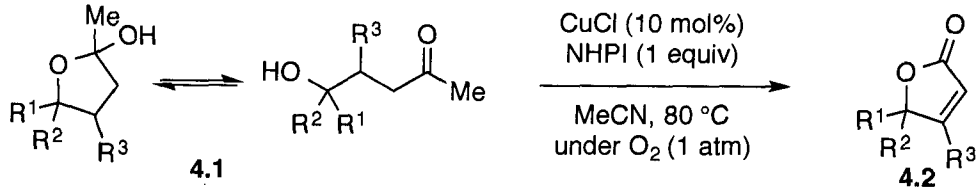


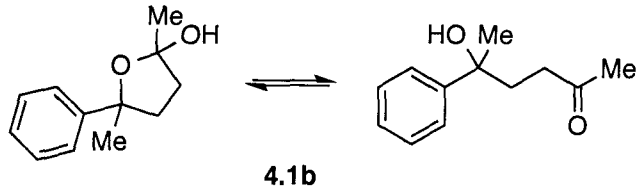
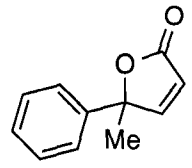
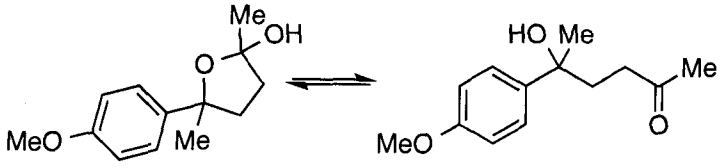
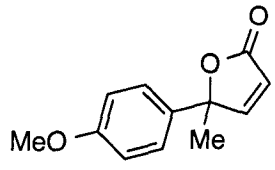
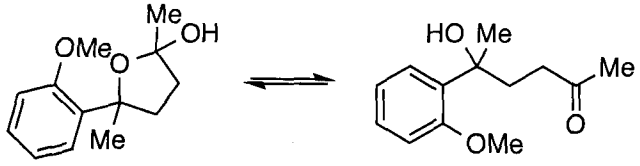
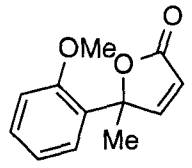
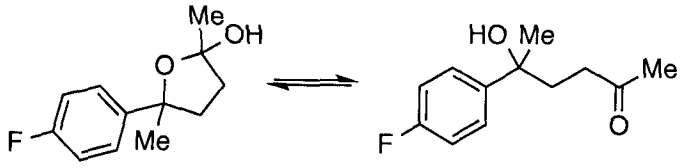
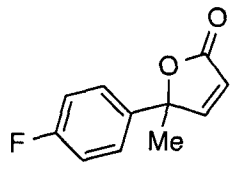
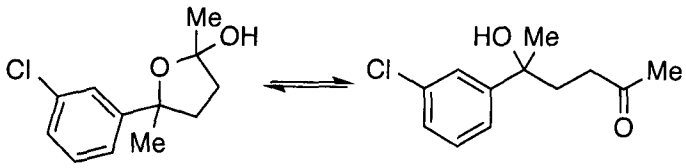
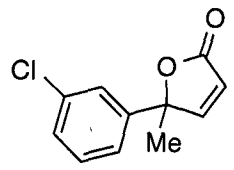
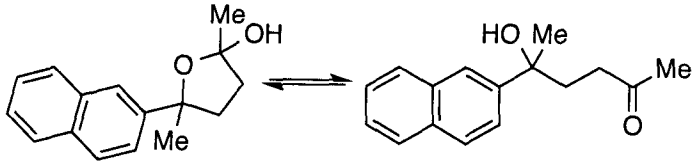
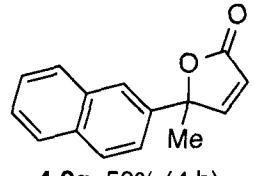
Scheme 4-15. *NHPI-catalyzed metal free oxidative C-C double bond cleavage of substituted styrene to ketone under an oxygen atmosphere.*

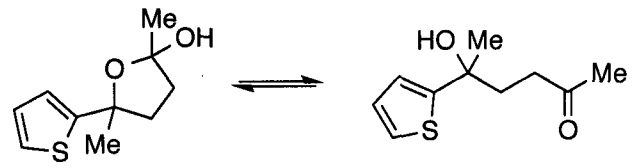
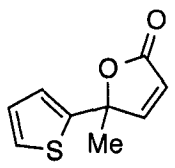
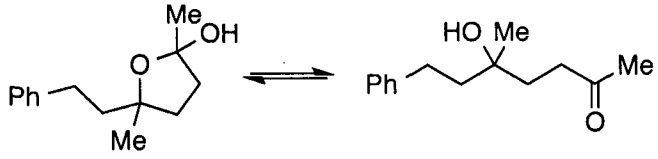
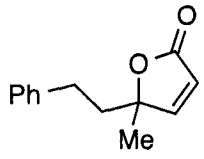
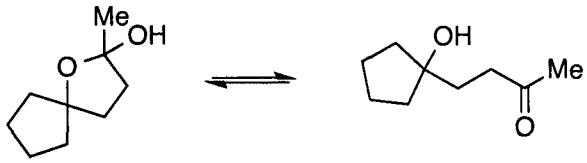
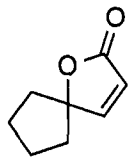
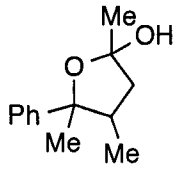
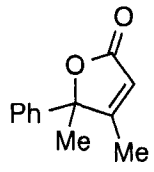
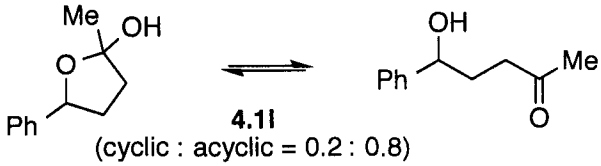
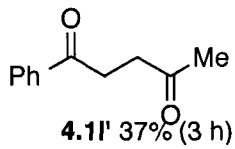
4.2.2.2 Scope and limitation

With the optimized reaction conditions in hand (Table 4-1, entry 10 with 10 mol% of CuCl), the substrate scope of lactols **4.1** was investigated (Table 4-2). Various aryl groups including thienyl moiety could be installed at the γ-position (R^1 and R^2) to afford the corresponding lactone **4.2** in good to moderate yields (entries 1-7). The reactions of γ-dialkyl lactols **4.1i** and **4.1j** also proceeded to afford the corresponding α,β-unsaturated lactones **4.2i** and **4.2j** in acceptable yields (entries 8 and 9). Installation of a methyl group at the β -position (R^3) did not disturb the transformation, affording lactone **4.2k** in 62% yield (entry 10). It was found that the γ-position should be fully substituted (R^1 and R^2) for enabling the present catalytic C-C bond fission and α,β-unsaturation for synthesis of lactone **4.2**, as the reaction of lactol **4.1l** only resulted in the oxidation of secondary benzylic alcohol to 1,4-diketone **4.1l'** (entry 11).[15]

Table 4-2. Substrate scope of α,β−unsaturated-γ-butyrolactones **4.2**.

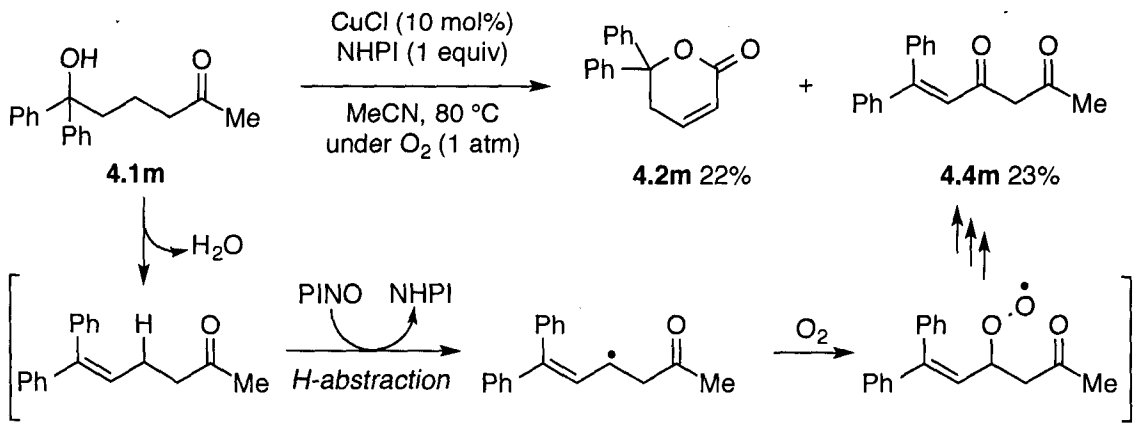


Entry[a]	Substrate	Product[b]
1	 **4.1b** (cyclic : acyclic = 0.3 : 0.7)	 **4.2b** 60% (8 h)
2	 **4.1c** (cyclic : acyclic = 0.4 : 0.6)	 **4.2c** 57% (12 h)
3	 **4.1d** (cyclic : acyclic = 0.3 : 0.7)	 **4.2d** 59% (12 h)
4	 **4.1e** (cyclic : acyclic = 0.4 : 0.6)	 **4.2e** 58% (8 h)
5	 **4.1f** (cyclic : acyclic = 0.4 : 0.6)	 **4.2f** 64% (4 h)
6	 **4.1g** (cyclic : acyclic = 0.3 : 0.7)	 **4.2g** 50% (4 h)

Entry[a]	Substrate	Product[b]
7	 **4.1h** (cyclic : acyclic = 0.3 : 0.7)	 **4.2c** 45% (4 h)
8	 **4.1i** (cyclic : acyclic = 0.3 : 0.7)	 **4.2i** 46% (6 h)
9	 **4.1j** (cyclic : acyclic = 0.3 : 0.7)	 **4.2j** 52% (6 h)
10	 **4.1k**	 **4.2k** 62% (4 h)
11	 **4.1l** (cyclic : acyclic = 0.2 : 0.8)	 **4.1l'** 37% (3 h)

[a] The reactions were carried out using 0.5 mmol of **4.1** with NHPI (1 equiv) in MeCN (5 mL) at 80 °C under an O_2 atmosphere (1 atm). [b] Isolated yields were recorded.

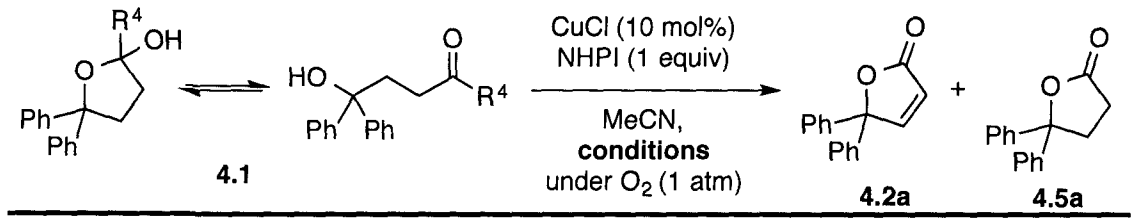
When δ-hydroxy ketone **4.1m** (that is observed as a sole acyclic form without 6-membered ring hemiacetal) was subjected to the present reaction conditions, only 22% yield of the desired α,β-unsaturated lactone **4.2m** was obtained along with 1,3-diketone **4.4m** in 23% yield (Scheme 4-16). The formation of **4.4m** is most likely due to consecutive dehydration followed by allylic oxygenation. [16]

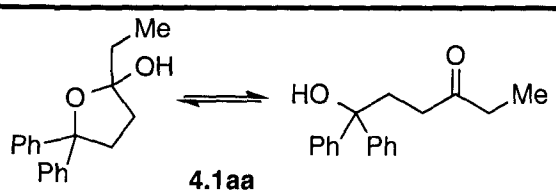
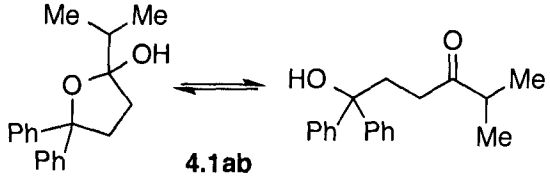


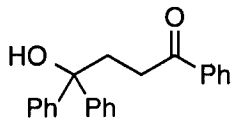
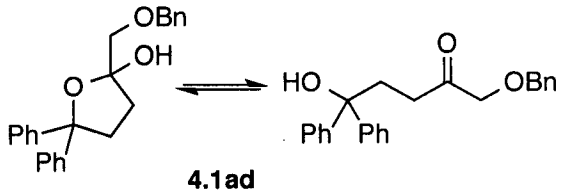
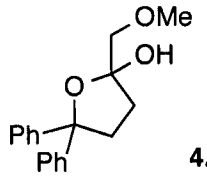
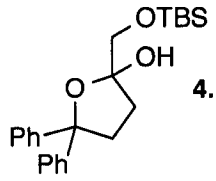
Scheme 4-16. *The reaction of d-hydroxy ketone **4.1m**.*

The effect of the lactol substituent R^4 was then examined (Table 4-3). By changing the methyl group (for **4.1a**) as R^4 to ethyl (for **4.1aa**) and isopropyl (**4.1ab**) lowered the mass-balance of the products (entries 1 and 2), but intriguingly delivered not only α,β-unsaturated lactone **4.2a** but also γ,γ-disubstituted-butyrolactone **4.5a** in the ratio of about 2:1. Lactol **4.1ac** having a phenyl group could not undergo the transformation at all (entry 3). It is noteworthy that the reactions of lactols **4.1ad-4.1af** bearing alkoxymethyl functions as R^4 delivered saturated γ,γ-disubstituted-butyrolactone **4.5a** as major product despite longer reaction time (entries 4-7).

Table 4-3. Effect of hemiacetal substituent for the formation of lactones **4.2a** and **4.5a**.

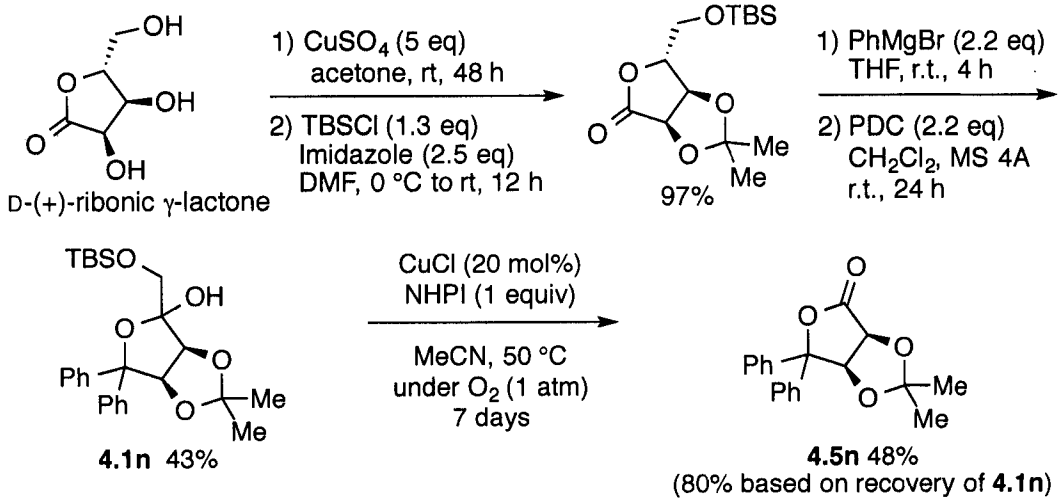


Entry[a]	Substrate	Temp. [°C]	time [h]	Yield[b] 4.2a	Yield[b] 4.5a
1	 **4.1aa** (cyclic : acyclic = 0.5 : 0.5)	80	7	25	13
2	 **4.1ab** (cyclic : acyclic = 0.5 : 0.5)	80	3	24	10

Entry[a]	Substrate	Temp. [°C]	time [h]	Yield[b] 4.2a	Yield[b] 4.5a
3	 **4.1ac**	80	8	0	0
4	 **4.1ad** (cyclic : acyclic = 0.8 : 0.2)	80	48	20	60
5	 **4.1ae**	80	24	8	52
6		50	72	5	70
7	 **4.1af**	50	168	1	61

[a] The reactions were carried out using 0.5 mmol of **4.1** with NHPI (1 equiv) in MeCN (5 mL) at 80 °C under an O_2 atmosphere (1 atm). [b] ^1H NMR yields based on 1,1,2,2-tetrachloroethane were recorded.

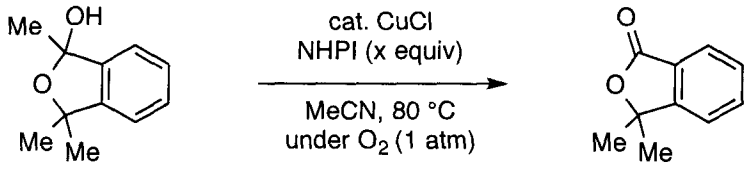
This saturated lactone synthesis was applied for transformation of optically active lactol **4.1n** derived from D-(+)-ribonic γ-lactone. The reaction proceeded selectively to produce the desired lactone **4.5n**, although the reaction was very slow and did not complete even after stirring over 7 days (Scheme 4-17).



Scheme 4-17. *Synthesis of lactone **4.5n**.*

4.2.2.3 Mechanistic investigation

To gain the mechanistic insights especially on the C-C bond fission process, the reaction of benzoannulated lactol **4.6** was examined and revealed that the C-C bond cleavage of **4.6** also proceeded smoothly even though 2 equiv of NHPI was required to achieve higher yields of phthalide **4.7** (Scheme 4-18).



4.6

CuCl	NHPI	**4.7**
20 mol%	1 equiv	53% (3 h)
20 mol%	2 equiv	77% (4 h)
10 mol%	**2 equiv**	**71% (9 h)**

Scheme 4-18. *Reactions of benzoannulated lactol* ***4.6.***

In order to understand the present C–C fission process, the reaction progress of benzoannulated lactol **4.6** was monitored by ^{1}H NMR over a period of 120 minutes and the kinetic profile of the reaction is shown in Figures 4-1 and 4-2. It was found that lactol **4.6** was consumed rapidly within 10-15 min along with generation of several derivatives, while the lactone **4.7** was steadily generated over the 120 min period. Thus, the reaction of **4.6** was conducted and stopped at 10 min to isolate these derivatives, with the aim to isolate some potential reaction intermediates (Scheme 4-19). Besides the isolation of phthalide **4.7** and phthalimide (**4.3**) from the reaction mixture, acetal **4.8** having two *N*-oxy-phthalimide units and lactol **4.9** bearing one *N*-oxyphthalimide moiety were isolated and identified in 15% and 13% yields, respectively. The structure of **4.8** was confirmed by X-ray crystallographic analysis.

Figure 4-1 Kinectic profile for the reaction of **4.6**

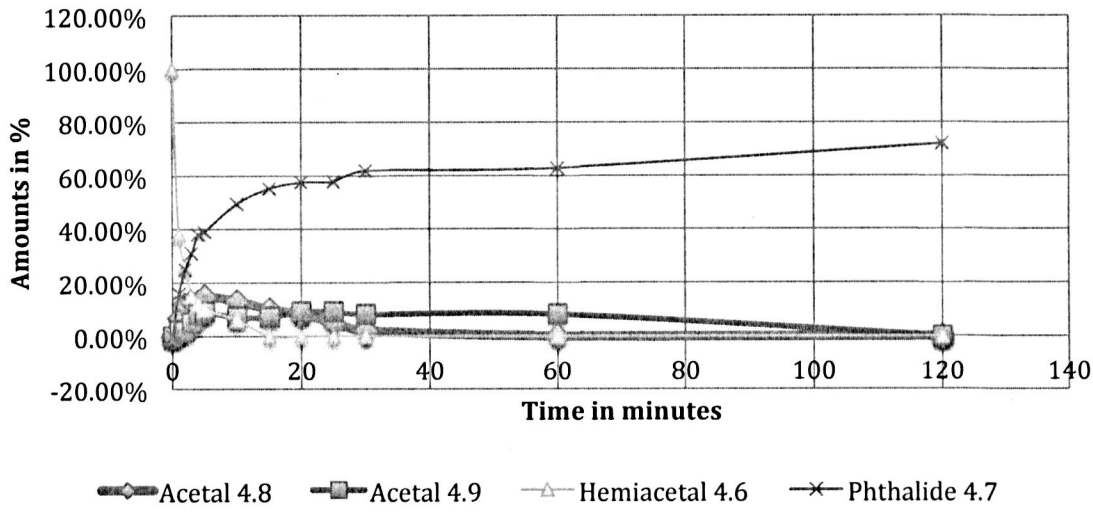
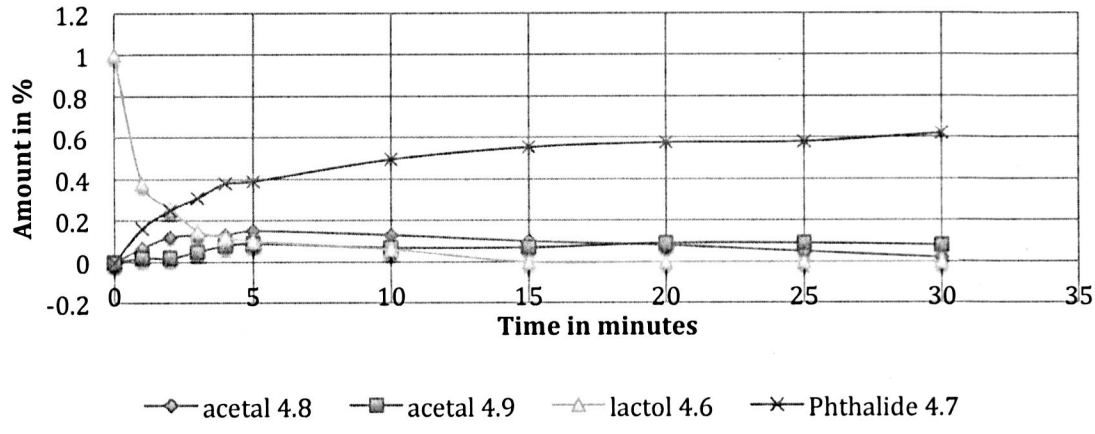
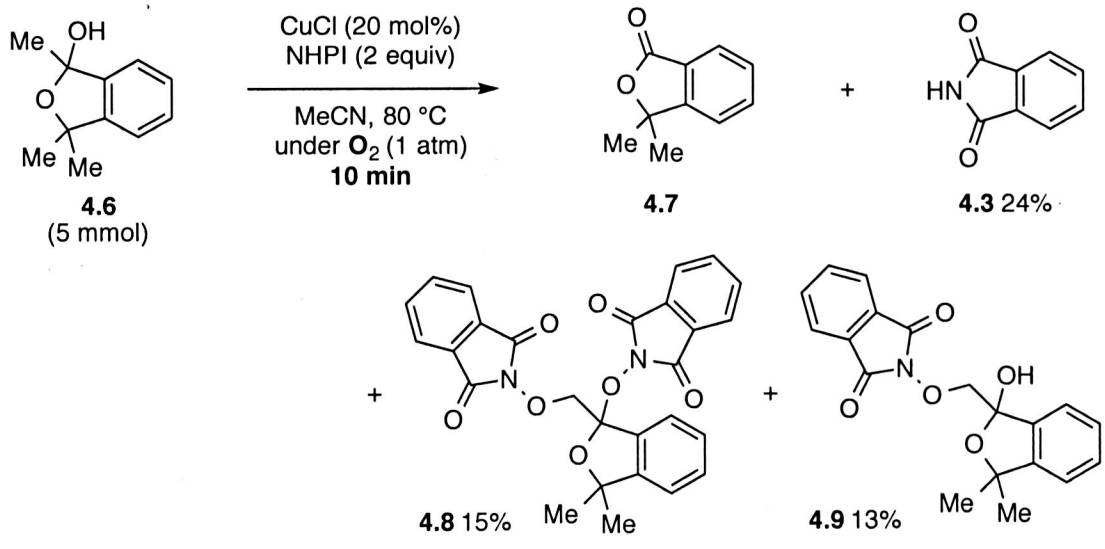


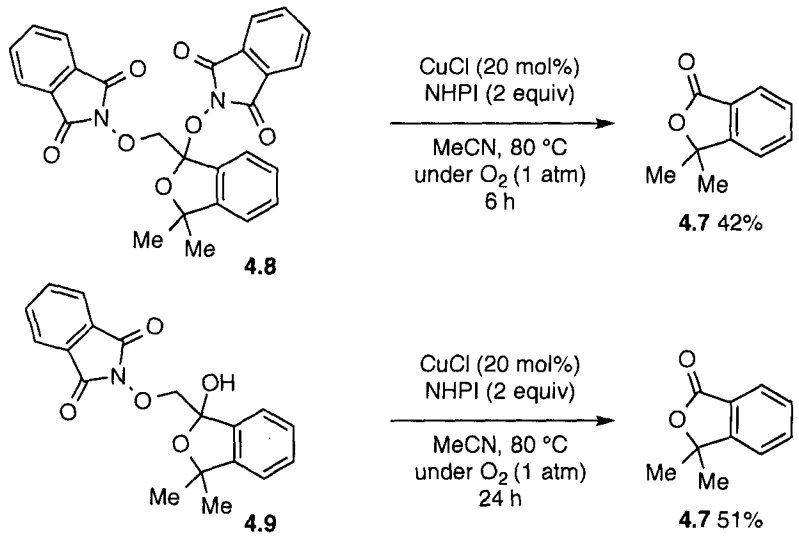
Figure 4-2. Kinetic profile of reaction of 4.6 in the first 30 min





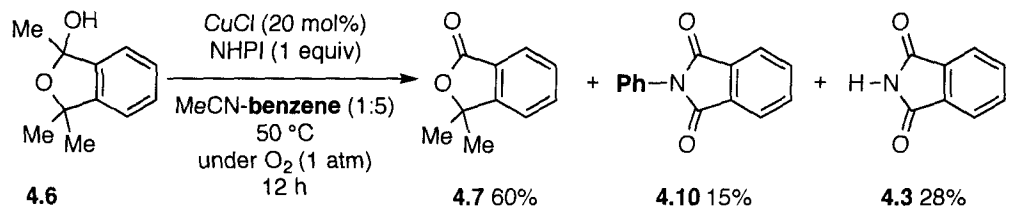
Scheme 4-19. *Isolation of acetals **4.8** and **4.9**.*

Next, acetals **4.8** and **4.9** were subjected to the Cu-catalyzed aerobic reaction conditions to see if they are the key intermediates in the mainstream of the present catalytic cycle for formation of phthalide **4.7** (Scheme 4-20). Although, both of the reactions provided phthalide **4.7** in moderate yields of 42% and 51%, respectively, longer reaction times were required, especially for the reaction of **4.9**. These experimental results implied that *N*-oxyphthalimide incorporated acetals **4.8** and **4.9** should not be the key intermediates for the present C-C bond cleavage, but the side-products formed during the course of the major catalytic pathway.



Scheme 4-20. *Conversion of acetals **4.8**and **4.9** to **4.7** under the standard conditions.*

When the reaction of **4.6** was carried out in the presence of benzene as co-solvent, *N*-phenylphthalimide (**4.10**) was isolated in 15% yield along with the formation of phthalide **4.7a** as well as phthalimide (**4.3**) (Scheme 4-21). It was presumed that *N*-phenylphthalimide (**4.10**) was generated via addition of putative phthalimide radical to benzene. Thus, the present C-C bond cleavage transformation might involve free radical processes.



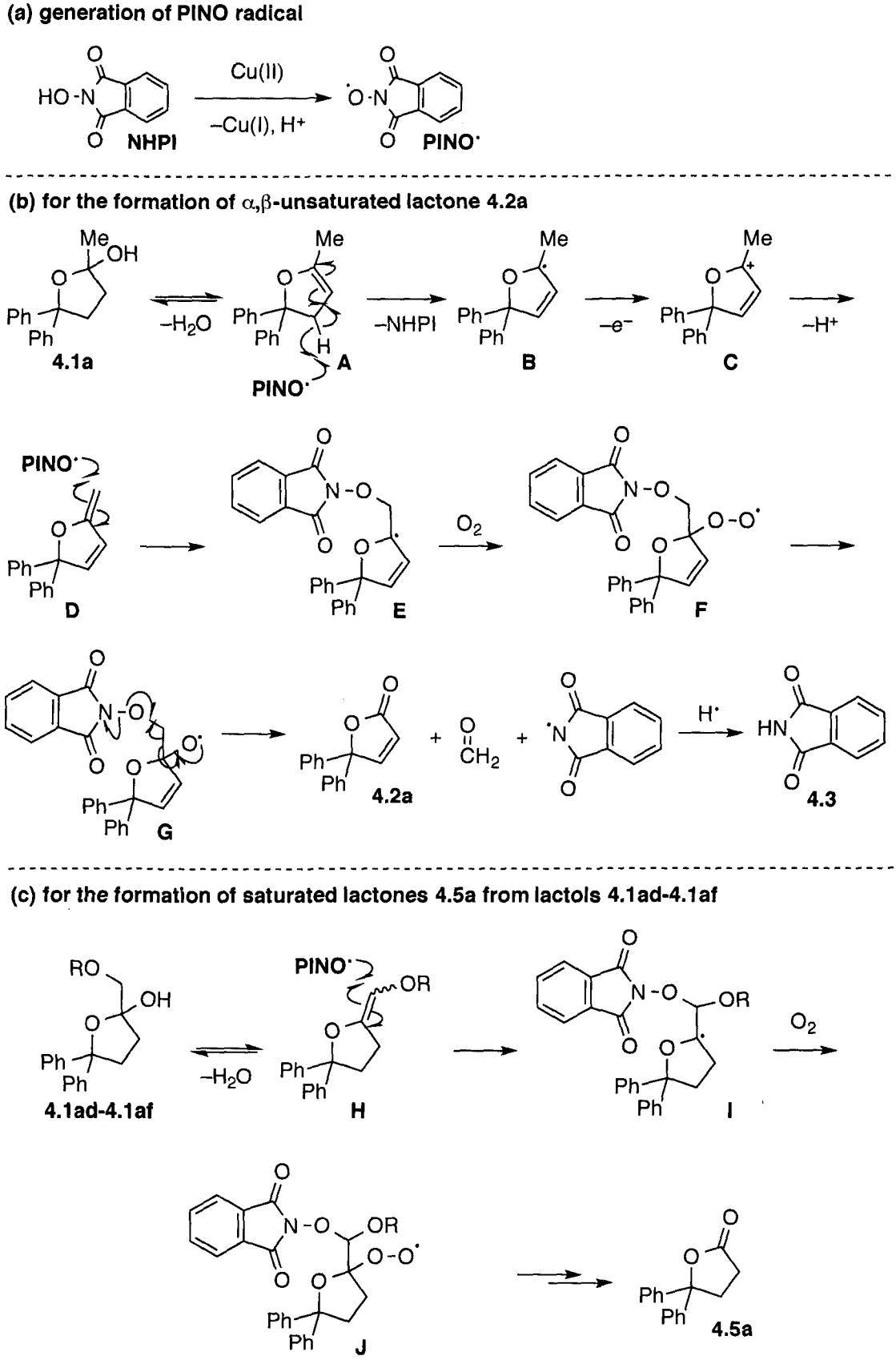
Scheme 4-21. *The reaction of lactol **4.6** in the prescence of benzene.*

Taking these findings into consideration, the proposed reaction pathways for the lactone formation via C-C bond cleavage are summarized in Scheme 4-23. Firstly, NHPI could be oxidized under Cu-catalyzed aerobic reaction conditions to generate the corresponding O-radical (the PINO radical) (Scheme 4-22a).[17,18] Concerning the formation of α,β-unsaturated lactones **4.2**, α,β-unsaturation most likely occurs prior to the C-C bond fission. Hence, lactol **4.1a** first undergoes dehydration to give *endo*-cyclic enol ether **A**, which is thermodynamically more stable than the corresponding *exo*-cyclic enol ether (Scheme 4-22b). In the presence of PINO radical, abstraction of H-radical at the allylic position occurs readily,[16] followed by alkene migration to generate α-oxy radical **B**. Subsequent single-electron-oxidation of α-oxy radical **B** to carbocation **C** under the present reaction conditions. Deprotonation of **C** forms exo-cyclic alkene **D**, which is trapped with the PINO radical, resulting in installation of the *N*-oxy-phthalimide moiety and regeneration of α-oxy radical **E**. Dioxygenation of the α-oxy radical **E** with molecular O_2 gives peroxy radical **F**, which undergoes *Fenton*-type reduction[19] to form alkoxy-radical **G**. Finally, β-radical fragmentation[20] of alkoxy-radical **G** result in consecutive C-C and O-N bond cleavage to form α,β-unsaturated lactone **4.2a**, formaldehyde, and phthalimidoyl radical, which abstracts a hydrogen radical to form phthalimide (**4.3**).[21]

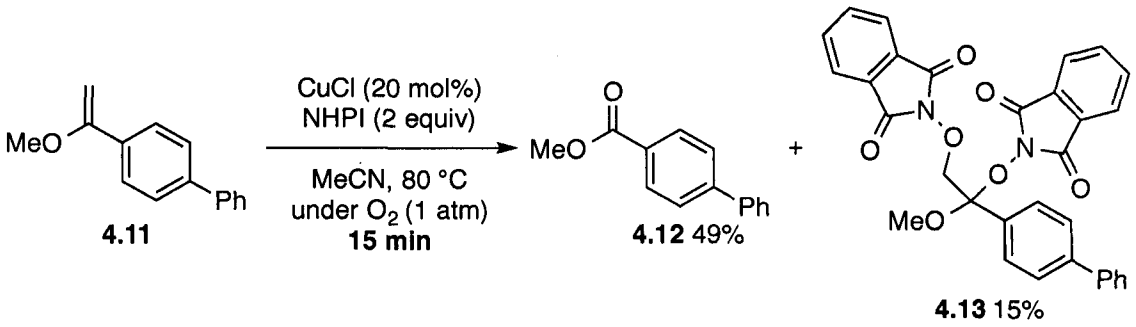
As for the reactions of alkoxymethyl lactols **4.1ad-4.1af** (Table 4-3, entries 4-7), the initial dehydration selectively generates exo-cyclic enol ether **H**, which is trapped by the PINO radical to form α-oxy radical **I** (Scheme 4-22c). The same transformation including dioxygenation and radical fragmentation takes place, resulting in formation of saturated lactone **4.5a** as a major product.

These proposed reaction pathways include enol ethers as one of the key intermediates. To confirm this possibility, methyl enol ether **4.11** was prepared and treated with the present reaction conditions (Scheme 4-23). Indeed, the reaction

proceeded very quickly within 15 min to give methyl ester **4.12** in 49% yield via the C–C bond cleavage along with NHPI-installed acetal **4.13** in 15% yield.

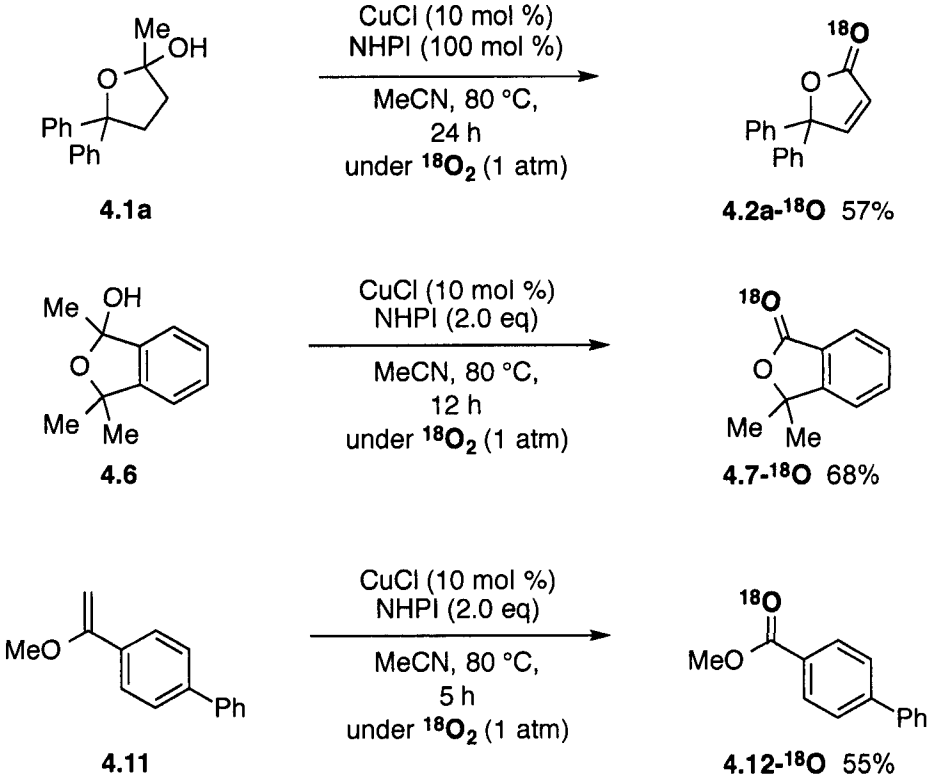


Scheme 4-22. *Proposed mechanism for the reaction of lactol* ***4.1****.*



Scheme 4-23. *The reaction of enol ether* ***4.11***

To further support the proposed mechanistic pathways, ^{18}O-labelling experiments were conducted by treatments of **4.1a**, **4.6**, and **4.11** under an $^{18}O_2$ atmosphere. These experiments delivered the corresponding lactones **4.2a** and **4.7** as well as ester **4.12** with incorporation of an ^{18}O atom (Scheme 4-24). These results are in agreement with the proposed reaction mechanism involving peroxy radicals such as **F** and **J** as the reaction intermediate.



Scheme 4-24. *Incorporation of molecular* O_2 *shown by* $^{18}O_2$ *experiment.*

4.3 Conclusions

In conclusion, unprecedented aerobic Cu-catalyzed NHPI–mediated synthesis of lactones from the corresponding lactols has been developed through radical–mediated C–

C bond cleavage. The intriguing multi-step process involving: 1) formation of *exo*-cyclic enol ethers, 2) addition of PINO radicals to the enol ethers, 3) trapping of the resulting C-radicals with molecular oxygen to generate of akoxy radicals and 4) subsequent β-radical fragmentation to result in the C–C bond cleavage. Further investigation on application of this radical strategy for more practical C–C bond cleavage and other types of molecular transformation could be done in the near future.

4.4 References

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Chapter 5: Experimental Section

5.1 General

^{1}H NMR (300 MHz, 400 MHz and 500 MHz) spectra were recorded on Bruker Avance 300 spectrometer, Bruker Avance 400 spectrometer, and Bruker Avance 500 spectrometer in $CDCl_3$ [using $(CH_3)_4Si$ (for ^{1}H, δ = 0.00) as internal standard], respectively. ^{13}C NMR (75 MHz, 100 MHz and 125 MHz) spectra were recorded on Bruker Avance 300 spectrometer, Bruker Avance 400 spectrometer and Bruker Avance 500 spectrometer in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, δ = 77.00) as internal standard], respectively. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet, sept = septet, m = multiplet, br = broad.

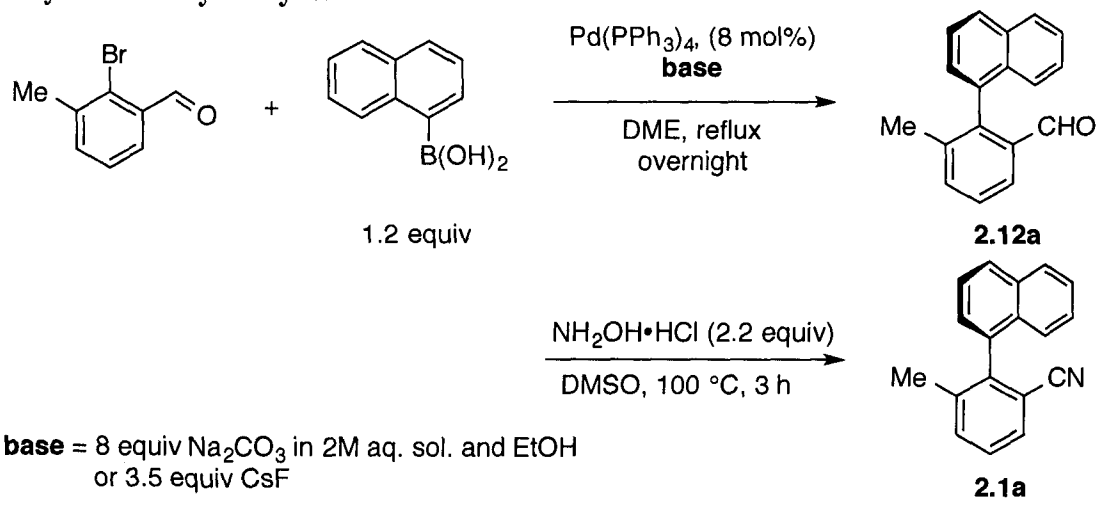
IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Q-Tof Premier LC HR mass spectrometer (Waters). X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus.

Flash column chromatography was performed using Merck silica gel 60 with distilled solvents. Acetonitrile (MeCN), tetrahydrofuran (THF), diethyl ether (Et_2O) were taken from a solvent purification system (PS-400-5, innovative technology Inc.). Dimethyl sulfoxide (DMSO) anhydrous, *N*,*N*-dimethylformamide (DMF) anhydrous, 1,2-Dimethoxyethane (DME) anhydrous, copper(II) acetate (98%), copper(I) Iodide (98%), copper(I) chloride (reagent grade, 97%), methyl lithium (3.0 M in diethoxymethane), methylmagnesium bromide (3.0 M in Et_2O), isopropylmagnesium bromide (2.0 M in THF) and phenylmagnesium bromide (3.0 M in Et_2O) were purchased from Sigma-Aldrich Co., Inc. All other Grignard reagents were prepared according to the general procedure[1] and were used after the titration by following the literature method.[2]

5.2 Experimental data for Chapter 2

5.2.1 Synthesis of biaryl nitriles

5.2.1.1 Method A: Pd(0)-catalyzed Suzuki–Miyaura cross coupling reaction of 2-bromoaryl aldehydes and aryl boronic acids[3] followed by treatment of biaryl aldehydes with hydroxylamine[4]



Scheme 5-1. *A representative scheme for preparation of biaryl-2-carbonitrile* ***2.1a*** *via method A.*

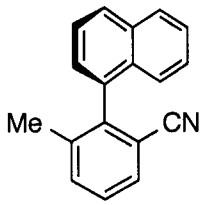
A typical procedure for synthesis of 3-methyl-2-(naphthalen-1-yl)benzonitrile (2.1a)

A mixture of 2-bromo-3-methylbenzaldehyde (1.00 g, 5.02 mmol, prepared according to reported procedure[5]), 1-naphthylboronic acid (1.04 g, 6.02 mmol), 2 M aqueous solution of Na_2CO_3 (20 mL, 40.2 mmol) with EtOH (10 mL) [or CsF (2.66 g, 17.6 mmol)], and $Pd(PPh_3)_4$ (0.46 g, 0.402 mmol) in DME (15 mL) was stirred under reflux overnight under an inert atmosphere. Upon completion, the reaction mixture was cooled to room temperature, and the solvents were removed in *vacuo*. The organic materials were then extracted with a mixture of EtOAc-H_2O (1:1). The combined organic extract was washed with 5% aqueous NaOH followed by water and brine. After drying with $MgSO_4$, the solution was concentrated in *vacuo* to yield the crude residue, which was purified by flash column chromatography (hexane : EtOAc = 95 : 5) to give 3-methyl-2-(naphthalen-1-yl)benzaldehyde (**2.12a**) (1.15 g, 4.67 mmol) in 93% yield.

3-Methyl-2-(naphthalen-1-yl)benzaldehyde (**2.12a**) (1.15 g, 4.67 mmol) was added to a solution of hydroxylamine hydrochloride (0.71 g, 10.3 mmol) in DMSO (10 mL), and the resulting reaction solution was stirred and heated at 100 °C for 3 h. After

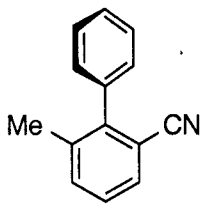
cooling to 0 °C, water was added to the reaction mixture, which was then extracted with CH_2Cl_2 twice. The combined organic extracts were washed with water followed by brine, dried with $MgSO_4$, and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (hexane : EtOAc = 90 : 10) to give 3-methyl-2-(naphthalen-1-yl)benzonitrile (**2.1a**) (0.89 g, 3.66 mmol) in 79% yield (74% overall yield in two steps).

3-Methyl-2-(naphthalen-1-yl)benzonitrile (2.1a)



Yellow solid; mp 100-102 °C; IR (ATR) 2225, 1593, 1390, 777, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (3H, s), 7.28 (1H, d, J = 8.4 Hz), 7.39-7.47 (3H, m), 7.52 (1H, ddd, J = 1.2, 6.8, 8.0 Hz), 7.56-7.62 (2H, m), 7.67 (1H, d, J = 7.2 Hz), 7.96 (2H, dd, J = 7.2, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 114.0, 118.1, 124.7, 125.4, 126.0, 126.6, 126.8, 128.0, 128.5, 128.9, 130.4, 131.2, 133.5, 134.1, 135.2, 138.8, 143.6; HRMS (ESI): Found: m/z 244.1126. Calcd for $C_{18}H_{14}N$: $(M+H)^+$ 244.1126.

6-Methyl-[1,1'-biphenyl]-2-carbonitrile (2.1b)

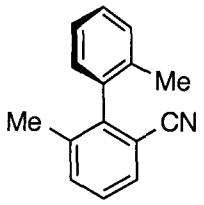


Prepared from phenylboronic acid and 2-bromo-3-methylbenzaldehyde with CsF, and purified by flash column chromatography (hexanes : EtOAc = 90 : 10) in 70% overall yield in two steps.

Clear oil; IR (ATR) 2223, 1458, 1273, 1010, 786, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 7.25-7.29 (2H, m), 7.33 (1H, dd, J = 7.6, 8.0 Hz), 7.42-7.49 (4H, m), 7.57 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 113.1, 118.4, 127.6,

128.3, 128.5, 128.9, 130.4, 134.3, 137.5, 137.6, 145.2; HRMS (ESI): Found: m/z 194.0974. Calcd for $C_{14}H_{12}N$: $(M+H)^+$ 194.0970.

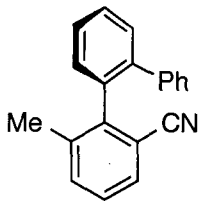
2',6-Dimethyl-[1,1'-biphenyl]-2-carbonitrile (2.1c)



Prepared from 2-methylphenylboronic acid and 2-bromo-3-methylbenzaldehyde with CsF, and purified by flash column chromatography (hexanes : EtOAc = 90 : 10) in 63% overall yield in two steps.

Clear oil; IR (ATR) 2225, 1456, 1274, 1004, 788, 746, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (3H, s), 2.06 (3H, s), 7.08 (1H, d, J = 7.6 Hz), 7.24-7.36 (4H, m), 7.49 (1H, d, J = 7.6 Hz), 7.57 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 19.9, 113.2, 118.1, 126.1, 127.6, 128.5, 128.6, 130.2, 130.3, 134.2, 135.5, 137.2, 137.7, 145.0; HRMS (ESI): Found: m/z 208.1125. Calcd for $C_{15}H_{14}N$: $(M+H)^+$ 208.1126.

6-Methyl-[1,1':2',1''-terphenyl]-2-carbonitrile (2.1d)

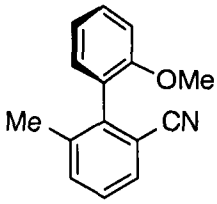


Prepared from 2-biphenylylboronic acid and 2-bromo-3-methylbenzaldehyde with CsF and purified by flash column chromatography (hexane : EtOAc = 95 : 5) in 70% overall yield in two steps

White solid; mp 153-154 °C; IR (ATR): 2226, 1558, 1541, 1506, 1473, 1456, 1252, 1192, 1111, 785, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, s), 7.11-7.22 (6H, m), 7.26 (2H, dd, J = 6.4, 7.2 Hz), 7.42-7.51 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 113.8, 118.5, 126.8, 127.45, 127.48, 127.7, 128.8, 129.1, 129.94, 130.07, 130.3, 134.0, 135.9,

137.8, 140.5, 141.3, 144.8; HRMS (ESI): Found: 270.1286. Calcd for $C_{20}H_{16}N$: $(M+H)^+$ 270.1283.

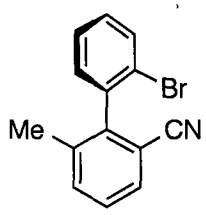
2'-Methoxy-6-methyl-[1,1'-biphenyl]-2-carbonitrile (2.1e)



Prepared from 2-methoxyphenylboronic acid and 2-bromo-3-methylbenzaldehyde with Na_2CO_3, and purified by flash column chromatography (hexanes : EtOAc = 90 : 10) in 83% overall yield in two steps.

White solid; mp 60-62 °C; IR (ATR) 2225, 1460, 1261, 1022, 794, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (3H, s), 3.77 (3H, s), 7.01 (1H, d, J = 8.0 Hz), 7.06 (1H, ddd, J = 0.8, 7.6, 8.0 Hz), 7.14 (1H, dd, J = 2.0, 7.6 Hz), 7.31 (1H, dd, J = 7.6, 7.6 Hz), 7.41 (1H, ddd, J = 2.0, 7.6, 9.2 Hz), 7.47 (1H, dd, J = 0.4, 7.6 Hz), 7.55 (1H, J = 0.4, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 55.4, 111.1, 113.7, 118.5, 120.7, 126.2, 127.5, 130.0, 130.1, 130.5, 133.9, 138.4, 142.1, 156.3; HRMS (ESI): Found: m/z 224.1071. Calcd for $C_{15}H_{14}NO$: $(M+H)^+$ 224.1075.

2'-Bromo-6-methyl-[1,1'-biphenyl]-2-carbonitrile (2.1f)

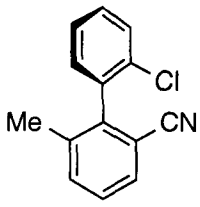


Prepared from 2-bromophenylboronic acid and 2-bromo-3-methylbenzaldehyde with Na_2CO_3 and purified by flash column chromatography (hexane : EtOAc = 95 : 5) in 40% overall yield in two steps.

White solid; mp 59-61°C; IR (ATR): 2226, 1558, 1541, 1522, 1506, 1489, 1456, 1026, 787, 760, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 7.22-7.25 (1H, m), 7.29-7.33 (1H, ddd, J = 1.2, 7.6, 8.8 Hz), 7.37-7.45 (2H, m), 7.51 (1H, d, J = 7.7 Hz), 7.59

(1H, d, J = 7.7 Hz), 7.71 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 113.1, 117.7, 123.1, 127.8, 128.3, 130.1, 130.2, 130.3, 133.0, 134.2, 138.0, 138.6, 144.1; HRMS (ESI): Found: 272.0068. Calcd for $C_{14}H_{11}N\,^{79}Br$: $(M+H)^+$ 272.0075.

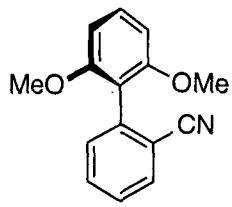
2'-Chloro-6-methyl-[1,1'-biphenyl]-2-carbonitrile (2.1g)



Prepared from 2-chlorophenylboronic acid and 2-bromo-3-methylbenzaldehyde with Na_2CO_3, and purified by flash column chromatography (hexanes : EtOAc = 90 : 10) in 60% overall yield in two steps.

Yellow solid; mp 58-59 °C; IR (ATR) 2225, 1454, 1265, 1033, 786, 750, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (3H, s), 7.22-7.26 (1H, m), 7.36-7.41 (3H, m), 7.49-7.54 (2H, m), 7.59 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 113.3, 117.8, 127.1, 128.3, 129.8, 130.0, 130.2, 130.5, 133.1, 134.2, 136.5, 138.1, 142.5; HRMS (ESI): Found: m/z 228.0581. Calcd for $C_{14}H_{11}NCl$: $(M+H)^+$ 228.0580.

2',6'-Dimethoxy-[1,1'-biphenyl]-2-carbonitrile (2.1h)[6]

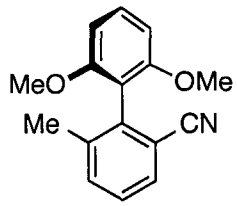


Prepared from 2,6-dimethoxyphenylboronic acid and 2-bromobenzyaldehyde with Na_2CO_3, and purified by flash column chromatography (hexanes : EtOAc = 90 : 10) in 75% overall yield in two steps.

White solid; mp 97-99 °C; IR (ATR) 2229, 1579, 1469, 1246, 1101, 779, 752, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (6H, s), 6.68 (2H, d, J = 8.4 Hz), 7.36 (1H, t, J = 8.4 Hz), 7.40-7.43 (2H, m), 7.61 (1H, ddd, J = 1.2, 7.6, 9.0 Hz), 7.73 (1H, dd, J = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 104.0, 114.3, 115.5, 118.6, 127.0, 130.3, 131.8,

132.0, 132.4, 138.6, 157.4; HRMS (ESI): Found: m/z 240.1030. Calcd for $C_{15}H_{14}NO_2$: $(M+H)^+$ 240.1025.

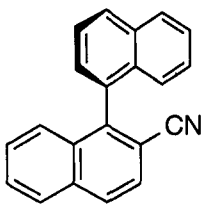
2',6'-Dimethoxy-6-methyl-[1,1'-biphenyl]-2-carbonitrile (2.1p)



Prepared from 2,6-dimethoxyphenylboronic acid and 2-bromo-3-methylbenzaldehyde with Na_2CO_3 and purified by flash column chromatography (hexane : EtOAc = 95 : 5) in 49% overall yield in two steps.

White solid; mp 137-139 °C; IR (ATR): 2228, 1558, 1541, 1506, 1456, 1449, 1412, 1190, 847, 791, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (3H, s), 3.75 (6H, s), 6.67 (2H, d, J = 8.0 Hz), 7.29-7.39 (2H, m), 7.47 (1H, d, J = 6.8 Hz), 7.56 (1H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 55.7, 104.0, 114.4, 114.6, 118.7, 127.3, 129.9, 130.3, 133.7, 138.5, 139.2, 157.3; HRMS (ESI): Found: 254.1185. Calcd for $C_{16}H_{16}NO_2$: $(M+H)^+$ 254.1181.

[1,1'-Binaphthalene]-2-carbonitrile (2.1q)

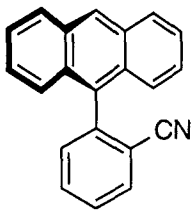


Prepared from naphthalen-1-ylboronic acid and 1-bromo-2-naphthaldehyde[7] with Na_2CO_3 and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 50% overall yield in two steps.

Light yellow solid; mp 169-172 °C; IR (ATR): 2226, 1558, 1541, 1522, 1506, 1489, 1456, 816, 785, 764, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (1H, d, J = 8.4 Hz), 7.32-7.38 (3H, m), 7.50-7.56 (2H, m), 7.62-7.69 (2H, m), 7.80 (1H, d, J = 8.6 Hz), 7.99-8.07 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 111.0, 118.4, 125.3, 125.4, 126.2, 126.6,

126.7, 127.5, 127.6, 128.1, 128.2, 128.5, 128.7, 128.8, 129.4, 132.2, 132.4, 133.6, 134.0, 134.6, 145.0; HRMS (ESI): Found: 280.1132. Calcd for $C_{21}H_{14}N$: $(M+H)^+$ 280.1126.

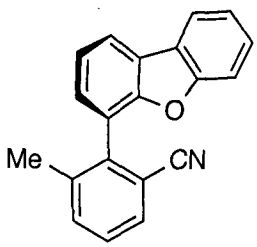
2-(Anthracen-9-yl)benzonitrile (2.1r)



Prepared from anthracen-9-ylboronic acid and 2-bromobenzaldehyde with Na_2CO_3 and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 46% overall yield in two steps.

Light yellow solid; mp 192-193 °C; IR (ATR): 2228, 1558, 1541, 1522, 1506, 1489, 1474, 1456, 768, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.46 (4H, m), 7.50 (2H, ddd, J = 1.5, 6.0, 7.6 Hz), 7.55 (1H, d, J = 7.6 Hz), 7.65 (1H, ddd, J = 1.1, 7.8, 8.8 Hz), 7.80 (1H, ddd, J = 1.2, 7.7, 8.9 Hz), 7.95 (1H, dd, J = 0.7, 7.8 Hz), 8.09 (2H, d, J = 8.5 Hz), 8.60 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.0, 117.6, 125.2, 125.4, 126.3, 128.2, 128.3, 128.7, 130.1, 131.2, 131.9, 132.4, 132.7, 133.1, 143.0; HRMS (ESI): Found: 280.1128. Calcd for $C_{21}H_{14}N$: $(M+H)^+$ 280.1126.

2-(dibenzo[b,d]furan-4-yl)-3-methylbenzonitrile (2.1s)

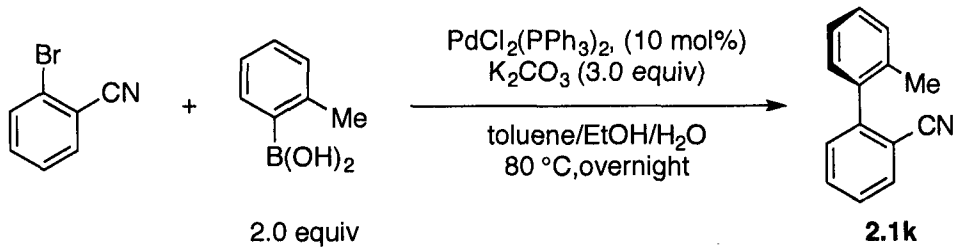


Prepared from dibenzofuran-4-boronic acid and 2-bromo-3-methylbenzaldehyde, and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 82% overall yield in two steps.

Light yellow solid; mp 127-128 °C; IR (ATR): 2226, 1449, 1412, 1261, 1188, 1107, 1057, 1015, 849, 791, 760, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 7.36-

7.54 (6H, m), 7.60 (1H, d, J = 7.7 Hz), 7.69 (1H, d, J = 7.7 Hz), 8.02 (1H, d, J = 7.7 Hz), 8.07 (1H, dd, J = 1.1, 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 111.8, 113.8, 118.3, 120.8, 121.2, 121.7, 122.96, 123.01, 124.1, 124.6, 127.4, 128.1, 128.4, 130.6, 134.4, 138.8, 139.7, 153.2, 156.2; HRMS (ESI): Found: 284.1061. Calcd for $C_{20}H_{14}NO$: $(M+H)^+$ 284.1075.

5.2.1.2 Method B: Pd(II)-catalyzed Suzuki–Miyaura cross coupling reaction of 2-bromobenzonitriles and aryl boronic acids[8]

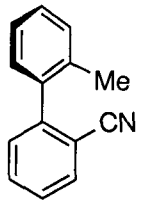


Scheme 5-2. *A representative scheme for preparation of biaryl-2-carbonitrile* ***2.1k*** *via method B.*

A typical procedure for synthesis of 2'-methyl-[1,1'-biphenyl]-2-carbonitrile (2.1k)

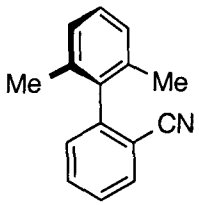
To a suspension of 2-bromobenzonitrile (0.26 g, 1.43 mmol), 2-methylphenylboronic acid (0.39 g, 2.88 mmol), K_2CO_3 (0.59 g, 4.29 mmol) in a mixture of toluene (5 mL), EtOH (1 mL) and H_2O (1 mL), was added $PdCl_2(PPh_3)_2$ (0.10 g, 0.143 mmol). The mixture was stirred at 80 °C overnight under an inert atmosphere. The reaction mixture was cooled to room temperature, quenched with H_2O and extracted with CH_2Cl_2 twice. The combined organic extracts was washed with water, followed by brine, dried over $MgSO_4$, and concentrated in *vacuo*. The crude residue was purified by flash column chromatography (hexane : EtOAc = 95 : 5) to give 2'-methyl-[1,1'-biphenyl]-2-carbonitrile (**2.1k**) (0.26 g, 1.35 mmol) in 94% yield.

2'-Methyl-[1,1'-biphenyl]-2-carbonitrile (2.1k)[9]



Clear oil; IR (ATR) 2225, 1473, 1217, 1006, 756, 744, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (3H, s), 7.20 (1H, dd, J = 0.8, 7.0 Hz), 7.26-7.34 (3H, m), 7.37 (1H, dd, J = 0.8, 7.6 Hz), 7.45 (1H, ddd, J = 1.2, 7.6, 8.8 Hz), 7.63 (1H, ddd, J = 1.2, 7.6, 9.0 Hz), 7.75 (1H, dd, J = 1.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 112.8, 118.1, 125.8, 127.5, 128.7, 129.4, 130.3, 130.4, 132.3, 132.8, 135.6, 138.0, 145.8; HRMS (ESI): Found: m/z 194.0967. Calcd for $C_{14}H_{12}N$: $(M+H)^+$ 194.0970.

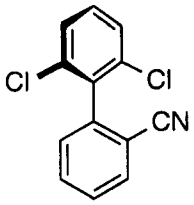
2',6'-dimethyl-[1,1'-biphenyl]-2-carbonitrile (2.1i)[10]



Prepared from 2,6-dimethylphenylboronic acid and 2-bromobenzonitrile, and purified by flash column chromatography (hexane : EtOAc = 95 : 5) followed by recrystallization from hexanes/EtOAc once in 28% yield.

Yellow oil; IR (ATR) 2225, 1593, 1463, 1253, 1112, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.01 (6H, s), 7.14 (2H, d, J = 7.6 Hz), 7.23 (1H, dd, J = 8.0, 9.2 Hz), 7.29 (1H, dd, J = 0.5, 7.6 Hz), 7.46 (1H, ddd, J = 1.2, 2.8, 7.6 Hz), 7.66 (1H, ddd, J = 1.2, 7.6, 9.0 Hz), 7.77 (1H, dd, J = 0.8, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 113.0, 117.7, 127.5, 127.6, 128.4, 130.2, 132.8, 132.9, 135.7, 137.6, 145.3; HRMS (ESI): Found: m/z 208.1133. Calcd for $C_{15}H_{14}N$: $(M+H)^+$ 208.1126.

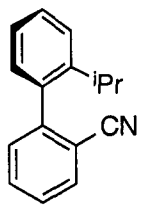
2',6'-dichloro-[1,1'-biphenyl]-2-carbonitrile (2.1j)



Prepared from 2,6-dichlorophenylboronic acid and 2-bromobenzonitrile, and purified by flash column chromatography (hexane : EtOAc = 95 : 5) followed by recrystallization from hexanes/EtOAc once in 13% yield.

White solid; mp 77-79 °C; IR (ATR) 2227, 1427, 1192, 1114, 1097, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, dd, J = 7.6, 8.8 Hz), 7.37 (1H, d, J = 8.0 Hz), 7.45 (2H, dd, J = 0.4, 8.0 Hz), 7.54 (1H, ddd, J = 1.2, 8.0, 9.2 Hz), 7.70 (1H, ddd, J = 1.2, 7.6, 9.2 Hz), 7.80 (1H, dd, J = 0.8, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3, 117.1, 128.2, 128.7, 130.5, 130.6, 132.7, 132.8, 134.8, 135.9, 140.7; HRMS (ESI): Found: m/z 248.0033. Calcd for $C_{13}H_8NCl_2$: $(M+H)^+$ 248.0034.

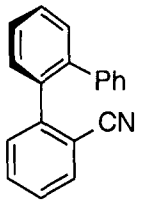
2'-isopropyl-[1,1'-biphenyl]-2-carbonitrile (2.1l)



Prepared from (2-isopropylphenyl)boronic acid and 2-bromobenzonitrile, and purified by flash column chromatography (hexane : EtOAc = 95 : 5) in 83% yield.

Yellow oil; IR (ATR) 2962, 2225, 1473, 1033, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, J = 6.8 Hz), 1.20 (3H, d, J = 6.8 Hz), 2.73 (1H, sept, J = 6.8 Hz), 7.14 (1H, d, J = 7.6 Hz), 7.22-7.28 (1H, m), 7.36 (1H, d, J = 7.6 Hz), 7.42-7.48 (3H, m), 7.61 (1H, t, J = 7.6 Hz), 7.74 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 24.3, 30.0, 113.1, 117.9, 125.5, 125.7, 127.4, 129.1, 129.4, 130.5, 132.1, 132.6, 136.9, 145.9, 146.4; HRMS (ESI): Found: m/z 222.1280. Calcd for $C_{16}H_{16}N$: $(M+H)^+$ 222.1283.

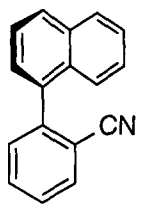
[1,1':2',1''-terphenyl]-2-carbonitrile (2.1m)[11]



Prepared from 2-biphenylylboronic acid and 2-bromobenzonitrile, and purified by flash column chromatography (hexane : EtOAc = 95 : 5) followed by recrystallization from hexanes/EtOAc once in 83% yield.

White solid; mp 125-127 °C; IR (ATR) 3018, 2223, 1469, 1215, 759, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-7.12 (2H, m), 7.16-7.22 (4H, m), 7.30 (1H, ddd, J = 0.8, 7.6, 8.8 Hz), 7.39-7.53 (5H, m), 7.58 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.8, 118.2, 126.7, 127.1, 127.3, 127.8, 128.9, 129.8, 130.4, 130.5, 131.4, 131.9, 132.7, 136.7, 140.3, 141.2, 145.6; HRMS (ESI): Found: m/z 256.1124. Calcd for $C_{19}H_{14}N$: $(M+H)^+$ 256.1126.

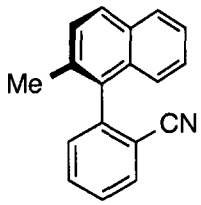
2-(naphthalen-1-yl)benzonitrile (2.1n)[12]



Prepared from 1-naphthylboronic acid and 2-bromobenzonitrile, and purified by flash column chromatography (hexane : EtOAc = 95 : 5) in 70% yield.

White solid; mp 124-126 °C; IR (ATR) 2226, 1558, 1541, 1506, 1489, 1473, 1456, 1192, 1111, 787, 750, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.63 (7H, m), 7.69 (1H, t, J = 7.6 Hz), 7.86 (1H, d, J = 7.6 Hz), 7.98 (2H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.4, 118.0, 125.0, 125.1, 126.0, 126.5, 127.4, 127.8, 128.4, 129.1, 131.3, 131.4, 132.2, 133.1, 133.6, 135.8, 144.2; HRMS (ESI): Found: 230.0967. Calcd for $C_{17}H_{12}N$: $(M+H)^+$ 230.0970.

2-(2-methylnaphthalen-1-yl)benzonitrile (2.1o)

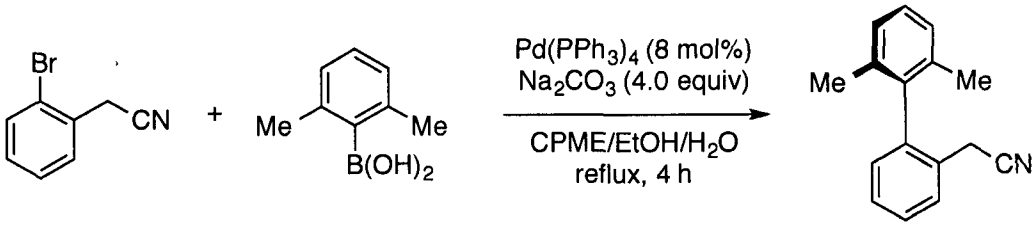


Prepared from (2-methylnaphthalen-1-yl)boronic acid and 2-bromobenzonitrile, and purified by flash column chromatography (hexane : EtOAc = 95 : 5) in 19% yield.

White solid; mp 89.7-92.6 °C; IR (ATR) 2226, 1558, 1541, 1506, 1456, 1435, 1028, 787, 760, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s), 7.19 (1H, d, J = 8.4 Hz), 7.36-7.48 (4H, m), 7.56 (1H, t, J = 7.7 Hz), 7.73 (1H, t, J = 7.7 Hz), 7.85-7.90 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 114.0, 117.7, 124.9, 125.1, 126.4, 127.8, 128.0, 128.5, 128.7, 131.3 131.9, 132.3, 132.7, 133.0, 133.76, 133.81, 144.0; HRMS (ESI): Found: 244.1126. Calcd for $C_{18}H_{14}N$: $(M+H)^+$ 244.1126.

5.2.1.3 Synthesis of biaryl-2-methane carbonitrile 2.4

Step 1: A procedure for synthesis of 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)acetonitrile (2.14)

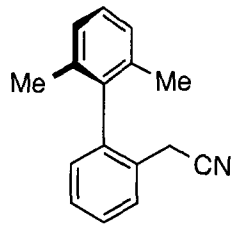


2.13 1.2 eq **2.14**

Scheme 5-3. Step 1: *Preparation of biaryl-2-acetonitrile **2.14**.*

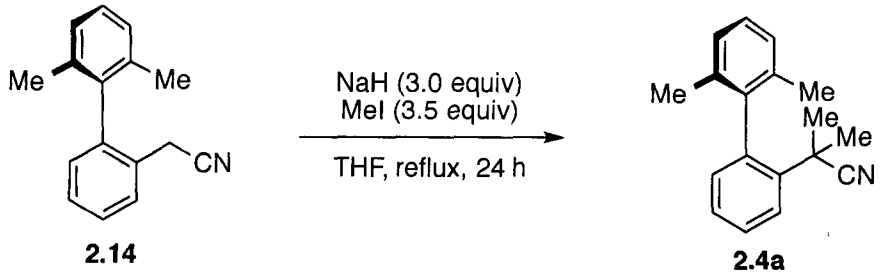
A mixture of 2-bromobenzyl cyanide (12.3 g, 62.7 mmol, prepared by the literature procedure[13]), 2,6-dimethylphenyl)boronic acid (11.2 g, 75.2 mmol), 2 M aqueous solution of Na_2CO_3 (125 mL, 250 mmol) with EtOH (50 mL), and $Pd(PPh_3)_4$ (2.90 g, 2.51 mmol) in cyclopentyl methyl ether (CPME) (50 mL) was refluxed overnight under an inert atmosphere. Upon completion, the reaction mixture was cooled to room

temperature, and the solvents were removed in *vacuo*. The organic materials were then extracted with a mixture of Et_2O-H_2O (1:1). The combined organic extract was washed with 5% aqueous NaOH followed by water and brine. After drying with $MgSO_4$, the solution was concentrated in *vacuo* to yield the crude residue, which was purified by flash column chromatography (hexane : EtOAc = 98 : 2) to give 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)acetonitrile (**2.14**) (9.72 g, 43.9 mmol) in 70% yield.



White solid, mp 80-81 °C; IR (NaCl) 3062, 2951, 1464, 1448, 1413, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (6H, s), 3.31 (2H, s), 7.11-7.14 (3H, m), 7.21 (1H, dd, J = 6.4, 8.4 Hz), 7.40-7.43 (2H, m), 7.59 (1H, dd, J = 3.6, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.2, 117.8, 127.8 (overlapped), 127.9, 128.0, 128.1, 128.7, 129.7, 135.8, 138,7, 140,2; HRMS (ESI): Found: m/z 222.1288. Calcd for $C_{16}H_{16}N$: $(M+H)^+$ 222.1283.

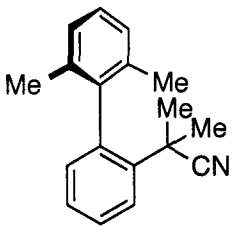
Step 2: Method A: A typical procedure for synthesis of 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)acetonitrile (2.4a)



Scheme 5-4. Step 2: *Dimethylation of biaryl-2-acetonitrile **2.14**.*

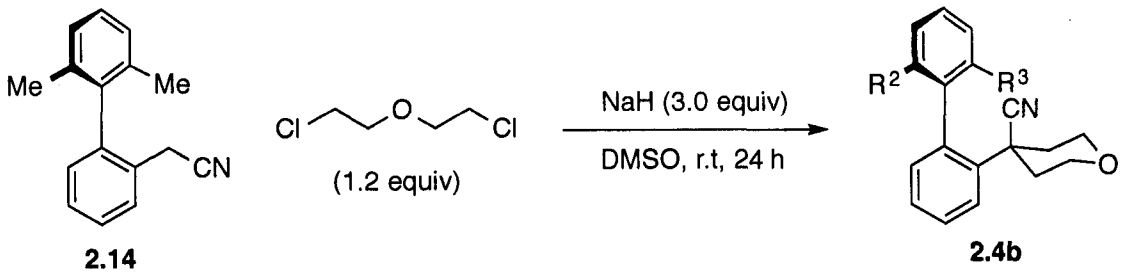
A solution of 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)acetonitrile (**2.14**) (6.8 g, 30.7 mmol) and methyl iodide (15.3 g, 107.5 mmol) in anhydrous THF (50 mL) was dropped into a refluxing mixture of NaH (3.68 g, 92.1 mmol, 60% dispersion in mineral oils) in

anhydrous THF (50 mL) over 30 min under an inert atmosphere. The resulting mixture was left to be stirred under reflux for 24 h. Upon completion, the reaction mixture was cooled to 0 °C, and carefully quenched with H_2O. The organic materials were then extracted with Et_2O, and the combined organic extract was washed with brine. After drying with $MgSO_4$, the solution was concentrated in *vacuo* to yield the crude residue, which was purified by flash column chromatography (hexane : EtOAc = 95 : 5) to give 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)acetonitrile (**2.4a**) (5.74 g, 23.0 mmol) in 75% yield.



White solid, mp 57-58 °C; IR (NaCl) 3059, 2929, 2235, 1446, 1381, 1182, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (6H, s), 1.99 (6H, s), 6.97 (1H, dd, J = 2.0, 7.6 Hz), 7.09 (2H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.34 (1H, dt, J = 1.6, 7.2 Hz), 7.40 (1H, dt, J = 1.6, 7.6 Hz), 7.66 (1H, dd, J = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.2, 117.8, 127.8 (overlapped), 127.9, 128.0, 128.1, 128.7, 129.7, 135.8, 138,7, 140,2; HRMS (ESI): Found: m/z 250.1592. Calcd for $C_{18}H_{20}N$: $(M+H)^+$ 250.1596.

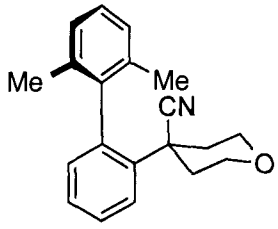
Step 2: Method B: A typical procedure for synthesis of 2-(2',6-dimethyl-[1,1'-biphenyl]-2-yl)-2-methylpropanenitrile (2.4b)



Scheme 5-5. Step 2: Method B: *Dialkylation of biaryl-2-acetonitrile* ***2.14***.

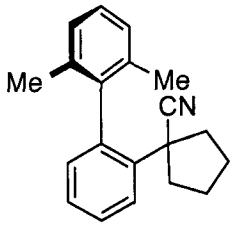
A solution of 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)acetonitrile (**2.14**) (0.66 g, 3.00 mmol) and 1-chloro-2-(2-chloroethoxy)ethane (0.51 g, 3.62 mmol) in anhydrous DMSO (5 mL) was dropped into a mixture of NaH (0.36 g, 9.00 mmol, 60% dispersion in mineral oil) in DMSO (10 mL) over 30 min at room temperature under an inert atmosphere. The resulting mixture was left to be stirred at room temperature for 24 h. Upon completion, the reaction mixture was carefully quenched with H_2O. The organic materials were then extracted with Et_2O, and the combined organic extract was washed with brine. After drying with $MgSO_4$, the solution was concentrated in *vacuo* to yield the crude residue, which was purified by flash column chromatography (hexane : EtOAc = 90 : 10) to give 4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)tetrahydro-2*H*-pyran-4-carbonitrile (**2.4b**) (0.65 g, 2.25 mmol) in 75% yield.

4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)tetrahydro-2*H*-pyran-4-carbonitrile (2.4b)



White solid, mp 102-104 °C; IR (NaCl) 3061, 2968, 1469, 1438, 1124, 1111, 1029, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.87-1.98 (4H, m), 1.99 (6H, s), 3.34 (2H, dd, J = 2.4, 12.4 Hz), 3.84-3.88 (2H, m), 6.98 (1H, dd, J =1.6, 7.6 Hz), 7.08 (2H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.37 (1H, dt, J = 1.2, 7.6 Hz), 7.42 (1H, dt, J = 1.6, 7.6 Hz), 7.64 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 36.3, 41.8, 64.7, 121.2, 127.3, 127.9, 128.0, 128.1, 128.5, 132.1, 136.3, 136.4, 139.3, 140.6; HRMS (ESI): Found: m/z 292.11694. Calcd for $C_{20}H_{22}NO$: $(M+H)^+$ 292.1701.

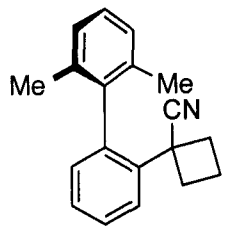
1-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)cyclopentane-1-carbonitrile (2.4c)



Prepared with 1,4-dibromobutane and purified by flash column chromatography (hexane : EtOAc = 95 : 5) in 59% yield.

White solid, mp 119-120 °C; IR (NaCl) 3061, 2960, 2225, 1454, 1377, 1165, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.73-1.86 (6H, m), 2.02 (6H, s), 2.15-2.18 (2H, m), 7.00-7.02 (1H, m), 7.09 (2H, d, J = 7.2 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.34-7.40 (2H, m), 7.56-7.59 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 22.7, 39.0, 47.7, 123.6, 127.2 (overlapped), 127.7, 128.2, 129.0, 131.5, 136.4, 136.5, 139.9, 140.9; HRMS (ESI): Found: m/z 276.1756. Calcd for $C_{20}H_{22}N$: $(M+H)^+$ 276.1752.

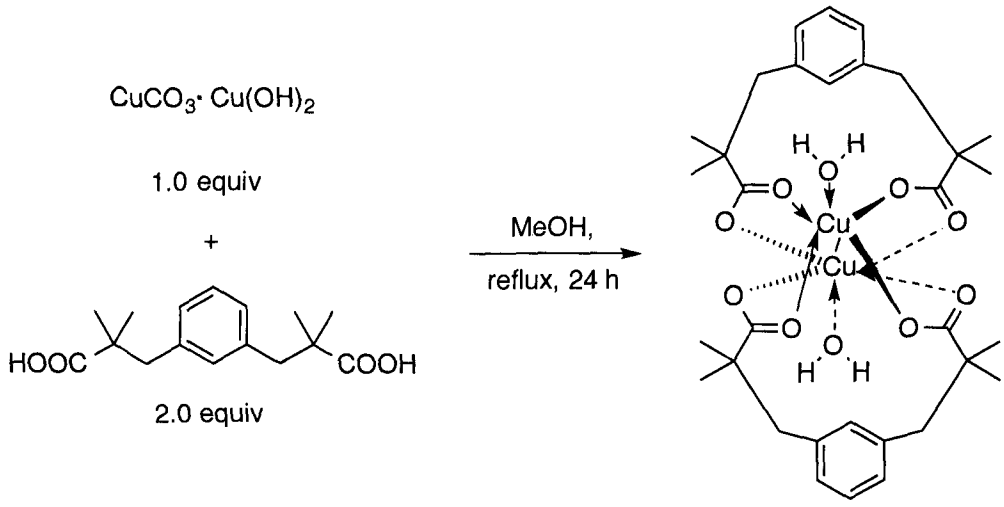
1-(2',6'-Dimethyl-[1,1'-biphenyl]-2-yl)cyclobutane-1-carbonitrile (2.4d)



Prepared with 1,3-dibromopropane and purified by flash column chromatography (hexane : EtOAc = 95 : 5) in 35% yield.

White solid, mp 76-78 °C; IR (NaCl) 3062, 2954, 2358, 1458, 927, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70-1.76 (1H, m), 2.04 (6H, s), 2.11-2.37 (5H, m), 7.03-7.07 (1H, m), 7.09 (2H, d, J = 7.2 Hz), 7.18 (1H, t, J = 6.8 Hz), 7.28-7.31 (1H, m), 7.33-7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 21.1, 34.6, 40.9, 124.4, 127.3, 127.4, 127.7, 127.8, 128.3, 130.8, 136.3, 137.0, 139.2, 139.4; HRMS (ESI): Found: m/z 262.1597. Calcd for $C_{19}H_{20}N$: $(M+H)^+$ 262.1596.

5.2.2. Synthesis of $Cu_2(esp)_2•2H_2O$



Scheme 5-6. *Preparation of* $Cu_2(esp)_2•2H_2O$

$\alpha,\alpha,\alpha',\alpha'$-Tetramethyl-1,3-benzenedipropionic acid ($espH_2$) was synthesized according to a reported procedure.[14] A mixture of $CuCO_3•Cu(OH)_2$ (0.39 g, 1.80 mmol), $espH_2$ (1.00 g, 3.60 mmol) and methanol (100 mL) was heated to reflux under an inert atmosphere for 24 h. The reaction mixture was cooled to room temperature and passed through celite. Then the filtrate was concentrated in *vacuo* to afford a dark green powder. Recrystallization from hexanes/EtOAc afforded the desired product $Cu_2(esp)_2•2H_2O$ (0.50 g, 0.700 mmol) in 40% yield.

$Cu_2(esp)_2•2H_2O$

Dark green crystal (CCDC 874165); mp 277-279 °C; IR (ATR): 1688, 1593, 1474, 1412, 1377, 1359, 1263, 1248, 1098, 710 cm^{-1}; HRMS (ESI) Found: 679.1393. Calcd for $C_{32}H_{41}O_8Cu_2$: $(M+H)^+$ 679.1393.

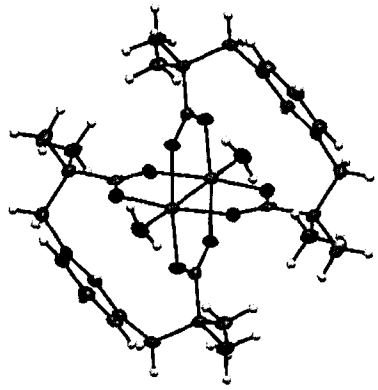
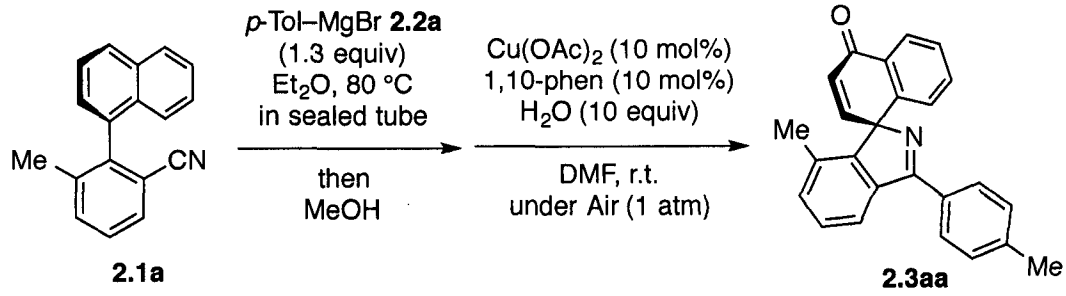


Figure 5-1. X-ray of $Cu^{II}_2(esp)_2•2H_2O$

5.2.3 Synthesis of azaspirocyclohexadienones derivatives

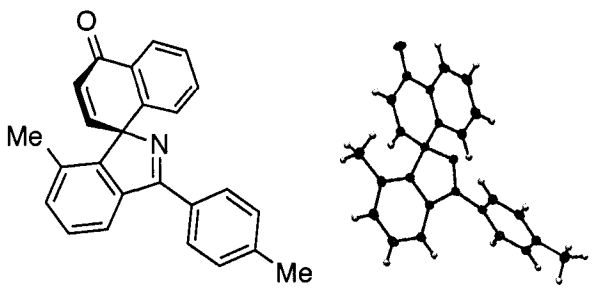
A typical procedure for synthesis of (±)-7-methyl-3-(p-tolyl)-4'H-spiro [isoindole-1,1'-naphthalen]-4'-one (2.3aa)



Scheme 5-7. *Synthesis of azaspirocyclohexadienone* ***2.3aa.***

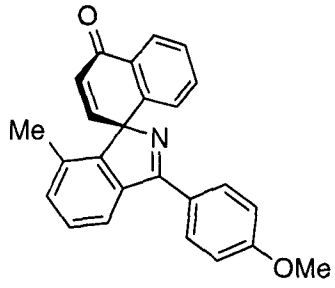
To an ice-cooled solution of 3-methyl-2-(naphthalen-1-yl)benzonitrile (**2.1a**) (122 mg, 0.500 mmol) in Et_2O (0.5 mL) was added an Et_2O solution of *p*-tolylmagnesium bromide (**2.2a**) (0.96 M, 0.67 mL, 0.650 mmol). The reaction mixture was stirred at 80 °C in a sealed tube for 2 h, and then anhydrous methanol (60 μL) was added at 0 °C. $Cu(OAc)_2$ (9.1 mg, 0.050 mmol), 1,10-phenanthroline (9.0 mg, 0.050 mmol), H_2O (90 μL, 5.00 mmol), and anhydrous DMF (5 mL) were then added. The reaction mixture was stirred at room temperatures under an air atmosphere. Upon completion, the reaction was quenched by addition of aqueous 1N HCl solution and organic materials were extracted with EtOAc twice. The combined organic extracts were washed with water and brine, and then dried over $MgSO_4$. After removal of the solvents, the resulting crude material was purified by flash column chromatography (hexane : EtOAc = 70 : 30) to give (±)-7-methyl-3-(p-tolyl)-4'H-spiro [isoindole-1,1'-naphthalen]-4'-one (**2.3aa**) (139.6 mg, 0.399 mmol) in 80% yield.

(±)-7-methyl-3-(p-tolyl)-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3aa)



Clear crystal (CCDC 874162); mp 216-218 °C; IR (ATR) 1656, 1544, 1350, 1300, 777, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (3H, s), 2.45 (3H, s), 6.30 (1H, d, J = 10.0 Hz), 6.56 (1H, d, J = 7.4 Hz), 6.76 (1H, d, J = 10.0 Hz), 7.16 (1H, d, J = 7.6 Hz), 7.32-7.36 (3H, m), 7.40-7.45 (2H, m), 7.77 (1H, d, J = 7.6 Hz), 7.92 (2H, d, J = 8.0 Hz), 8.25 (1H, dd, J = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 21.4, 77.2, 121.2, 126.3, 126.8, 128.2, 128.3, 129.2, 129.4, 130.7, 130.9, 131.5, 132.0, 132.9, 134.1, 138.6, 139.4, 141.1, 145.0, 152.5, 173.9, 184.9; HRMS (ESI): Found: m/z 350.1542. Calcd for $C_{25}H_{20}NO$: $(M+H)^+$ 350.1545.

(±)-3-(4-methoxyphenyl)-7-methyl-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3ab)

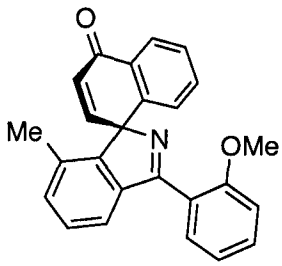


Synthesized from **2.1a** and (4-methoxyphenyl)magnesium bromide (**2.3b**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 80% yield.

Yellow solid; mp 189-191 °C; IR (ATR): 1667, 1599, 1543, 1508, 1456, 1298, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (3H, s), 3.88 (3H, s), 6.30 (1H, d, J = 10.0 Hz), 6.56 (1H, d, J = 7.8 Hz), 6.75 (1H, d, J = 10.0 Hz), 7.05 (2H, d, J = 8.8 Hz), 7.16 (1H, d, J = 7.4 Hz), 7.34 (1H, dd, J = 7.6, 7,6 Hz), 7.39-7.45 (2H, m), 7.77 (1H, d, J = 7.6 Hz), 8.00 (2H, d, J = 8.8 Hz), 8.25 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 55.4, 77.1, 114.2, 121.2, 126.4, 126.9, 128.2, 129.2, 130.0, 130.7, 131.5, 132.0, 132.9, 134.1, 138.8, 139.4, 145.2, 152.6, 161.7, 173.3, 185.0; HRMS (ESI): Found: 366.1497. Calcd for $C_{25}H_{20}NO_2$: $(M+H)^+$ 366.1494.

(±)-3-(2-methoxyphenyl)-7-methyl-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one

(2.3ac)

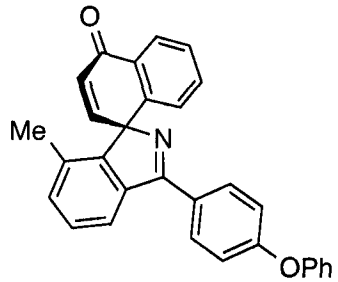


Synthesized from **2.1a** and (2-methoxyphenyl)magnesium bromide (**2.2c**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 75% yield.

Yellow solid; mp 127-129 °C; IR (ATR): 1661, 1599, 1582, 1551, 1508, 1489, 1456, 1437, 1381, 1346, 1298, 1273, 1246, 1119, 1022, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (3H, s), 3.86, (3H, s), 6.37 (1H, d, J = 10.0 Hz), 6.65 (1H, d, J = 8.0 Hz), 6.77 (1H, d, J = 10.0 Hz), 7.06-7.13 (3H, m), 7.33-7.44 (4H, m), 7.50 (1H, ddd, J = 1.2, 8.0, 9.2 Hz), 7.58 (1H, d, J = 7.2 Hz), 8.25 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 55.4, 77.7, 111.2, 120.8, 121.6, 123.3, 126.4, 126.8, 128.1, 128.9, 130.4, 130.7, 131.3, 131.6, 132.0, 132.9, 133.5, 138.6, 140.8, 145.2, 151.4, 157.5, 174.6, 185.1; HRMS (ESI): Found: 366.1494. Calcd for $C_{25}H_{20}NO_2$: $(M+H)^+$ 366.1494.

(±)-7-methyl-3-(4-phenoxyphenyl)-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one

(2.3ad)

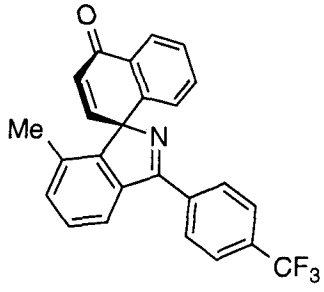


Synthesized from **2.1a** and (4-phenoxyphenyl)magnesium bromide (**2.2d**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 77% yield.

Pink solid; mp 191-193 °C; IR (ATR): 1665, 1599, 1585, 1545, 1487, 1456, 1437, 1381, 1346, 1298, 1238, 1152, 1024, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (3H, s),

6.30 (1H, d, J = 10 Hz), 6.57 (1H, dd, J = 0.8, 7.8 Hz), 6.77 (1H, d, J = 10 Hz), 7.08 (2H, dd, J = 0.8, 7.6 Hz), 7.13-7.19 (4H, m), 7.33-7.46 (5H, m), 7.78 (1H, d, J = 7.6 Hz), 8.01 (2H, dt, J = 2.0, 8.8 Hz), 8.26 (1H, dd, J = 1.2, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 77.1, 118.4, 119.5, 121.1, 124.0, 126.3, 126.9, 128.2, 128.4, 129.2, 129.9, 130.1, 130.8, 131.6, 132.0, 132.9, 134.2, 138.6, 139.2, 144.9, 152.5, 156.2, 159.8, 173.2, 184.9; HRMS (ESI): Found: 428.1653. Calcd for $C_{30}H_{22}NO_2$: $(M+H)^+$ 428.1651.

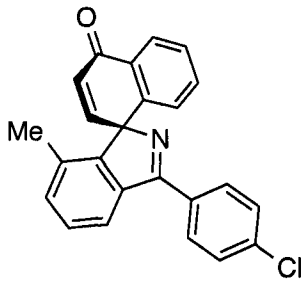
(±)-7-methyl-3-(4-(trifluoromethyl)phenyl)-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3ae)



Synthesized from **2.1a** and (4-(trifluoromethyl)phenyl)magnesium bromide (**2.2e**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 80% yield.

Yellow solid; mp 215-217 °C; IR (ATR): 1662, 1599, 1555, 1489, 1456, 1381, 1348, 1321, 1300, 1275, 1246, 1165, 1153, 1128, 1067, 1016, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (3H, s), 6.30 (1H, d, J = 10 Hz), 6.56 (1H, d, J = 7.6 Hz), 6.80 (1H, d, J = 10 Hz), 7.22 (1H, d, J = 7.6 Hz), 7.37 (1H, ddd, J = 1.2, 7.6, 8.8 Hz), 7.43-7.49 (2H, m), 7.72 (1H, d, J = 7.6 Hz), 7.82 (2H, d, J = 8.4 Hz), 8.13 (2H, d, J = 8.0 Hz), 8.27 (1H, dd, J = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 77.7, 120.8, 123.8 (1C, q, J = 271.0 Hz), 125.8 (1C, q, J = 4.0 Hz), 126.2, 127.1, 128.5, 128.8, 129.5, 131.2, 132.0, 132.1, 132.6 (1C, q, J = 32.0 Hz), 133.0, 133.1, 134.5, 137.1, 138.0, 138.7, 144.2, 152.7, 173.1, 184.8; HRMS (ESI): Found: 404.1262. Calcd for $C_{25}H_{17}NOF_3$: $(M+H)^+$ 404.1262.

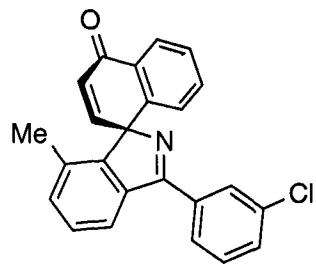
(±)-3-(4-chlorophenyl)-7-methyl-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3af)



Synthesized from **2.1a** and (4-chlorophenyl)magnesium bromide (**2.2f**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 72% yield.

Yellow solid; mp 216-217 °C; IR (ATR): 1668, 1601, 1543, 1489, 1456, 1381, 1346, 1325, 1298, 1169, 1015, 851, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (3H, s), 6.29 (1H, d, J = 10.0 Hz), 6.54 (1H, d, J = 7.6 Hz), 6.78 (1H, d, J = 10.0 Hz), 7.19 (1H, d, J = 7.6 Hz), 7.36 (1H, ddd, J = 1.2, 7.6, 8.8 Hz), 7.42-7.47 (2H, m), 7.52-7.54 (2H, m), 7.73 (1H, d, J = 7.6 Hz), 7.97 (2H, dd, J = 1.6, 8.4 Hz), 8.27 (1H, dd, J = 1.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 77.4, 120.9, 126.2, 127.0, 128.4, 129.1, 129.4, 129.7, 131.0, 131.9, 132.0, 132.2, 133.0, 134.3, 137.1, 138.2, 138.9, 144.5, 152.6, 173.0, 184.9; HRMS (ESI): Found: 370.0999. Calcd for $C_{24}H_{17}NOCl$: $(M+H)^+$ 370.0999.

(±)-3-(3-chlorophenyl)-7-methyl-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3ag)

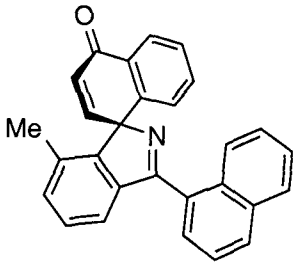


Synthesized from **2.1a** and (3-chlorophenyl)magnesium bromide (**2.2g**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 73% yield.

Yellow solid; mp 160-162 °C; IR (ATR): 1663, 1601, 1545, 1456, 1427, 1381, 1341, 1298, 1215, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (3H, s), 6.28 (1H, d, J = 10.0 Hz), 6.55 (1H, dd, J = 0.8, 7.6 Hz), 6.79 (1H, d, J = 10.0 Hz), 7.20 (1H, d, J = 7.6 Hz), 7.36 (1H, ddd, J = 1.2, 7.2, 8.8 Hz), 7.42-7.56 (4H, m), 7.74 (1H, d, J = 8.0 Hz), 7.91

(1H, dt, J = 1.2, 7.6 Hz), 8.01 (1H, t, J = 1.2 Hz), 8.26 (1H, dd, J = 1.6, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 77.4, 120.9, 126.2, 126.4, 127.0, 128.4, 129.4, 130.1, 130.8, 131.0, 131.89, 131.93, 133.0, 134.3, 134.9, 135.3, 138.0, 138.7, 144.3, 152.6, 172.9, 184.8; HRMS (ESI): Found: 370.1000. Calcd for $C_{24}H_{17}NOCl$: $(M+H)^+$ 370.0999.

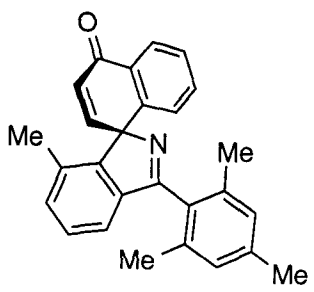
(±)-7-methyl-3-(naphthalen-1-yl)-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3ah)



Synthesized from **2.1a** and 1-naphthalenylmagnesium bromide (**2.2h**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 85% yield.

Yellow solid; mp 146-148 °C; IR (ATR): 1663, 1599, 1541, 1456, 1382, 1298, 1215, 1152, 962, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, s), 6.46 (1H, d, J = 10.0 Hz), 6.76 (1H, dd, J = 1.2, 7.6 Hz), 6.83 (1H, d, J = 10.0 Hz), 7.18 (1H, d, J = 7.2 Hz), 7.34-7.56 (6H, m), 7.62 (1H, dd, J = 7.2, 8.4 Hz), 7.86 (1H, d, J = 7.0 Hz), 7.94 (1H, d, J = 7.7 Hz), 8.02 (1H, d, J = 8.2 Hz), 8.25 (1H, d, J = 8.3 Hz), 8.29 (1H, dd, J= 1.6, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 78.3, 121.4, 125.0, 125.5, 126.2, 126.3, 126.9, 127.1, 127.3, 128.4, 128.5, 129.3, 130.6, 130.8, 131.0, 131.8, 132.1, 133.0, 133.9, 134.1, 138.5, 141.0, 144.8, 152.0, 175.0, 184.9; HRMS (ESI): Found: 386.1545. Calcd for $C_{28}H_{20}NO$: $(M+H)^+$ 386.1545.

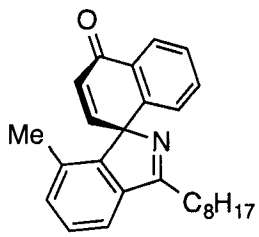
(±)-3-mesityl-7-methyl-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3ai)



Synthesized from **2.1a** and mesitylmagnesium bromide (**2.2i**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 65% yield.

Yellow solid; mp 166-167 °C; IR (ATR): 1661, 1614, 1599, 1555, 1454, 1300, 1150, 839, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (3H, s), 2.18 (3H, s), 2.27 (3H, s), 2.35 (3H, s), 6.31 (1H, d, *J* = 10 Hz), 6.70 (1H, dd, *J* = 0.8, 7.6 Hz), 6.79 (1H, d, *J* = 10 Hz), 6.98 (2H, s), 7.12-7.17 (2H, m), 7.34 (1H, t, *J* = 7.6 Hz), 7.38-7.48 (2H, m), 8.28 (1H, dd, *J* = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 19.8, 20.2, 21.2, 78.6, 120.4, 126.3, 127.0, 128.3, 128.47, 128.48, 129.5, 130.0, 130.9, 131.6, 132.0, 132.9, 134.0, 135.6, 138.56, 138.59, 141.1, 145.0, 151.5, 176.9, 184.9; HRMS (ESI): Found: 378.1858. Calcd for $C_{27}H_{24}NO$: $(M+H)^+$ 378.1858.

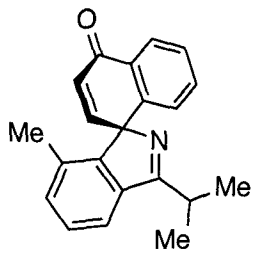
(±)-7-methyl-3-octyl-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3aj)



Synthesized from **2.1a** and octylmagnesium bromide (**2.2j**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 65% yield.

White solid; mp 96-98 °C; IR (ATR): 2955, 2928, 2857, 1665, 1601, 1570, 1456, 1300, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.8 Hz), 1.27-1.38 (8H, m), 1.44-1.51 (2H, m), 1.85-1.93 (5H, m), 2.94 (2H, t, *J* = 6.0 Hz), 6.19 (1H, d, *J* = 10.0 Hz), 6.46 (1H, d, *J* = 7.6 Hz), 6.72 (1H, d, *J* = 10.0 Hz), 7.12 (1H, d, *J* = 7.6 Hz), 7.34-7.42 (3H, m), 7.50 (1H, d, *J* = 7.6 Hz), 8.23 (1H, d, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 16.9, 22.6, 26.9, 29.2, 29.3, 29.6, 31.0, 31.8, 77.3(overlapped), 119.3, 126.2, 126.9, 128.2, 129.2, 130.6, 131.5, 132.0, 132.8, 133.8, 138.8, 140.6, 145.5, 151.6, 177.8, 185.0; HRMS (ESI): Found: 348.2314. Calcd for $C_{24}H_{30}NO$: $(M+H)^+$ 348.2327.

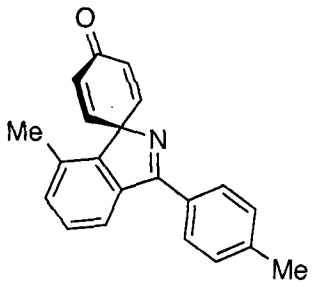
(±)-3-isopropyl-7-methyl-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3ak)



Synthesized from **2.1a** and isopropylmagnesium bromide (**2.2k**) and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 29% yield.

White solid; mp 148-150 °C; IR (ATR): 2953, 2928, 2855, 1663, 1599, 1568, 1543, 1524, 1456, 1300, 772, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (6H, t, J = 6.8 Hz), 1.84 (3H, s), 3.35 (1H, sept, J = 6.8 Hz), 6.17 (1H, d, J = 10.0 Hz), 6.43 (1H, d, J = 7.6 Hz), 6.72 (1H, d, J = 10.0 Hz), 7.11 (1H, d, J = 7.6 Hz), 7.32-7.43 (3H, m), 7.53 (1H, d, J = 7.6 Hz), 8.23 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 20.3, 20.5, 30.1, 76.9, 119.5, 126.1, 126.8, 128.1, 129.0, 130.6, 131.5, 132.1, 132.8, 133.9, 138.8, 139.9, 145.5, 151.8, 182.2, 185.1; HRMS (ESI): Found: 302.1544. Calcd for $C_{21}H_{20}NO$: $(M+H)^+$ 302.1545.

(±)-7'-methyl-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3ba)

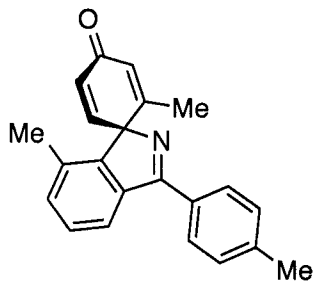


Synthesized from 6-methyl-[1,1'-biphenyl]-2-carbonitrile (**2.1b**) and **2.2a** under an O_2 atmosphere without addition of water, and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 37% yield.

Yellow solid; mp 239-240 °C; IR (ATR): 2968, 2929, 1666, 1568, 1456, 1298, 771, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (3H, s), 2.45 (3H, s), 6.31 (2H, d, J = 10.0 Hz), 6.61 (2H, d, J = 10.0 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.35 (2H, d, J = 7.6 Hz), 7.44 (1H, dd, J =

7.6, 7.6 Hz), 7.72 (1H, d, J = 7.6 Hz), 7.86 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 21.5, 76.4, 121.4, 128.3, 129.4, 129.5, 130.8, 131.3, 131.6, 134.6, 139.8, 141.2, 144.8, 148.4, 175.0, 185.8; HRMS (ESI): Found: 300.1388. Calcd for $C_{21}H_{18}NO$: $(M+H)^+$ 300.1388.

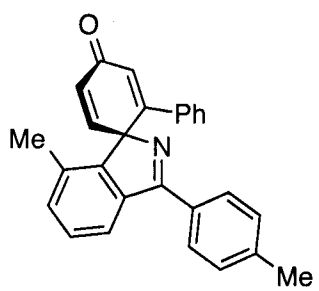
(±)-2,7'-dimethyl-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3ca)



Synthesized from 2',6-dimethyl-[1,1'-biphenyl]-2-carbonitrile (**2.1c**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 78% yield.

Yellow solid; mp 188-190 °C; IR (ATR): 1666, 1541, 1348, 881, 831, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (3H, d, J= 1.2 Hz), 2.21 (3H, s), 2.45 (3H, s), 6.17 (1H, d, J = 9.6 Hz), 6.50 (1H, d, J = 1.2 Hz), 6.56 (1H, dd, J = 1.6, 9.6 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.36 (2H, d, J = 8.0 Hz), 7.44 (1H, dd, J = 7.6, 7.6 Hz), 7.73 (1H, d, J = 7.6 Hz), 7.88 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 17.7, 21.4, 78.7, 121.2, 128.1, 129.2, 129.4, 129.6, 130.5, 130.7, 131.5, 134.1, 139.9, 141.1, 144.7, 149.3, 154.7, 175.1, 186.5; HRMS (ESI): Found: 314.1549. Calcd for $C_{22}H_{20}NO$: $(M+H)^+$ 314.1545.

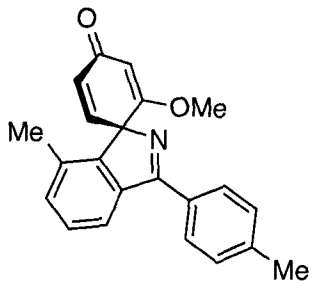
(±)-7'-methyl-1-phenyl-3'-(p-tolyl)spiro[cyclohexa[3,6]diene-2,1'-isoindol]-5-one (2.3da)



Synthesized from 6-methyl-[1,1':2',1''-terphenyl]-2-carbonitrile (**2.1d**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 82% yield.

Light yellow solid; mp 189-191 °C; IR (ATR): 1651, 1620, 1535, 1346, 1277, 1184, 824, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.43 (3H, s), 6.18 (1H, d, J = 9.8 Hz), 6.64 (1H, dd, J = 1.4, 9.8 Hz), 6.68 (1H, d, J = 1.4 Hz), 6.86 (2H, d, J = 7.5 Hz), 7.04 (2H, dd, J = 7.4, 8.0 Hz), 7.13 (1H, t, J = 7.4 Hz), 7.21 (1H, d, J = 7.5 Hz), 7.31 (2H, d, J = 7.9 Hz), 7.37 (1H, t, J = 7.6 Hz), 7.57 (1H, d, J = 7.6 Hz), 7.70 (2H, d, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 21.5, 78.8, 121.3, 126.7, 127.7, 128.0, 128.7, 129.3, 129.4, 130.1, 130.8, 130.9, 131.6, 134.3, 137.0, 140.5, 141.1, 145.5, 148.9, 156.0, 175.4, 186.8; HRMS (ESI): Found: 376.1705. Calcd for $C_{27}H_{22}NO$: $(M+H)^+$ 376.1701.

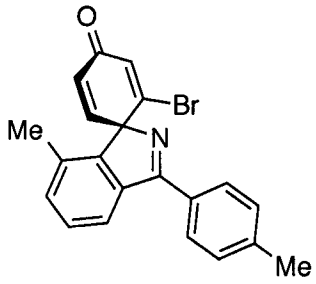
(±)-2-methoxy-7'-methyl-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3ea)



Synthesized from 2'-methoxy-6-methyl-[1,1'-biphenyl]-2-carbonitrile (**2.1e**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 60% yield.

White solid; mp 236-238 °C; IR (ATR): 1656, 1595, 1346, 1222, 852, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (3H, s), 2.42 (3H, s), 3.55 (3H, s), 5.89 (1H, d, J = 1.2 Hz), 5.91 (1H, d, J = 10.0 Hz), 6.48 (1H, dd, J = 1.2, 10.0 Hz), 7.20 (1H, d, J = 7.6 Hz), 7.31 (2H, d, J = 7.6 Hz), 7.40 (1H, dd, J = 7.2, 7.6 Hz), 7.67 (1H, d, J = 7.6 Hz), 7.85 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 21.4, 55.8, 77.7, 104.1, 121.2, 128.2, 129.1, 129.3, 130.1, 130.7, 131.3, 133.9, 140.0, 140.6, 141.0, 149.0, 170.8, 175.3, 188.1; HRMS (ESI): Found: 330.1494. Calcd for $C_{22}H_{20}NO_2$: $(M+H)^+$ 330.1494.

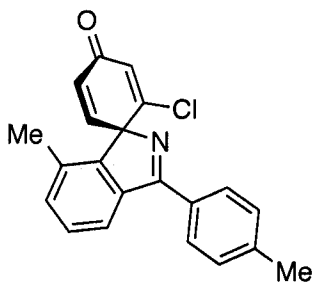
(±)-2-bromo-7'-methyl-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3fa)



Synthesized from 2'-bromo-6-methyl-[1,1'-biphenyl]-2-carbonitrile (**2.1f**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 81% yield.

Light yellow solid; mp 186-189 °C; IR (ATR): 1667, 1547, 1508, 1375, 1350, 1300, 1265, 951, 880, 835, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (3H, s), 2.46 (3H, s), 6.35 (1H, d, J = 9.8 Hz), 6.62 (1H, dd, J = 1.3, 9.8 Hz), 7.07 (1H, d, J = 1.3 Hz), 7.27 (1H, d, J = 7.4 Hz), 7.36 (2H, d, J = 7.9 Hz), 7.47 (1H, t, J = 7.6 Hz), 7.73 (1H, d, J = 7.6 Hz), 7.89 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 21.5, 79.5, 121.5, 128.3, 129.5, 129.8, 130.0, 130.6, 131.9, 134.4, 135.2, 140.3, 141.5, 144.7, 144.8, 148.5, 176.3, 184.0; HRMS (ESI): Found: 378.0491. Calcd for $C_{21}H_{17}NO^{79}Br$: $(M+H)^+$ 378.0494.

(±)-2-chloro-7'-methyl-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3ga)

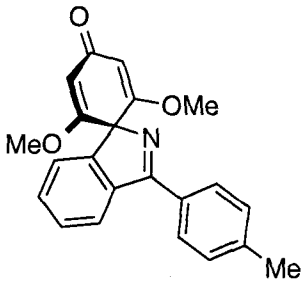


Synthesized from 2'-chloro-6-methyl-[1,1'-biphenyl]-2-carbonitrile (**2.1g**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 74% yield.

Orange solid; mp 189-191 °C; IR (ATR): 1660, 1543, 1508, 1350, 972, 879, 758; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (3H, s), 2.44 (3H, s), 6.26 (1H, d, J = 9.6 Hz), 6.58 (1H,

dd, J = 1.2, 9.6 Hz), 6.79 (1H, d, J = 1.2 Hz), 7.26 (1H, d, J = 7.6 Hz), 7.35 (2H, d, J = 7.6 Hz), 7.46 (1H, dd, J = 7.6, 7.6 Hz), 7.72 (1H, d, J = 8.0 Hz), 7.88 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 21.4, 79.0, 121.4, 128.2, 129.4, 129.7, 130.0, 130.4, 130.8, 131.7, 134.3, 140.2, 141.4, 144.3, 147.7, 152.1, 176.4, 184.8; HRMS (ESI): Found: 334.0999. Calcd for $C_{21}H_{17}NOCl$: $(M+H)^+$ 334.0999.

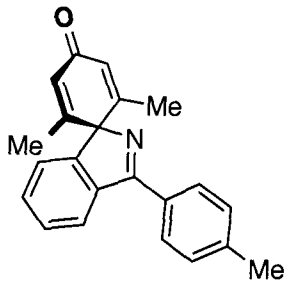
(±)-2,6-dimethoxy-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3ha)



Synthesized from 2',6'-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (**2.1h**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 50 : 50) in 48% yield.

Brown solid; mp 243-245 °C; IR (ATR): 1653, 1593, 1355, 1242, 1209, 1101, 846, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (3H, s), 3.47 (6H, s), 5.71 (2H, s), 7.35 (2H, d, J = 8.0 Hz), 7.34 (1H, d, J = 7.2 Hz), 7.43 (1H, dd, J = 7.2, 7.2 Hz), 7.49 (1H, dd, J = 7.2, 7.6 Hz), 7.83 (1H, d, J = 7.6 Hz), 7.92 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 56.0, 79.5, 101.7, 121.2, 123.2, 128.3, 128.5, 129.3, 129.3 (overlapped), 130.7, 139.9, 141.1, 151.8, 168.5, 175.7, 188.2; HRMS (ESI): Found: 346.1453. Calcd for $C_{22}H_{20}NO_3$: $(M+H)^+$ 346.1443.

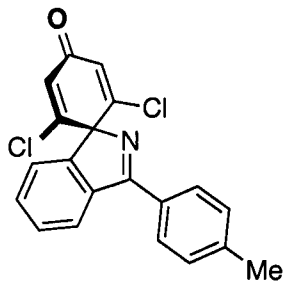
(±)-2,6-dimethyl-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3ia)



Synthesized from 2',6'-dimethyl-[1,1'-biphenyl]-2-carbonitrile (**2.1i**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 68% yield.

Yellow solid; mp 143-145 °C; IR (ATR): 1664, 1633, 1543, 1346, 1001, 891, 827, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (6H, s), 2.48 (3H, s), 6.38 (2H, s), 7.26 (1H, d, J = 7.2 Hz), 7.39 (2H, d, J = 8.0 Hz), 7.47 (1H, ddd, J = 1.2, 7.6, 8.4 Hz), 7.52 (1H, ddd, J = 1.2, 7.6, 8.4 Hz), 7.90 (1H, d, J = 7.6 Hz), 7.94 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 21.4, 81.9, 122.0, 123.3, 128.0, 128.1, 128.7, 129.5, 129.8, 130.5, 139.5, 141.4, 152.9, 156.0, 175.2, 186.6; HRMS (ESI): Found: 314.1541. Calcd for $C_{22}H_{20}NO$: $(M+H)^+$ 314.1545.

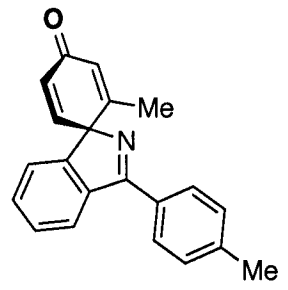
(±)-2,6-dichloro-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3ja)



Synthesized from 2',6'-dichloro-[1,1'-biphenyl]-2-carbonitrile (**2.1j**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 69% yield.

Orange solid; mp 153-155 °C; IR (ATR): 1651, 1595, 1350, 1321, 993, 827, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (3H, s), 6.73 (2H, s), 7.37-7.41 (3H, m), 7.52-7.60 (2H, m), 7.90 (1H, d, J = 7.2 Hz), 7.94 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 82.0, 122.0, 123.7, 128.3, 129.2, 129.6, 129.8, 130.0, 130.3, 140.6, 141.9, 149.9, 152.4, 177.8, 182.6; HRMS (ESI): Found: 354.0446. Calcd for $C_{20}H_{14}NOCl_2$: $(M+H)^+$ 354.0452.

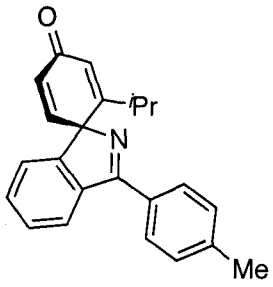
(±)-2-methyl-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3ka)



Synthesized from 2'-methyl-[1,1'-biphenyl]-2-carbonitrile (**2.1k**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 49% yield.

Yellow solid; mp 141-143 °C; IR (ATR): 1666, 1544, 1508, 1348, 1280, 997, 833, 758, 669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, d, J = 1.2 Hz), 2.47 (3H, s), 6.22 (1H, d, J = 10.0 Hz), 6.42 (1H, q, J = 1.2 Hz), 6.48 (1H, dd, J = 1.2, 10.0 Hz), 7.31 (1H, dd, J = 1.2, 6.8 Hz), 7.38 (2H, d, J = 8.0 Hz), 7.46-7.54 (2H, m), 7.89-7.94 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 21.4, 79.2, 122.5, 123.5, 128.1, 128.6, 128.8, 129.3, 129.5, 129.8, 130.5, 139.4, 141.3, 146.3, 151.8, 155.9, 174.8, 186.7; HRMS (ESI): Found: 300.1386. Calcd for $C_{21}H_{18}NO$: $(M+H)^+$ 300.1388.

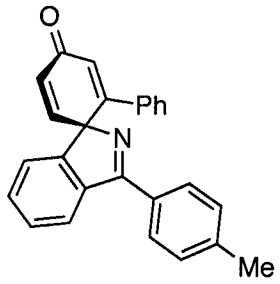
(±)-2-isopropyl-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3la)



Synthesized from 2'-isopropyl-[1,1'-biphenyl]-2-carbonitrile (**2.1l**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 42% yield.

Yellow solid; mp 136-138 °C; IR (ATR): 1662, 1539, 1508, 1346, 1004, 891, 827, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (3H, d, J = 6.8 Hz), 1.07 (3H, d, J = 6.8 Hz), 1.32 (1H, sept, J = 6.8 Hz), 2.46 (3H, s), 6.16 (1H, d, J = 10.0 Hz), 6.44 (1H, dd, J = 1.6, 10.0 Hz), 6.53 (1H, d, J = 1.6 Hz), 7.31 (1H, d, J = 7.2 Hz), 7.37 (2H, d, J = 8.0 Hz), 7.46 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.51 (1H, ddd, J = 1.2, 7.6, 8.4 Hz), 7.90-7.93 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.0, 23.6, 28.7, 79.7, 122.9, 123.6, 126.1, 128.2, 128.8, 129.1, 129.5, 129.6, 130.7, 140.0, 141.4, 146.3, 151.4, 166.4, 175.0, 187.2; HRMS (ESI): Found: 328.1701. Calcd for $C_{23}H_{22}NO$: $(M+H)^+$ 328.1701.

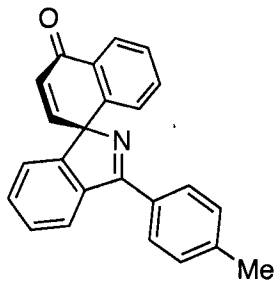
(±)-1-phenyl-3'-(p-tolyl)spiro[cyclohexa[3,6]diene-2,1'-isoindol]-5-one (2.3ma)



Synthesized from [1,1':2',1''-terphenyl]-2-carbonitrile (**2.1m**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 50 : 50) in 36% yield.

White solid; mp 135-137 °C; IR (ATR): 1658, 1508, 1340, 1006, 893, 769, 756, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, s), 6.25 (1H, d, J = 9.6 Hz), 6.55 (1H, dd, J = 1.6, 9.6 Hz), 6.59 (1H, d, J = 1.6 Hz), 6.81-6.83 (2H, m), 7.01-7.05 (2H, m), 7.12 (1H, tt, J = 1.2, 7.2 Hz), 7.31 (2H, d, J = 8.0 Hz), 7.42-7.47 (3H, m), 7.72 (3H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 79.2, 122.8, 123.5, 127.2, 127.5, 128.0, 128.5, 128.8, 128.9, 129.4, 129.8, 129.9, 130.6, 136.5, 140.0, 141.2, 147.1, 151.3, 157.4, 174.9, 186.9; HRMS (ESI): Found: 362.1544. Calcd for $C_{26}H_{20}NO$: $(M+H)^+$ 362.1545.

(±)-3-(p-tolyl)-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3na)

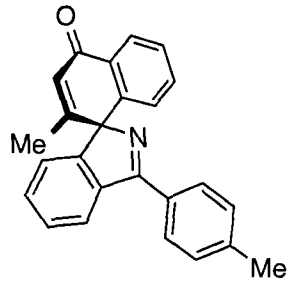


Synthesized from 2-(naphthalen-1-yl)benzonitrile (**2.1n**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 41% yield.

White solid; mp 129-132 °C; IR (ATR): 1653, 1595, 1361, 1242, 1211, 1099, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (3H, s), 6.40 (1H, d, J = 10.0 Hz), 6.59 (1H, d, J = 7.8 Hz), 6.69 (1H, d, J = 10.0 Hz), 7.18 (1H, d, J = 7.6 Hz), 7.34-7.44 (5H, m), 7.49 (1H, dd, J = 7.6, 7.2 Hz), 7.93 (2H, d, J = 7.6 Hz), 7.98 (1H, d, J = 8.0 Hz), 8.26 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 77.6, 123.3, 123.6, 126.4, 127.0, 128.2, 128.4,

128.5, 129.6, 129.7, 130.0, 130.9, 131.4, 132.9, 138.7, 139.6, 141.4, 146.7, 155.1, 174.0, 185.1; HRMS (ESI): Found: 336.1389. Calcd for $C_{24}H_{18}NO$: $(M+H)^+$ 336.1388.

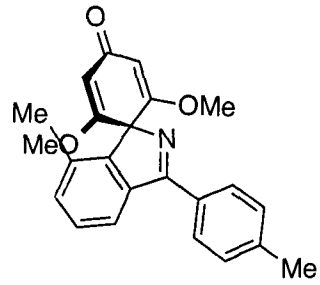
(±)-2'-methyl-3-(p-tolyl)-4'H-spiro[isoindole-1,1'-naphthalen]-4'-one (2.3oa)



Synthesized from 2-(2-methylnaphthalen-1-yl)benzonitrile (**2.1o**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 32% yield.

Light yellow solid; mp 151-155 °C; IR (ATR): 1657, 1597, 1531, 1456, 1341, 1302, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.52 (3H, d, J = 1.3 Hz), 2.49 (3H, s), 6.57 (1H, d, J = 8.0 Hz), 6.63 (1H, d, J = 1.3 Hz), 7.11 (1H, d, J = 7.6 Hz), 7.29 (1H, ddd, J = 1.5, 8.0, 8.5 Hz), 7.35-7.41 (4H, m), 7.47 (1H, ddd, J = 1.0, 8.0, 8.5 Hz), 7.92 (1H, d, J = 8.0 Hz), 8.00 (2H, d, J = 8.0 Hz), 8.24 (1H, dd, J = 1.5, 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 21.6, 80.3, 122.6, 123.4, 125.9, 126.7, 127.9, 128.3, 128.4, 128.7, 129.6, 130.0, 130.8, 131.0, 132.6, 138.7, 140.1, 141.5, 156.1, 156.6, 174.4, 184.9; HRMS (ESI): Found: 350.1548. Calcd for $C_{25}H_{20}NO$: $(M+H)^+$ 350.1545.

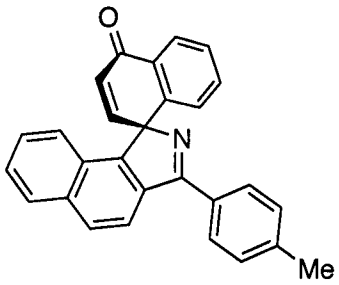
(±)-2,6-dimethoxy-7'-methyl-3'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,1'-isoindol]-4-one (2.3pa)



Synthesized from 2',6'-dimethoxy-6-methyl-[1,1'-biphenyl]-2-carbonitrile (**2.1p**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 20 : 80) in 61% yield.

Light yellow solid; mp 272 °C (decomp.); IR (ATR): 1651, 1591, 1358, 1209, 1096, 858, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (3H, s), 2.43 (3H, s), 3.50 (6H, s), 5.78 (2H, s), 7.18 (1H, d, J = 7.4 Hz), 7.32 (2H, d, J = 7.9 Hz), 7.38 (1H, dd, J = 7.6, 7.6 Hz), 7.63 (1H, d, J = 7.6 Hz), 7.85 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 21.5, 56.2, 79.5, 102.9, 120.9, 128.3, 128.9, 129.3, 130.8, 131.0, 133.3, 140.8, 141.0, 149.2, 167.6, 175.9, 188.1; HRMS (ESI): Found: 360.1601. Calcd for $C_{23}H_{22}NO_3$: $(M+H)^+$ 360.1600.

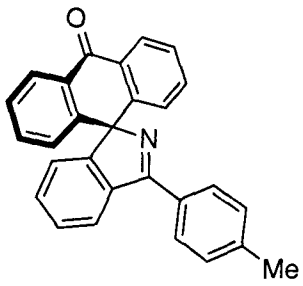
(±)-3-(p-tolyl)-4'H-spiro[benzo[e]isoindole-1,1'-naphthalen]-4'-one (2.3qa)



Synthesized from [1,1'-binaphthalene]-2-carbonitrile (**2.1q**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 87% yield.

Light yellow solid; mp 241 °C (decomp.); IR (ATR): 1659, 1599, 1452, 1341, 1298, 841, 827, 772, 754, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.48 (3H, s), 6.35 (1H, d, J = 10.0 Hz), 6.49 (1H, d, J = 7.9 Hz), 6.82 (1H, d, J = 10.0 Hz), 7.25-7.28 (1H, m), 7.35-7.44 (5H, m), 7.51 (1H, dd, J = 7.0, 8.1 Hz), 7.96 (1H, d, J = 8.3 Hz), 7.99 (2H, d, J = 7.6 Hz), 8.03 (2H, s), 8.35 (1H, d, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 77.5, 120.1, 123.6, 126.4, 127.38, 127.45, 127.57, 127.63, 128.5, 128.9, 129.6, 130.5, 130.6, 131.0, 131.5, 133.1, 133.8, 137.3, 139.5, 141.3, 146.9, 152.6, 174.1, 185.2; HRMS (ESI): Found: 386.1551. Calcd for $C_{28}H_{20}NO$: $(M+H)^+$ 386.1545.

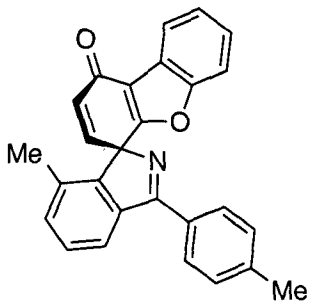
(±)-3'-(p-tolyl)-10H-spiro[anthracene-9,1'-isoindol]-10-one (2.3ra)



Synthesized from 2-(anthracen-9-yl)benzonitrile (**2.1r**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 80% yield.

White solid; mp 204-207 °C; IR (ATR): 1665, 1597, 1549, 1508, 1452, 1346, 1317, 1261, 1186, 1157, 1014, 833, 773, 729, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (3H, s), 6.83 (2H, d, J = 7.6 Hz), 7.00 (1H, d, J = 7.4 Hz), 7.27 (1H, d, J = 6.0), 7.38-7.49 (7H, m), 7.96 (1H, d, J = 7.6 Hz), 8.12 (2H, d, J = 7.9 Hz), 8.46 (2H, d, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 78.5, 123.0, 123.4, 126.0, 127.8, 128.1, 128.3, 129.6, 129.9, 130.8, 131.1, 133.4, 137.1, 140.0, 141.3, 159.6, 173.5, 184.0; HRMS (ESI): Found: 386.1548. Calcd for $C_{28}H_{20}NO$: $(M+H)^+$ 386.1545.

(±)-7'-methyl-3'-(p-tolyl)-1H-spiro[dibenzo[b,d]furan-4,1'-isoindol]-1-one (2.3sa)

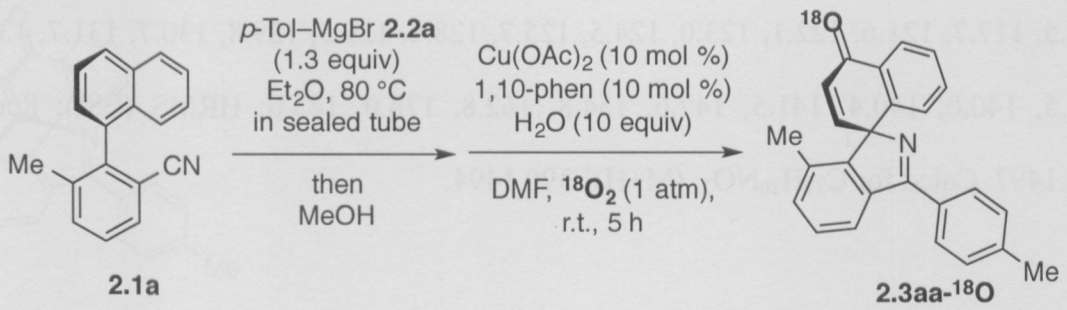


Synthesized from 2-(dibenzo[b,d]furan-4-yl)-3-methylbenzonitrile (**2.1s**) and **2.2a**, and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 77% yield.

White solid; mp 184-186 °C; IR (ATR): 1668, 1641, 1611, 1599, 1541, 1508, 1375, 1348, 1300, 1265, 951, 881, 829, 760, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.02 (3H, s), 2.46 (3H, s), 6.20 (1H, d, J = 9.8 Hz), 6.72 (1H, d, J = 9.8 Hz), 7.23 (1H, d, J = 7.3 Hz), 7.29-7.40 (5H, m), 7.49 (1H, dd, J = 7.6, 7.6 Hz), 7.82 (1H, d, J = 7.7 Hz), 7.94 (2H, d, J

= 8.1 Hz), 8.22 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 21.5, 75.2, 111.5, 117.7, 121.6, 122.1, 123.0, 124.5, 125.7, 128.4, 129.5, 129.8, 130.7, 131.7, 131.9, 134.5, 140.0, 140.4, 141.5, 147.6, 154.8, 162.8, 176.0, 183.6; HRMS (ESI): Found: 390.1497. Calcd for $C_{27}H_{20}NO_2$: $(M+H)^+$ 390.1494.

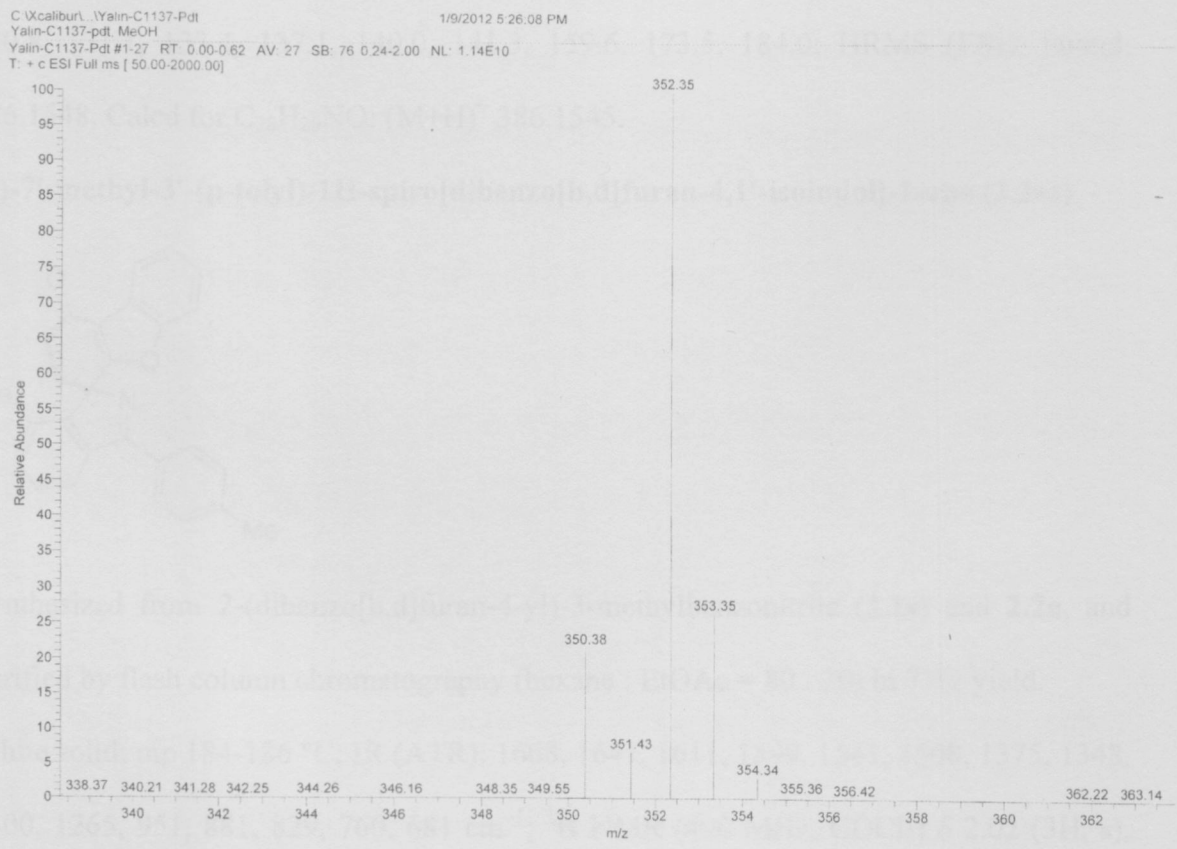
5.2.4. Labelling experiments



Scheme 5-8. ***Isotope labelling experiment using $^{18}O_2$***

By subjecting the reaction of **2.1a** under an $^{18}O_2$ atmosphere, we observed that the ^{18}O incorporated **2.3aa** was obtained mainly by mass spectroscopy. When comparing the IR-spectrums of **2.3aa** and **2.3aa-^{18}O**, a rightward shift of the C=O stretching was also observed in **2.3aa-^{18}O**.

Spectrum of ESI (LRMS) of **2.3aa-^{18}O**



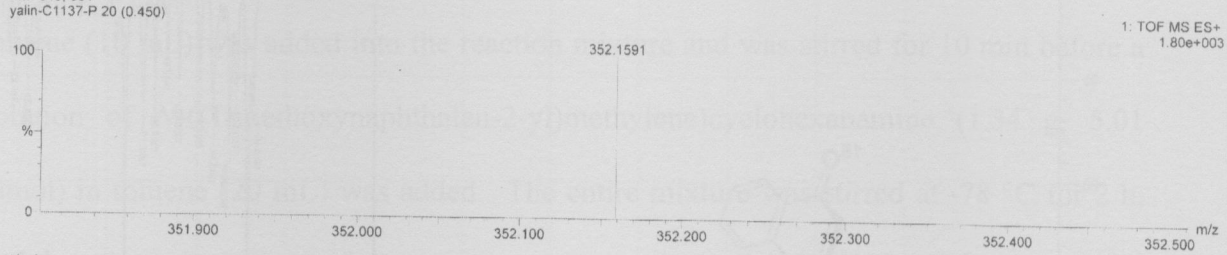
Spectrum of ESIHRMS of **2.3aa-^{18}O**

Elemental Composition Report

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.8, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
24 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-30 H: 0-23 N: 0-3 18O: 0-2

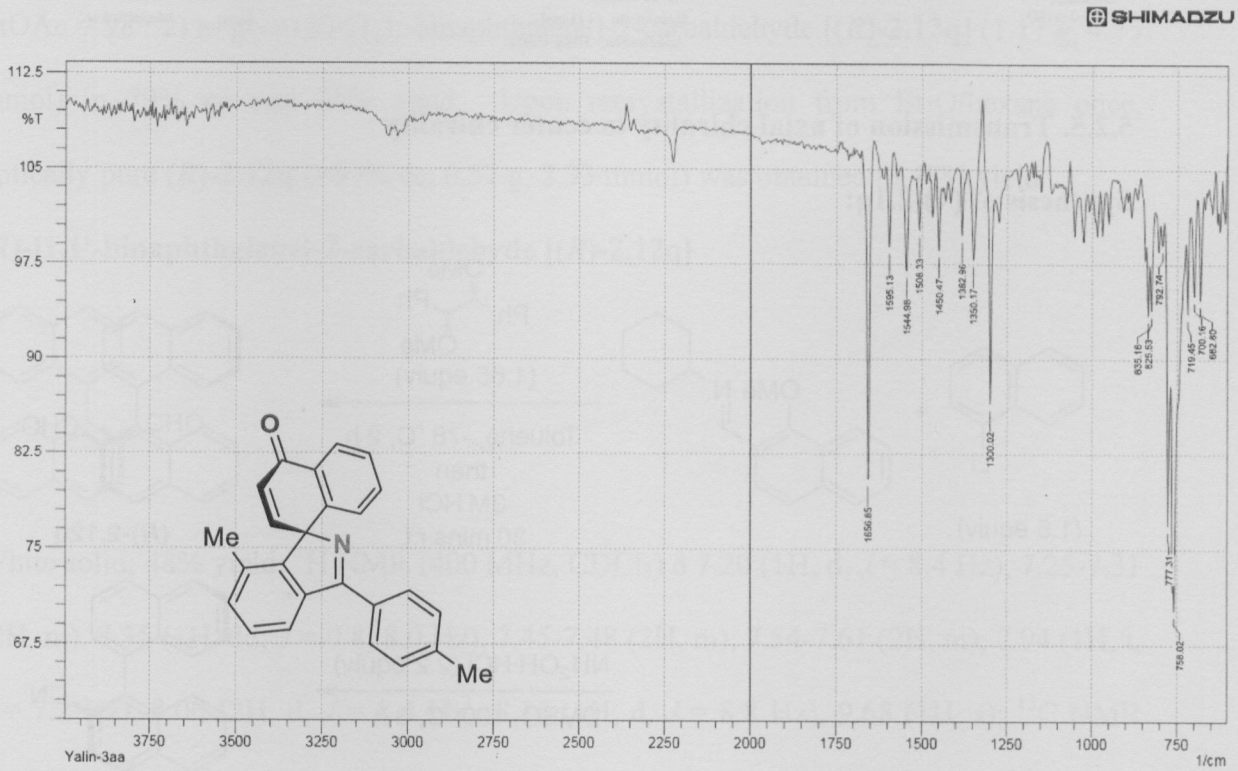
mw: 349, 351
yalin-C1137-P 20 (0.450)



Minimum:				-1.8			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
352.1591	352.1587	0.4	1.1	16.5	25.4	0.0	C25 H20 N 18O

IR Spectrum of **2.3aa**

IR 1656 (C=O) cm^{-1}



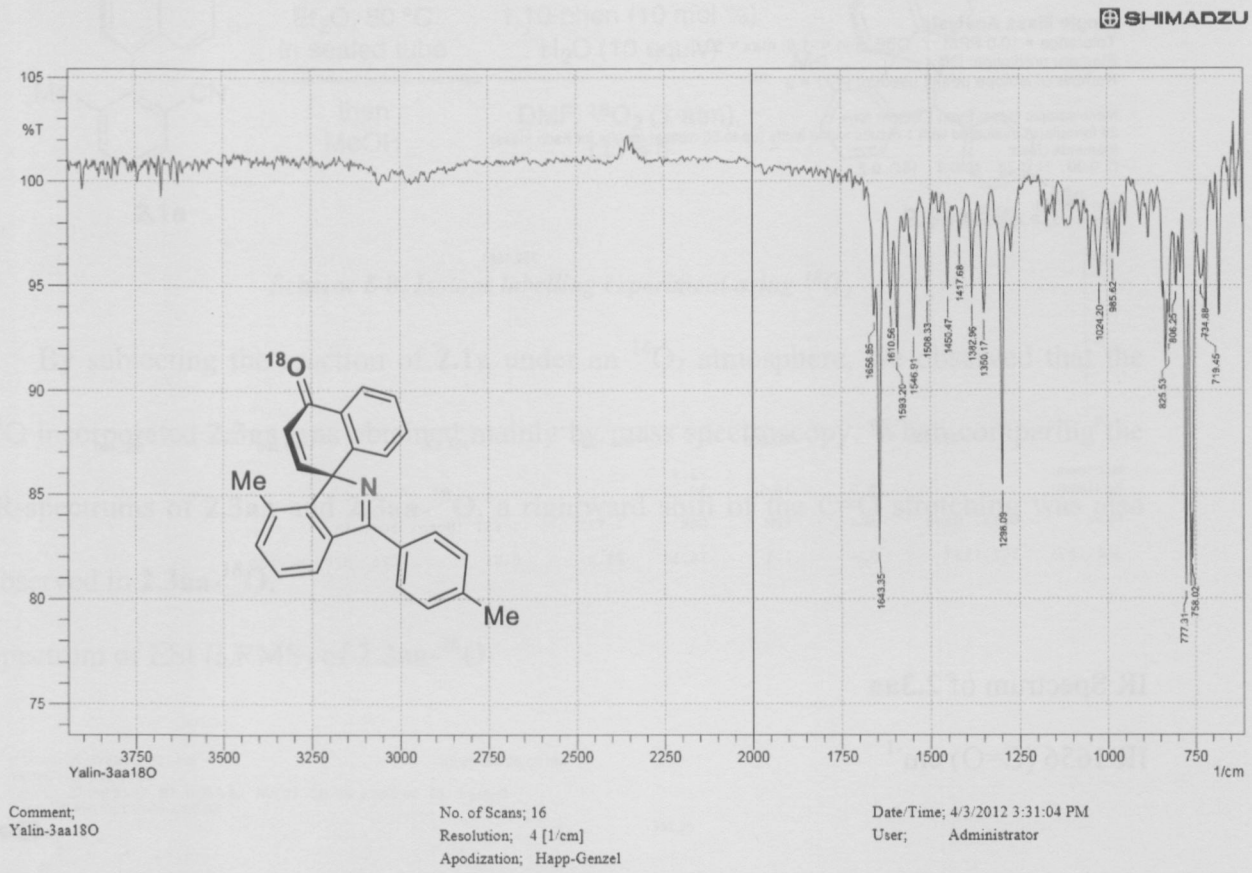
Comment;
Yalin-3aa

No. of Scans; 16
Resolution; 4 [1/cm]
Apodization; Happ-Genzel

Date/Time; 3/28/2012 11:53:01 PM
User; Administrator

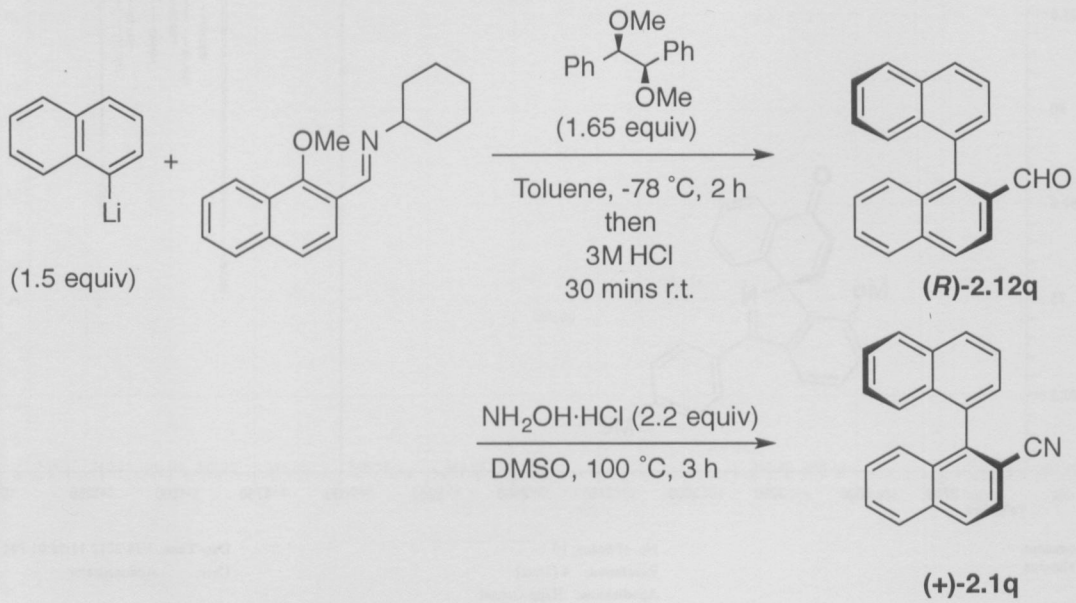
IR Specrtum of **2.3aa-^{18}O**

IR 1643 (C=O) cm^{-1}



5.2.5. Transmission of axial chirality to center chirality

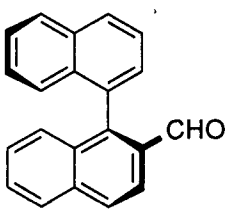
Synthesis of (+)-2.1q:



Scheme 5-9. *Synthesis of optically pure (+)-2.1q.*

(*R*)-[1,1'-binaphthalene]-2-carbaldehyde **(*R*)-2.12q** was prepared according to the reported procedure with slight modification as follows.[15] *n*-BuLi (1.6 M in hexanes, 5.2 mL, 8.25 mmol) was dropped into a solution of 1-bromonaphthalene (1.55 g, 7.50 mmol) in anhydrous toluene (30 mL) at -78 °C and left to be stirred under an inert atmosphere for 1 h. A solution of (1*R*,2*R*)-1,2-dimethoxy-1,2-diphenylethane (1.99 g, 8.25 mmol) in toluene (10 mL) was added into the reaction mixture and was stirred for 10 min before a solution of *N*-((1-methoxynaphthalen-2-yl)methylene)cyclohexanamine (1.34 g, 5.01 mmol) in toluene (20 mL) was added. The entire mixture was stirred at -78 °C for 2 h, and the mixture was warmed to room temperature. Aqueous 3 M HCl solution was added to the mixture and then stirred for 30 min to ensure complete hydrolysis of the resulting binapthyl imine into aldehyde. The organic materials were extracted with EtOAc thrice, and the combined organic extracts were washed with water and brine, and dried over $MgSO_4$. The crude material was purified by flash column chromatography (hexane : EtOAc = 98 : 2) to give (*R*)-[1,1'-binaphthalene]-2-carbaldehyde [**(*R*)-2.12q**] (1.17 g, 4.75 mmol) in 79% ee and 95% yield. Upon recrystallization from Et_2O/hexane once, optically pure **(*R*)-2.12q** (>99% ee, 0.57 g, 2.33 mmol) was obtained in 47% yield.

(*R*)-[1,1'-binaphthalene]-2-carbaldehyde [(*R*)-2.12q]



White solid; 48% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, d, *J* = 8.4 Hz), 7.25-7.31 (2H, m), 7.35 (1H, dd, *J* = 0.8, 8.0 Hz), 7.45-7.48 (2H, m), 7.54-7.61 (2H, m), 7.94 (1H, t, *J* = 7.2 Hz), 8.00 (2H, d, *J* = 8.4 Hz), 8.15 (1H, d, *J* = 8.8 Hz), 9.68 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.0, 124.9, 126.1, 126.2, 126.7, 126.9, 127.6, 128.1, 128.3, 128.6, 128.8, 128.9, 129.1, 132.0, 132.8, 132.9, 133.2, 133.4, 136.0, 144.8, 192.4; HPLC

analysis using chiral column Daicel ChiralPak IA hexane/isopropyl alcohol (9/1), flow rate 0.5 mL/min, retention time: 9.4 min.

HPLC analysis chart of 79% ee (*R*)-[1,1'-binaphthalene]-2-carbaldehyde [(*R*)-2.12q]

4/4/2012 21:23:34 1 / 1

==== Shimadzu LCsolution Analysis Report ====

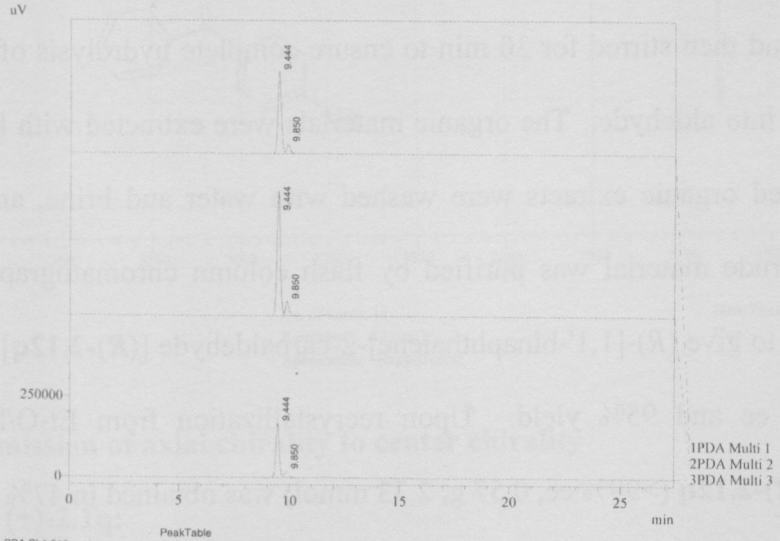
C:\...\User\Desktop\Yalin\azaspiro\Yalin-C2049-b4recryst.lcd

Acquired by	: Admin
Sample Name	: Yalin-C2049-b4recryst
Sample ID	: Yalin-C2049-b4recryst
Tray#	: 1
Vail #	: 21
Injection Volume	: 0.2 uL
Data File Name	: Yalin-C2049-b4recryst.lcd
Method File Name	: 5 membered CN SO2Ph try.lcm
Batch File Name	:
Data Acquired	: 4/3/2012 3:42:28 PM

<<Pump>>

Pump Mode	: Low pressure gradient
Pump A	: LC-20AD
Total Flow	: 0.5000 mL/min
B.Conc	: 10.0 %
C.Conc	: 0.0 %
D.Conc	: 0.0 %

<Chromatogram>



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	9.444	2702798	252038	89.246
2	9.850	325696	28500	10.754
Total		3028494	280538	100.000

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	9.444	4148947	386850	89.014
2	9.850	512083	43876	10.986
Total		4661030	430725	100.000

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	9.444	1810483	168871	89.199
2	9.850	219219	19037	10.801
Total		2029702	187908	100.000

C:\Documents and Settings\User\Desktop\Yalin\azaspiro\Yalin-C2049-b4recryst.lcd

HPLC analysis chart of pure (*R*)-[1,1'-binaphthalene]-2-carbaldehyde [(*R*)-2.12q]

==== Shimadzu LCsolution Analysis Report ====

C:\...\User\Desktop\Yalin\azaspiro\Yalin-C2049-recryst.lcd

Acquired by	: Admin	<<Pump>>	
Sample Name	: Yalin-C2049-recryst	Pump Mode	: Low pressure gradient
Sample ID	: Yalin-C2049-recryst	Pump A	: LC-20AD
Tray#	: 1	Total Flow	: 0.5000 mL/min
Vail #	: 22	B.Conc	: 10.0 %
Injection Volume	: 0.2 uL	C.Conc	: 0.0 %
Data File Name	: Yalin-C2049-recryst.lcd	D.Conc	: 0.0 %
Method File Name	: 5 membered CN SO2Ph try.lcm		
Batch File Name	:		
Data Acquired	: 4/3/2012 4:10:55 PM		

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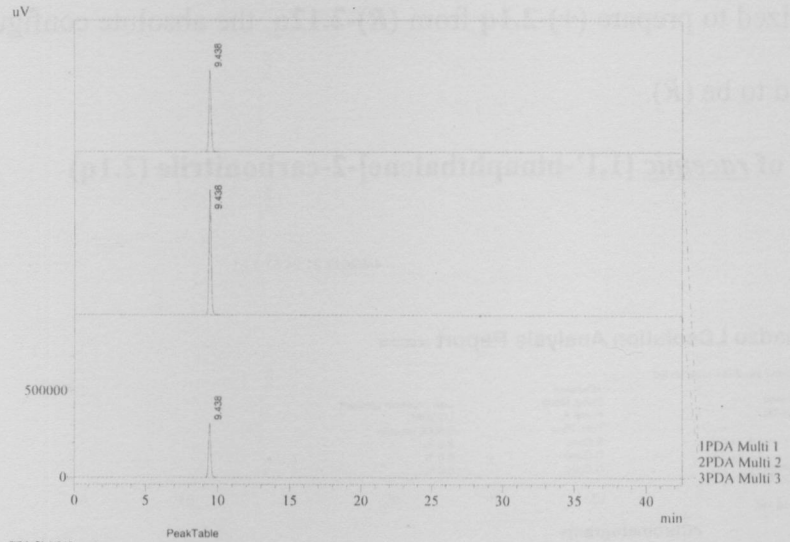

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	9.438	5083957	470000	100.000
Total		5083957	470000	100.000

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	9.438	7803874	719160	100.000
Total		7803874	719160	100.000

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	9.438	3410330	315702	100.000
Total		3410330	315702	100.000

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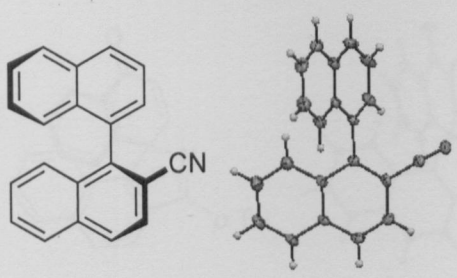
(+)-[1,1'-binaphthalene]-2-carbonitrile [(+)-2.1q]



The optically pure aldehyde **(*R*)-2.12q** was then converted into optically pure (+)-[1,1'-binaphthalene]-2-carbonitrile according to the same method as described in Section 5.2.1.1, where **(+)-2.1q** ($[\alpha]^{20}_{D}$ +102.5° (c = 0.051, $CHCl_3$)) was obtained. Optical purity of **(+)-2.1q** was tested by HPLC analysis using chiral column Daicel ChiralPak IB hexane/isopropyl alcohol (98/2), flow rate 0.5 mL/min, retention time: 17.3 min. The structure was confirmed by X-ray crystallographic analysis (CCDC 874163). Based on the transformation utilized to prepare **(+)-2.1q** from **(*R*)-2.12q**, the absolute configuration of **(+)-2.1q** is presumed to be (*R*).

HPLC analysis chart of *racemic* [1,1'-binaphthalene]-2-carbonitrile (2.1q)

4/4/2012 21:24:57 1 / 1

==== Shimadzu LCsolution Analysis Report ====

C:\...\User\Desktop\Yalin\azaspiro\Yalin-2051-racemic.lcd

Acquired by	: Admin	<<Pump>>	
Sample Name	: Yalin-2051-racemic	Pump Mode	: Low pressure gradient
Sample ID	: Yalin-2051-racemic	Pump A	: LC-20AD
Tray#	: 1	Total Flow	: 0.5000 mL/min
Vail #	: 23	B.Conc	: 2.0 %
Injection Volume	: 0.2 uL	C.Conc	: 0.0 %
Data File Name	: Yalin-2051-racemic.lcd	D.Conc	: 0.0 %
Method File Name	: 5 membered CN SO2Ph try.lcm		
Batch File Name	:		
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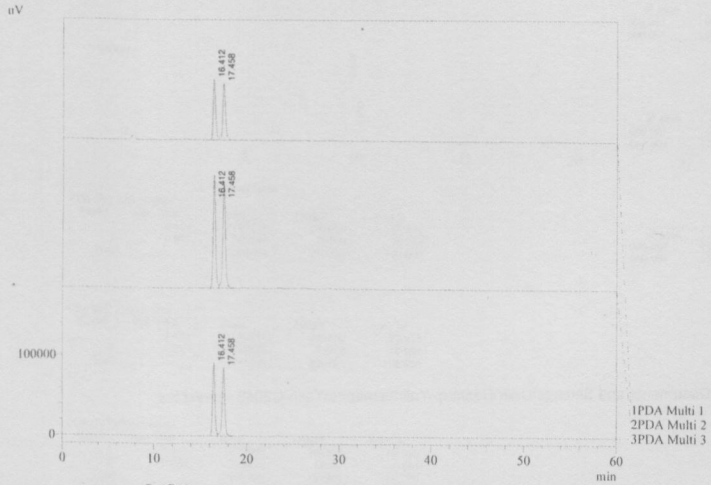

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	16.412	1367831	75924	49.056
2	17.458	1420453	71136	50.944
Total		2788283	147060	100.000

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	16.412	2551497	141745	48.980
2	17.458	2657791	132902	51.020
Total		5209288	274647	100.000

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	16.412	1643659	91382	48.776
2	17.458	1726178	85724	51.224
Total		3369837	177106	100.000

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HPLC analysis chart of (+)-[1,1'-binaphthalene]-2-carbonitrile [(+)-2.1q]

==== Shimadzu LCsolution Analysis Report ====

C:\Documents and Settings\User\Desktop\Yalin\azaspiro\Yalin-2051.lcd

Acquired by	: Admin	<<Pump>>	
Sample Name	: Yalin-2051	Pump Mode	: Low pressure gradient
Sample ID	: Yalin-2051	Pump A	: LC-20AD
Tray#	: 1	Total Flow	: 0.5000 mL/min
Vail #	: 24	B.Conc	: 2.0 %
Injection Volume	: 0.2 uL	C.Conc	: 0.0 %
Data File Name	: Yalin-2051.lcd	D.Conc	: 0.0 %
Method File Name	: 5 membered CN SO2Ph try.lcm		
Batch File Name	:		
Data Acquired	: 4/4/2012 9:11:48 PM		

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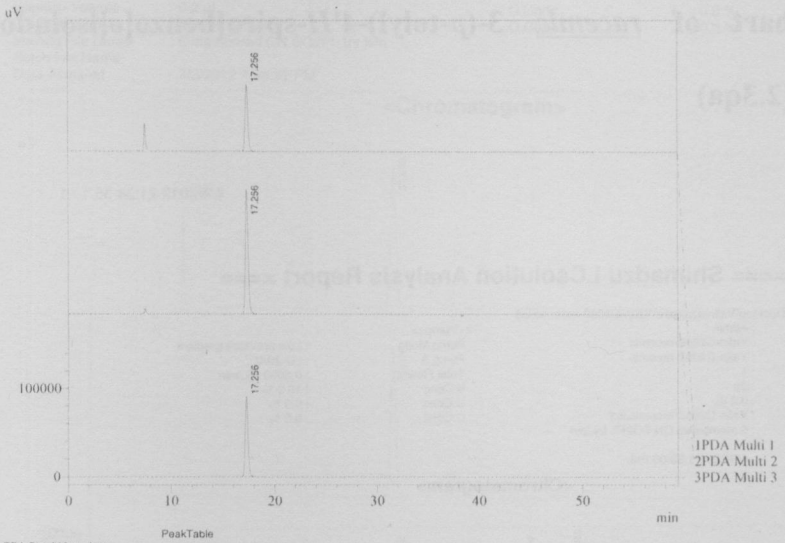

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	17.256	1421485	75181	100.000
Total		1421485	75181	100.000

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	17.256	2666490	140536	100.000
Total		2666490	140536	100.000

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	17.256	1714216	90539	100.000
Total		1714216	90539	100.000

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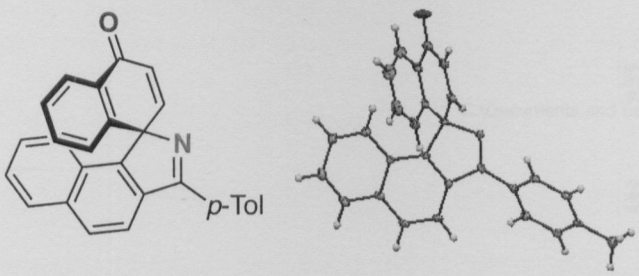
(+)-3-(*p*-tolyl)-4'*H*-spiro[benzo[*e*]isoindole-1,1'-naphthalen] -4'-one [(+)-2.3qa]



(+)-[1,1'-binaphthalene]-2-carbonitrile [**(+)-2.1q**] was then subjected to the reaction conditions as described in Section 5.2.3 to provide (+)-3-(*p*-tolyl)-4'*H*-spiro[benzo[*e*]isoindole-1,1'-naphthalen] -4'-one [**(+)-2.3qa**] ($[\alpha]^{20}_{D}$ +156.8° (c = 0.044, $CHCl_3$)). Optical purity of **(+)-2.3qa** was tested by HPLC analysis using chiral column Daicel ChiralPak IA hexane/isopropyl alcohol (9/1), flow rate 0.5 mL/min, retention time: 23.4 min. The structure was confirmed by X-ray crystallography (CCDC 874164).

HPLC analysis chart of *racemic* 3-(*p*-tolyl)-4'*H*-spiro[benzo[*e*]isoindole-1,1'-naphthalen] -4'-one (2.3qa)

4/4/2012 21:24:35 1 / 1

==== Shimadzu LCsolution Analysis Report ====

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Acquired by	: Admin	<<Pump>>	
Sample Name	: Yalin-C2052-racemic	Pump Mode	: Low pressure gradient
Sample ID	: Yalin-C2052-racemic	Pump A	: LC-20AD
Tray#	: 1	Total Flow	: 0.5000 mL/min
Vail #	: 25	B.Conc	: 10.0 %
Injection Volume	: 0.2 uL	C.Conc	: 0.0 %
Data File Name	: Yalin-C2052-racemic.lcd	D.Conc	: 0.0 %
Method File Name	: 5 membered CN SO2Ph try.lcm		
Batch File Name	:		
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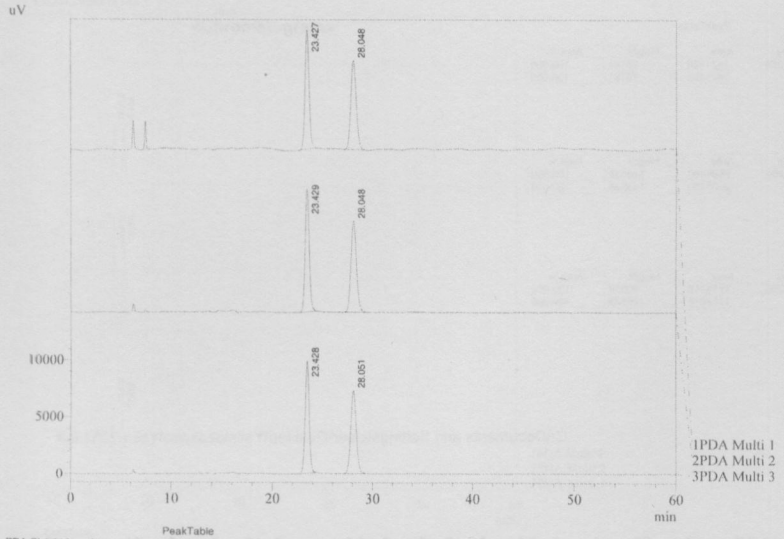

PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	23.427	292758	10461	49.750
2	28.048	295699	7744	50.250
Total		588456	18205	100.000

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	23.429	300706	10710	49.754
2	28.048	303677	7904	50.246
Total		604383	18615	100.000

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	23.428	277241	9867	49.801
2	28.051	279452	7281	50.199
Total		556693	17148	100.000

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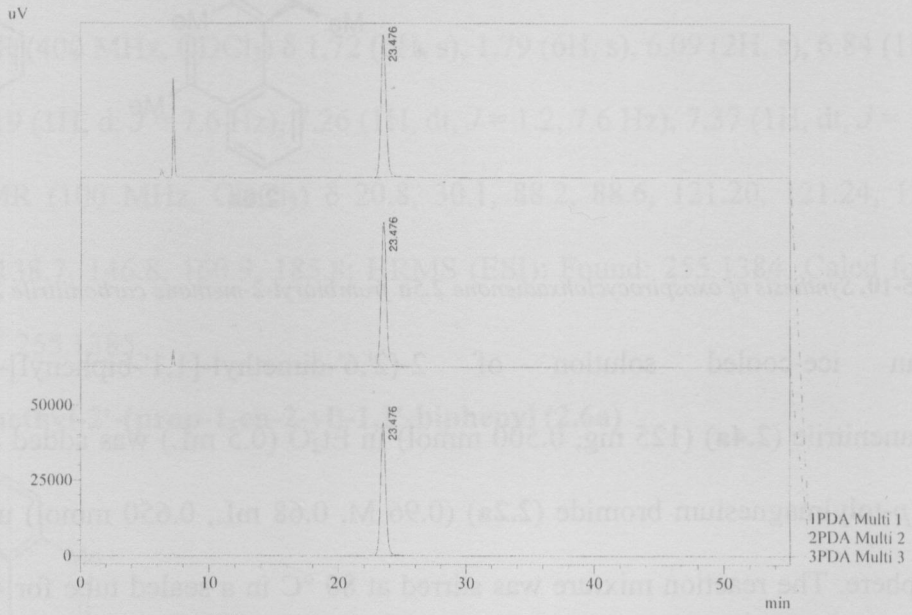
HPLC analysis chart of (+)-3-(*p*-tolyl)-4'*H*-spiro[benzo[*e*]isoindole-1,1'-naphthalen]-4'-one [(+)-2.3qa]

==== Shimadzu LCsolution Analysis Report ====

C:\Documents and Settings\User\Desktop\Yalin\azaspiro\Yalin-C2052.lcd

Acquired by	: Admin	<<Pump>>	
Sample Name	: Yalin-C2052	Pump Mode	: Low pressure gradient
Sample ID	: Yalin-C2052	Pump A	: LC-20AD
Tray#	: 1	Total Flow	: 0.5000 mL/min
Vail #	: 26	B.Conc	: 10.0 %
Injection Volume	: 0.2 uL	C.Conc	: 0.0 %
Data File Name	: Yalin-C2052.lcd	D.Conc	: 0.0 %
Method File Name	: 5 membered CN SO2Ph try.lcm		
Batch File Name	:		
Data Acquired	: 4/3/2012 4:55:22 PM		

<Chromatogram>



PeakTable

PDA Ch1 210nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	23.476	1314539	46920	100.000
Total		1314539	46920	100.000

PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	23.476	1356697	47943	100.000
Total		1356697	47943	100.000

PDA Ch3 230nm 4nm

Peak#	Ret. Time	Area	Height	Area %
1	23.476	1250624	44181	100.000
Total		1250624	44181	100.000

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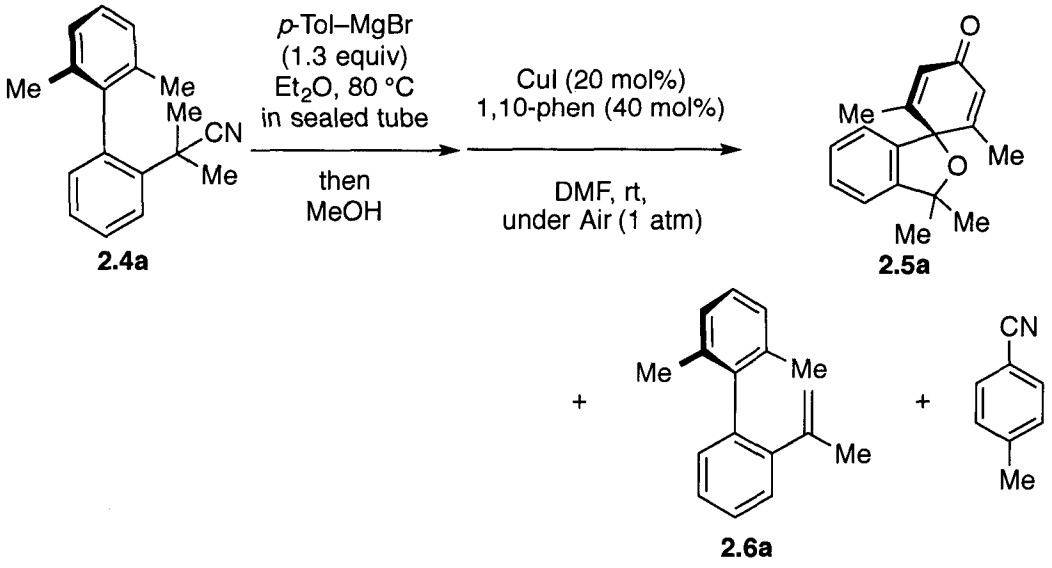
5.2.6 Synthesis of oxospirocyclohexadienones derivatives

A typical procedure for synthesis of 2,3',3',6-tetramethyl-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran]-2,5-dien-4-one (2.5a)

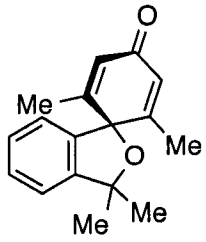


Scheme 5-10. *Synthesis of oxospirocyclohxadienone **2.5a** from biaryl-2-methane carboniitrile **2.4a**.*

To an ice-cooled solution of 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)-2-methylpropanenitrile (**2.4a**) (125 mg, 0.500 mmol) in Et_2O (0.5 mL) was added an Et_2O solution of *p*-tolylmagnesium bromide (**2.2a**) (0.96 M, 0.68 mL, 0.650 mmol) under an inert atmosphere. The reaction mixture was stirred at 80 °C in a sealed tube for 4 h, and then anhydrous methanol (60 μL) was added at 0 °C. CuI (19.1 mg, 0.100 mmol), 1,10-phenanthroline (36 mg, 0.200 mmol) and anhydrous DMF (5 mL) were then added. The reaction mixture was stirred at room temperatures under an air atmosphere. Upon completion, the reaction was quenched by addition of pH 9 buffer solution and organic materials were extracted with EtOAc twice. The combined organic extracts were washed with water and brine, and then dried over $MgSO_4$. After removal of the solvents, the resulting crude material was purified by flash column chromatography (from hexane : EtOAc = 100 : 0 to hexane : EtOAc = 90 : 10) to give 2,3',3',6-tetramethyl-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran]-2,5-dien-4-one **(2.5a)** (58.5 mg, 0.229 mmol) and

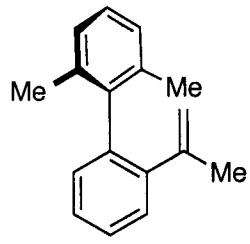
2,6-dimethyl-2'-(prop-1-en-2-yl)-1,1'-biphenyl (**2.6a**) (30.9 mg, 0.139 mmol) in 46% and 28% yield, respectively.

2,3',3',6-tetramethyl-3'*H*-spiro[cyclohexane-1,1'-isobenzofuran]-2,5-dien-4-one (2.5a)



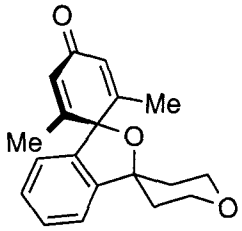
White solid, mp 135-137 °C; IR (NaCl): 3072, 2976, 1670, 1627, 1377, 1008, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (6H, s), 1.79 (6H, s), 6.09 (2H, s), 6.84 (1H, d, J = 8.0 Hz), 7.19 (1H, d, J = 7.6 Hz), 7.26 (1H, dt, J = 1.2, 7.6 Hz), 7.37 (1H, dt, J = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 30.1, 88.2, 88.6, 121.20, 121.24, 126.1, 128.4, 129.2, 138.7, 146.8, 160.9, 185.8; HRMS (ESI): Found: 255.1384. Calcd for $C_{17}H_{19}O_2$: $(M+H)^+$ 255.1385.

2,6-dimethyl-2'-(prop-1-en-2-yl)-1,1'-biphenyl (2.6a)



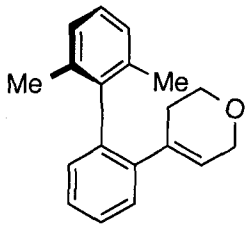
Colourless oil; IR (NaCl): 3059, 2953, 2920, 1629, 1462, 1375, 1002, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.69 (3H, s), 2.02 (6H, s), 4.82 (1H, d, J = 1.2 Hz), 4.94-4.94 (1H, m), 7.05-7.10 (3H, m), 7.16 (1H, dd, J = 6.4, 8.0 Hz), 7.31-7.38 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 22.6, 115.3, 126.9, 127.0, 127.1, 127.2, 128.7, 129.9, 136.2, 138.4, 141.4, 142.6, 145.9; HRMS (ESI): Found: 223.1488. Calcd for $C_{17}H_{19}$: $(M+H)^+$ 223.1487.

2,6-dimethyl-2'',3'',5'',6''-tetrahydrodispiro[cyclohexane-1,1'-isobenzofuran-3',4''-pyran]-2,5-dien-4-one (2.5b)



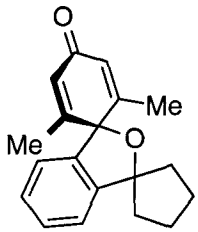
Yellow solid; mp 193-195 °C; IR (NaCl): 3072, 2972, 2866, 1670, 1629, 1429, 1377, 1008, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.77 (6H, s), 2.02-2.21 (4H, m), 3.97-4.00 (4H, m), 6.12 (2H, s), 6.87 (1H, d, J = 7.6 Hz), 7.24 (1H, d, J = 7.6 Hz), 7.30 (1H, t, J = 7.2 Hz), 7.38 (1H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 38.5, 64.1, 86.6, 88.9, 121.5, 121.6, 126.3, 129.0, 129.4, 139.1, 145.0, 160.5, 185.7; HRMS (ESI): Found: 297.1490. Calcd for $C_{19}H_{21}O_3$: $(M+H)^+$ 297.1491.

4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)-3,6-dihydro-2H-pyran (2.6b)



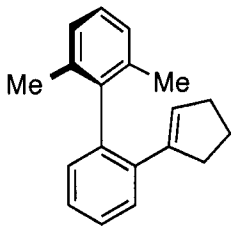
Pale yellow solid; mp 83-84 °C; IR (NaCl): 3059, 2964, 1608, 1462, 1130, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.93-1.96 (2H, m), 1.98 (6H, s), 3.57 (2H, t, J = 5.2 Hz), 4.10 (2H, dd, J = 2.8, 5.2 Hz), 5.52 (1H, s), 7.03-7.06 (3H, m), 7.13 (1H, dd, J = 6.8, 8.4 Hz), 7.29-7.33 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 28.1, 64.3, 65.6, 124.8, 127.0, 127.1, 127.2, 127.3, 128.4, 130.1, 135.0, 136.5, 138.5, 141.1, 141.3; HRMS (ESI) Found: 265.1593. Calcd for $C_{19}H_{21}O$: $(M+H^+)$ 265.1592.

2,6-dimethyldispiro[cyclohexane-1,1'-isobenzofuran-3',1''-cyclopentane]-2,5-dien-4-one (2.5c)



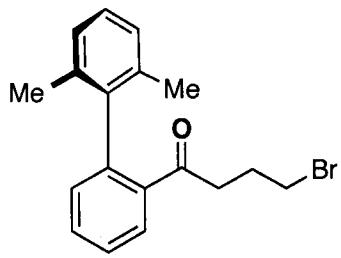
Pale yellow solid; mp 136-137 °C; IR (NaCl): 2960, 2872, 1670, 1627, 1377, 1010, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (6H, s), 1.85-2.11 (6H, m), 2.32-2.39 (2H, m), 6.08 (2H, s), 6.82 (1H, d, J = 7.6 Hz), 7.21-7.28 (2H, m), 7.36 (1H, dt, J = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 25.1, 42.5, 88.4, 98.1, 120.8, 121.1, 125.9, 128.2, 129.3, 138.8, 146.9, 160.8, 185.9; HRMS (ESI): Found: 281.1544. Calcd for $C_{19}H_{21}O_2$: $(M+H)^+$ 281.1542.

2'-(cyclopent-1-en-1-yl)-2,6-dimethyl-1,1'-biphenyl (2.6c)



Colourless oil; IR (NaCl): 2953, 2922, 1685, 1462, 1440, 1004, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72-1.76 (2H, m), 1.95 (6H, s), 2.22-2.28 (4H, m), 5.31 (1H, t, J = 2.0 Hz), 7.04 (1H, dd, J = 1.6, 7.2 Hz), 7.08-7.01 (2H, m), 7.16 (1H, dd, J = 6.8, 8.4 Hz), 7.27-7.34 (2H, m), 7.43 (1H, dd, J = 1.6, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 23.6, 33.4, 34.8, 126.7, 126.8, 126.9, 127.2, 128.2, 129.1, 129.9, 136.0, 136.7, 138.7, 142.1, 142.7; HRMS (ESI): Found: 249.1646. Calcd for $C_{19}H_{21}$: $(M+H)^+$ 249.1643.

4-bromo-1-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)butan-1-one (2.7)

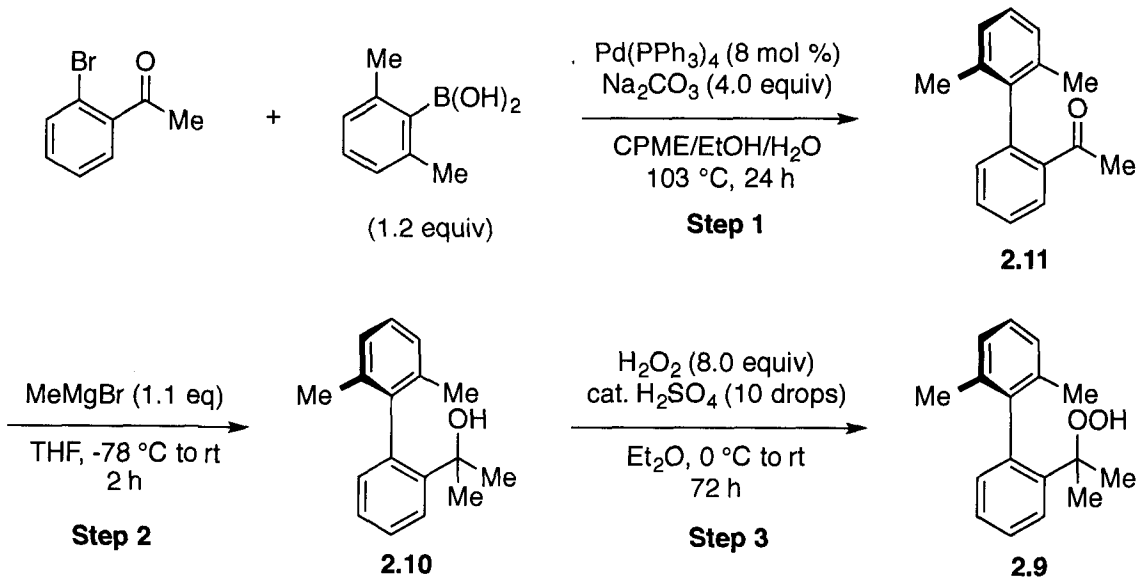


Colourless oil; IR (NaCl): 3053, 2983, 1683, 1463, 1265, 908, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95-201 (2H, m), 1.98 (6H, s), 2.53 (2H, t, J = 6.8 Hz), 3.23 (1H, t, J = 6.4 Hz), 7.09-7.21 (4H, m), 7.44 (1H, dt, J = 0.8, 7.6 Hz), 7.54 (1H, dt, J = 1.2, 7.6 Hz), 7.72 (1H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 26.8, 33.2, 39.3, 127.4,

127.5, 127.7, 128.3, 130.5, 131.5, 135.7, 139.3, 139.4, 140.2, 203.2; HRMS (ESI) Found: 331.698. Calcd for $C_{18}H_{20}O^{79}Br$: $(M+H)^+$ 331.0698.

5.2.7 Synthesis of oxospirocyclohexadienone 2.5a from biaryl hydroperoxide 2.9

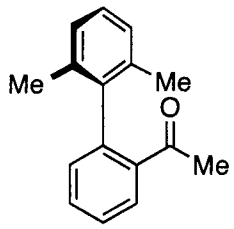
5.2.7.1 Synthesis of biaryl hydroperoxide 2.9



Scheme 5-11. *Preparation of biaryl hydroperoxide* ***2.9***

Step 1: Preparation of 1-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)ethan-1-one (2.11):

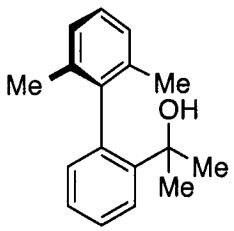
A mixture of 2-bromobenzaldehyde (2.98 g, 15.0 mmol), 2,6-dimethylphenyl)boronic acid (2.70 g, 18.0 mmol), 2 M aqueous solution of Na_2CO_3 (30 mL, 60.0 mmol) with EtOH (10 mL), and $Pd(PPh_3)_4$ (1.38 g, 1.2 mmol) in cyclopentyl methyl ether (CPME) (20 mL) was stirred at reflux under an inert atmosphere for 24 h. The reaction mixture was cooled to room temperature, and the solvents were removed in *vacuo*. The organic materials were then extracted with a mixture of Et_2O-H_2O (1:1). The organic extract was washed with 5% aqueous NaOH followed by water and brine. After drying with $MgSO_4$, the solution was concentrated in *vacuo* to yield the crude residue, which was purified by flash column chromatography (hexane : EtOAc = 98 : 2) to afford 1-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)ethan-1-one (**2.11**) (2.86 g, 12.7 mmol) in 85% yield.



Pale yellow oil; IR (NaCl) 3061, 2920, 1681, 1462, 1354, 1276, 1244, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.98 (6H, s), 1.99, (3H, s), 7.10 (2H, d, J = 7.6 Hz), 7.20-7.14 (1H, dd, J = 1.2, 7.6 Hz), 7.19 (1H, dd, J = 6.8 Hz), 7.43 (1H, dt, J = 1.2, 7.6 Hz), 7.54 (1H, dt, J = 1.6, 7.6 Hz), 7.77 (1H, dd, J = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 29.2, 127.3, 127.5, 127.6, 128.7, 130.4, 131.6, 135.7, 139.4, 139.7, 140.5, 202.1; HRMS (ESI): Found: 225.1282. Calcd for $C_{16}H_{17}O$: $(M+H)^+$ 225.1279.

Step 2: Preparation of 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)propan-2-ol (2.10):

Methylmagnesium bromide (3.7 mL, 11.0 mmol, 3.0 M in Et_2O) was dropped into a solution of 1-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)ethan-1-one (**2.11**) (2.24 g, 10.0 mmol) in Et_2O (25 mL) at -78 °C under an inert atmosphere. The mixture was then allowed to warm to room temperature and left to be stirred for 1 h. The reaction mixture was quenched with 1 M HCl and organic materials were extracted thrice with Et_2O. The combined organic extracts were washed with brine and dried over $MgSO_4$ Concentration of the solution in *vacuo* yield the crude residue, which was purified by flash column chromatography (hexane : EtOAc = 98 : 2) to afford 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)propan-2-ol (**2.10**) (2.11 g, 8.77 mmol) in 88% yield.

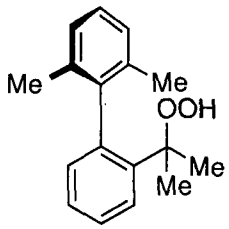


White solid; mp 81-82 °C; IR (NaCl) 3566, 3061, 2978, 1460, 1436, 1328, 954, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (6H, s), 1.79 (1H, s), 2.02 (6H, s), 6.89 (1H, dd, J =

1.2, 7.2 Hz), 7.08-711 (2H, m), 7.17 (1H, dd, J = 6.8, 8.4 Hz), 7.27 (1H, dt, J = 1.6, 7.6 Hz), 7.34 (1H, dt, J = 1.6, 7.6 Hz), 7.53 (1H, dd, J = 1.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2. 32.0, 74.3, 126.88, 126.90, 127.2, 127.3, 127.4, 131.0, 136.3, 137.2, 142.2, 145.5; HRMS (ESI): Found: 241.1589. Calcd for $C_{17}H_{21}O$: $(M+H)^+$ 241.1592.

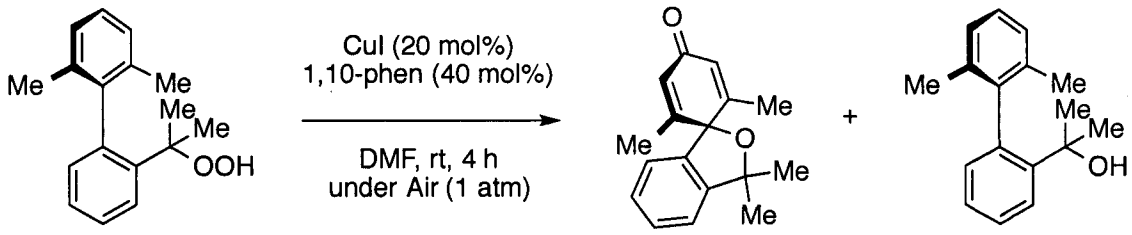
Step 3: Preparation of 2'-(2-hydroperoxypropan-2-yl)-2,6-dimethyl-1,1'-biphenyl (2.9)

To a cooled solution of 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)propan-2-ol (**2.10**) (2.10 g, 8.70 mmol) in Et_2O (3 ml) was added H_2O_2 (6.0 mL, 69.6 mmol, 35% by wt. in H_2O) and concentrated H_2SO_4 (10 drops). The reaction mixture was allowed to warm to room temperature and left to be stirred for 72 h. The reaction was quenched with water and organic materials were extracted thrice with Et_2O. The combined organic extracts were washed twice with water and once with brine. After drying over $MgSO_4$, the solution was concentrated in vacuo and the crude was purified by flash column chromatography (hexane : EtOAc = 95 : 5) to afford 2'-(2-hydroperoxypropan-2-yl)-2,6-dimethyl-1,1'-biphenyl (**2.9**) (0.66 g, 2.59 mmol) in 30% yield.



White solid; mp 105-106 °C; IR (NaCl) 3444, 3059, 2989, 2941, 1463, 1379, 1147, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (6H, s), 1.98 (6H, s), 6.95 (1H, dd, J = 1.2, 7.6 Hz), 7.06-7.8 (2H, m), 7.16 (1H, dd, J = 6.8, 8.0 Hz), 7.23 (1H, brs), 7.32 (1H, dt, J = 1.2, 7.6 Hz), 7.42 (1H, dt, J = 1.6, 7.2 Hz), 7.76 (1H, dd, J = 1.2, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 26.7, 85.7, 127.10, 127.12, 127.5, 127.6, 127.7, 131.4, 136.0, 139.1, 141.8, 142.7; HRMS (ESI): Found: 257.1543. Calcd for $C_{17}H_{21}O_2$: $(M+H)^+$ 257.1542.

5.2.7.2 Synthesis of oxospirocyclohexadienone 2.5a



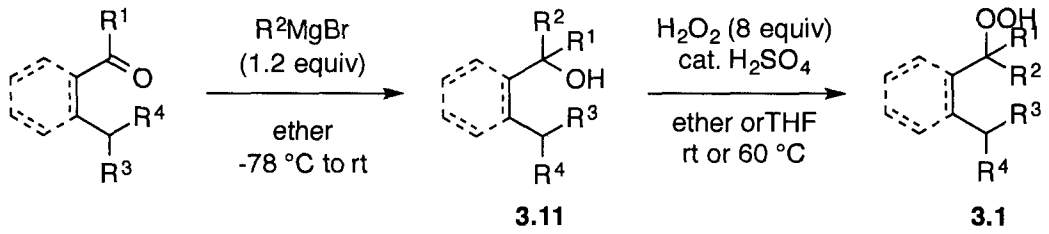
2.9 **2.5a** 24% **2.10** 25%

Scheme 5-12. *The reaction of biaryl hydroperoxide* ***2.9***

To a solution of 2'-(2-hydroperoxypropan-2-yl)-2,6-dimethyl-1,1'-biphenyl (**2.9**) (66.7 mg, 0.260 mmol) in DMF (3 mL) was added CuI (9.9 mg, 0.052 mmol), 1,10-phenanthroline (18.7 mg, 0.104 mmol). The reaction mixture was allowed to stir at room temperature under ambient air. Upon consumption of **2.9** judged by TLC analysis, the reaction mixture was quenched with pH 9 buffer and organic material was extracted thrice with EtOAc. Combined organic extracts were washed twice with water and once with brine. After drying with $MgSO_4$, the solution was concentrated in *vacuo* and the crude mixture was purified by flash column chromatography (hexane : EtOAc = 95 : 5) to afford 2,3',3',6-tetramethyl-3'H-spiro[cyclohexane-1,1'-isobenzofuran]-2,5-dien-4-one (**2.5a**) (15.8 mg, 0.062 mmol) in 24% yield, and 2-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)propan-2-ol (**2.10**) (15.6 g, 0.065 mmol) in 25% yield.

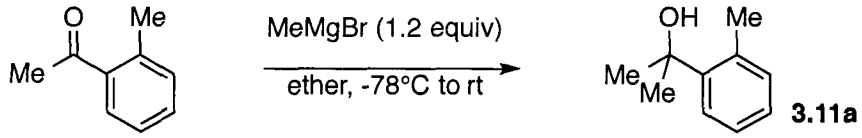
5.3. Experimental data for Chapter 3

5.3.1. Synthesis of alkyl hydroperoxide derivatives 3.1



Scheme 5-13. *A general scheme for the preparation of tertiary hyroperoxides **3.1**.*

5.3.1.1. Preparation of alkyl alcohols 3.11a–3.11s:

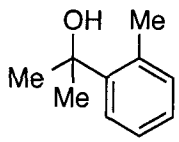


Scheme 5-14. *Synthesis of 2-(o-tolyl)propan-2-ol (**3.11a**).*

A typical procedure for the synthesis of 2-(o-tolyl)propan-2-ol (3.11a)

To a solution of 1-(2-methylphenyl)ethanone (2.01g, 15.0 mmol) in anhydrous diethyl ether (15 mL) was added 5.5 mL of MeMgBr (3.0 M in ether; 1.97g, 16.5 mmol) dropwise at −78 °C. The reaction was then allowed to warm up to room temperature and stirred for 1 h. After completion, the reaction was quenched with 1 N aqueous HCl at 0 °C and the organic materials were extracted twice with diethyl ether. The combined extracts were washed with brine, and dried over $MgSO_4$. Volatile materials were removed in *vacuo* and the crude material was purified by flash column chromatography (hexane : EtOAc = 90 : 10) to give 2-(o-tolyl)propan-2-ol (**3.11a**) (1.94 g, 12.9 mmol) in 86% yield

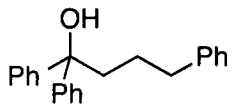
2-(o-tolyl)propan-2-ol (3.11a)[16]



White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (6H, s), 1.78 (1H, s), 2.58 (3H, s), 7.12-7.16 (3H, m), 7.41-7.46 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 30.8, 73.6, 125.2,

125.6, 127.0, 132.6, 135.9, 145.7.

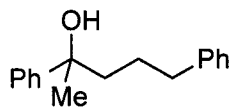
1,1,4-Triphenylbutan-1-ol (3.11b)[17]



Prepared from benzophenone and $Ph(CH_2)_3MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 42% yield.

White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 1.58-1.68 (2H, m), 2.06 (1H, brs), 2.26-2.33 (2H, m), 2.62 (2H, t, J = 7.6 Hz), 7.10-7.25 (7H, m), 7.28 (4H, dd, J = 7.6, 8.0 Hz), 7.36 (4H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 36.0, 41.3, 78.2, 125.7, 126.0, 126.8, 128.1, 128.3, 128.4, 142.1, 147.0.

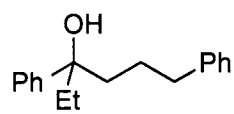
2,5-Diphenylpentan-2-ol (3.11c)



Prepared from 1-phenylethanone and $Ph(CH_2)_3MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 94% yield.

Colorless oil; IR (NaCl) 910, 1030, 1101, 1373, 1447, 1495, 1601, 2941, 2972, 3026, 3418 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40-1.55 (1H, m), 1.53 (3H, s), 1.55-1.68 (1H, m), 1.78-1.90 (2H, m), 2.55 (2H, t, J = 7.6 Hz), 7.10 (2H, d, J = 7.2 Hz), 7.15 (1H, dd, J = 7.2, 7.6 Hz), 7.19-7.26 (3H, m), 7.32 (2H, ddd, J = 2.0, 7.6, 8.0 Hz), 7.39 (2H, dd, J = 1.2, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 30.2, 36.0, 43.6, 74.6, 124.7, 125.7, 126.5, 128.1, 128.2, 128.4, 142.2, 147.8; HRMS (ESI): Found: m/z 241.1590. Calcd for $C17H_{21}O$: $(M+H)^+$ 241.1592.

3,6-Diphenylhexan-3-ol (3.11d)

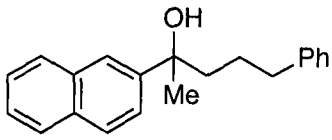


Prepared from propiophenone and $Ph(CH_2)_3MgBr$ and purified by flash column

chromatography (hexane : EtOAc = 90 : 10) in quantitative yield;

Colorless oil; IR (NaCl) 953, 1030, 1447, 1454, 1495, 1603, 2938, 2967, 3024, 3470 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (3H, t, J = 7.6 Hz), 1.33-1.45 (1H, m), 1.57-1.70 (2H, m), 1.74-1.91 (4H, m), 2.48-2.61 (2H, m), 7.09 (2H, dd, J = 1.2, 8.0 Hz), 7.14 (1H, dd, J = 7.2, 7.6 Hz), 7.18-7.26 (3H, m), 7.28-7.35 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 25.2, 35.4, 36.1, 42.1, 77.1, 125.3, 125.7, 126.3, 128.0, 128.2, 128.3, 142.2, 145.8; HRMS (ESI): Found: m/z 255.1759. Calcd for $C_{18}H_{23}O$: $(M+H)^+$ 255.1749.

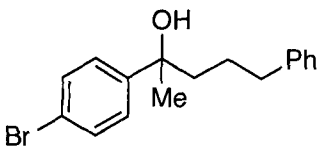
2-(Naphthalen-2-yl)-5-phenylpentan-2-ol (3.11e)



Prepared from 1-(2-naphthyl)ethanone and $Ph(CH_2)_3MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 90% yield.

Colorless oil; IR (NaCl) 1123, 1273, 1371, 1454, 1495, 1504, 1601, 2860, 2940, 2970, 3389 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41-1.53 (1H, m), 1.58-1.70 (1H, m), 1.62 (3H, s), 1.84 (1H, brs), 1.92 (2H, dtt, J = 1.2, 11.6, 14.0 Hz), 2.55 (2H, ddd, J = 2.0, 7.0, 8.2 Hz), 7.08 (2H, d, J = 7.2 Hz), 7.14 (1H, ddd, J = 1.2, 7.2, 7.6 Hz), 7.18-7.25 (2H, m), 7.41-7.50 (3H, m), 7.77-7.84 (3H, m), 7.85 (1H, d, J = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 30.3, 36.0, 43.4, 74.8, 123.1, 123.6, 125.6, 125.7, 126.0, 127.4, 127.8, 128.1, 128.2, 128.4, 132.2, 133.1, 142.1, 145.1; HRMS (ESI): Found: m/z 291.1754. Calcd for $C_{21}H_{23}O$: $(M+H)^+$ 291.1749.

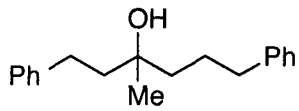
2-(4-Bromophenyl)-5-phenylpentan-2-ol (3.11f)



Prepared from 1-(4-bromophenyl)ethanone and $Ph(CH_2)_3MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 91% yield.

Colorless oil; IR (NaCl) 1395, 1452, 1487, 1495, 1591, 1603, 2860, 2941, 2972, 3416 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39-1.50 (1H, m), 1.51 (3H, s), 1.55-1.67 (2H, m), 1.80 (2H, dtt, J = 5.6, 10.8, 11.2 Hz); 2.55 (2H, ddd, J = 2.4, 6.4, 8.8 Hz), 7.10 (2H, d, J = 6.8 Hz), 7.16 (1H, dd, J = 7.2, 7.6 Hz), 7.23-7.28 (4H, m), 7.43 (2H, td, J = 2.4, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 30.3, 35.9, 43.5, 74.4, 120.4, 125.8, 126.7, 128.27, 128.34, 131.1, 142.0, 146.8; HRMS (ESI): Found: m/z 319.0695. Calcd for $C_{17}H_{20}O^{79}Br$: $(M+H)^+$ 319.0698.

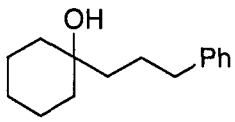
3-Methyl-1,6-diphenylhexan-3-ol (3.11g)



Prepared from 4-phenylbutan-2-one and $Ph(CH_2)_3MgBr$ and purified by flash column chromatography (hexane : EtOAC = 90 : 10) in 99% yield.

Colorless oil; IR (NaCl) 910, 1373, 1454, 1495, 1603, 2862, 2940, 3026, 3406 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.22 (3H, s), 1.52-1.57 (2H, m), 1.64-1.78 (4H, m), 2.59-2.66 (4H, m), 7.14-7.21 (6H, m), 7.24-7.31 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.9, 30.3, 36.3, 41.5, 43.7, 72.6, 125.7, 125.8, 128.29, 128.31, 128.4, 142.3, 142.5; HRMS (ESI): Found: m/z 269.1901. Calcd for $C_{19}H_{25}O$: $(M+H)^+$ 269.1905.

1-(3-Phenylpropyl)cyclohexanol (3.11h)

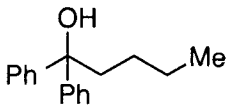


Prepared from cyclohexanone and $Ph(CH_2)_3MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 81% yield.

Colorless oil; IR (NaCl) 968, 1171, 1256, 1454, 1495, 1603, 1697, 2857, 2932, 3404 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36-1.60 (12H, m), 1.66-1.74 (2H, m), 2.61 (2H, t, J = 7.6 Hz), 7.18 (1H, t, J = 8.0 Hz), 7.19 (2H, d, J = 7.6 Hz), 7.27 (2H, dd, J = 7.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 24.8, 25.8, 36.4, 37.4, 42.0, 71.4, 125.7, 128.2,

128.4, 142.5; HRMS (ESI): Found: m/z 219.1752. Calcd for $C_{15}H_{23}O$: $(M+H)^+$ 219.1749.

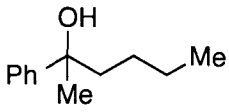
1,1-Diphenylpentan-1-ol (3.11i)[18]



Prepared from benzophenone and *n*-BuLi (1.6 M in hexanes) and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 48% yield

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 7.2 Hz), 1.20-1.30 (2H, m), 1.30-1.40 (2H, m), 2.10 (1H, s), 2.27 (2H, t, *J* = 8.0 Hz), 7.21 (2H, dd, *J* = 6.8, 7.6 Hz), 7.30 (4H, dd, *J* = 7.2, 8.0 Hz), 7.41 (4H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 23.1, 25.9, 41.7, 78.2, 126.0, 126.7, 128.1, 147.2.

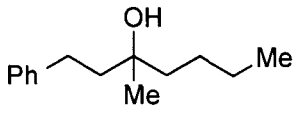
2-Phenylhexan-2-ol (3.11j)[19]



Prepared from 2-hexanone and PhMgBr and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in quantitative yield.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, t, J = 7.2 Hz), 1.06-1.17 (1H, m), 1.18-1.31 (3H, m), 1.55 (3H, s), 1.74 (1H, s), 1.75-1.88 (2H, m), 7.23 (1H, d, *J* = 7.2, 7.6 Hz), 7.33 (2H, dd, *J* = 7.2, 8.0 Hz), 7.43 (2H, dd, *J* = 1.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 23.0, 26.1, 30.1, 43.9, 74.7, 124.8, 126.4, 128.1, 148.1.

3-Methyl-1-phenylheptan-3-ol (3.11k)[20]

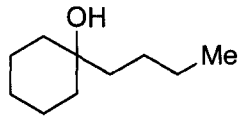


Prepared from 2-hexanone and $Ph(CH_2)_3MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in quantitative yield.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.2 Hz), 1.24 (3H, s), 1.25 (1H, s), 1.30-1.39 (4H, m), 1.48-1.56 (2H, m), 1.73-1.80 (2H, m), 2.64-2.70 (2H, m),

7.16-7.22 (3H, m), 7.28 (2H, ddd, J = 1.6, 7.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 23.3, 26.2, 26.9, 30.3, 41.8, 43.7, 72.7, 125.7, 128.3, 128.4, 142.6.

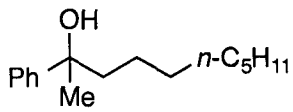
1-Butylcyclohexanol (3.11l)[21]



Prepared from cyclohexanone and *n*-BuLi (1.6 M in hexanes) and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 90% yield.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.2 Hz), 1.20-1.37 (6H, m), 1.37-1.60 (11H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.3, 23.3, 25.1, 25.9, 37.4, 42.2, 71.4.

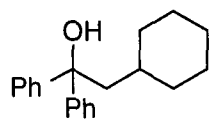
2-Phenyldecan-2-ol (3.11m)[21]



Prepared from 1-phenylethanone and $CH_3(CH_2)_7MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 98% yield.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 6.8 Hz), 1.08-1.18 (1H, m), 1.18-1.30 (11H, m), 1.55 (3H, s), 1.75 (1H, s), 1.72-1.84 (2H, m), 7.23 (1H, tt, J = 1.2, 7.6 Hz), 7.33 (2H, dt, J = 1.6, 7.6 Hz), 7.42 (2H, dd, J = 1.2, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 23.9, 29.2, 29.5, 29.9 30.1, 31.8, 44.2, 74.7, 124.7, 126.4, 128.1, 148.1.

2-Cyclohexyl-1,1-diphenylethanol (3.11n)

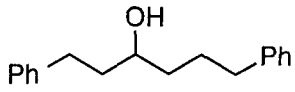


Prepared from ethyl 2-cyclohexylacetate and PhMgBr (2.2 equiv) and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in quantitative yield.

Colorless oil; IR (NaCl) 1032, 1059, 1447, 1493, 1599, 2849, 2922, 3445 (brs) cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 0.90-1.05 (2H, m), 1.05-1.20 (3H, m), 1.38-1.48 (1H, m), 1.48-1.62 (5H, m), 2.03 (1H, s), 2.21 (2H, d, J = 5.2 Hz), 7.20 (2H, t, J = 7.2 Hz), 7.29 (4H, dd, J = 7.2, 8.0 Hz), 7.41 (4H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 26.3, 33.5, 35.2, 49.2, 78.8, 126.0, 126.6, 128.0, 147.7; HRMS (ESI): Found: m/z 281.1911. Calcd for $C_{20}H_{25}O$: $(M+H)^+$ 281.1905.

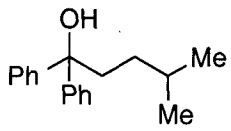
1,6-Diphenylhexan-3-ol (3.11o)



Prepared from 3-phenylpropanal and $Ph(CH_2)_3MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 95% yield.

White solid; mp 37–38 °C; IR (NaCl) 1454, 1495, 1603, 2860, 2938, 3015, 3429 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (1H, brs), 1.47-1.57 (2H, m), 1.57-1.82 (4H, m), 2.55-2.67 (3H, m), 2.76 (1H, ddd, J = 5.6, 9.6, 13.6 Hz), 3.57-3.65 (1H, m), 7.12-7.22 (6H, m), 7.22-7.30 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 32.0, 35.8, 37.0, 39.0, 71.1, 125.7, 125.8, 128.26, 128.35 (overlapped×2), 142.1, 142.3; HRMS (ESI): Found: m/z 255.1754. Calcd for $C_{18}H_{23}O$: $(M+H)^+$ 255.1749.

4-Methyl-1,1-diphenylpentan-1-ol (3.11p)

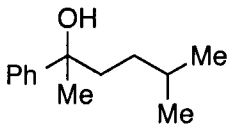


Prepared from benzophenone and $(CH_3)_2CH(CH_2)_2MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 29% yield.

White solid; mp 49–50 °C; IR (NaCl) 1032, 1165, 1447, 1599, 1653, 2868, 2953, 3472 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (6H, d, J = 6.4 Hz), 1.14-1.20 (2H, m), 1.50-1.60 (1H, m), 2.11 (1H, s), 2.25-2.30 (2H, m), 7.21 (2H, tt, J = 1.2, 7.6 Hz), 7.29 (4H, ddd, J = 2.0, 6.4, 7.6 Hz), 7.38-7.43 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 28.4, 32.6, 39.8, 78.2, 126.0, 126.7, 128.1, 147.1; HRMS (ESI): Found: m/z 255.1754.

Calcd for $C_{18}H_{23}O$: $(M+H)^+$ 255.1749.

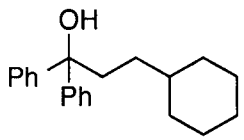
5-Methyl-2-phenylhexan-2-ol (3.11q)[22]



Prepared from 1-phenylethanone and $(CH_3)_2CH(CH_2)_2MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in quantitative yield.

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, d, J = 6.4 Hz), 0.84 (3H, d, J = 6.4 Hz), 0.96-1.07 (1H, m), 1.10-1.20 (1H, m), 1.40-1.51 (1H, m), 1.55 (3H, s), 1.73-1.87 (2H, m), 1.76 (1H, s), 7.23 (1H, tt, J = 1.6, 7.6 Hz), 7.33 (2H, dt, J = 1.6, 8.0 Hz), 7.42 (2H, dd, J = 1.6, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 22.6, 28.3, 30.2, 32.8, 41.9, 74.7, 124.8, 126.4, 128.1, 148.1.

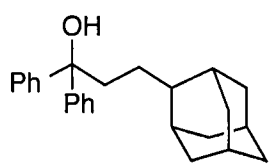
3-Cyclohexyl-1,1-diphenylpropan-1-ol (3.11r)



Prepared from benzophenone and $Cy(CH_2)_2MgBr$ and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 28% yield.

White solid; mp 61–62 °C; IR (NaCl) 1279, 1319, 1447, 1493, 1655, 2849, 2922, 3472 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80-0.90 (2H, m), 1.08-1.27 (7H, m), 1.60-1.73 (4H, m), 2.13 (1H, brs), 2.25-2.31 (2H, m), 7.20 (2H, dd, J = 6.8, 7.2 Hz), 7.29 (4H, dd, J = 7.2, 7.6 Hz), 7.40 (4H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 26.6, 31.2, 33.3, 38.1, 39.3, 78.3, 126.0, 126.7, 128.1, 147.2; HRMS (ESI): Found: m/z 295.2061. Calcd for $C_{21}H_{27}O$: $(M+H)^+$ 295.2062.

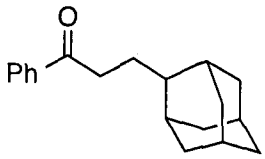
3-(Adamantan-2-yl)-1,1-diphenylpropan-1-ol (3.11s)



Prepared from 3-(adamantan-2-yl)-1-phenylpropan-1-one (see below) and PhMgBr and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 94% yield.

White solid; mp 114–115 °C; IR (NaCl) 1031, 1057, 1447, 1493, 1597, 2849, 2905, 3447 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38-1.46 (4H, m), 1.62 (1H, t, J = 7.2 Hz), 1.66-1.76 (9H, m), 1.78.1.87 (3H, m), 2.14 (1H, s), 2.23-2.28 (2H, m), 7.21 (2H, tt, J = 1.2, 7.2 Hz), 7.30 (4H, ddd, J = 2.0, 6.4, 7.2 Hz), 7.40-7.45 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 28.0, 28.3, 31.6, 31.9, 38.4, 39.2, 40.2, 44.8, 78.3, 126.0, 126.7, 128.1, 147.2; HRMS (ESI): Found: m/z 347.2373. Calcd for $C_{25}H_{31}O$: $(M+H)^+$ 347.2375.

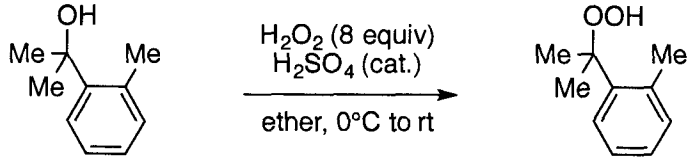
3-(Adamantan-2-yl)-1-phenylpropan-1-one



Prepared from (2-(adamantan-2-yl)ethyl)magnesium bromide and benzonitrile in THF and followed by hydrolysis with 1 mL HCl at reflux temperature for 2 days.

White solid; mp 109–111 °C; IR (NaCl) 1447, 1580, 1597, 1682, 2849, 2899 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (2H, d, J = 12.4 Hz), 1.68-1.79 (7H, m), 1.79-1.95 (8H, m), 2.96 (2H, t, J = 8.0 Hz), 7.46 (2H, dt, J = 1.2, 6.4 Hz), 7.55 (1H, tt, J = 1.6, 7.2 Hz), 7.95-8.00 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 28.0, 28.3, 31.6, 31.9, 37.0, 38.3, 39.2, 44.3, 128.1, 128.5, 132.8, 137.1, 200.9; HRMS (ESI): Found: m/z 269.1919. Calcd for $C_{19}H_{25}O$: $(M+H)^+$ 269.1905.

5.3.1.2 Preparation of 2-(o-tolyl)propyl 2-hydroperoxide (3.1a)



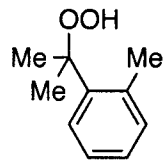
3.11a **3.1a**

Scheme 5-15. *Synthesis of 2-(o-tolyl)propyl-2-hydroperoxide (**3.1a**).*

To a stirred solution of 2-(o-tolyl)propan-2-ol (**3.11a**) (1.94 g, 12.9 mmol) in 3

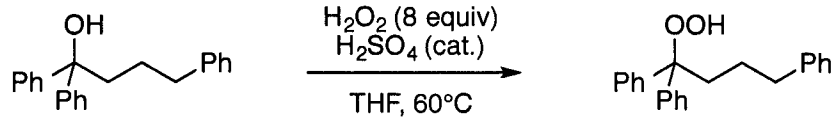
mL of diethyl ether at 0 °C was added 11.7 mL of H_2O_2 (30 wt % in H_2O; 3.51 g, 103.2 mmol) and 13 drops of H_2SO_4 (conc) dropwise. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched with water and the organic materials were extracted three times with diethyl ether. The combined extracts were washed with H_2O (3 times) and dried over $MgSO_4$. Volatile materials were removed in *vacuo* and the crude material was purified by flash column chromatography (hexane : EtOAc = 90 : 10) to give hydroperoxide **3.1a** (1.72 g, 10.3 mmol) in 80% yield.

2-(o-Tolyl)propyl 2-hydroperoxide (3.1a)[23]



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (6H, s), 2.58 (3H, s), 7.16-7.20 (3H m), 7.31 (1H, s), 7.34-7.38 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 26.1, 85.5, 125.9, 126.9, 127.6, 132.8, 136.0, 141.5.

5.3.1.3 Preparation of alkyl peroxides 3.1b–3.1n, 3.1p–3.1s



3.11b **3.1b**

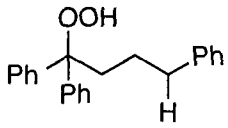
Scheme 5-16. *Typical procedure for synthesis of 1,1,4-triphenylbutyl 1-hydroperoxide (**3.1b**).*

A typical procedure for the synthesis of 1,1,4-triphenylbutyl 1-hydroperoxide (3.1b)

To a stirred solution of 1,1,4-triphenylbutan-1-ol (**3.11b**) (2.54 g, 8.4 mmol) in 3 mL of THF at 0 °C was added 7.6 mL of H_2O_2 (30 wt % in H_2O; 2.29 g, 67.2 mmol) and 8 drops of H_2SO_4 (conc) dropwise. The reaction mixture was stirred at 60 °C for 24 h. The reaction was quenched with H_2O and the organic materials were extracted three times with diethyl ether. The combined extracts were washed with H_2O (3 times) and dried over $MgSO_4$. (The combined aqueous extracts were quenched with an excess amount of $Na_2S_2O_2$.) Volatile materials were removed in *vacuo* and the crude material was purified

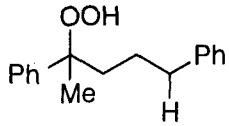
by flash column chromatography (hexane : EtOAc = 90 : 10) to give hydroperoxide **3.1b** (2.59 g, 8.1 mmol) in 97% yield.

1,1,4-Triphenylbutyl hydroperoxide (3.1b)



White solid; mp 61–62 °C; IR (NaCl) 1030, 1059, 1337, 1447, 1495, 1601, 2955, 3061, 3472 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57-1.67 (2H, m), 2.43-2.49 (2H, m), 2.62 (2H, t, J = 7.6 Hz), 7.04 (1H, s), 7.10-7.18 (3H, m), 7.22-7.27 (4H, m), 7.27-7.33 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 35.6, 35.9, 89.5, 125.7, 126.8, 127.3, 128.15, 128.24, 128.4, 142.2, 143.1; HRMS (ESI): Found: m/z 319.1705. Calcd for $C_{22}H_{23}O_2$: $(M+H)^+$ 319.1698.

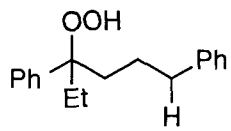
2,5-Diphenylpentyl 2-hydroperoxide (3.1c)



Prepared from 1-phenylethanone and 2,5-diphenylpentan-2-ol (**3.11c**) for 12 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 85% yield.

Colorless oil; IR (NaCl) 1030, 1373, 1447, 1495, 2862, 2945, 3024, 3424 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46-1.58 (1H, m), 1.58-1.71 (1H, m), 1.63 (3H, s), 1.78-1.90 (2H, m), 2.49-2.62 (2H, m), 7.11 (2H, d, J = 7.2 Hz), 7.15 (1H, dd, J = 7.2, 7.6 Hz), 7.19 (1H, s), 7.22-7.30 (3H, m), 7.33-7.41 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 25.6, 36.0, 39.2, 86.3, 125.6, 125.8, 127.3, 128.27, 128.34, 128.5, 142.0, 143.8; HRMS (ESI): Found: m/z 257.1553. Calcd for $C_{17}H_{21}O_2$: $(M+H)^+$ 257.1542.

3,6-Diphenylhexyl 3-hydroperoxide (3.1d)

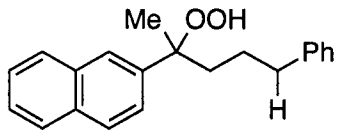


Prepared from 3,6-diphenylhexan-3-ol (**3.11d**) for 4 days and purified by flash column

chromatography (hexane : EtOAc = 90 : 10) in 86% yield.

Colorless oil; IR (NaCl) 1030, 1327, 1447, 1495, 1603, 2878, 2941, 2967, 3474 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, t, J = 7.2 Hz), 1.45-1.55 (1H, m), 1.55-1.67 (1H, m), 1.83-1.98 (4H, m), 2.59 (2H, t, J = 7.6 Hz), 7.01 (1H, s), 7.12-7.19 (3H, m), 7.22-7.30 (3H, m), 7.30-7.38 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.6, 24.9, 27.8, 34.0, 36.0, 88.5, 125.8, 125.9, 127.1, 128.3, 128.4, 142.2, 142.9; HRMS (ESI): Found: m/z 271.1690. Calcd for $C_{18}H_{23}O_2$: $(M+H)^+$ 271.1698.

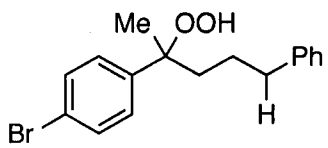
2-(Naphthalen-2-yl)-5-phenylpentyl 2-hydroperoxide (3.1e)



Prepared from 2-(naphthalen-2-yl)-5-phenylpentan-2-ol (**3.11e**) for 7 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 34% yield.

Colorless oil; IR (NaCl) 1375, 1454, 1495, 1601, 2862, 2945, 2982, 3059, 3441(brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47-1.57 (1H, m), 1.61-1.73 (1H, m), 1.74 (3H, s), 1.90-1.97 (2H, m), 2.50-2.63 (2H, m), 7.09 (2H, dd, J = 1.2, 7.2 Hz), 7.15 (1H, tt, J = 2.0, 7.2 Hz), 7.20-7.28 (3H, m), 7.44-7.52 (2H, m), 7.55 (1H, dd, J = 2.0, 8.4 Hz), 7.79-7.87 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 25.7, 36.0, 39.1, 86.5, 123.7, 124.8, 125.8, 126.0, 126.2, 127.5, 128.2, 128.26, 128.35 (overlapped), 132.6, 133.1, 141.2, 142.0; HRMS (ESI): Found: m/z 307.1703. Calcd for $C_{21}H_{23}O_2$: $(M+H)^+$ 307.1698.

2-(4-Bromophenyl)-5-phenylpentyl 2-hydroperoxide (3.1f)

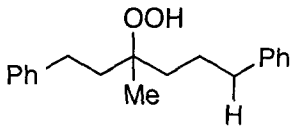


Prepared from 2-(4-bromophenyl)-5-phenylpentan-2-ol (**3.11f**) and 1 mL of H_2SO_4 (conc) for 24 h and purified by flash column chromatography (hexane : EtOAC = 90 : 10) in 68% yield.

Colorless oil; IR (NaCl) 1009, 1086, 1396, 1452, 1487, 1591, 1603, 2862, 2945, 3416

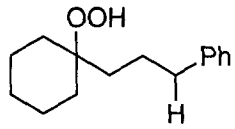
(brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43-1.54 (1H, m), 1.54-1.67 (1H, m), 1.60 (3H, s), 1.74-1.85 (2H, m), 2.50-2.61 (2H, m), 7.11 (2H, dd, J = 1.2, 7.2 Hz), 7.17 (1H, tt, J = 2.0, 7.2 Hz), 7.21-7.28 (5H, m), 7.48 (2H, dt, J = 1.6, 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 25.5, 35.9, 39.0, 85.9, 121.3, 125.8, 127.5, 128.30, 128.32, 131.5, 141.8, 143.0; HRMS (ESI): Found: m/z 335.0640. Calcd for $C_{17}H_{20}O_2{}^{79}Br$: $(M+H)^+$ 335.0647.

3-Methyl-1,6-diphenylhexyl 3-hydroperoxide (3.1g)[24]



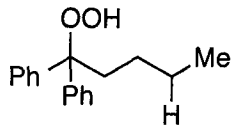
Prepared from 3-methyl-1,6-diphenylhexan-3-ol (**3.11g**) and 1 mL of H_2SO_4 (conc) for 24 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 51% yield. Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) 1.22 (3H, s), 1.60-1.75 (4H, m), 1.78-1.92 (2H, m), 2.57-2.65 (4H, m), 6.99 (1H, s), 7.15-7.22 (6H, m), 7.24-7.31 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 25.5, 29.9, 36.0, 36.2, 38.4, 84.4, 125.79, 125.82, 128.30, 128.34, 128.4, 142.3, 142.5.

1-(3-Phenylpropyl)cyclohexyl hydroperoxide (3.1h)



Prepared from 1-(3-phenylpropyl)cyclohexanol (**3.11h**) and 1 mL of H_2SO_4 (conc) for 18 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 26% yield. White solid; mp 35–36 °C; IR (NaCl) 1315, 1452, 1495, 1603, 2862, 2936, 3024, 3406 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21-1.45 (5H, m), 1.48-1.62 (5H, m), 1.62-1.78 (4H, m), 2.62 (2H, t, J = 7.6 Hz), 6.93 (1H, brs), 7.15-7.22 (3H, m), 7.28 (2H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 24.6, 25.8, 32.5, 35.8, 36.2, 83.1, 125.7, 128.3, 128.4, 142.5; HRMS (ESI): Found: m/z 235.1705. Calcd for $C_{15}H_{23}O_2$: $(M+H)^+$ 235.1698.

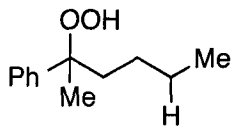
1,1-Diphenylpentan hydroperoxide (3.1i)



Prepared from 1,1-diphenylpentan-1-ol (**3.11i**) for 8 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 82% yield.

Colorless oil; IR (NaCl) 1032, 1337, 1447, 1493, 1599, 2870, 2955, 3470 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.2 Hz), 1.19-1.28 (2H, m), 1.28-1.38 (2H, m), 2.38-2.45 (2H, m), 7.11 (1H, brs), 7.23-7.29 (2H, m), 7.29-7.38 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 23.0, 25.5, 36.1, 89.6, 126.9, 127.2, 128.1, 143.3; HRMS (ESI): Found: m/z 257.1531. Calcd for $C_{17}H_{21}O_2$: $(M+H)^+$ 257.1542.

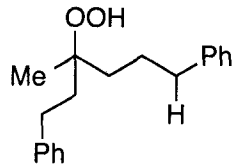
2-Phenylhexyl 2-hydroperoxide (3.1j)[25]



Prepared from 2-phenylhexan-2-ol (**3.11j**) for 5 h and purified by flash column chromatography (hexane : EtOAC = 90 : 10) in 90% yield.

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz), 1.08-1.17 (1H, m), 1.20-1.33 (3H, m), 1.65 (3H, s), 1.72-1.84 (2H, m), 7.22 (1H, s), 7.29 (1H, tt, J = 1.6, 7.2 Hz), 7.38 (2H, ddd, J = 1.6, 7.2, 8.0 Hz), 7.43 (2H, dd, J = 1.2, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.4, 23.0, 26.0, 39.6, 86.5, 125.7, 127.3, 128.5, 144.0.

3-Methyl-1-phenylheptyl 3-hydroperoxide (3.1k)

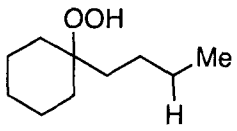


Prepared from 3-methyl-1-phenylheptan-3-ol (**3.11k**) and 1 mL of H_2SO_4 (conc) for 48 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 42% yield.

Colorless oil; IR (NaCl) 1373, 1454, 1495, 1603, 1705, 2868, 2936, 2953, 3393 (brs) cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.2 Hz), 1.24 (3H, s), 1.28-1.38 (4H, m),

1.56-1.64 (2H, m), 1.86 (2H, ddd, J = 1.6, 6.4, 10.4 Hz), 2.65 (2H, t, J = 8.4 Hz), 7.11 (1H, brs), 7.15-7.23 (3H, m), 7.28 (2H, dd, J = 7.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.5, 23.2, 25.9, 29.9, 36.3, 38.4, 84.5, 125.8, 128.3, 128.4, 142.6; HRMS (ESI): Found: m/z 223.1707. Calcd for $C_{14}H_{23}O_2$: $(M+H)^+$ 223.1698.

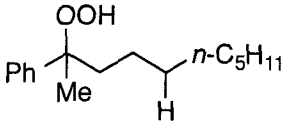
1-Butylcyclohexyl hydroperoxide (3.1l)



Prepared from 1-butylcyclohexanol (**3.11l**) for 2 days and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 35% yield.

Colorless oil; IR (NaCl) 959, 1150, 1260, 1377, 1447, 2860, 2932, 3385 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 6.8 Hz), 1.24-1.48 (9H, m), 1.48-1.60 (5H, m), 1.72-1.80 (2H, m), 7.03 (1H, t, J = 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.9, 23.3, 25.1, 25.8, 32.5, 36.1, 83.2; HRMS (ESI): Found: m/z 173.1550. Calcd for $C_{10}H_{21}O_2$ $(M+H)^+$ 173.1542.

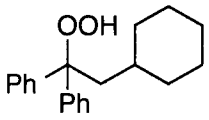
2-Phenyldecyl 2-hydroperoxide (3.1m)



Prepared from 2-phenyldecan-2-ol (**3.11m**) for 20 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 79% yield.

Colorless oil; IR (NaCl) 1028, 1070, 1373, 1447, 1466, 1495, 2853, 2924, 3416(brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 6.8 Hz), 1.00-1.18 (1H, m), 1.18-1.32 (11H, m), 1.65 (3H, s), 1.72-1.83 (2H, m), 7.16 (1H, s), 7.29 (1H, t, J = 7.2 Hz), 7.38 (2H, dd, J = 7.2, 8.0 Hz), 7.43 (2H, dd, J = 1.6, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.4, 22.6, 23.8, 29.2, 29.4, 30.0, 31.8, 39.8, 86.5, 125.7, 127.3, 128.5, 144.1; HRMS (ESI): Found: m/z 251.2010. Calcd for $C_{16}H_{27}O_2$: $(M+H)^+$ 251.2011.

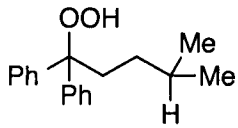
2-Cyclohexyl-1,1-diphenylethyl hydroperoxide (3.1n)



Prepared from 2-cyclohexyl-1,1-diphenylethanol (**3.11n**) for 24 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 94% yield.

White solid; mp 60–62 °C; IR (NaCl) 1339, 1449, 1491, 2851, 2924, 3474 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82-1.00 (3H, m), 1.02-1.14 (3H, m), 1.28-1.40 (1H, m), 1.50-1.60 (4H, m), 2.33 (2H, d, J = 5.2 Hz), 7.04 (1H, s), 7.24 (2H, tt, J = 1.6, 7.2 Hz), 7.31 (4H, ddd, J = 1.6, 6.8, 8.0 Hz), 7.35 (4H, dd, J = 2.0, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.28. 26.35, 32.9, 34.7, 43.4, 89.9, 126.9, 127.2, 128.1, 143.7; HRMS (ESI): Found: m/z 297.1849. Calcd for $C_{20}H_{25}O_2$: $(M+H)^+$ 297.1855.

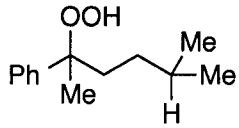
4-Methyl-1,1-diphenylpentyl hydroperoxide (3.1p)



Prepared from 4-methyl-1,1-diphenylpentan-1-ol (**3.11p**) for 10 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 83% yield.

White solid; mp 63–65 °C; IR (NaCl) 1337, 1447, 1468, 1493, 2870, 2932, 2957, 3472 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (6H, d, J = 6.8 Hz), 1.10-1.18 (2H, m), 1.53 (1H, sept, J = 2.8 Hz), 2.40-2.45 (2H, m), 7.09 (1H, s), 7.25 (2H, tt, J = 1.6, 7.2 Hz), 7.28-7.37 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 28.3, 32.1, 34.1, 89.6, 126.9, 127.2, 128.1, 143.3; HRMS (ESI): Found: m/z 271.1709. Calcd for $C_{18}H_{23}O_2$: $(M+H)^+$ 271.1698.

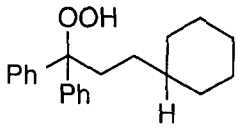
5-Methyl-2-phenylhexyl 2-hydroperoxide (3.1q)[23]



Prepared from 5-methyl-2-phenylhexan-2-ol (**3.11q**) for 5 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 94% yield.

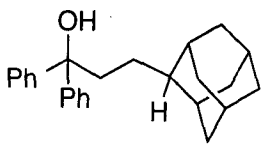
Colorless *oil*; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, d, J = 6.8 Hz), 0.84 (3H, d, J = 6.8 Hz), 0.98-1.07 (1H, m), 1.14-1.24 (1H, m), 1.40-1.50 (1H, m), 1.65 (3H, s), 1.72-1.84 (2H, m), 7.19 (1H, s), 7.29 (1H, dd, J = 6.8, 7.2 Hz), 7.38 (2H, dd, J = 7.2, 8.0 Hz), 7.43 (2H, dd, J = 1.6, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.36, 22.44, 22.5, 28.3, 32.7, 37.6, 86.5, 125.7, 127.3, 128.5, 144.1.

3-Cyclohexyl-1,1-diphenylpropyl hydroperoxide (3.1r)



Prepared from 3-cyclohexyl-1,1-diphenylpropan-1-ol (**3.11r**) for 24 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 86% yield; Colorless oil; IR (NaCl) 1032, 1059, 1325, 1447, 1493, 2849, 2922, 3470 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78-0.90 (2H, m), 1.07-1.25 (6H, m), 1.58-1.72 (5H, m), 2.40-2.46 (2H, m), 7.10 (1H, s), 7.24 (2H, dd, J = 6.0, 7.6 Hz), 7.31 (4H, dd, J = 7.2, 7.6 Hz), 7.34 (4H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 26.6, 30.6, 33.3, 33.7, 38.0, 89.6, 126.9, 127.2, 128.1, 143.3; HRMS (ESI): Found: m/z 311.2015. Calcd for $C_{21}H_{27}O_2$: $(M+H)^+$ 311.2011.

3-(Adamantan-2-yl)-1,1-diphenylpropyl hydroperoxide (3.1s)

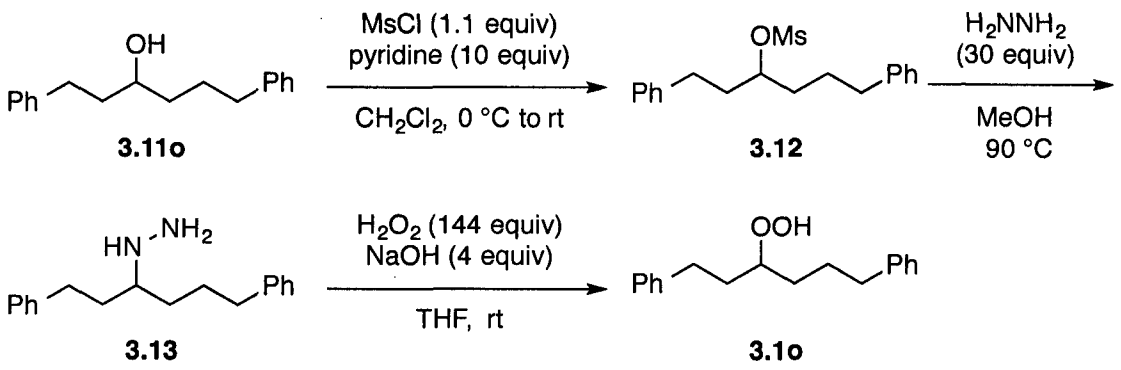


Prepared from 3-(adamantan-2-yl)-1,1-diphenylpropan-1-ol (**3.11s**) for 8 h and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 91% yield.

White solid; mp 146–148 °C; IR (NaCl) 1337, 1446, 1493, 2849, 2905, 3480 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36-1.45 (4H, m), 1.59 (1H, t, J = 7.2 Hz), 1.65-1.75 (9H, m), 1.78.1.88 (3H, m), 2.37-2.43 (2H, m), 7.11 (1H s), 7.24 (2H, tt, J = 1.6, 7.2 Hz), 7.31 (4H, ddd, J = 2.0, 7.2, 7.6 Hz), 7.35-7.39 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 28.0, 28.3, 31.5, 31.9, 34.4, 38.4, 39.2, 44.6, 89.6, 126.8, 127.2, 128.1, 143.3; HRMS

(ESI): Found: m/z 363.2332. Calcd for $C_{25}H_{31}O_2$: $(M+H)^+$ 363.2324.

5.3.1.4 Preparation of 1,6-diphenylhexyl 3-hydroperoxide (3.1o)



Scheme 5-17. *Synthesis of 1,6-diphenylhexyl 3-hydroperoxide (**3.1o**).*

Previously reported procedure from literature[26] for the synthesis of analogous compounds was employed for the synthesis of 1,6-diphenylhexyl 3-hydroperoxide (**3.1o**). To a solution of 1,6-diphenylhexan-3-ol (**3.11o**) (1.27 g, 5.0 mmol) in CH_2Cl_2 (2 mL), was added 0.43 mL of methanesulfonyl chloride (0.63 g, 5.5 mmol) and followed by 0.8 mL of pyridine (0.79 g, 10.0 mmol). After completion (2 h), the reaction was quenched with 10% HCl (40 mL). The organic layer was extracted with ether and the combined extracts were washed with saturated $NaHCO_3$, followed by brine and water. After drying over magnesium sulfate, volatile materials were removed in *vacuo* to afford 1,6-diphenylhexan-3-yl methanesulfonate (**3.12**). The crude product was used directly for the subsequent step without purification.

Partial characterization data of **3.12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68-1.82 (4H, m), 1.92-2.08 (2H, m), 2.58-2.78 (4H, m), 2.94 (3H, s), 4.78 (1H, tt, J = 5.6, 6.0 Hz), 7.13-7.22 (6H, m), 7.22-7.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 31.2, 33.9, 35.4, 36.0, 38.7, 82.9, 126.0, 126.1, 128.3, 128.4 (overlapped), 128.5, 140.8, 141.6.

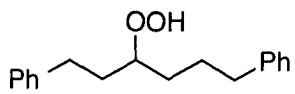
A reaction mixture of methanesulfonate **3.12** along with hydrazine monohydrate (50–60%; 4.7 mL, 150 mmol) and methanol (8 mL) in sealed tube was heated at 90 °C for 4 h. After consumption of starting material, the reaction mixture was extracted with ether and washed with KOH (50 wt % aq soln), followed by washing with water and brine. The

organic extracts were dried oyer magnesium sulfate and volatile materials were removed in vacuo to give (1,6-diphenylhexan-3-yl)hydrazine (**3.13**). The crude product was immediately used for the next step without any purification.

Partial characterization data of **3.13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.58 (2H, m), 1.58-1.80 (4H, m), 2.55 (1H, tt, J = 6.0, 6.0 Hz), 2.62 (4H, t, J = 7.6 Hz), 2.89 (2H, brs), 7.14-7.24 (6H, m), 7.24-7.30 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 31.2, 31.9, 33.5, 36.0, 62.2, 125.75, 125.79, 128.2, 128.28, 128.33, 128.4, 142.1.

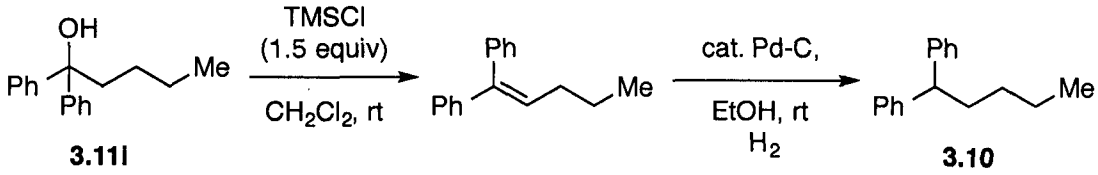
To a solution of hydrazine **3.13** in 50 mL of THF, NaOH (0.8 g, 20.0 mmol) was added, followed by hydrogen peroxide (90 mL, 30 wt % aq soln). The reaction mixture was stirred at rt for 3 d. The reaction mixture was extracted with ether, and the combined organic phase was washed with water (100 mL × 5) and brine and dried over magnesium sulfate. Volatile materials were removed in *vacuo* and the resulting crude material was subjected to flash column chromatography (hexane:ethyl acetate = 90:10) to furnish 1,6-diphenylhexyl 3-hydroperoxide (**3.1o**) (0.81 g, 3.0 mmol) in 60% yield over 3 steps.

1,6-Diphenylhexyl 3-hydroperoxide (3.1o)



Colorless oil; IR (NaCl) 1344, 1454, 1495, 1603, 2860, 2940, 3024, 3404 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-1.63 (1H, m), 1.63-1.86 (4H, m), 1.90-2.00 (1H, m), 2.62 (2H, t, J = 7.2 Hz), 2.65-2.78 (2H, m), 3.90-3.97 (1H, m), 7.14-7.22 (6H, m), 7.22-7.30 (4H, m), 7.40 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 31.5, 31.6, 33.7, 35.8, 84.6, 125.78, 125.85, 128.3, 128.4 (overlapped×2), 142.0, 142.2; HRMS (ESI): Found: m/z 271.1698. Calcd for $C_{18}H_{23}O_2$: $(M+H)^+$ 271.1698.

5.3.2 Preparation of 1,1-diphenylpentane (3.10)

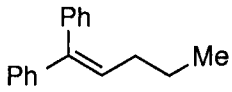


3.11i **3.10**

Scheme 5-18. *Synthesis of 1,1-diphenylpentane (**3.10**).*

To a stirring solution 1,1-diphenylpentan-1-ol (**3.11i**) (2.4 g, 10 mmol) in CH_2Cl_2 (20 mL), was added 1.9 mL of $ClSiMe_3$ (1.6 g, 15 mmol). The reaction mixture was allowed to stir for 2 h and then the solvent was removed in vacuo and the crude material was subjected to flash column chromatography (100% hexane) to afford 1,1-diphenylpent-1-ene (2.0 g, 9 mmol) in 90% yield.

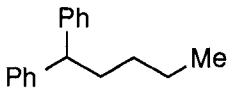
1,1-Diphenylpent-1-ene[27]



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.2 Hz), 1.46 (2H, qt, J = 7.2, 7.6 Hz), 2.09 (2H, td, J = 7.6, 7.6 Hz), 6.08 (1H, t, J = 7.6 Hz), 7.15-7.25 (7H, m), 7.28 (1H, t, J = 7.2 Hz), 7.35 (2H, dd, J = 6.8, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 23.1, 31.8, 126.7, 126.8, 127.2, 128.0, 128.1, 129.9, 130.1, 140.3, 141.6, 142.9.

To a 2-neck flask with Pd (10 wt % on carbon) (0.19 g, 0.18 mmol) under a hydrogen atmosphere, was added a solution of 1,1-diphenylpent-1-ene (1.96 g, 8.8 mmol) in EtOH (44 mL). The reaction mixture was stirred for 6 h and then filtered through a pad of celite. Afterward, solvent was removed in vacuo, and the crude material was subjected to flash column chromatography (100% hexane) to afford 1,1-diphenylpentane (10) in quantitative yield.

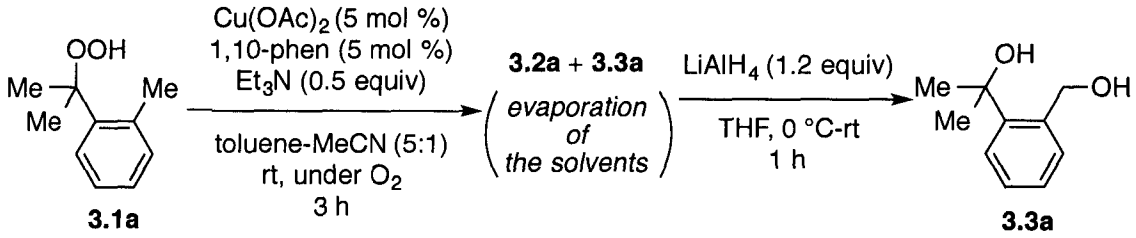
1,1-Diphenylpentane (3.10)



Colorless oil; IR (NaCl) 1450, 1493, 1599, 2857, 2928, 2955, 3024, 3059 cm^{-1}; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 0.85 (3H,-t, J = 7.2 Hz), 1.18-1.28 (2H, m), 1,32 (2H, tt, J = 7.2, 7.4 Hz), 2.03 (2H, td, J = 7.2, 8.0 Hz), 3.87 (1H, t, J = 8.0 Hz), 7.14 (2H, t, J = 6.8 Hz), 7.20-7.28 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.7, 30.2, 35.4, 51.4, 126.0, 127.9, 128.3, 145.4; HRMS (ESI): Found: m/z 225.1632. Calcd for $C_{17}H_{21}$: $(M+H)^+$ 225.1643.

5.3.3 Copper-catalyzed aerobic aliphatic C–H oxygenation with hydroperoxides 3.1.

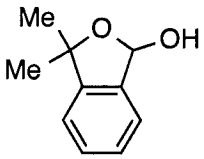


Scheme 5-19. *The reaction of hydroperoxide **3.1a**.*

A typical procedure for the reaction of hydroperoxide 3.1a

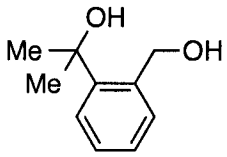
To a stirring solution of $Cu(OAc)_2$ (4.5 mg, 0.025 mmol), 1,10-phenanthroline (4.5 mg, 0.025 mmol) and hydroperoxide **3.1a** (83.1 mg, 0.50 mmol) in 5.0 mL of solvent (toluene:MeCN = 5:1), were added Et_3N (35 μL, 0.25 mmol) and the reaction mixture was stirred at room temperature under an oxygen atmosphere for 3 h. After the complete consumption of hydroperoxide **3.1a**, the solvent was removed in *vacuo*. The crude residue was subjected to $LiAlH_4$ (22.8 mg, 0.6 mmol) at 0 °C in THF. The reaction was stirred at room temperature for another 1 h before quenching with pH 9 buffer at 0 °C and the organic materials were extracted three times with diethyl ether. The combined extracts were washed with brine, and dried over $MgSO_4$. Volatile materials were removed in *vacuo* and the resulting crude material was subjected to flash column chromatography (hexane:ethyl acetate = 60:40) to afford 2-(2-(hydroxymethyl)phenyl) propan-2-ol (**3.3a**) (75.0 mg, 0.45 mmol) in 90% yield.

3,3-Dimethyl-1,3-dihydroisobenzofuran-1-ol (3.2a)[28]



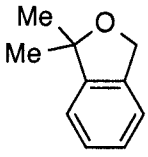
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (3H, s), 1.61 (3H, s), 3.65 (1H, d, J = 6.8 Hz), 6.44 (1H, d, J = 6.8 Hz), 7.17 (1H, d, J = 7.2 Hz), 7.31-7.42 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 30.9, 85.8, 99.7, 120.5, 123.0, 127.9, 129.4, 138.4, 147.5.

2-(2-(Hydroxymethyl)phenyl)propan-2-ol (3.3a)[29]



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (6H, s), 3.97 (2H, brs), 4.76 (2H, s), 7.17-7.30 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.4, 65.3, 74.5, 126.2, 127.2, 127.9, 132.0, 137.9, 146.3.

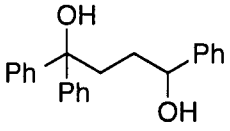
1,1-Dimethyl-1,3-dihydroisobenzofuran (3.4a)[30]



Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (6H, s), 5.07 (2H, s), 7.10-7.15 (1H, m), 7.17-7.21 (1H, m), 7.22-7.29 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 70.7, 85.7, 120.5, 121.0, 127.1, 127.3, 138.5, 146.9.

Compound Data in Table 3-2

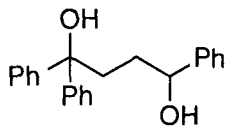
1,1,4-Triphenylbutane-1,4-diol (3.3b)



White solid; mp 97–99 °C; IR (NaCl) 1449, 1493, 2872, 2929, 2955, 3404 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (3H, s), 1.80 (2H, dt, J = 7.2, 7.6 Hz), 2.21 (1H, brs),

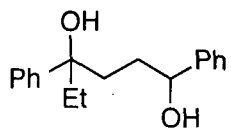
2.35-2.52 (2H, m), 2.86 (1H, brs), 4.72 (1H, t, J = 6.0 Hz), 7.18-7.24 (2H, m), 7.24-7.35 (9H, m), 7.36-7.42 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.3, 37.9, 74.5, 77.9, 125.8, 126.0, 126.1, 126.66, 126.72, 127.4, 128.07, 128.09, 128.4, 144.4, 146.8, 147.1; HRMS (ESI): Found: m/z 319.1709. Calcd for $C_{22}H_{23}O_2$: $(M+H)^+$ 319.1698.

1,4-Diphenylpentane-1,4-diol (3.3c)



A mixture of 2 diastereomers in 0.5:0.5 (1:1) ratio. Yellowish oil; IR (NaCl) 1028, 1057, 1454, 1493, 2930, 2972, 3362 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (3H×1.0, s), 1.60-1.88 (2.5H×1.0, m), 1.94-2.05 (1.5H×1.0, m), 2.45 (2H×1.0, brs), 4.60-4.69 (1H×1.0, m), 7.20-7.36 (8H×1.0, m), 7.38-7.43 (2H×1.0, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 30.9, 33.4, 33.6, 39.8, 40.4, 74.2, 74.3, 74.4, 74.7, 124.7, 124.8, 125.8 (overlapped), 126.35, 126.45, 127.3, 127.4, 128.08, 128.10, 128.3 (overlapped), 144.5, 144.6, 147.6, 147.8; HRMS (ESI): Found: m/z 257.1549. Calcd for $C_{17}H_{21}O_2$: $(M+H)^+$ 257.1542.

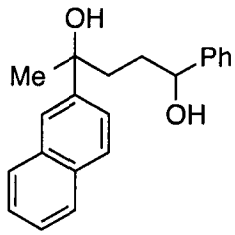
1,4-Diphenylhexane-1,4-diol (3.3d)



A mixture of 2 diastereomers in 0.5:0.5 (1:1) ratio. Yellowish oil; IR (NaCl) 1028, 1057, 1309, 1454, 1493, 1603, 2934, 2967, 3362 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (3H×0.5, t, J = 7.6 Hz), 0.72 (3H×0.5, t, J = 7.2 Hz), 1.48-1.87 (4.5H×1.0, m), 1.92-2.02 (1.5H×1.0, m), 2.82 (2H×1.0, brs), 4.56 (1H×0.5, dd, J = 4.4, 8.8 Hz), 4.63 (1H×0.5, dd, J = 4.8, 7.2 Hz), 7.16-7.35 (10H×1.0, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 7.8, 32.9, 33.3, 35.6, 36.1, 38.0, 39.1, 74.1, 75.0, 76.89, 76.93, 125.4, 125.5, 125.7, 125.8, 126.2, 126.3, 127.3, 127.4, 127.97, 128.01, 128.3 (overlapped), 144.5, 144.6, 145.7 (overlapped); HRMS (ESI): Found: m/z 271.1693. Calcd for $C_{18}H_{23}O_2$: $(M+H)^+$

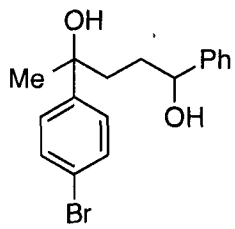
271.1698.

4-(Naphthalen-2-yl)-1-phenylpentane-1,4-diol (3.3e)



A mixture of 2 diastereomers in 0.5:0.5 (1:1) ratio. Yellowish oil; IR (NaCl) 820, 858, 1055, 1273, 1375, 1452, 1504, 2974, 3011, 3362 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (3H×1.0, s), 1.57-1.67 (1H×0.5, m), 1.67-1.81 (3H×0.5, m), 1.91 (1H×0.5, ddd, J = 5.6, 9.2, 14.8 Hz), 2.03-2.16 (3H×0.5, m), 2.66 (2H×1.0, brs), 4,63 (1H×0.5, dd, J = 4.4, 8.4 Hz), 4.66 (1H×0.5, dd, J = 4.8, 7.2 Hz), 7.20-7.32 (5H×1.0, m), 7.42-7.50 (3H×1.0, m), 7.77-7.84 (3H×1.0, m), 7.89 (1H×1.0, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3, 31.0, 33.4, 33.6, 39.5, 40.2, 74.1, 74.48, 74.53, 74.8, 123.1, 123.3, 123.61, 123.63, 125.5, 125.6, 125.73, 125.74, 125.91, 125.95, 127.3, 127.4 (overlapped), 127.77, 127.82, 128.1, 128.29, 128.31, 132.09, 132.14, 133.11, 133.13, 144.4, 144.5, 145.0, 145.2; HRMS (ESI): Found: m/z 307.1702. Calcd for $C_{21}H_{23}O_2$: $(M+H)^+$ 307.1698.

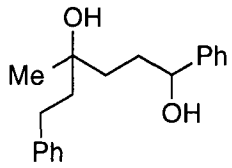
4-(4-Bromophenyl)-1-phenylpentane-1,4-diol (3.3f)



A mixture of 2 diastereomers in 0.5:0.5 (1:1) ratio. Yellowish oil; IR (NaCl) 827, 1009, 1078, 1393, 1454, 1487, 1589, 2930, 2972, 3345 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (3H×1.0, s), 1.53-1.84 (5H×0.5, m), 1.90-2.00 (3H×0.5, m), 2.69 (2H×1.0, brs), 4.61 (1H×0.5, dd, J = 4.4, 8.4 Hz), 4.65 (1H×0.5, dd, J = 4.8, 7.2 Hz), 7.21-7.35 (7H×1.0, m), 7.40-7.45 (2H×1.0, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.2, 31.0, 33.2, 33.5, 39.6, 40.4, 74.0, 74.1 (overlapped), 74.7, 120.2, 120.3, 125.68, 125.71, 126.7, 126.9, 127.4,

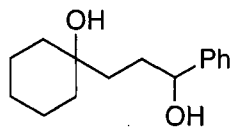
127.5, 128.4 (overlapped), 131.09, 131.11, 144.2, 144.4, 146.7, 147.0; HRMS (ESI): Found: m/z 335.0641. Calcd for $C_{17}H_{20}O_2{}^{79}Br$ $(M+H)^+$ 335.0647.

1,4,6-Triphenylhexane-1,4-diol (3.3g)



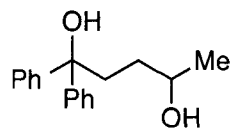
A mixture of 2 diastereomers in 0.5:0.5 (1:1) ratio. Yellowish oil; IR (NaCl) 1057, 1373, 1454, 1495, 2864, 2945, 3026, 3350 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.20 (3H×0.5, s), 1.21 (3H×0.5, s), 1.47-1.57 (1H×1.0, m), 1.63-1.93 (5H×1.0, m), 2.40-2.98 (4H×1.0, m), 4.64 (1H×0.5, t, J = 7.6 Hz), 4.65 (1H×0.5, t, J = 7.6 Hz), 7.13-7.19 (3H×1.0, m), 7.22-7.28 (3H×1.0, m), 7.30-7.35 (4H×1.0, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 26.9, 30.26, 30.33, 33.4, 33.5, 37.8, 37.9, 43.6, 44.2, 72.28, 72.32, 74.6, 74.8, 125.7, 125.8, 127.42, 127.43, 128.27, 128.35 (overlapped), 128.39, 142.40, 142.44, 144.70, 144.74; HRMS (ESI): Found: m/z 285.1854. Calcd for $C_{19}H_{25}O_2$: $(M+H)^+$ 285.1855.

1-(3-Hydroxy-3-phenylpropyl)cyclohexanol (3.3h)[31]



White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19-1.30 (1H, m), 1.32-1.65 (11H, m), 1.75-1.92 (2H, m), 2.65 (2H, brs), 4.65 (1H, dd, J = 4.8, 8.0 Hz), 7.22-7.28 (1H, m), 7.29-7.36 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 22.2, 25.7, 32.6, 37.1, 37.7, 38.1, 71.1, 74.7, 125.8, 127.3, 128.3, 144.9.

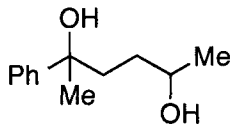
1,1-Diphenylpentane-1,4-diol (3.3i)



White solid; mp 77–79 °C; IR (NaCl) 988, 1032, 1061, 1377, 1447, 1493, 1599, 2967,

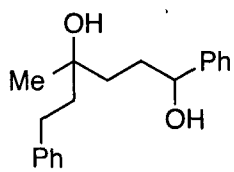
3011, 3412 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, d, J = 6.0 Hz), 1.39-1.58 (2H, m), 1.59 (2H, brs), 2.44 (2H, t, J = 7.6 Hz), 3.81-3.89 (1H, m), 7.19-7.24 (2H, m), 7.28-7.34 (4H, m), 7.43 (4H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 33.2, 38.0, 68.3, 77.8, 126.0, 126.1, 126.6, 126.7, 128.0, 147.0, 147.3; HRMS (ESI): Found: m/z 257.1544. Calcd for $C_{17}H_{21}O$: $(M+H)^+$ 257.1542.

2-Phenylhexane-2,5-diol (3.3j)



A mixture of 2 diastereomers in 0.56:0.44 (1.27:1) ratio. Yellowish oil; IR (NaCl) 1028, 1061, 1128, 1375, 1447, 1495, 2930, 2970, 3374 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H×0.56, d, *J* = 6.0 Hz), 1.16 (3H×0.44, d, *J* = 6.4 Hz), 1.30-1.52 (2H×1.0, m), 1.56 (3H×0.56, s), 1.58 (3H×0.44, s), 1.84-2.05 (2H×1.0, m), 3.73-3.83 (1H×1.0, m), 7.24 (1H×1.0, t, *J* = 6.8 Hz), 7.34 (2H×1.0, ddd, *J* = 2.0, 7.6, 8.0 Hz), 7.41-7.47 (2H×1.0, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 23.7, 30.3, 31.0, 33.3, 33.4, 39.8, 40.6, 67.9, 68.5, 74.3, 74.4, 124.8, 124.9, 126.3, 126.4, 128.08, 128.09, 147.8, 148.1; HRMS (ESI): Found: m/z 195.1384. Calcd for $C_{12}H_{19}O_2$: $(M+H)^+$ 195.1385.

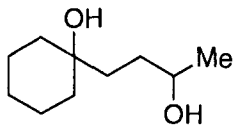
5-Methyl-7-phenylheptane-2,5-diol (3.3k)



A mixture of 2 diastereomers in 0.5:0.5 (1:1) ratio. Yellowish oil; IR (NaCl) 1053, 1070, 1375, 1454, 1495, 1603, 2934, 2968, 3362 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.215 (3H×0.5, d, J = 6.4 Hz), 1.218 (3H×0.5, d, *J* = 6.4 Hz), 1.25 (3H×1.0, s), 1.52-1.70 (4H×1.0, m), 1.75-1.82 (2H×1.0, m), 2.37 (2H×1.0, brs), 2.64-2.72 (2H×1.0, m), 3.77-3.86 (1H×1.0, m), 7.16-7.22 (3H×1.0, m), 7.25-7.30 (2H×1.0, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 23.7, 26.6, 27.0, 30.35, 30.41, 33.2, 33.3, 37.9, 38.0, 43.7, 44.3, 68.4,

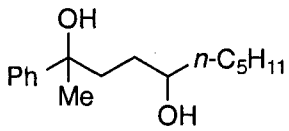
68.5, 72.3, 72.4, 125.7 (overlapped), 128.3 (overlapped), 128.4 (overlapped), 142.4, 142.5; HRMS (ESI): Found: m/z 223.1701. Calcd for $C_{14}H_{23}O_2$: $(M+H)^+$ 223.1698.

1-(3-Hydroxybutyl)cyclohexanol (3.3l)[32]



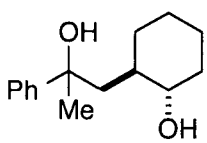
Yellowish solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, d, J = 6.4 Hz), 1.23-1.35 (1H, m), 1.38-1.62 (13H, m), 3.76-3.85 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 22.3, 23.6, 25.8, 32.4, 37.2, 37.9, 38.1, 68.5, 71.2.

2-Phenyldecane-2,5-diol (3.3m)



A mixture of 2 diastereomers in 0.56:0.44 (1.27:1) ratio. White solid; mp. 50–53 °C; IR (NaCl) 1028, 1063, 1375, 1445, 1495, 2857, 2930, 3331 (brs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H×0.56, t, J = 6.8 Hz), 0.87 (3H×0.44, t, J = 6.8 Hz), 1.18-1.52 (10H×1.0, m), 1.55 (3H×0.56, s), 1.56 (3H×0.44, s), 1.83-2.07 (2H×1.0, m), 2.69 (2H×1.0, brs), 3.50-3.60 (1H×1.0, m), 7.19-7.25 (1H×1.0, m), 7.33 (2H×1.0, dd, J = 7.6, 8.0 Hz), 7.40-7.45 (2H×1.0, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 25.3, 25.4, 30.5, 31.1, 31.5, 31.6, 31.77, 31.79, 37.2, 37.6, 39.8, 40.6, 71.9, 72.6, 74.4 (overlapped), 124.8, 124.9, 126.3, 126.4, 128.1 (overlapped), 148.0, 148.1; HRMS (ESI): Found: m/z 251.2013. Calcd for $C_{16}H_{27}O_2$ $(M+H)^+$ 251.2011.

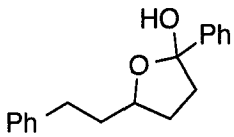
trans-2-(2-Hydroxy-2,2-diphenylethyl)cyclohexanol (3n-major)



The NMR reported is the major isomer of compound 3n (trans:cis = 1.37:1). White solid; mp 143–144 °C; IR (NaCl) 1003, 1061, 1447, 1493, 2857, 2930, 3331 (brs) cm^{-1}; ^{1}H

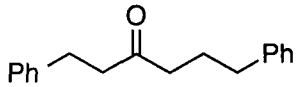
NMR (400 MHz, $CDCl_3$) δ 0.90-1.03 (1H, m), 1.04-1.24 (3H, m), 1.25-1.35 (1H, m), 1.48-1.68 (3H, m), 1.83-1.90 (1H, m), 2.35 (1H, dd, *J* = 6.0, 14.8 Hz), 2.41 (1H, dd, *J* = 2.4, 14.8 Hz), 2.84 (1H, brs), 3.23 (1H, dt, J = 4.0, 10.0 Hz), 5.57 (1H, brs), 7.14-7.23 (2H, m), 7.26 (2H, dd, *J* = 7.2, 8.0 Hz), 7.32 (2H, t, *J* = 7.6 Hz), 7.42 (2H, dd, *J* = 1.2, 8.8 Hz), 7.47 (2H, dd, *J* = 1.2, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 25.5, 34.3, 35.8, 40.6, 48.4, 76.1, 77.1, 125.9, 126.3, 126.4, 126.6, 127.9, 128.0, 146.7, 149.1; HRMS (ESI): Found: m/z 297.1861. Calcd for $C_{20}H_{25}O_2$: $(M+H)^+$ 297.1855.

Compound Data in Scheme 3-20 for 4-Hydroxy-1,6-diphenylhexan-1-one (3.2o)



White solid; mp 77–78 °C; IR (NaCl) 1449, 1495, 1599, 1682, 2928, 3017, 3063, 3445 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78-1.92 (3H, m), 1.96-2.05 (2H, m), 2.70 (1H, td, *J* = 8.0, 16.0 Hz), 2.82 (1H, td, *J* = 8.0, 13.6 Hz), 3.13 (1H, td, *J* = 7.2, 17.6 Hz), 3.18 (1H, td, J = 7.2, 17.2 Hz), 3.67-3.75 (1H, m), 7.18 (1H, t, *J* = 7.2 Hz), 7.21 (2H, d, *J* = 6.8 Hz), 7.26-7.31 (2H, m), 7.45 (2H, dd, *J* = 7.2, 8.0 Hz), 7.56 (1H, tt, *J* = 1.2, 7.6 Hz), 7.97 (2H, dd, *J* = 1.6, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 32.1, 34.9, 39.5, 70.9, 125.8, 128.1, 128.40, 128.41, 128.6, 133.1, 136.8, 141.9; HRMS (ESI): Found: m/z 269.1542. Calcd for $C_{18}H_{21}O_2$: $(M+H)^+$ 269.1542.

1,6-Diphenylhexan-3-one (3.8o)



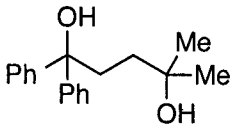
Colorless oil; IR (NaCl) 1369, 1452, 1497, 1603, 1699, 2859, 2928, 3024, 3059 cm^{-1}; ^1H NMR (400 MHz, v) δ 1.89 (2H, tt, *J* = 7.2, 7.6 Hz), 2.38 (2H, t, *J* = 7.2 Hz), 2.58 (2H, t, *J* = 7.6 Hz), 2.69 (2H, t, *J* = 7.6 Hz), 2.87 (2H, t, *J* = 7.6 Hz), 7.11-7.20 (6H, m), 7.26 (4H, dd, *J* = 7.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 29.7, 35.0, 42.0, 44.3, 125.9, 126.0, 128.27, 128.33, 128.4 (overlapped), 141.1, 141.5, 209.8; HRMS (ESI): Found: m/z

253.1591. Calcd for $C_{18}H_{21}O$: $(M+H)^+$ 253.1592.

Compound Data in Table 3-3

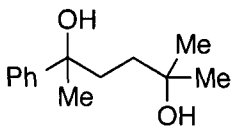
Reactions were carried out using 0.5 mmol of hydroperoxides **3.1** with $Cu(OAc)_2$ (5 mol %), 1,10-phen (5 mol %), and Et_3N (0.5 equiv) in toluene/MeCN (5:1, 0.1 M) at room temperature under an O_2 atmosphere. After stirring 5–7 h, the reaction mixture was further treated with PPh_3 (1 equiv) at rt.

4-Methyl-1,1-diphenylpentane-1,4-diol (3.3p)



White solid; mp 128–131 °C; IR (NaCl) 702, 1026, 1049, 1371, 1446, 1493, 2932, 2972, 3370 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (6H, s), 1.48 (2H, t, J = 7.6 Hz), 1.92 (1H, brs), 2.40 (2H, t, J = 7.6 Hz), 3.42 (1H, brs), 7.19 (2H, t, J = 7.2 Hz), 7.28 (4H, t, J = 7.6 Hz), 7.41 (4H, dd, J = 1.2, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.4, 36.1, 37.3, 70.8, 77.8, 126.0, 126.6, 128.1, 147.2; HRMS (ESI): Found: m/z 271.1693. Calcd for $C_{18}H_{23}O_2$: $(M+H)^+$ 271.1698.

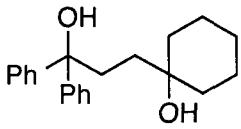
2-Methyl-5-phenylhexane-2,5-diol (3.3q)



White solid; mp 63–65 °C; IR (NaCl) 1067, 1375, 1445, 1493, 2932, 2974, 3393 (brs), 3599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, s), 1.18 (3H, s), 1.34 (1H, ddd, J = 6.4, 9.2, 15.6 Hz), 1.46 (1H, ddd, J = 6.0, 9.2, 15.6 Hz), 1.55 (3H, s), 1.91 (1H, ddd, J = 6.0, 9.2, 15.6 Hz), 1.97 (1H, ddd, J = 6.4, 9.2, 15.6 Hz), 2.29 (2H, brs), 7.22 (1H, t, J = 7.2 Hz), 7.33 (2H, ddd, J = 1.6, 7.2, 8.0 Hz), 7.43 (2H, dd, J = 1.2, 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 29.8, 30.7, 37.5, 38.2, 70.7, 74.3, 124.8, 126.4, 128.1, 148.0;

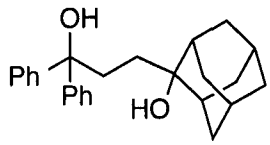
HRMS (ESI): Found: m/z 209.1544. Calcd for $C_{13}H_{21}O_2$: $(M+H)^+$ 209.1542.

1-(3-Hydroxy-3,3-diphenylpropyl)cyclohexanol (3.3r)



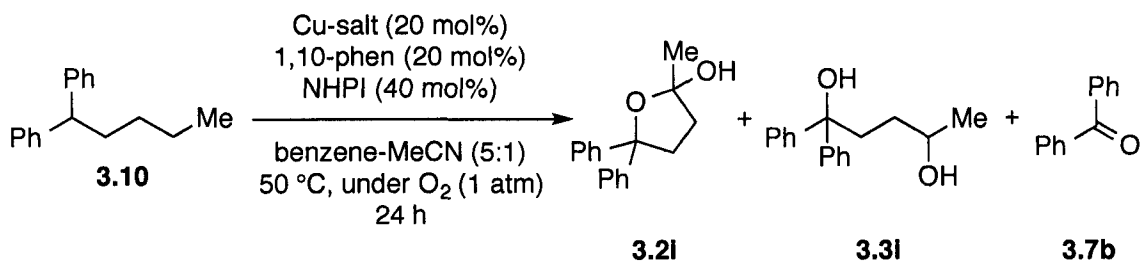
White solid; mp 87–90 °C; IR (NaCl) 1007, 1059, 1260, 1449, 1491, 2857, 2934, 3393 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18-1.30 (1H, m), 1.30-1.58 (11H, m), 1.64 (1H, brs), 2.42 (2H, t, J = 7.2 Hz), 3.34 (1H, brs), 7.20 (2H, t, J = 7.2 Hz), 7.30 (4H, ddd, J = 1.6, 7.2, 8.0 Hz), 7.44 (4H, dd, J = 1.6, 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 25.7, 34.8, 35.6, 37.5, 71.5, 77.7, 126.0, 126.5, 128.0, 147.3; HRMS (ESI): Found: m/z 311.2003. Calcd for $C_{21}H_{27}O_2$: $(M+H)^+$ 311.2011.

2-(3-Hydroxy-3,3-diphenylpropyl)adamantan-2-ol (3.3s)



White solid; mp 47–50 °C; IR (NaCl) 700, 980, 1032, 1449, 2857, 2911, 3447 (brs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50-1.83 (16H, m), 2.10 (2H, d, J = 12.0 Hz), 2.41 (2H, t, J = 7.2 Hz), 7.20 (2H, t, J = 7.2 Hz), 7.30 (4H, dd, J = 7.2, 8.0 Hz), 7.45 (4H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 27.3, 32.1, 32.9, 34.46, 34.51, 36.9, 38.2, 75.2, 77.9, 126.1, 126.6, 128.1, 147.4; HRMS (ESI): Found: m/z 363.2321. Calcd for $C_{25}H_{31}O_2$: $(M+H)^+$ 363.2324.

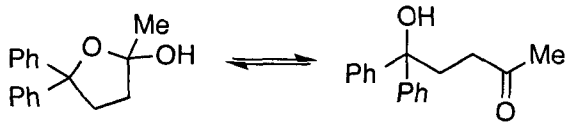
5.3.3. A procedure for the reaction of alkane 10 under CuCl-NHPI catalytic system



Scheme 5-20. *The reaction of alkane **3.1a** for direct oxygenation.*

A solution of alkane **3.10** (67.3 mg, 0.30 mmol) in 3.0 mL of solvent (toluene:MeCN = 5:1) was added to a mixture of CuCl (5.9 mg, 0.060 mmol), 1,10-phenanthroline (10.8 mg, 0.060 mmol) and *N*-hydroxyphthalimide (NHPI) (19.6 mg, 0.12 mmol) at room temperature under an oxygen atmosphere, then heated to 50 °C and left to be stirred for 24 h. The reaction was then allowed to cool to room temperature before quenching with pH 9 buffer and the organic materials were extracted three times with ethyl acetate. The combined extracts were washed with brine, and dried over $MgSO_4$. Volatile materials were removed in *vacuo* and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 70 : 30) to afford 5-hydroxy-5,5-diphenylpentan-2-one (**3.2i**) (31.2 mg, 0.123 mmol), 1,1-diphenylpentane-1,4-diol (**3.3i**) (3.8 mg, 0.015 mmol) and benzophenone (**3.7b**) (13.1 mg, 0.072 mmol) in 41%, 5%, and 24% yields respectively.

2.2i: Equilibrium mixture of 2-methyl-5,5-diphenyltetrahydrofuran-2-ol (cyclic) and 5-hydroxy-5,5-diphenylpentan-2-one (acyclic)[33]

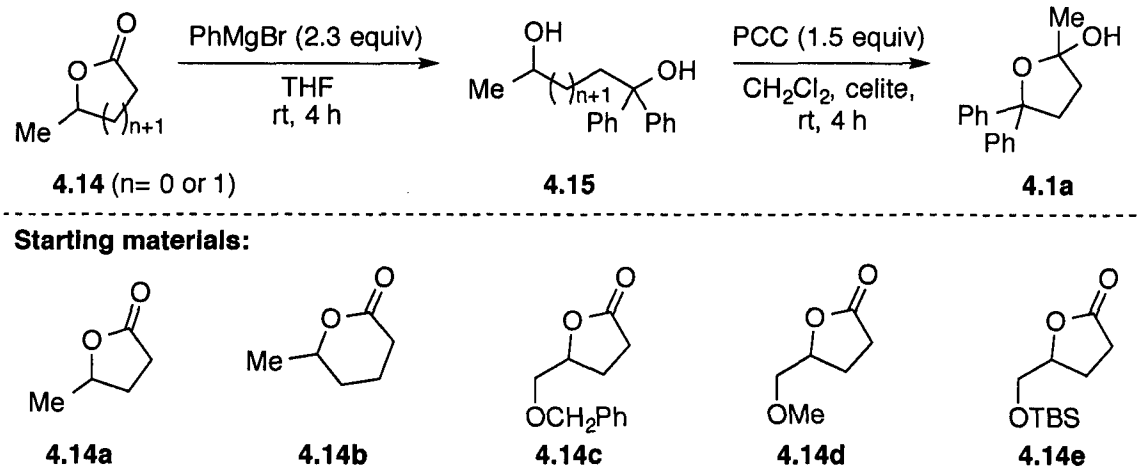


A mixture of 2 equilibrium acyclic and cyclic isomers in 0.5:0.5 (1:1) ratio White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (3H×0.5, s), 1.89 (1H×0.5, dt, J = 6.8, 11.6 Hz), 2.08 (3H×0.5, s), 2.05-2.12 (1H×0.5, m), 2.40 (1H×0.5, s), 2.47 (2H×0.5, t, J = 7.2 Hz), 2.59 (2H×0.5, t, J = 7.2 Hz), 2.66 (1H×0.5, ddd, J = 2.8, 7.2, 12.4 Hz), 2.76 (1H×0.5, s), 2.87 (1H×0.5, dt, J = 6.8, 11.6 Hz), 7.15-7.36 (12H×0.5, m), 7.38-7.46 (8H×0.5, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 30.1, 35.0, 38.0, 38.4, 38.6, 77.4, 89.2, 105.7, 125.6, 125.9 (overlapped), 126.1, 126.6, 126.8, 126.9 (overlapped), 128.0, 128.1, 128.2 (overlapped), 146.3, 146.7 (overlapped), 147.2, 209.9.

5.4 Experimental data for Chapter 4

5.4.1 Synthesis of Hemiacetals

5.4.1.1 Method A: For the synthesis of hemiacetals 4.1a, 4.1j, 4.1m and 4.1ad-4.1af



Scheme 5-20. *General scheme for preparation of hemiacetal* ***4.1*** *using* ***Method A.***

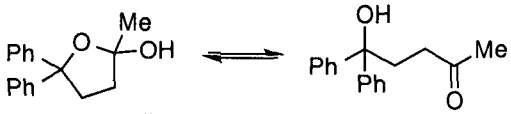
A typical procedure for synthesis of 2-methyl-5,5-diphenyltetrahydrofuran-2-ol (4.1a):

To an ice-cooled solution of γ-valerolactone (**4.14a**) (3.00 g, 29.9 mmol) in THF (60 mL) was added an Et_2O solution of phenylmagnesium bromide (3.0 M, 22.9 mL, 68.9 mmol), under an inert atmosphere. The reaction mixture was then warmed to room temperature, and left to stir for 4 h. After the consumption of **4.14a**, judged by thin layer chromatography analysis, the reaction was cooled in an ice-water bath before quenching with aqueous 1 M HCl solution and the organic materials were extracted three times with Et_2O. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude 1,4-diol **4.15** was used directly for next step.

The crude 1,4-diol **4.15** obtained was dissolved in CH_2Cl_2 (300 mL) and added to a 500 mL round bottomed flask, a third filled with celite. Pyridinium chlorochromate (PCC) (9.67 g, 44.9 mmol) was added to the mixture and stirred rigorously at room temperature for 4 h. Upon consumption of 1,4-diol by thin layer chromatography

analysis, the reaction mixture was filtered over a celite pad and the filtrate was concentrated in *vacuo* to yield the crude residue, which was purified by flash column chromatography (hexane : EtOAc = 80 : 20) to give 2-methyl-5,5-diphenyltetrahydrofuran-2-ol (**4.1a**) (4.95 g, 19.5 mmol) as an equilibrium mixture with 5-hydroxy-5,5-diphenylpentan-2-one (acyclic form) in 0.5:0.5 ratio, in 65% yield over two steps. The resulting white solid was recrystallized from EtOAc-hexane before use.

2-Methyl-5,5-diphenyltetrahydrofuran-2-ol (4.1a)[34]



cyclic : acyclic = 0.5 : 0.5

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (3H×0.5, s), 1.90 (1H×0.5, dt, J = 6.8, 11.6 Hz), 2.09 (3H×0.5, s), 2.07-2.13 (1H×0.5, m), 2.49 (2H×0.5, t, J = 6.8 Hz), 2.61 (2H×0.5, t, J = 7.2 Hz), 2.68 (1H×0.5, ddd, J = 2.8, 7.2, 12.4 Hz), 2.81 (1H×0.5, s), 2.89 (1H×0.5, dt, J = 6.8, 11.6 Hz), 7.20-7.33 (12H×0.5, m), 7.42-7.48 (8H×0.5, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 30.1, 35.0, 38.0, 38.4, 38.6, 77.4, 89.2, 105.7, 125.6, 125.9 (overlapped), 126.1, 126.6, 126.8, 126.9 (overlapped), 128.0, 128.1, 128.2 (overlapped), 146.3, 146.7 (overlapped), 147.2, 209.9.

2-Methyl-1-oxaspiro[4.4]nonan-2-ol (4.1j)

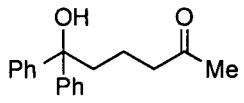
cyclic : acyclic = 0.3 : 0.7

Prepared from γ-valerolactone (**4.14a**) and 1,4-bis(bromomagnesium)butane (0.25 M in THF), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 31% overall yield in two steps as an equilibrium mixture with 4-(1-hydroxycyclopentyl)butan-2-one (acyclic form) in 0.3:0.7 ratio.

Yellow oil; IR (NaCl) 3414, 2958, 2870, 1701, 1166, 985 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (3H×0.3, s), 1.52-1.92 (8H×0.7 + 12H×0.3, m), 1.86 (2H×0.7, t, J = 7.2

Hz), 2.18 (3H×0.7, s), 2.63 (2H×0.7, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 23.75, 23.79, 28.2, 30.0, 34.7, 36.0, 38.5, 39.0, 39.4, 39.7, 39.9, 81.7, 92.6, 104.8, 209.9; HRMS (ESI): Found: m/z 157.1224. Calcd for $C_9H_{17}O_2$: $(M+H)^+$ 157.1229.

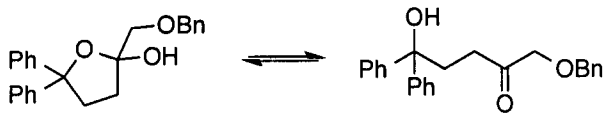
6-Hydroxy-6,6-diphenylhexan-2-one (4.1m)



Prepared from δ-hexalactone (**4.14b**) and phenylmagnesium bromide (3.0 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 44% overall yield in two steps.

White solid, mp 103-105 °C; IR (NaCl) 3388, 2960, 1703, 1651, 1446 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.65 (2H, m), 2.07 (3H, s), 2.24-2.28 (2H, m), 2.34 (2H, t, J = 7.2 Hz), 7.20 (2H, t, J = 7.6 Hz), 7.29 (4H, t, J = 7.6 Hz), 7.40 (4H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 29.7, 41.1, 43.5, 78.0, 125.9, 126.8, 128.1, 146.9, 209.1; HRMS (ESI): Found: m/z 269.1545. Calcd for $C_{18}H_{21}O_2$: $(M+H)^+$ 269.1542.

2-((Benzyloxy)methyl)-5,5-diphenyltetrahydrofuran-2-ol (4.1ad)



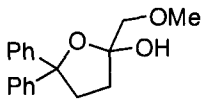
cyclic : acyclic = 0.8 : 0.2

Prepared from 5-((benzyloxy)methyl) dihydrofuran-2(3*H*)-one (**4.14c**) [35], and phenylmagnesium bromide (3.0 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 24% overall yield in two steps as an equilibrium mixture with 2-((benzyloxy)methyl)-5,5-diphenyltetrahydrofuran-2-ol (acyclic form) in 0.8:0.2 ratio.

White solid, mp 54-55 °C; IR (NaCl) 3535, 3062, 2864, 1774, 1490, 1448, 1097, 991 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (1H×0.8, ddd, J = 1.2, 7.2, 12.0 Hz), 2.04 (1H×0.8, ddd, J = 3.6, 6.8, 12.4 Hz), 2.58 (2H×0.2, t, J = 7.6 Hz), 2.67 (1H×0.8, ddd, J = 3.2, 7.2, 12.4 Hz), 2.81 (1H×0.8, ddd, J = 6.8, 10.8, 12.4 Hz), 2.91 (2H×0.2, t, J = 7.6 Hz), 3.341

(2H×0.2, s), 3.344 (2H×0.2, s), 3.60 (2H×0.8, s), 4.70 (2H×0.8, d, J = 3.6 Hz), 7.18-7.46 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) (for the cyclic isomer) δ 35.0, 37.8, 73.6, 74.8, 89.8, 105.3, 125.4, 125.9, 162.2, 126.7, 126.8, 127.8, 128.0, 128.4, 128.6, 137.9, 145.9, 147.0; HRMS (ESI): Found: m/z 361.1804. Calcd for $C_{24}H_{25}O_3$: $(M+H)^+$ 361.1804.

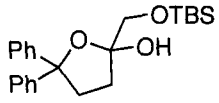
2-(Methoxymethyl)-5,5-diphenyltetrahydrofuran-2-ol (4.1ae)



Prepared from 5-(methoxymethyl) dihydrofuran-2(3*H*)-one (**4.14d**) [36] and phenylmagnesium bromide (3.0 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 27% overall yield in two steps

White solid, mp 115-116 °C; IR (NaCl) 3527, 2929, 2856, 1597, 1446, 1074, 921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (1H, dt, J = 7.6, 11.6 Hz), 2.06 (1H, ddd, J = 3.2, 6.8, 12.4 Hz), 2.71 (1H, ddd, J = 3.2, 7.2, 12.4 Hz), 2.82 (1H, dt, J = 6.8, 7.2 Hz), 3.35 (1H, s), 3.51 (3H, s), 3.53 (2H, d, J = 4.0 Hz), 7.16-7.31 (6H, m), 7.43 (4H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.0, 37.7, 59.8, 89.7, 105.1, 125.8, 126.2, 126.7, 126.8, 127.9, 128.0, 145.9, 146.9; HRMS (ESI): Found: m/z 285.1494. Calcd for $C_{18}H_{21}O_3$: $(M+H)^+$ 285.1491.

2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5,5-diphenyltetrahydrofuran-2-ol (4.1af)

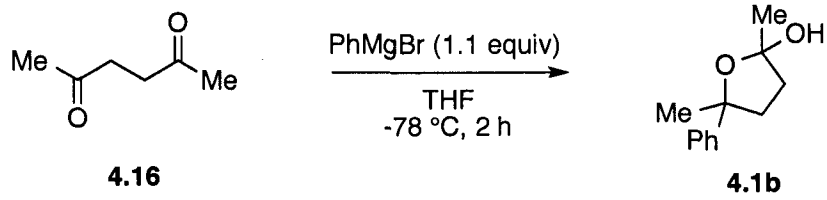


Prepared from 5-(((*tert*-butyldimethylsilyl)oxy)methyl) dihydrofuran-2(3*H*)-one (**4.14e**)[37] and phenylmagnesium bromide (3.0 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 29% overall yield in two steps

White solid, mp 67-68 °C; IR (NaCl,) 3527, 2954, 2929, 2856, 1490, 1446, 1253, 1095, 921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (3H, s), 0.13 (3H, s), 0.93 (9H, s), 1.91 (1H, ddd, J = 7.2, 8.0, 11.6 Hz), 2.01 (1H, ddd, J = 3.6, 7.2, 12.8 Hz), 2.71 (1H, ddd, J = 3.6, 7.2, 12.4 Hz), 2.82 (1H, ddd, J = 6.8, 10.8, 12.4 Hz), 3.41 (1H, s), 3.71 (2H, d, J = 2.4

Hz), 7.17-7.21 (2H, m), 7.29 (4H, t, J = 7.6 Hz), 7.45-7.48 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, -5.3, 18.4, 25.6, 25.9, 34.5, 37.8, 68.4, 89.3, 105.6, 125.9, 126.0, 126.1, 126.7, 127.9, 128.0, 146.2, 147.3; HRMS (ESI): Found: m/z 385.2199. Calcd for $C_{23}H_{36}O_3Si$: $(M+H)^+$ 385.2199.

5.4.1.2 Method B: For the synthesis of hemiacetals 4.1b-4.1i



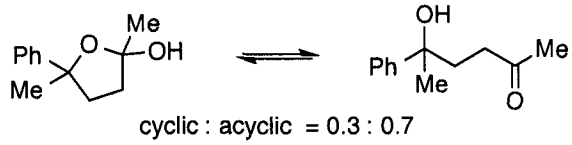
4.16 **4.1b**

Scheme 5-22. *Preparation of hemiacetal **4.1** using **Method B**.*

A typical procedure for synthesis of 2,5-dimethyl-5-phenyltetrahydrofuran-2-ol (4.1b)

A solution of hexane-2,5-dione (**4.16**) (1.14 g, 10.0 mmol) in THF (20 mL) was cooled to -78 °C in a dry ice-acetone bath under an inert atmosphere. An Et_2O/THF solution of phenylmagnesium bromide (3.0 M, 3.7 mL, 11.0 mmol, diluted with anhydrous THF (7.5 mL)) was then added drop wise via a dropping funnel over 30 min and left to stir for 2 h at the same temperature. After the consumption of **4.16** judged by thin layer chromatography analysis, the reaction was quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted three times with Et_2O. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (hexane : EtOAc = 70 : 30) to give 2,5-dimethyl-5-phenyltetrahydrofuran-2-ol (**4.1b**) (0.96 g, 5.02 mmol) in 50% yield as an equilibrium mixture with 5-hydroxy-5-phenylhexan-2-one (acyclic form) in 0.3:0.7 ratio.

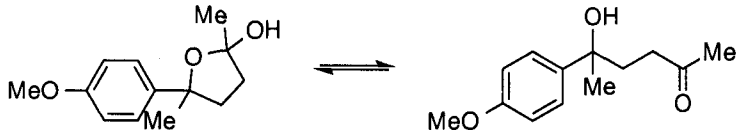
2,5-dimethyl-5-phenyltetrahydrofuran-2-ol (4.1b)



cyclic : acyclic = 0.3 : 0.7

Yellow oil; IR (NaCl) 3451, 3059, 2974, 2931, 1712, 1600, 1492, 1444, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (3H×0.1, s), 1.56 (3H×0.7, s), 1.62 (3H×0.1, s), 1.63 (3H×0.2, s), 1.65 (3H×0.2, s), 2.08 (3H×0.7, s), 2.04-2.49 (4H×0.7 + 4H×0.3, m), 2.50 (1H, brs), 7.21-7.26 (1H×0.7 + 1H×0.3, m), 7.30-7.38 (2H×0.7 + 2H×0.3, m), 7.40-7.47 (2H×0.7 + 2H×0.3, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.1, 30.0, 30.3, 31.2, 31.8, 37.3, 37.6, 38.2, 38.5, 38.8, 39.4, 73.9, 85.7, 85.9, 105.5, 105.6, 124.5, 124.6, 124.8, 126.3, 126.4, 126.6, 128.0, 128.1, 128.2, 147.1, 148.1, 149.1, 210.0; HRMS (ESI): Found: m/z 193.1228. Calcd for $C_{12}H_{17}O_2$: $(M+H)^+$ 193.1229.

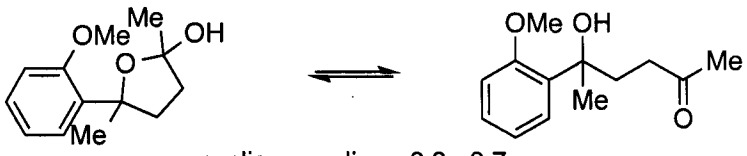
5-(4-methoxyphenyl)-2,5-dimethyltetrahydrofuran-2-ol (4.1c)



cyclic : acyclic = 0.4 : 0.6

Prepared with (4-methoxyphenyl)magnesium bromide (1.3 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 57% yield as an equilibrium mixture with 5-hydroxy-5-(4-methoxyphenyl)hexan-2-one (acyclic form) in 0.4:0.6 ratio. Yellow solid, mp 66-78 °C; IR (NaCl) 3595, 3016, 2837, 1708, 1610, 1510, 1247, 1033, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (3H×0.1, s), 1.54 (3H×0.6, s), 1.61 (3H×0.1, s), 1.62 (3H×0.3, s), 1.63 (3H×0.3, s), 2.08 (3H×0.6, s), 2.03-2.25 (2H×0.6 + 2H×0.4, m), 2.32-2.47 (2H×0.6 + 2H×0.4, m), 3.79 (3H×0.1, s), 3.80 (3H×0.3, s), 3.81 (3H×0.6, s), 6.85-6.89 (2H×0.6 + 2H×0.4, m), 7.29-7.39 (2H×0.6 + 2H×0.4, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.1, 30.0, 30.3, 31.2, 31.8, 37.3, 37.7, 38.3, 38.6, 38.9, 39.4, 55.2 (overlapped), 73.7, 85.5, 85.8, 105.5, 105.6, 113.3, 113.4, 113.5, 125.7, 125.8, 125.9, 139.3, 140.3, 141.2, 158.1, 158.2, 158.3, 210.0; HRMS (ESI): Found: m/z 223.1334. Calcd for $C_{13}H_{19}O_3$: $(M+H)^+$ 223.1334.

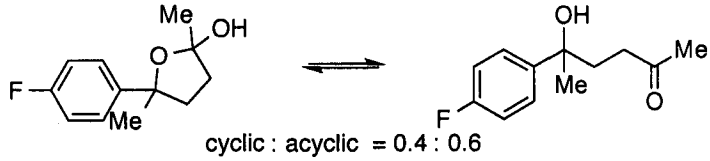
5-(2-methoxyphenyl)-2,5-dimethyltetrahydrofuran-2-ol (4.1d)



cyclic : acyclic = 0.3 : 0.7

Prepared with (2-methoxyphenyl)magnesium bromide (1.5 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 58% yield as an equilibrium mixture with 5-hydroxy-5-(2-methoxyphenyl)hexan-2-one (acyclic form in 0.4:0.6 ratio. White solid, mp 71-77°C; IR (NaCl) 3595, 3010, 2937, 2837, 1707, 1597, 1485, 1236, 1043, 927 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (3H×0.1, s), 1.56 (3H×0.7, s), 1.63 (3H×0.3, s), 1.69 (3H×0.2, s), 2.07 (3H×0.7, s), 2.01-2.11 (2H×0.7 m), 2.32-2.48 (2H×0.7 + 2H×0.3, m), 3.82 (3H×0.1, s), 3.83 (3H×0.2, s), 3.88 (3H×0.7, s), 4.11 (1H, brs), 6.86-6.70 (2H×0.7 + 2H×0.3, m), 7.19-7.21 (2H×0.2, m), 7.23 (1H×0.7, dd, J = 2.0, 7.2 Hz), 7.34 (1H ×0.7, dd, J = 1.6, 7.6 Hz), 7.56 (1H ×0.1, dd, J = 2.0, 7.6 Hz), 7.68 (1H ×0.1, dd, J = 2.0, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 27.6, 27.7, 27.9, 29.3, 29.9, 35.1, 37.1, 37.2, 37.8, 37.9, 39.3, 55.0, 55.1, 55.3; 74.2, 84.9, 85.4, 105.1 (overlapped), 110.8, 110.9, 111.3, 120.1, 120.3, 120.8, 125.7, 126.2, 126.7, 127.7, 127.8, 128.2, 134.2, 135.6, 137.4, 155.3 (overlapped), 156.6, 209.8; HRMS (ESI): Found: m/z 223.1333. Calcd for $C_{13}H_{19}O_3$: $(M+H)^+$ 223.1334.

5-(4-fluorophenyl)-2,5-dimethyltetrahydrofuran-2-ol (4.1e)

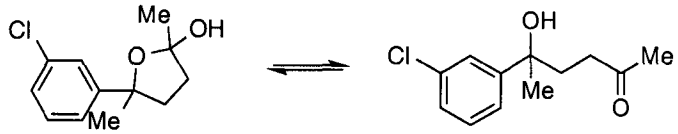


cyclic : acyclic = 0.4 : 0.6

Prepared with (4-fluorophenyl)magnesium bromide (1.1 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 59% yield as an equilibrium mixture with 5-(4-fluorophenyl)-5-hydroxyhexan-2-one (acyclic form) in 0.4:0.6 ratio.

Yellow oil; IR (NaCl) 3415, 2976, 1701, 1600, 1508, 1014, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H×0.2, s), 1.53 (3H×0.6, s), 1.61 (3H×0.2, s), 1.62 (3H×0.2, s), 1.63 (3H×0.2, s), 2.08 (3H×0.6, s), 2.01-2.16 (2H×0.6 +2H×0.4, m), 2.33-2.46 (2H×0.6 + 2H×0.4, m), 2.63 (1H, brs), 6.96-7.05 (2H×0.6 + 2H×0.4, m), 7.32-7.44 (2H×0.6 + 2H×0.4, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.1, 30.0, 30.2, 31.3, 31.8, 37.3, 37.6, 38.1, 38.6, 38.7, 39.5, 73.7, 85.3, 85.6, 105.6, 105.7, 114.6 (d, J = 17.0 Hz), 114.8 (d, J = 17.0 Hz), 115.3 (d, J = 18.0 Hz), 126.1 (d, J = 6.0 Hz), 126.3 (d, J = 6.0 Hz), 126.5 (d, J = 6.0 Hz), 142.9 (d, J = 2.0 Hz), 143.9 (d, J = 2.0 Hz), 144.9 (d, J = 2.0 Hz), 161.5 (d, J = 194.0 Hz), 161.6 (d, J = 194.0 Hz) (overlapped), 210.0; HRMS (ESI): Found: m/z 211.1137. Calcd for $C_{12}H_{16}O_2F$: $(M+H)^+$ 211.1134.

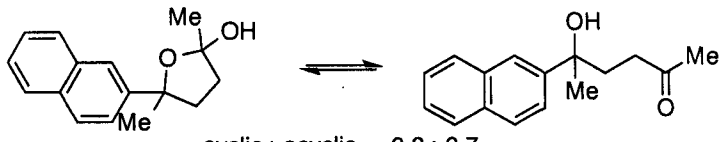
5-(3-chlorophenyl)-2,5-dimethyltetrahydrofuran-2-ol (4.1f)



cyclic : acyclic = 0.4 : 0.6

Prepared with (3-chlorophenyl)magnesium bromide (1.2 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 43% yield as an equilibrium mixture with 5-(3-chlorophenyl)-5-hydroxyhexan-2-one (acyclic form) in 0.4:0.6 ratio. Yellow oil; IR (NaCl) 3439, 3066, 2976, 2931, 1712, 1595, 1105, 927, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (3H×0.2, s), 1.54 (3H×0.6, s), 1.62 (3H×0.2, s), 1.625 (3H×0.2, s), 1.63 (3H×0.2, s) 2.09 (3H×0.6, s), 2.01-2.24 (2H×0.6 +2H×0.4, m), 2.33-2.51 (2H×0.6 + 2H×0.4, m), 2.78 (1H, brs), 7.19-7.27 (3H×0.6 + 3H×0.4, m), 7.38 (1H×0.2, s), 7.43 (1H×0.6, s), 7.46 (1H ×0.2, t, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.1, 30.1, 30.2, 31.1, 31.6, 37.1, 37.6, 38.0, 38.5, 38.7, 39.4, 73.7, 85.2, 85.5, 105.7 (overlapped), 122.8, 122.9, 123.1, 125.0, 125.1, 125.3, 126.6 (overlapped), 126.8, 129.3, 129.4, 129.6, 134.0, 134.05, 134.3, 149.5, 150.4, 151.4, 210.1; HRMS (ESI): Found: m/z 227.0843. Calcd for $C_{12}H_{16}O_2Cl$: $(M+H)^+$ 227.0839.

2,5-dimethyl-5-(naphthalen-2-yl)tetrahydrofuran-2-ol (4.1g)

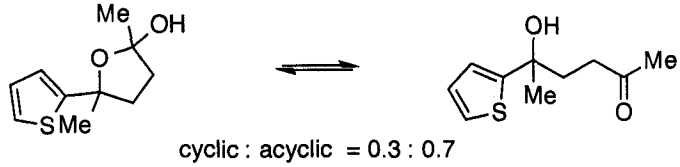


cyclic : acyclic = 0.3 : 0.7

Prepared with (2-naphthyl)magnesium bromide (1.2 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 47% yield as an equilibrium mixture with 5-hydroxy-5-(naphthalen-2-yl)hexan-2-one (acyclic form) in 0.3:0.7 ratio.

Yellow solid, mp 62-65 °C; IR (NaCl) 3595, 3433, 3016, 1707, 1506, 1373, 1099, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (3H×0.1, s), 1.67 (3H×0.7, s), 1.70 (3H×0.1, s), 1.71 (3H×0.2, s), 1.77 (3H×0.2, s), 2.07 (3H×0.7, s), 2.10-2.57 (2H×0.7 +4H×0.3, m), 2.23 (2H×0.7, dt, J = 1.6, 6.8 Hz), 2.81 (1H, brs), 7.47-7.52 (3H×0.7 + 3H×0.3, m), 7.83-7.89 (3H×0.7 + 3H×0.3, m), 7.90 (1H×0.2, s), 7.96 (1H×0.7, s), 7.97 (1H×0.1, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.1, 30.0, 30.2, 31.2, 31.7, 37.0, 37.6, 38.2, 38.3, 38.8, 39.1, 74.1, 85.7, 86.0, 105.6, 105.7, 122.6, 122.7, 123.3, 123.4, 123.6, 123.8, 125.5, 125.54, 125.7, 125.9, 126.0, 126.1, 127.4 (overlapped), 127.8, 127.9, 128.0, 128.05, 128.1 (overlapped), 132.2 (overlapped), 123.3, 133.0, 133.1, 133.3, 144.4, 145.3, 146.4, 210.1; HRMS (ESI): Found: m/z 243.1382. Calcd for $C_{16}H_{19}O_2$: $(M+H)^+$ 243.1385.

2,5-dimethyl-5-(thiophen-2-yl)tetrahydrofuran-2-ol (4.1h)



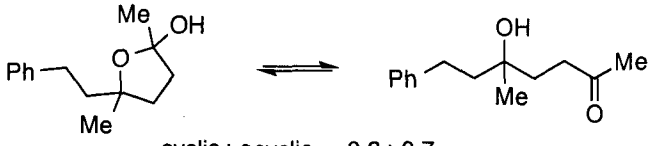
cyclic : acyclic = 0.3 : 0.7

Prepared with (2-thienyl)magnesium bromide (0.8 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 77% yield as an equilibrium mixture with 5-hydroxy-5-(thiophen-2-yl)hexan-2-one (acyclic form) in 0.3:0.7 ratio.

Brown oil; IR (NaCl) 3425, 3103, 2974, 1701, 1371, 1099, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (3H×0.1, s), 1.59 (3H×0.1, s), 1.63 (3H×0.7 + 3H×0.2, s), 1.75 (3H×0.2, s), 2.12 (3H×0.7, s), 1.92-2.28 (2H×0.7 + 4H×0.2 + 2H×0.1, m), 2.38-2.61 (2H×0.7 +

2H×0.1, m), 2.94 (1H, brs), 6.84 (1H×0.2, dd, J = 1.2, 3.6 Hz), 6.87 (1H×0.7, dd, J = 1.2, 3.2 Hz), 6.91-6.96 (1H×0.7 + 1H×0.3, 1H×0.1, m), 7.13 (1H×0.2, dd, J = 1.2, 4.8 Hz), 7.16 (1H×0.1, dd, J = 1.2, 4.8 Hz), 7.18 (1H×0.7, dd, J = 1.2, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.0, 29.9, 30.0, 31.5, 31.7, 37.7, 37.9, 38.4, 38.9, 39.7, 40.4, 73.3, 83.7, 84.7, 105.8, 105.9, 121.3, 122.2 (overlapped), 123.2, 123.6, 123.7, 126.7, 126.8, 126.84, 152.7, 153.4, 153.5, 209.8; HRMS (ESI): Found: m/z 199.0794. Calcd for $C_{10}H_{15}O_2S$: $(M+H)^+$ 199.0793.

2,5-dimethyl-5-phenethyltetrahydrofuran-2-ol (4.1i)

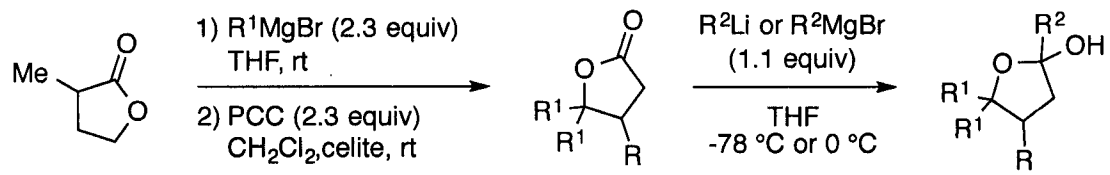


cyclic : acyclic = 0.3 : 0.7

Prepared with phenethylmagnesium bromide (0.35 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 42% yield as an equilibrium mixture with 5-hydroxy-5-methyl-7-phenylheptan-2-one (acyclic form) in 0.3:0.7 ratio.

Pale yellow oil; IR (NaCl) 3417, 2970, 1712, 1602, 1496, 1454, 1373,1107, 920 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H×0.7 + 3H×0.1, s), 1.42 (3H×0.2, s), 1.53 (3H×0.2, s), 1.71 (3H×0.1, s), 1.73-2.14 (5H, m), 2.17 (3H×0.7, s), 2.58-2.71 (3H, m), 7.17-7.20 (3H, m), 7.25-7.30 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 26.5, 28.0, 28.4, 28.5, 30.0, 30.3, 30.9, 31.2, 34.9, 35.9, 36.0, 37.7, 38.3, 38.4, 43.7, 44.3, 44.8, 71.8, 84.4, 84.7, 105.1, 105.4, 125.6, 125.7, 125.8, 128.24, 128.27 (overlapped), 128.3, 128.34, 128.4, 142.3, 142.5, 142.6, 209.7; HRMS (ESI): Found: m/z 221.1546. Calcd for $C_{14}H_{21}O_2$: $(M+H)^+$ 221.1542.

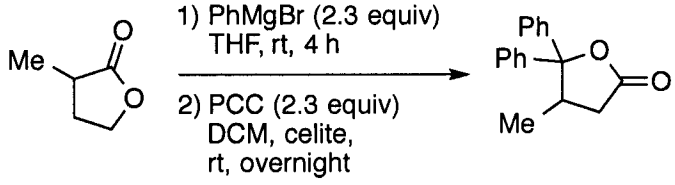
5.4.1.3 Method C: For the synthesis of hemiacetals 4.1k, 4.1l, 4.1aa-ac, and 4.6



4.17 **4.18** **4.1**

Scheme 5-23. *Preparation of lactols* ***4.1*** *using* ***Method C****.*

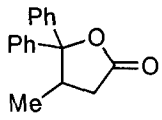
Step 1: A typical procedure for synthesis of 4-methyl-5,5-diphenyldihydrofuran-2(3*H*)-one (4.18a):



4.17a **4.18a**

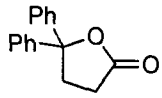
To an ice-cooled solution of α-methyl-γ-butyrolactone (**4.17a**) (1.89 mL, 20.0 mmol) in THF (40 mL) was added an Et_2O solution of phenylmagnesium bromide (3.0 M, 15.3 mL, 46.0 mmol), under an inert atmosphere. The reaction mixture was then warmed to room temperature, and left to stir for 4 h. After the complete consumption of **S-7** by thin layer chromatography analysis, the reaction was cooled in an ice-water bath before quenching with aqueous 1M HCl solution and the organic materials were extracted three times with Et_2O. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude 1,4-diol was then dissolved in CH_2Cl_2 (100 mL) and added to a 250 mL round bottomed flask, a third-filled with celite. Pyridinium chlorochromate (9.89 g, 46.0 mmol) was then added to mixture and stirred rigorously at room temperature overnight. After the complete consumption of diol by thin layer chromatography analysis, the reaction mixture was filtered over a celite pad and the filtrate was concentrated in *vacuo* to yield the crude residue, which was purified by flash column chromatography (hexane : EtOAc = 80 : 20) to give 4-methyl-5,5-diphenyldihydrofuran-2(3*H*)-one (**4.18a**) (3.83 g, 15.2 mmol) in 76% yield.

4-methyl-5,5-diphenyldihydrofuran-2(3*H*)-one (4.18a)[38]



White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, d, J = 6.8Hz), 2.32 (1H, dd, J = 5.2, 17.2 Hz), 2.71 (1H, dd, J = 7.2, 17.2 Hz), 3.42 (1H, qd, J = 2.4, 7.2 Hz), 7.23-7.38 (8H, m), 7.51-7.53 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 37.5, 38.1, 92.3, 125.6, 126.1, 127.4, 128.1, 128.2, 128.6, 140.5, 142.8, 175.7.

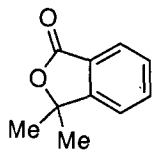
5,5-diphenyldihydrofuran-2(3*H*)-one (4.18b or 4.5a)[39]



Prepared from γ-butyrolactone and phenylmagnesium bromide (3.0 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 67% yield.

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (2H, t, J = 7.6 Hz), 2.90 (2H, t, J = 7.6 Hz), 7.25-7.29 (2H, m), 7.32-7.36 (4H, m), 7.41-7.43 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 35.6, 89.7, 125.3, 127.9, 128.6, 143.0, 176.0.

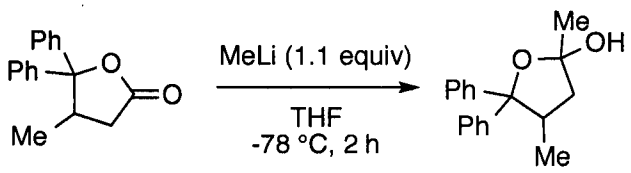
3,3-dimethylisobenzofuran-1(3*H*)-one (4.18c or 4.7)



Prepared from phthalide and methylmagnesium bromide (3.0 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 70 : 30) in 80% yield.

White solid, mp 69-73 °C; IR (NaCl) 3020, 2983, 2399, 1762, 1614, 1467, 1134, 1047, 906 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (6H, s), 7.42 (1H, d, J = 7.6 Hz), 7.51 (1H, t, J = 7.6 Hz), 7.68 (1H, dt, J = 0.8, 7.6 Hz), 7.86 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 85.3, 120.6, 125.2, 125.6, 128.8, 134.0, 154.9, 169.7; HRMS (ESI): Found: m/z 163.0760. Calcd for $C_{10}H_{11}O_2$: $(M+H)^+$ 163.0759.

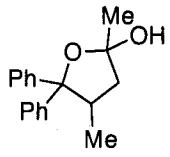
Step 2: Method 1: A typical procedure for synthesis of 2,4-dimethyl-5,5-diphenyltetrahydrofuran-2-ol (4.1k) using methyl lithium:



4.18a **4.1j**

A solution of **4.18a** (1.26 g, 5.0 mmol) in THF (10 mL) was cooled to -78 °C in a dry ice-acetone bath under an inert atmosphere. A diethoxymethane solution of methyl lithium (3.0 M, 1.8 mL, 5.5 mmol) was then added drop wise via syringe and left to stir for 2 h at the same temperature. After the consumption of **4.18a** judged by thin layer chromatography analysis, the reaction was quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted three times with Et_2O. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (hexane : EtOAc = 80 : 20) to give 2,4-dimethyl-5,5-diphenyltetrahydrofuran-2-ol (**4.1k**) (1.26 g, 4.69 mmol) as a equilibrium mixture with 5-hydroxy-4-methyl-5,5-diphenylpentan-2-one (acyclic form) in a 0.9:0.1 ratio, in 93% yield. The pure cyclic isomer can be obtained by recrystallization from Et_2O/hexanes.

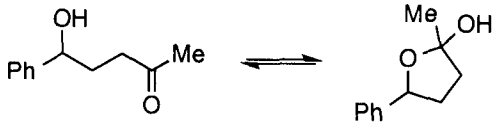
2,4-dimethyl-5,5-diphenyltetrahydrofuran-2-ol (4.1k)



Clear crystal, mp 117-120 °C; IR (NaCl) 3589, 3059, 2976, 2399, 1446, 1382, 1004, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, d, J = 6.8 Hz), 1.73 (3H, s), 1.77 (1H, t, J = 10.8 Hz), 2.11 (1H, d, J = 1.2 Hz), 2.2 (1H, dd, J = 8.0, 12.4 Hz), 3.47 (1H, qt, J = 4.0, 6.8 Hz), 7.10-7.17 (3H, m), 7.21-7.28 (3H, m), 7.32 (2H, t, J = 7.2 Hz), 7.47 (2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 27.0, 40.7, 46.1, 90.7, 104.1, 126.4,

126.5,126.8, 126.9, 127.5, 128.0, 143.9, 147.9; HRMS (ESI): Found: m/z 269.1583. Calcd for $C_{18}H_{20}O_2$: $(M+H)^+$ 269.1542.

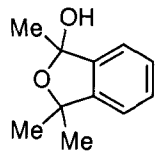
5-hydroxy-5-phenylpentan-2-one (4.1l)[40]



Prepared 5-phenyldihydrofuran-2(3H)-one (**4.18d**)[41] with and methyl lithium (3.0 M in diethoxymethane), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 45% yield as an equilibrium mixture with 2-methyl-5-phenyltetrahydrofuran-2-ol (cyclic form) in 0.8:0.2 ratio.

Yellow oil; (Only the major acyclic form is characterized): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (2H, t, J = 6.8 Hz), 2.13 (3H, s), 2.55 (2H, t, J = 6.8 Hz), 4.71 (1H, t, J = 6.4 Hz), 7.29-7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.0, 32.6, 39.8, 73.4, 125.7, 127.5, 128.5, 144.2, 209.4.

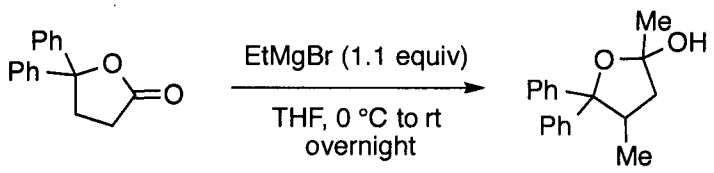
1,3,3-trimethyl-1,3-dihydroisobenzofuran-1-ol (4.6)



Prepared from 3,3-dimethylisobenzofuran-1(3H)-one (**4.18c**) with and methyl lithium (3.0 M in diethoxymethane), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 85% yield. Recrystallization from Et_2O/hexane before use.

White solid, mp 112-113 °C; IR (NaCl) 3610, 2978, 2399, 1384, 1132, 966, 927 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (3H, s), 1.56 (3H, s), 1.77 (3H, s), 7.15 (1H, d, J = 7.6 Hz), 7.31-7.39 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 29.3, 30.8, 84.5, 105.9, 120.6, 122.0, 128.0, 129.2, 141.3, 146.9; HRMS (ESI): Found: m/z 179.1075. Calcd for $C_{11}H_{15}O_2$: $(M+H)^+$ 178.1072.

Step 2: Method 2: A typical procedure for synthesis of 2-ethyl-5,5-diphenyl tetrahydrofuran-2-ol (1aa) using Grinard reagents:



4.18a **4.1k**

A solution of **4.18b** (1.19 g, 5.0 mmol) in THF (10 mL) was cooled to -0 °C in a dry ice-acetone bath under an inert atmosphere. An Et_2O solution of ethyl magnesium bromide (2.45 M, 2.25 mL, 5.5 mmol) was then added drop wise via syringe and left to stir to room temperature overnight. The reaction was then quenched with saturated aqueous NH_4Cl solution and the organic materials were extracted three times with Et_2O. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude residue was purified by flash column chromatography (hexane : EtOAc = 80 : 20) to give 2-ethyl-5,5-diphenyltetrahydrofuran-2-ol (**4.1aa**) (0.149 g, 0.55 mmol), as an equilibrium mixture with 6-hydroxy-6,6-diphenylhexan-3-one (acyclic form) in 0.5:0.5 ratio in 11% yield.

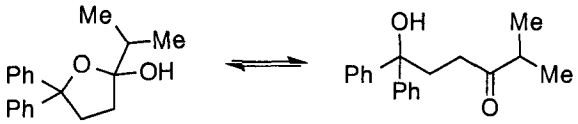
2-ethyl-5,5-diphenyltetrahydrofuran-2-ol (4.1aa)

cyclic : acyclic = 0.5 : 0.5

White solid, mp 64-67 °C; IR (NaCl) 3450, 3061, 2978, 2939, 2249, 1707, 1446, 1265, 1026, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H×0.5, t, J = 7.2 Hz), 1.03 (3H×0.5, t, J = 7.6 Hz), 1.08-1.93 (3H×0.5, m), 2.04 (1H×0.5, ddd, J = 2.8, 6.8, 12.4 Hz), 2.19 (1H×0.5, brs), 3.37 (2H×0.5, q, J = 7.6 Hz), 2.45 (2H×0.5, t, J = 6.4 Hz), 2.61 (2H×0.5, t, J = 7.2 Hz), 2.69 (1H×0.5, ddd, J = 3.2, 7.6, 12.4 Hz), 2.82 (1H, brs), 2.86 (1H×0.5, ddd, J = 1.2, 7.2, 12.4 Hz), 7.18-7.23 (2H, m), 7.24-7.32 (4H, m), 7.40-7.46 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 8.7, 33.8, 35.1, 36.1 (overlapped), 37.2, 38.0, 77.5, 88.9,

107.9, 125.7, 125.9, 126.0, 126.6, 126.7, 126.9, 128.0, 128.1, 128.2, 146.4, 146.7, 147.5, 212.7; HRMS (ESI): Found: m/z 291.1359. Calcd for $C_{18}H_{20}O_2Na$: $(M+Na)^+$ 291.1361.

2-isopropyl-5,5-diphenyltetrahydrofuran-2-ol (4.1ab)

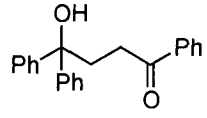


cyclic : acyclic = 0.5 : 0.5

Prepared with 5,5-diphenyldihydrofuran-2(3H)-one (**4.18b**) and isopropylmagnesium bromide (2.0 M in THF), and purified by flash column chromatography (hexane : EtOAc = 90 : 10) in 12% yield as an equilibrium mixture with 6-hydroxy-2-methyl-6,6-diphenylhexan-3-one (acyclic form) in 0.5:0.5 ratio.

White solid, mp 62-64 °C; IR (NaCl) 3448, 3059, 2970, 2933, 1701, 1446, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H×0.5, dd, J = 2.4, 6.8 Hz), 1.01 (6H×0.5, dd, J = 2.0, 6.8 Hz), 1.12 (3H×0.5, dd, J = 2.4, 6.8 Hz), 1.81-1.88 (1H×0.5, m), 1.93-2.04 (2H×0.5, m), 2.48 (2H×0.5, t, J = 7.2 Hz), 2.51 (1H×0.5, sep, J = 6.8 Hz), 2.59 (2H×0.5, t, J = 6.4 Hz), 2.71 (1H×0.5, ddt, J = 2.0, 7.6, 12.4 Hz), 2.821 (1H×0.5, ddd, J = 2.0, 6.8, 11.6 Hz), 2.93 (1H, brs), 7.14-7.22 (2H, m), 7.24-7.31 (4H, m), 7.40-7.44 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 17.9, 18.2, 35.1, 35.3, 35.4, 37.5, 37.9, 40.9, 77.5, 88.9, 109.4, 125.6, 125.9, 126.0, 126.55, 126.58, 126.8, 127.9, 128.0, 128.1, 146.4, 146.8, 147.9, 216.1; HRMS (ESI): Found: m/z 283.1698. Calcd for $C_{19}H_{23}O_2$: $(M+H)^+$ 283.1698.

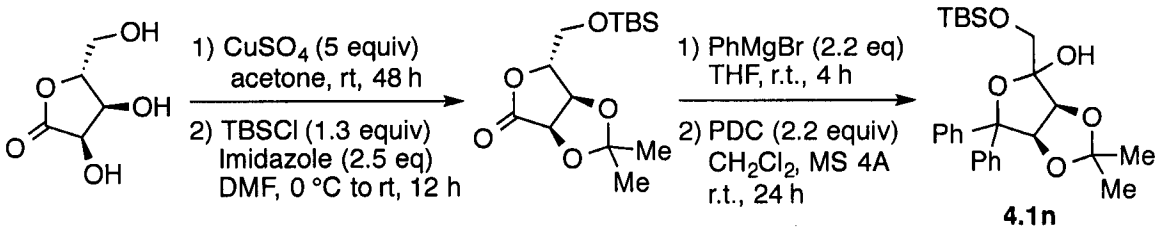
4-hydroxy-1,4,4-triphenylbutan-1-one (4.1ac)



Prepared with 5,5-diphenyldihydrofuran-2(3H)-one (**4.18b**) and phenylmagnesium bromide (3.0 M in Et_2O), and purified by flash column chromatography (hexane : EtOAc = 80 : 20) in 14% yield.

White solid, mp 92-93 °C; IR (NaCl) 3491, 3057, 2958, 1678, 1492, 1446, 1357, 1294 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.78 (2H, t, J = 7.2 Hz), 2.81 (1H, s), 3.03 (2H, t, J = 6.8 Hz), 7.22 (2H, tt, J = 1.2, 7.2 Hz), 7.30-7.33 (4H, m), 7.40 (2H, t, J = 8.0 Hz), 7.46-7.48 (4H, m), 7.52 (1H, tt, J = 2.0, 7.6 Hz), 7.86-7.88 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 35.5, 77.6, 126.0, 126.9, 128.1, 128.2, 128.5, 133.1, 136.8, 146.8, 201.1; HRMS (ESI): Found: m/z 317.1545. Calcd for $C_{22}H_{21}O_2$: $(M+H)^+$ 317.1542.

5.4.1.4 Synthesis of hemiacetal 4.1n



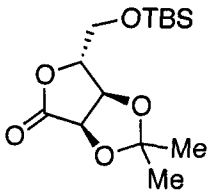
Scheme 5-24. *Preparation of lactol **4.1n**.*

Finely ground copper(II) sulfate pentahydrate (27.5 g, 110 mmol) was heated at 160 °C using a silicon oil bath in a 100 mL round bottomed flask under vacuum overnight to obtain anhydrous copper(II) sulfate. D-(+)-ribonic γ-lactone (3.26 g, 22.0 mmol) and acetone (50 mL) was then added and the reaction mixture was stirred at room temperature for 48 h under an inert atmostphere. Upon consumption of starting materials by thin layer chromatography analysis, the reaction mixture was filtered over a celite pad and the filtrate was concentrated in *vacuo* to provide 2,3-*O*-isopropylidene-D-ribonic γ-lactone in quatitative yields. This was then treated with imidazole (3.74 g, 55.0 mmol) and anhydrous DMF (10 mL) and cooled to 0 °C in an ice-water bath under an inert atmosphere. tert-Butyldimethylsilyl chloride (4.31 g, 28.6 mmol) was then added in one portion and left to be stirred at room temperature for 12 h. The reaction was quenched with H_2O and the organic materials were extracted three times with Et_2O. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude materials were purified

by flash column chromatography (hexane : EtOAc = 95 : 5) to give D-Ribonic acid, 5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-, γ-lactone (6.42 g, 21.3 mmol) in 97% yield.

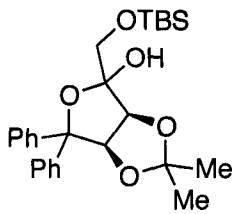
To an ice-cooled solution of (6.42g, 21.3 mmol) in anhydrous THF (50 mL) was added an Et_2O solution of phenylmagnesium bromide (3.0 M, 15.6 mL, 46.9 mmol), under an inert atmosphere. The reaction mixture was then warmed to room temperature, and left to stir for 4 h. After the completion of reaction judged by thin layer chromatography analysis, the reaction was cooled in an ice-water bath before quenching with sat. aqueous NH_4Cl solution and the organic materials were extracted three times with Et_2O. The combined extracts were washed with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* the resulting crude materials were purified by flash column chromatography (hexane : EtOAc = 90 : 10) to give (*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-((4*R*,5*R*)-5-(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (4.77 g, 10.4 mmol) in 49% yield. (*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-((4*R*,5*R*)-5-(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (4.59 g, 10.0 mmol) was then treated with pyridinium dichromate (8.28 g, 22.0 mmol) and Molecular Sieves 4A (1.5 g) in dry CH_2Cl_2 (50 mL) under an inert atmosphere. The reaction mixture was stirred rigoursly at room temperature for 24 h. After the complete consumption of starting materials by thin layer chromatography analysis, the reaction mixture was filtered over a celite pad and the filtrate was concentrated in *vacuo* to yield the crude residue, which was purified by flash column chromatography (hexane : EtOAc = 95 : 5) to give (3a*S*,6a*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-6,6-diphenyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (**4.1n**) (2.72 g, 4.27 mmol) in 43% yield as a mixture of two diastereomer in 1:1 ratio.

5-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,3-*O*-(1-methylethylidene)-, γ-lactone (S-11)[42]



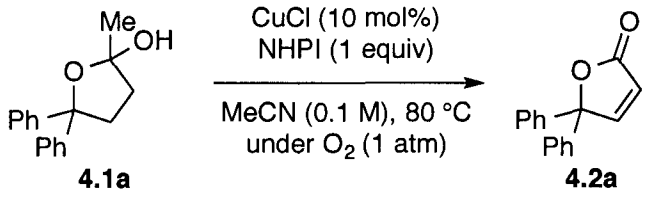
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (3H, s), 0.08 (3H, s), 0.86 (9H, s), 1.38 (3H, s), 1.46 (3H, s), 3.74 (1H, dd, J = 2.4, 11.2 Hz), 3.83 (1H, dd, J = 2.0, 11.2 Hz), 4.59 (1H, t, J = 1.6 Hz), 4.66 (2H, dd, J = 5.6, 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.8, -5.7, 18.2, 25.5, 25.7, 26.7, 62.9, 75.7, 78.4, 82.2, 112.9, 174.1.

(3a*S*,6a*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-6,6-diphenyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (4.1n)



Colourless oil; (one of the diastereomers was characterized): IR (NaCl) 3506, 2954, 2856, 1658, 1448, 1384, 1080, 1028, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.11 (3H, s), 0.87 (9H, s), 1.06 (3H, s), 1.18 (3H, s), 3.44, (1H, s), 3.84 (1H, d, J = 10.4 Hz), 3.91 (1H, d, J = 10.4 Hz), 4.59 (1H, d, J = 5.6 Hz), 5.10 (1H, d, J = 5.6 Hz), 7.03 (1H, t, J = 7.2 Hz), 7.11-7.15 (3H, m), 7.23 (4H, t, 8.0 Hz), 7.46 (2H, d, J = 7.6 HZ); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, -5.1, 18.3, 24.7, 25.4, 25.8, 65.2, 85.3, 86.3, 90.7, 104.2, 112.6, 126.3, 126.4, 126.7, 126.9, 127.2, 127.8, 142.7, 145.8; HRMS (ESI): Found: m/z 479.2231. Calcd for $C_{26}H_{36}O_5SiNa$: $(M+Na)^+$ 479.2230.

5.4.2 Synthesis of Unsaturated Lactones 4.2

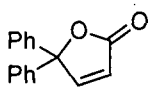


4.1a **4.2a**

Scheme 5-25. *The reaction of lactol* ***4.1a***

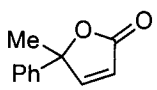
To a 25 mL Schlenk tube, CuCl (5.1 mg, 0.05 mmol), *N*-hydroxyphthalimide (81.5 mg, 0.5 mmol) and lactol **4.1a** (0.127 g, 0.50 mmol) was added and back filled with oxygen (1 atm) before addition of solvent, MeCN (5.0 mL). The reaction mixture was stirred at 80 °C under oxygen atmosphere for 12 h. Upon consumption of lactol **4.1a** by thin layer chromatography anyalysis, the reaction was cooled to room temperature before quenching with pH 9 buffer and the organic materials were extracted three times with EtOAc. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 80 : 20) to afford 5,5-diphenylfuran-2(5*H*)-one (**4.2a**) (85.0 mg, 0.36 mmol) in 72% yield as a white solid.

5,5-diphenylfuran-2(5*H*)-one (4.2a)



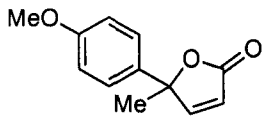
White solid, mp 133-134 °C; IR (NaCl) 3088, 3064, 2399, 1761, 1598, 1492, 1448, 1091, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (1H, d, J = 5.2 Hz), 7.25-7.88 (10H, m), 7.94 (1H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 92.1, 119.6, 126.5, 128.5, 128.6, 139.1, 158.8, 172.0; HRMS (ESI): Found: m/z 237.0913. Calcd for $C_{16}H_{13}O_2$: $(M+H)^+$ 237.0916.

5-methyl-5-phenylfuran-2(5H)-one (4.2b)



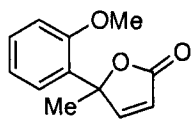
White solid, mp 34-36 °C; IR (NaCl) 3088-3064, 2987, 2399, 1749, 1602, 1496, 1446, 1116, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (3H, s), 6.04 (1H, d, J = 5.6 Hz), 7.27-7.39 (5H, m), 7.65 (1H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 88.8, 119.1, 124.6, 128.2, 128.7, 139.1, 160.4, 172.3; HRMS (ESI): Found: m/z 175.0759. Calcd for $C_{11}H_{11}O_2$: $(M+H)^+$ 175.0759.

5-(4-methoxyphenyl)-5-methylfuran-2(5H)-one (4.2c)



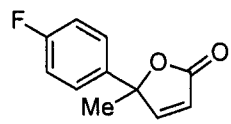
Pale yellow solid, mp 48-50 °C; IR (NaCl) 2935, 2893, 2399, 1751, 1610, 1514, 1303, 1253, 1101, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.81 (3H, s), 3.79 (3H, s), 6.04 (1H, d, J = 5.6 Hz), 6.89 (2H, dd, J = 2.0, 6.8 Hz), 7.28 (2H, dd, J = 2.0, 6.8 Hz), 7.61 (1H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 55.2, 88.7, 114.0, 119.0, 126.1, 130.9, 159.4, 160.6, 172.4; HRMS (ESI): Found: m/z 205.0865. Calcd for $C_{12}H_{13}O_3$: $(M+H)^+$ 205.0865.

5-(2-methoxyphenyl)-5-methylfuran-2(5H)-one (4.2d)



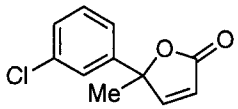
White solid, mp 56-57 °C; IR (NaCl) 2937, 2839, 2399, 1747, 1597, 1489, 1290, 1101, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (3H, s), 3.90 (3H, s), 5.92 (1H, d, J = 5.6 Hz), 6.91 (1H, d, J = 8.0 Hz), 6.96 (1H, t, J = 7.6 Hz), 7.29 (1H, dt, J = 1.6, 7.6 Hz), 7.55 (1H, dd, J = 1.6, 7.6 Hz), 8.11 (1H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 55.2, 88.8, 110.9, 118.4, 121.1, 125.5, 128.2, 129.4, 155.2, 160.2, 172.3; HRMS (ESI): Found: m/z 205.0866. Calcd for $C_{12}H_{13}O_3$: $(M+H)^+$ 205.0865.

5-(4-fluorophenyl)-5-methylfuran-2(5H)-one (4.2e)



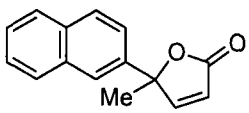
Yellow oil; IR (NaCl) 2985, 2252, 1749, 1602, 1510, 1234, 912, 732 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (3H, s), 6.07 (1H, d, J = 5.6 Hz), 7.07 (2H, tt, J = 2.4, 8.8 Hz), 7.34-7.37 (2H, m), 7.60 (1H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4. 88.4, 115.7 (d, J = 21.6 Hz), 119.5, 126.7 (d, J = 8.4 Hz), 135.1 (d, J = 3.4 Hz), 160.2, 162.5, (d, J = 246.4 Hz), 172.1; HRMS (ESI): Found: m/z 193.0666. Calcd for $C_{11}H_{10}O_2F$: $(M+H)^+$ 193.0665.

5-(3-chlorophenyl)-5-methylfuran-2(5H)-one (4.2f)



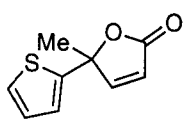
White solid, mp 40-41 °C; IR (NaCl, $CHCl_3$) 3072, 2987, 1757, 1597, 1575, 1423, 1234, 1118, 962, 891 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (3H, d, J = 1.6 Hz), 6.07 (1H, dd, J = 1.6, 5.6 Hz), 7.25-7.32 (3H, m), 7.38 (1H, s), 7.63 (1H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 88.1, 119.6, 122.9, 125.1, 128.4, 130.1, 134.7, 141.2, 159.8, 171.8; HRMS (ESI): Found: m/z 209.0365. Calcd for $C_{11}H_{10}O_2Cl$: $(M+H)^+$ 209.0369.

5-methyl-5-(naphthalen-2-yl)furan-2(5H)-one (4.2g)



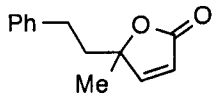
Yellow solid, mp 70-72 °C; IR (NaCl) 3059, 2987, 2399, 1755, 1600, 1508, 1377, 1109, 964 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (3H, s), 6.10 (1H, d, J = 5.6 Hz), 7.44 (1H, dd, J = 2.0, 8.8 Hz), 7.48-7.51 (2H, m), 7.72 (1H, d, J = 5.6 Hz), 7.82-7.87 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 89.0, 119.4, 122.5, 123.7, 126.6, 126.6, 127.6, 128.1, 128.7, 132.8, 133.1, 136.5, 160.4, 172.4; HRMS (ESI): Found: m/z 225.0919. Calcd for $C_{15}H_{13}O_2$: $(M+H)^+$ 225.0916.

5-methyl-5-(thiophen-2-yl)furan-2(5H)-one (4.2h)



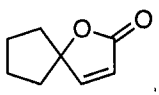
Yellow oil; IR (NaCl) 3109, 2985, 2252, 1757, 1604, 1448, 1375, 1242, 1105 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (3H, s), 6.12 (1H, d, J = 5.6 Hz), 6.98-7.03 (2H, m), 7.31 (1H, d, J = 5.2 Hz), 7.56 (1H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 86.3, 119.9, 124.9, 126.1, 127.2, 141.9, 159.3, 171.7; HRMS (ESI): Found: m/z 181.0323. Calcd for $C_9H_9O_2S$: $(M+H)^+$ 181.0323.

5-methyl-5-phenethylfuran-2(5H)-one (4.2i)



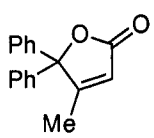
Yellow oil; IR (NaCl) 2931, 1751, 1602, 1496, 1454, 1105, 950, 821 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (3H, s), 2.01 (1H, ddd, J = 5.6, 11.6, 14.4 Hz), 2.15 (1H, ddd, J = 5.6, 11.6, 14.4 Hz), 2.54 (1H, ddd, J = 5.6, 11.6, 13.6 Hz), 2.64 (1H, ddd, J = 5.6, 12.0, 13.6 Hz), 6.03 (1H, d, J = 5.6 Hz), 7.13 (2H, d, J = 6.8 Hz), 7.19 (1H, t, J = 7.6 Hz), 7.25-7.29 (2H, m), 7.34 (1H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 29.9, 39.9, 88.5, 120.6, 126.2, 128.2, 128.5, 140.7, 160.1, 172.4; HRMS (ESI): Found: m/z 203.1072. Calcd for $C_{13}H_{15}O_2$: $(M+H)^+$ 203.1072.

1-oxaspiro[4.4]non-3-en-2-one (4.2j)



Yellow oil; IR (NaCl) 2960, 1754, 1600, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82-2.02 (8H, m), 6.00 (1H, d, J = 5.6 Hz), 7.41 (1H, d, J = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 36.7, 96.7, 120.1, 159.0, 172.5; HRMS (ESI): Found: m/z 139.0757. Calcd for $C_8H_{11}O_2$: $(M+H)^+$ 139.0759.

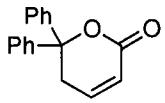
4-methyl-5,5-diphenylfuran-2(5H)-one (4.2k)



White solid, mp 92-96°C; IR (NaCl, $CHCl_3$) 3088, 3062, 1743, 1643, 1448, 1269, 929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, d, J = 1.2 Hz), 5.96 (1H, q, J = 1.2 Hz),

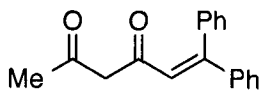
7.25-7.29 (4H, m), 7.34-7.38 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 94.1, 117.6, 127.5, 128.5, 128.7, 138.3, 170.8, 172.1; HRMS (ESI): Found: m/z 251.1071. Calcd for $C_{17}H_{15}O_2$: $(M+H)^+$ 251.1072.

6,6-diphenyl-5,6-dihydro-2H-pyran-2-one (4.2m)[43]



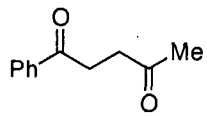
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (2H, dd, J = 1.6, 4.0 Hz), 6.01 (1H, dt, J = 1.6, 9.6 Hz), 6.88 (1H, dt, J = 4.4, 9.6 Hz), 7.24-7.29 (2H, m), 7.31-7.34 (4H, m), 7.37-7.40 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.8, 86.3, 122.8, 125.9, 127.8, 128.5, 143.1, 143.6, 163.6.

6,6-diphenylhex-5-ene-2,4-dione (4.4m)[44]



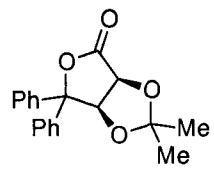
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.21 (2H, s), 5.31 (1H, s), 7.27-7.36 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 46.6, 87.2, 105.8, 125.9, 128.0, 128.4, 142.6, 171.7, 191.6.

1-phenylpentane-1,4-dione (4.1l')[45]



Clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (3H, s), 2.89 (2H, t, J = 6.8 Hz), 3.28 (2H, t, J = 6.8 Hz), 7.45 (2H, tt, J = 1.6, 6.8 Hz), 7.56 (1H, tt, J = 1.2, 7.6 Hz), 7.97-7.99 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.0, 32.4, 37.0, 128.0, 128.5, 133.1, 136.6, 198.5, 207.3.

(3aS,6aR)-2,2-dimethyl-6,6-diphenyldihydrofuro[3,4-d][1,3]dioxol-4(3aH)-one (4.5n)



White solid, mp 175-178 °C; IR (NaCl) 3062, 2995, 1789, 1494, 1450, 1377, 1105, 977 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, s), 1.42 (3H, s), 4.75 (1H, d, J = 4.4 Hz), 5.35 (1H, d J = 4.4 Hz), 7.27-7.38 (6H, m), 7.42-7.46 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 26.9, 76.3, 81.9, 88.4, 114.5, 125.4, 126.5, 128.0, 128.1, 128.6, 129.0, 138.5, 140.9, 173.7; HRMS (ESI): Found: m/z 311.1290. Calcd for $C_{19}H_{19}O_4$: $(M+H)^+$ 311.1283.

5.4.3 Isolation of reaction intermediates in the reaction of 4.6

5.4.3.1 Monitoring of reaction progress of 4.6 by 1H NMR spectroscopy

To a 10 mL Schlenk tube, using methyl benzoate (25.0 μL, 0.2 mmol) as an internal standard, CuCl (4.1 mg, 0.04 mmol), *N*-hydroxyphthalimide (65.3 mg, 0.4 mmol) and hemiacetal **4.6** (35.6 mg, 0.20 mmol) was added and back filled with molecular oxygen (1 atm) before addition of solvent, CD_3CN (2.0 mL). A stopwatch is started as soon as the reaction mixture was stirred at 80 °C under O_2 atmosphere. At the intended time intervals, a sample of 50 μL of the reaction mixture was collected by syringe and diluted with 0.3 mL of CD_3CN in a NMR tube and checked by ^{1}H NMR spectroscopy immediately. The reaction was monitored over a period of 120 minutes and the percentage of each compound present in the reaction is plotted against time as shown in Figure 5-1 and 5-2.

Figure 5-1 Kinectic profile for the reaction of **4.6**

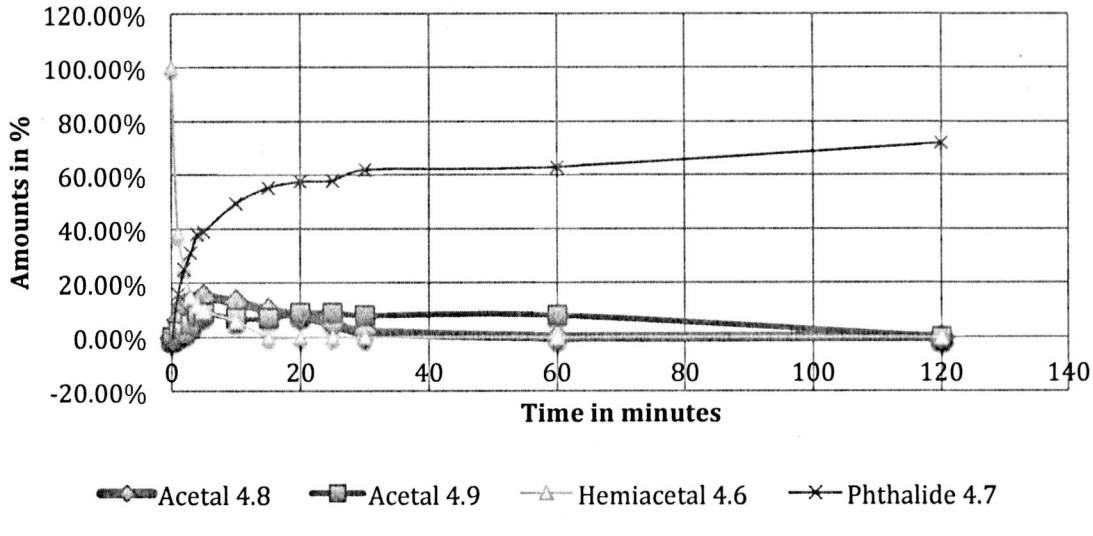
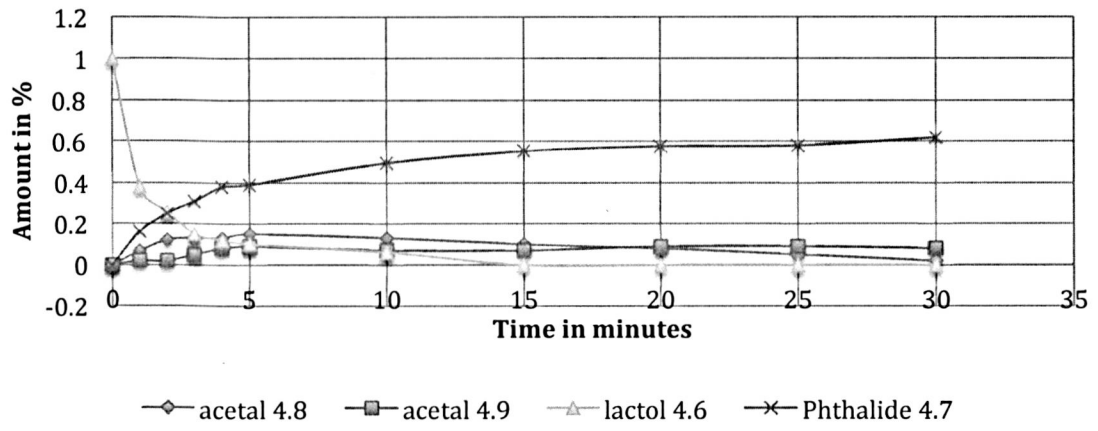
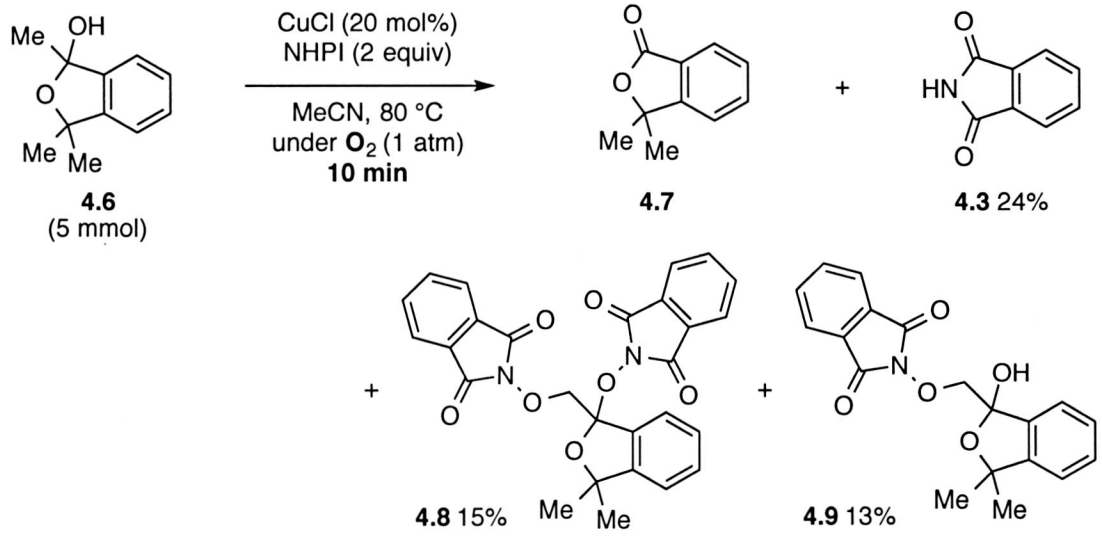


Figure 5-2. Kinetic profile of reaction of 4.6 in the first 30 min



From the charts, it is observed that hemiacetal **4.6** was consumed quickly in the first 15 minutes of the reaction progress, and acetals **4.8** and **4.9** can be observed to increase slowly and eventually consumed, contributing to the total yield of phthalide **7**. Thus, the reaction was stopped at 10 minutes time in effort to isolate acetal **4.8** and **4.9** for investigation.

5.4.3.2 Isolation of acetals 4.8 and 4.9

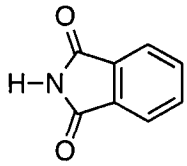


Scheme 5-25. *Isolation of acetals **4.8** and **4.9**.*

To a 100 mL Schlenk tube, CuCl (0.102 g, 1.00 mmol), *N*-hydroxyphthalimide (1.63 g, 10.0 mmol) and hemiacetal **4.6** (0.89 g, 5.00 mmol) was added and back filled with oxygen (1 atm) before addition of solvent, MeCN (50 mL). The reaction mixture was stirred at 80 °C under oxygen atmosphere for 10 minutes and then cooled to 0 °C

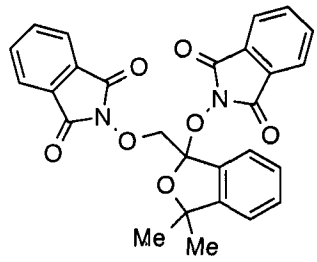
before removing MeCN in *vacuo*. The remaining crude materials was subjected to flash column chromatography (SiO_2, hexane : EtOAc = 70 : 30) to afford phthalide **4.7** (0.41 g, 2.55 mmol, 51% yield), phthalimide (**3**) (0.17 g, 1.20 mmol, 24% yield), acetal **4.9** (0.22 g, 0.65 mmol, 13% yield) and acetal **4.8** as a mixture with NHPI. The mixture of **4.8** and NHPI was then separated by flash column chromatography (Al_2O_3 (neutral), hexane : ethyl acetate = 70 : 30), providing **4.8** (0.36g, 0.74 mmol) in 15% yields.

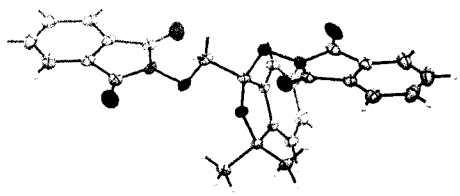
Phthalimide (4.3)[46]



White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, dd, J = 3.6, 5.6 Hz), 7.88 (2H, dd, J = 3.6, 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.6, 132.6, 134.3, 167.8.

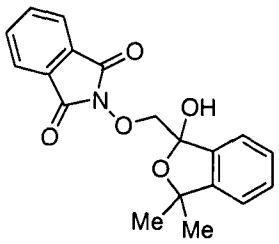
2-((1-((1,3-dioxoisoindolin-2-yl)oxy)-3,3-dimethyl-1,3-dihydroisobenzofuran-1-yl)methoxy)isoindoline-1,3-dione (4.8)





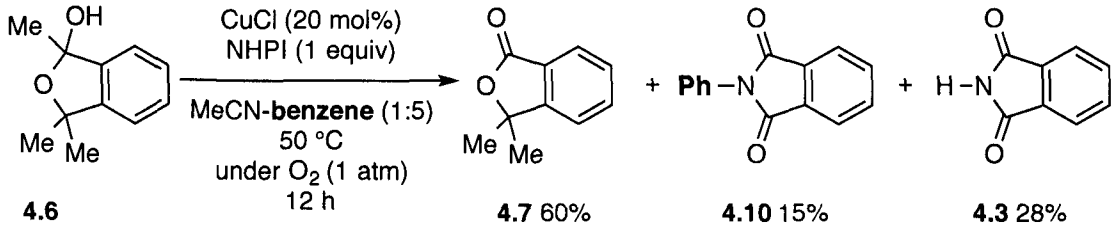
Colorless crystal (CCDC 1027434), mp 176-177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (3H, s), 1.66 (3H, s), 4.67 (1H, d, J = 9.2 Hz), 5.07 (1H, d, J = 9.6 Hz), 7.17 (1H, d, J = 6.8 Hz), 7.41-7.49 (2H, m), 7.69-7.73 (4H, m), 7.76-7.79 (4H, m), 7.84 (1H, d, J = 6.8Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1, 29.2, 77.5, 89.4, 114.6, 120.2, 123.4, 123.5, 125.0, 127.8, 128.8, 129.1, 130.8, 132.8, 134.4, 148.9, 162.7, 164.2; IR (NaCl, $CHCl_3$) 1793, 1735, 1467, 1367, 1080 cm^{-1}; ESI HRMS: Found: m/z 507.1166. Calcd for $C_{27}H_{20}N_2O_7Na$ $(M+Na)^+$ 507.1168.

2-((1-hydroxy-3,3-dimethyl-1,3-dihydroisobenzofuran-1-yl)methoxy)isoindoline-1,3-dione (4.9)



White foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.51 (3H, s), 4.41 (1H, d, J = 11.6 Hz), 4.54 (1H, d, J = 11.6 Hz), 5.04 (1H, s), 7.14 (1H, d, J = 7.2 Hz), 7.34-7.44 (3H, m), 7.78 (2H, dd, J = 3.2, 5.6 Hz), 7.87 (2H, dd, J = 3.2, 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 30.5, 82.1, 86.1, 104.4, 120.6, 122.7, 123.6, 128.0, 128.9, 129.9, 134.5, 137.3, 148.0, 163.7; IR (NaCl, $CHCl_3$) 3061, 2399, 1732, 1600, 1379, 1022 cm^{-1}; ESI HRMS: Found: m/z 340.1184. Calcd for $C_{19}H_{18}NO_5$ $(M+H)^+$ 340.1185.

5.4.3.3 Isolation of *N*-phenylphthalimide 4.10



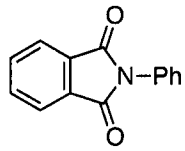
4.6 **4.7** 60% **4.10** 15% **4.3** 28%

Scheme 5-25. *The reaction of lactol **4.6** in the prescence of benzene.*

To a 25 mL Schlenk tube, CuCl (10.2 mg, 0.10 mmol), *N*-hydroxyphthalimide (81.5 mg, 0.5 mmol) and hemiacetal **4.6** (89.1 mg, 0.50 mmol) was added and back filled with oxygen (1 atm) before addition of solvents, MeCN : Benzene = 1 : 5 (5 mL). The reaction mixture was stirred at 50 °C under oxygen atmosphere for 12 h. After the complete consumption of hemiacetal **4.6** by thin layer chromatography anyalysis, the reaction was cooled to room temperature before quenching with pH 9 buffer and the organic materials were extracted three times with ethyl acetate. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile

materials were removed *in vacuo* and the resulting crude material was subjected to flash column chromatography (hexane : ethyl acetate = 80 : 20) to afford 3,3-dimethylisobenzofuran-1(3*H*)-one (**4.7**) (47.9 mg of 64.4 mg, 0.30 mmol, 60% yield) and *N*-phenylphthalimide (**4.10**) (16.5 mg of 64.4 mg, 0.07 mmol, 15% yield) as a inseperable mixture of 4:1 ratio, totally weighing 64.4 mg.

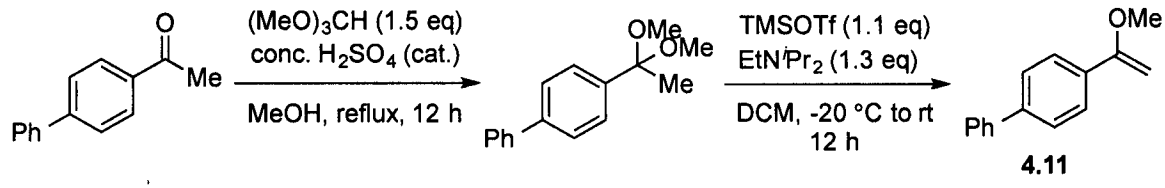
N-phenylphthalimide (4.10)[47]



Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.46 (3H, m), 7.49-7.53 (2H, m), 7.79 (1H, dd, J = 3.2, 5.6 Hz), 7.95 (1H, dd, J = 3.2, 5.6 Hz; ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.7, 126.5, 128.1, 129.1, 131.6, 131.7, 134.3, 167.2.

5.4.4 Synthesis of Ester 4.12 and isolation of acetal 4.13

A procedure for the synthesis of 4-(1-methoxyvinyl)-1,1'-biphenyl (4.11)

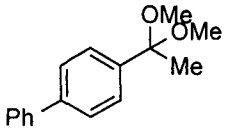


Scheme 5-26. *The preparation of enol ether **4.11**.*

To a mixture of 4-acetylbiphenyl (3.92 g, 20 mmol), triethyl orthoformate (3.2 mL, 30 mmol) in methanol (2 mL), was added 3 drops of concentrated H_2SO_4 and refluxed under inert atmosphere for 6 h. Upon consumption of 4-acetylbiphenyl judged by thin layer chromatography analysis, the purple mixture was then cooled to room temperature and neutralized with NaOMe (0.1 g). The crude material was then concentrated in *vacuo* and then subjected to flash column chromatography (Al_2O_3, hexane : EtOAc = 90 : 10) to afford 4-(1,1-dimethoxyethyl)-1,1'-biphenyl (4.18g, 17.26 mmol) as an orange oil in 86% yield.

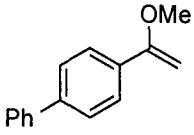
A mixture of 4-(1,1-dimethoxyethyl)-1,1'-biphenyl (2.42 g, 10.0 mmol), *N*,*N*-Diisopropylethylamine (2.26 mL, 13.0 mmol) and anhydrous CH_2Cl_2 (20 mL) was cooled in a Schlenk tube to -20 °C, under an inert atmosphere. Trimethylsilyl trifluoromethanesulfonate (1.99 mL, 11 mmol) was added to the cooled solution drop wise, and then warmed to room temperature and left to be stirred for 6 h. Upon reaction completion, judged by thin layer chromatography analysis, the reaction was quenched with saturated aqueous Na_2CO_3 solution and the organic materials were extracted three times with CH_2Cl_2. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude material was subjected to flash column chromatography (Al_2O_3, hexane : EtOAc = 90 : 10) to 4-(1-methoxyvinyl)-1,1'-biphenyl (4.**11**) (2.08 g, 9.87 mmol) as a white solid in 93 % yield.

4-(1,1-dimethoxyethyl)-1,1'-biphenyl[48]



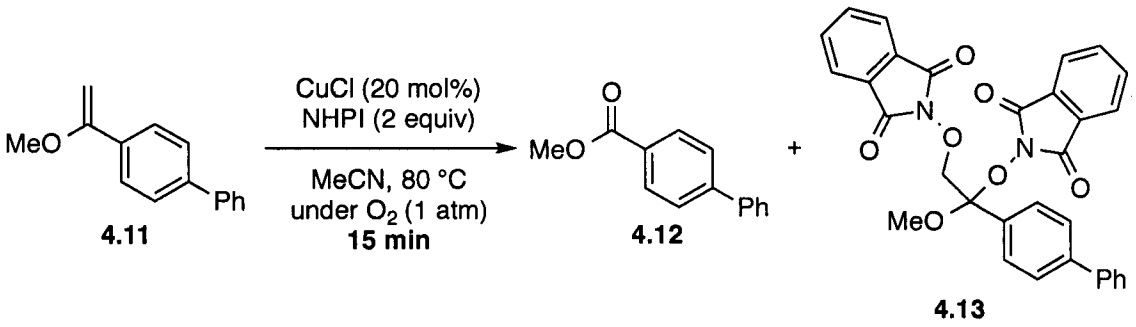
Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (3H, s), 3.22 (6H, s), 7.34 (1H, t, J = 7.6 Hz), 7.41-7.45 (2H, m), 7.55-7.61 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1, 49.0, 101.6, 126.7, 126.8, 127.1, 127.2, 128.7, 140.4, 140.8, 141.9.

4-(1-methoxyvinyl)-1,1'-biphenyl (4.11)



White solid, mp 68-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (3H, s), 4.23 (1H, d, J = 2.8 Hz), 4.58 (1H, d, J = 2.8 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.31 (2H, t, J = 7.2 Hz), 7.44-7.49 (4H, m), 7.56 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 81.8, 125.7, 126.8, 127.0, 128.7, 135.4, 140.7, 141.1, 160.5; IR (NaCl, $CHCl_3$) 2951, 1722, 1606, 1487, 1049 cm^{-1}; ESI HRMS: Found: m/z 211.1125. Calcd for $C_{15}H_{15}O$ $(M+H)^+$ 211.23.

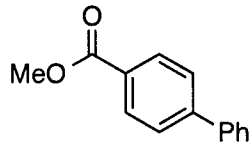
Synthesis of 4-(1-methoxyvinyl)-1,1'-biphenyl (4.12)



Scheme 5-27. *The reaction of enol ether* ***4.11***

To a 25 mL Schlenk tube, CuCl (10.2 mg, 0.10 mmol), *N*-hydroxyphthalimide (0.163 g, 1.0 mmol) and 4-(1-methoxyvinyl)-1,1'-biphenyl (**4.11**) (0.105, 0.50 mmol) was added and back filled with oxygen (1 atm) before addition of solvent, MeCN (5.0 mL). The reaction mixture was stirred at 80 °C under oxygen atmosphere. After the complete consumption of 4-(1-methoxyvinyl)-1,1'-biphenyl (**4.11**) by thin layer chromatography anyalysis, the reaction was cooled to room temperature before quenching with pH 9 buffer and the organic materials were extracted three times with EtOAc. The combined extracts were washed twice with water and once with brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude material was subjected to flash column chromatography (hexane : EtOAc = 80 : 20) to afford methyl [1,1'-biphenyl]-4-carboxylate (**4.12**) (52.1 mg, 0.24 mmol) in 49% yield as a white solid and 2,2'-((1-([1,1'-biphenyl]-4-yl)-1-methoxyethane-1,2-diyl)bis(oxy))bis(isoindoline-1,3-dione) (**4.13**) (0.73 mmol, 15% yield based on NMR ratio using 1,1,2,2-tetrachloroethane as internal standard).

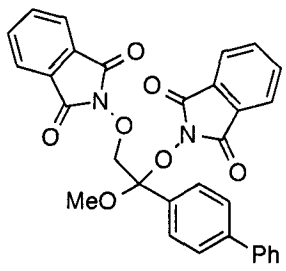
Methyl [1,1'-biphenyl]-4-carboxylate (4.12)



White solid, mp 113-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (3H, s), 7.38 (1H, tt, J = 1.2, 6.4 Hz), 7.45 (2H, t, J = 7.6 Hz), 7.60-7.42 (2H, m), 7.64 (2H, dd, J = 1.6, 6.8 Hz),

8.10 (2H, dd, J = 1.6, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 127.0, 127.2, 128.1, 128.9, 130.1, 139.9, 145.6, 166.9; IR (NaCl, $CHCl_3$) 2953, 2399, 1718, 1608, 1436, 1282, 1114 cm^{-1}; ESI HRMS: Found: m/z 213.0912. Calcd for $C_{14}H_{13}O_2$ $(M+H)^+$ 213.0916.

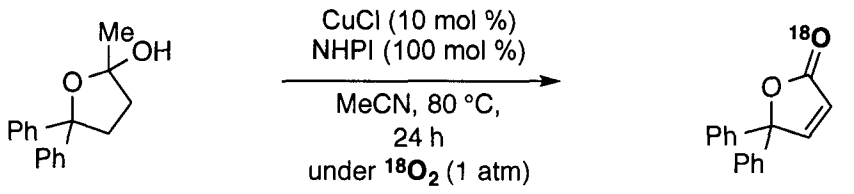
2,2'-((1-([1,1'-biphenyl]-4-yl)-1-methoxyethane-1,2-diyl)bis(oxy))bis(isoindoline-1,3-dione) (4.13)



White foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (3H, s), 4.76 (1H, d, J = 11.2 Hz), 4.79 (1H, d, J = 10.8 Hz), 7.35 (1H, tt, J = 1.2, 7.2 Hz), 7.43 (2H, t, J = 7.6 Hz), 7.58 (2H, d, J = 6.8 Hz), 7.64 (2H, d, J = 8.8 Hz), 7.67 (2H, dd, J = 3.2, 5.6 Hz), 7.72-7.76 (4H, m), 7.84 (2H, dd, J = 2.8, 5.6 Hz), 7.93 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 78.3, 108.8, 123.4, 123.5, 126.8, 127.5, 128.4, 128.71, 128.74, 129.4, 133.4, 134.33, 140.3, 142.1, 162.6, 164.5; IR (NaCl, $CHCl_3$) 2951, 2399, 1793, 1732, 1606, 1467 cm^{-1}; ESI HRMS: Found: m/z 535.1504. Calcd for $C_{31}H_{23}N_2O_7$ $(M+H)^+$ 535.1505.

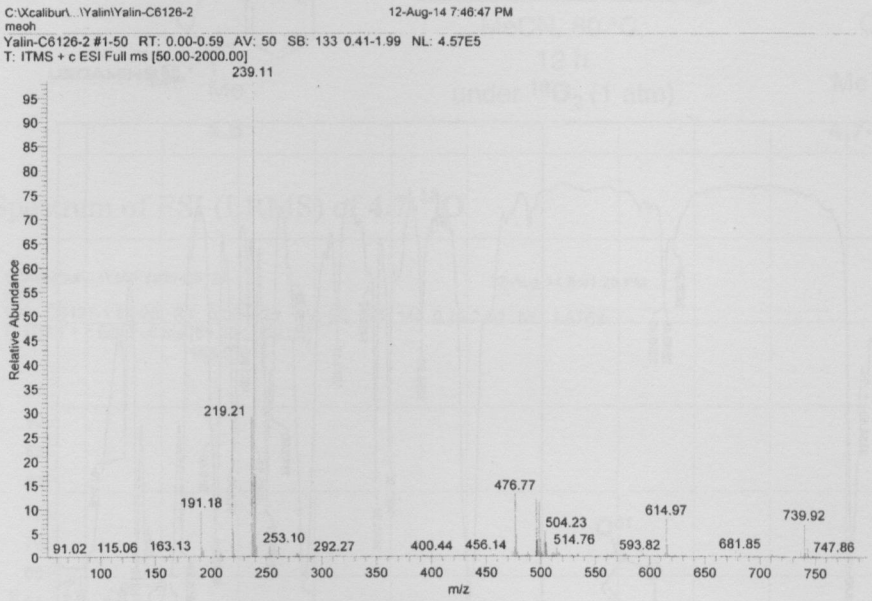
5.4.5 Labelling experiments

By subjecting the reaction of hemiacetal **4.1a**, **4.6** and methyl enol ether **4.11,** under an $^{18}O_2$ atmosphere, we observed that the ^{18}O incorporated products **4.2a-^{18}O**, **4.7-^{18}O** and **4.12-^{18}O** was obtained, mainly by mass spectroscopy. When comparing the IR-spectrums of normal **^{16}O** and **^{18}O** incorporated products, a rightward shift of the C=O stretching was also observed in **4.2a-^{18}O**, **4.7-^{18}O** and **4.12-^{18}O**.



4.1a **4.2a-^{18}O** 57%

Spectrum of ESI (LRMS) of **4.2a-^{18}O**



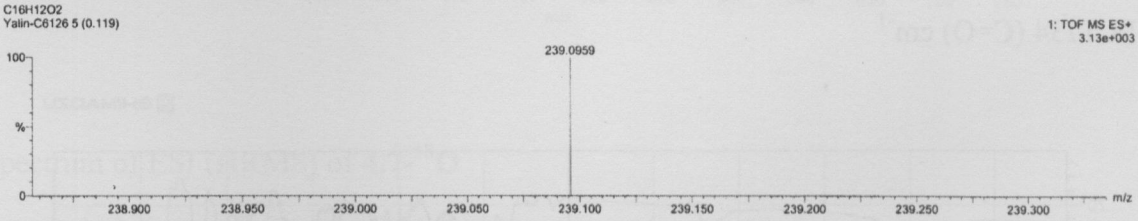
Spectrum of ESI (HRMS) of **4.2a-^{18}O**

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
31 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 0-25 H: 0-40 18O: 0-2 16O: 0-2

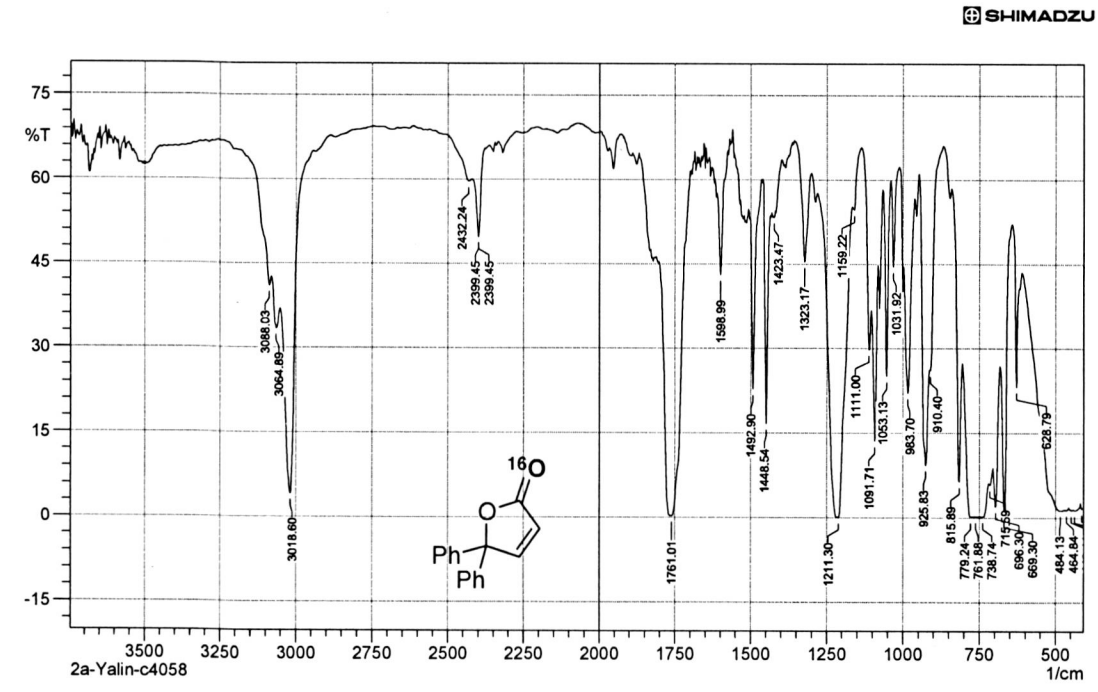
C16H12O2
Yalin-C6126 5 (0.119)



Minimum:				-1.5			
Maximum:		5.0	5.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
239.0959	239.0958	0.1	0.4	10.5	26.2	0.0	C16 H13 18O 16O

IR Spectrum of **4.2a**

IR 1761 (C=O) cm^{-1}



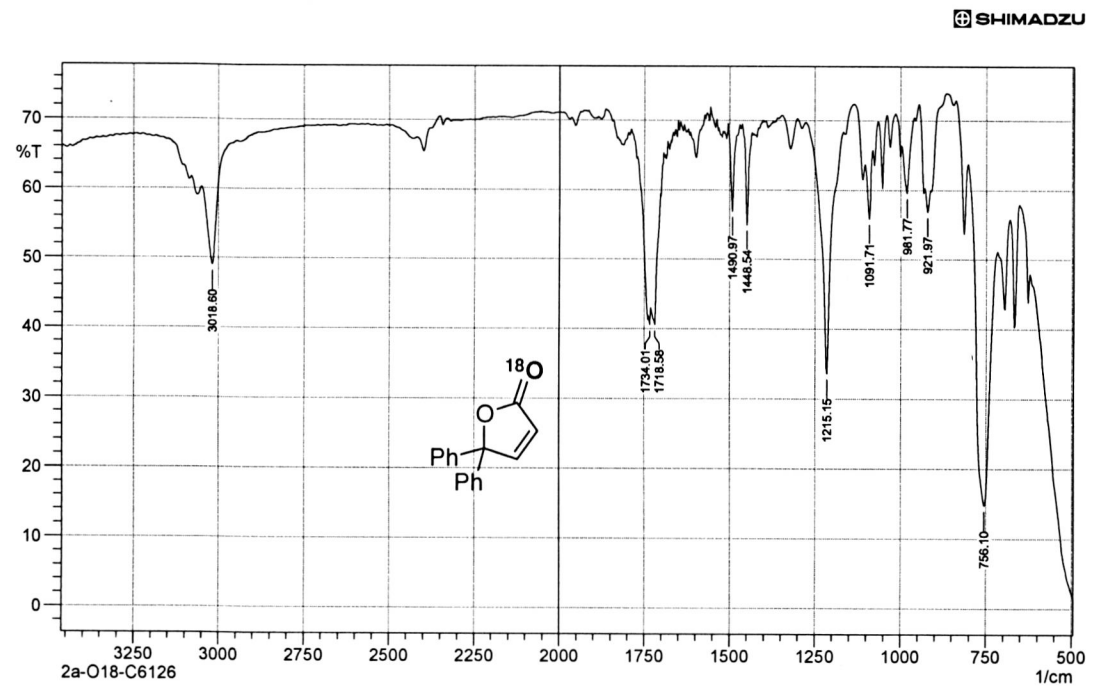
Comment;
2a-Yalin-c4058

No. of Scans; 8
Resolution; 4 [1/cm]
Apodization; Happ-Genzel

Date/Time; 8/28/2014 5:03:33 PM
User; Administrator

IR Specrtum of **2a-^{18}O**

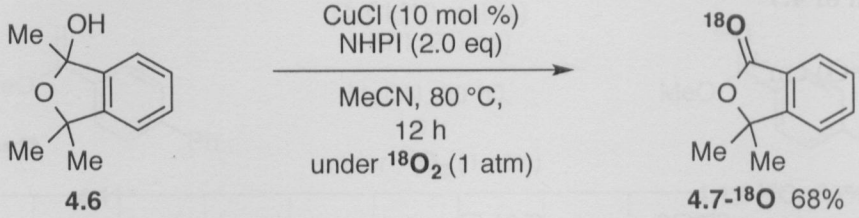
IR 1734 (C=O) cm^{-1}



Comment;
2a-O18-C6126

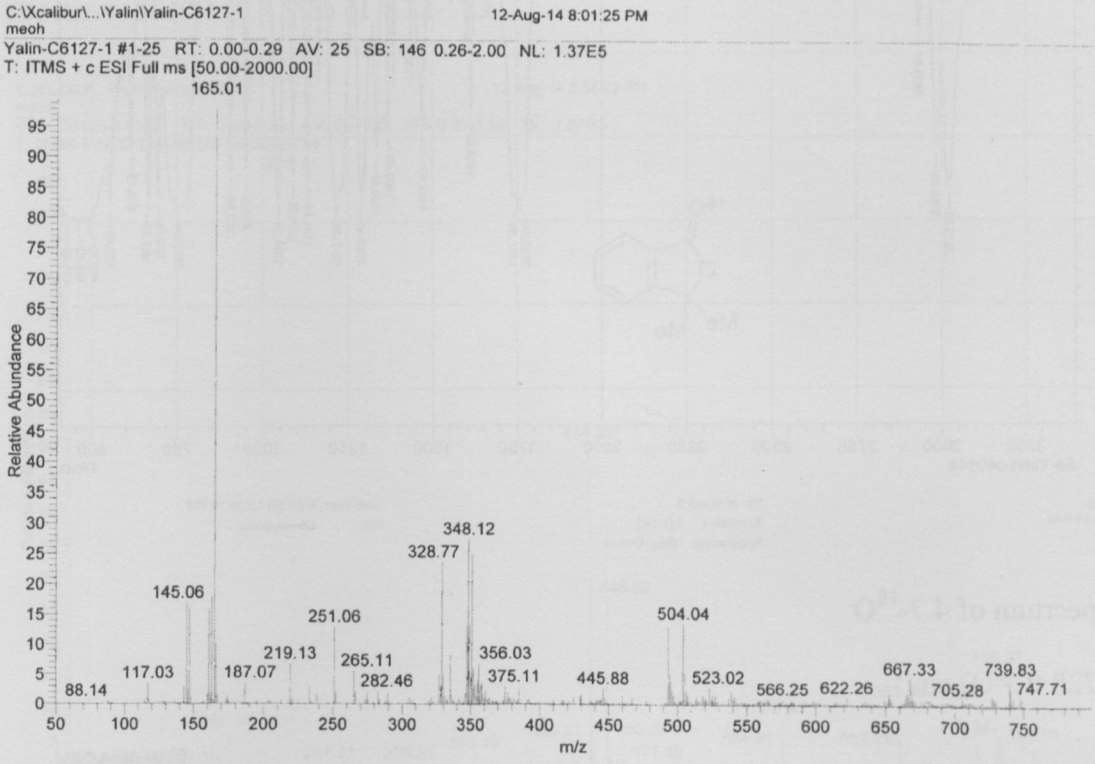
No. of Scans; 8
Resolution; 4 [1/cm]
Apodization; Happ-Genzel

Date/Time; 9/30/2014 10:29:49 AM
User; Administrator



4.6 **4.7-^{18}O** 68%

Spectrum of ESI (LRMS) of **4.7-^{18}O**



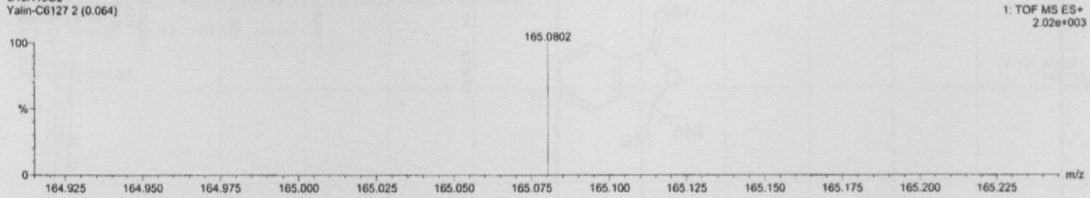
Spectrum of ESI (HRMS) of **4.7-^{18}O**

Elemental Composition Report Page 1

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
105 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-34 H: 0-30 N: 0-4 16O: 0-2 18O: 0-2

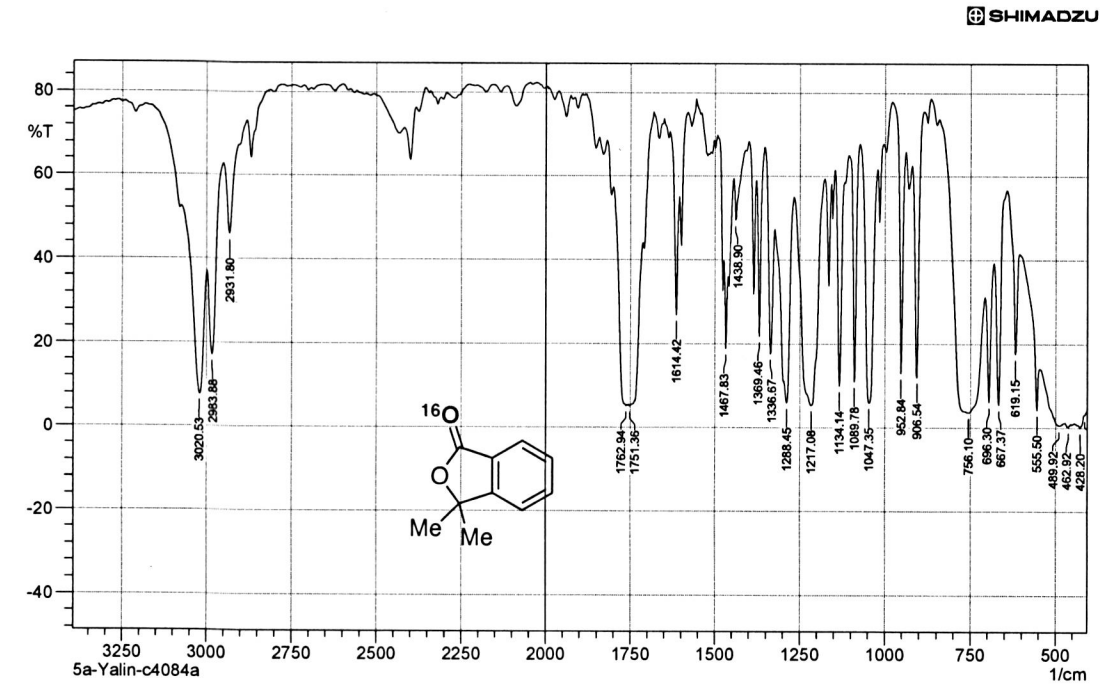
C10H10O2
Yalin-C6127 2 (0.064)



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
165.0802	165.0801	0.1	0.6	5.5	24.1	0.0	C10 H11 16O 18O

IR Spectrum of **4.7**

IR 1762 (C=O) cm^{-1}



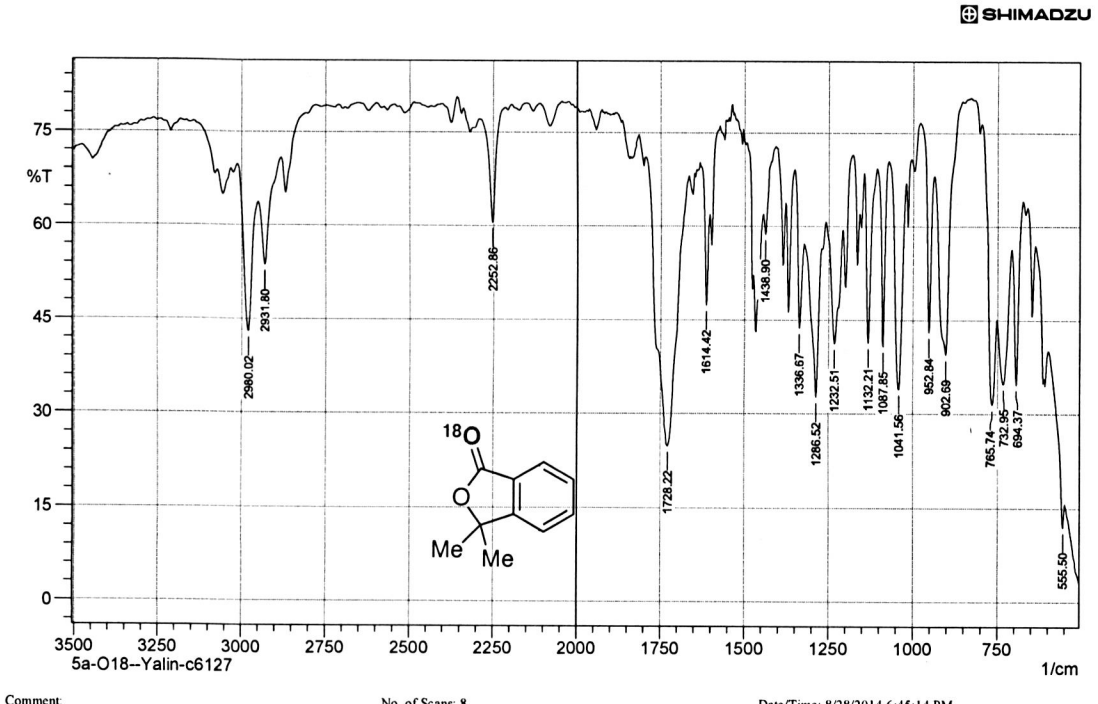
Comment;
5a-Yalin-c4084a

No. of Scans; 8
Resolution; 4 [1/cm]
Apodization; Happ-Genzel

Date/Time; 8/28/2014 5:36:59 PM
User; Administrator

IR Specrtum of **4.7-^{18}O**

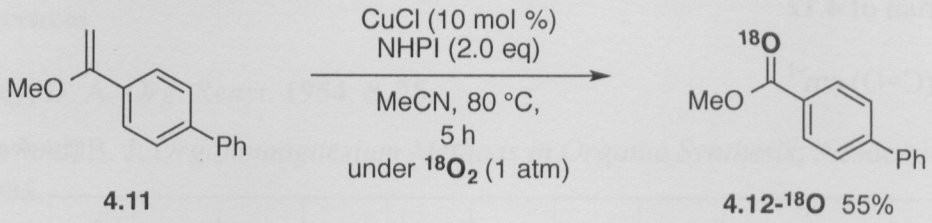
IR 1728 (C=O) cm^{-1}



Comment;
5a-O18--Yalin-c6127

No. of Scans; 8
Resolution; 4 [1/cm]
Apodization; Happ-Genzel

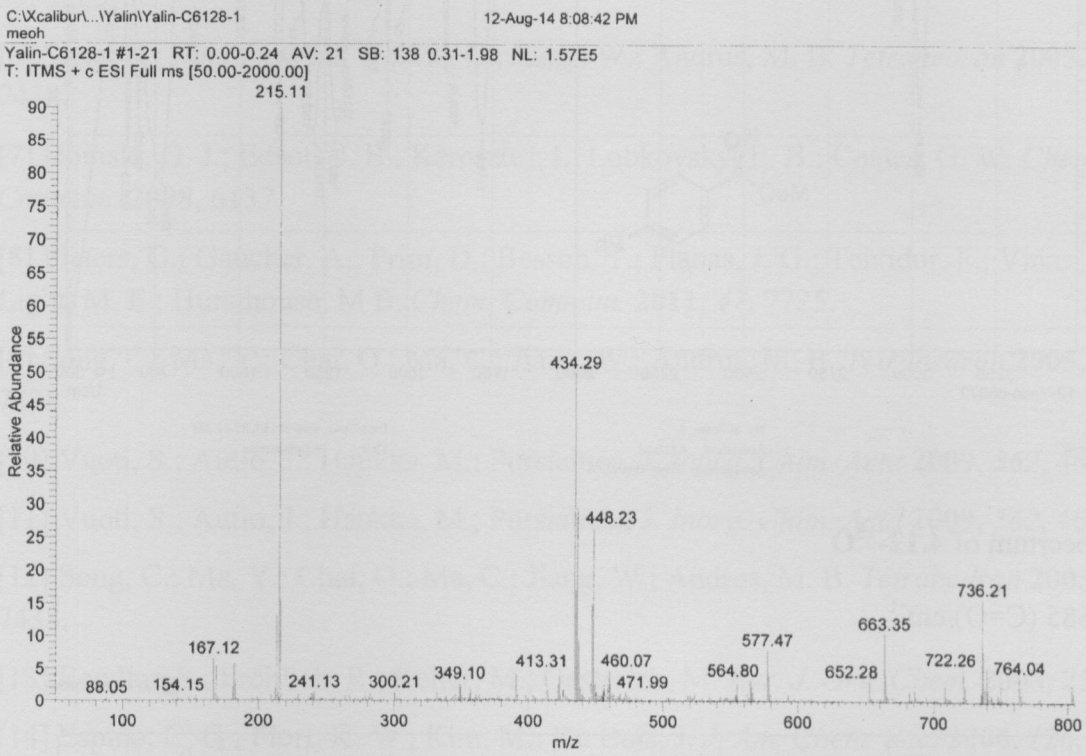
Date/Time; 8/28/2014 6:45:14 PM
User; Administrator



4.11

4.12-^{18}O 55%

Spectrum of ESI (LRMS) of **4.12-^{18}O**



Spectrum of ESI (HRMS) of **4.12-^{18}O**

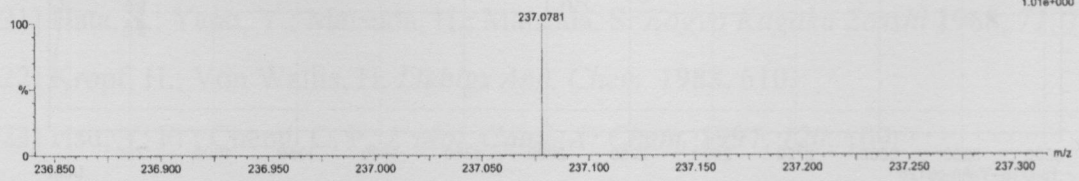
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
47 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-14 H: 0-30 16O: 0-2 18O: 0-2 Na: 0-2

C14H12O2
Yalin-C6128 32 (0.699)

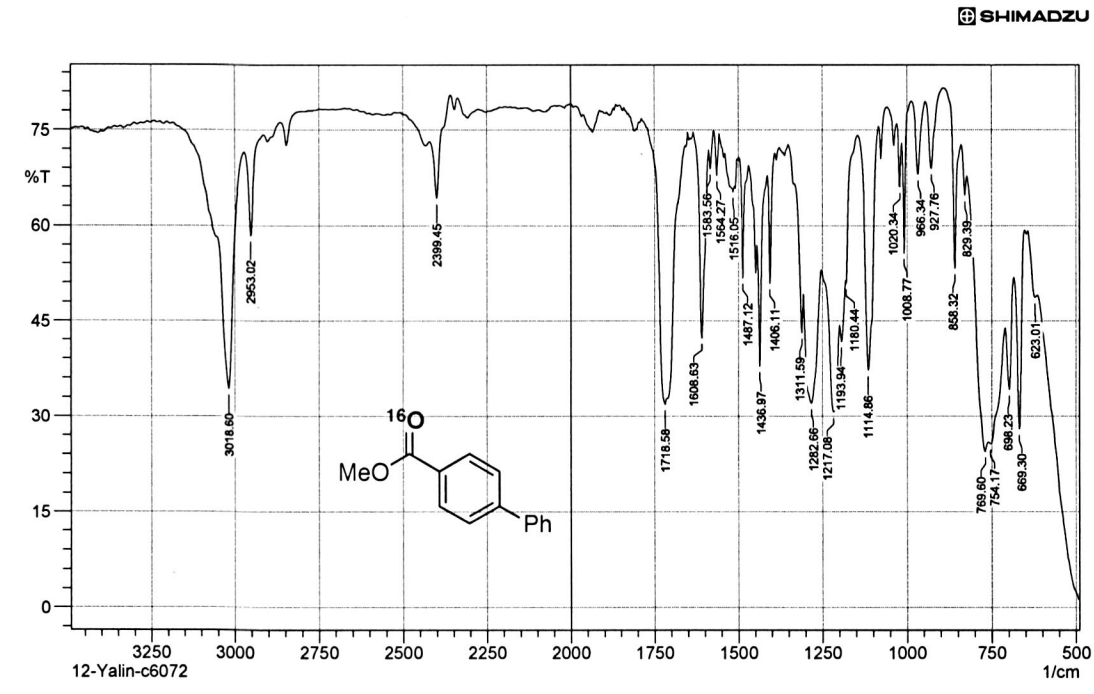
1: TOF MS ES+
1.01e+000



Minimum:				-1.5			
Maximum:		5.0	10.0	50.0			
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	i-FIT (Norm)	Formula
237.0781	237.0777	0.4	1.7	8.5	12.5	0.0	C14 H12 16O 18O Na

IR Spectrum of **4.12**

IR 1718 (C=O) cm^{-1}



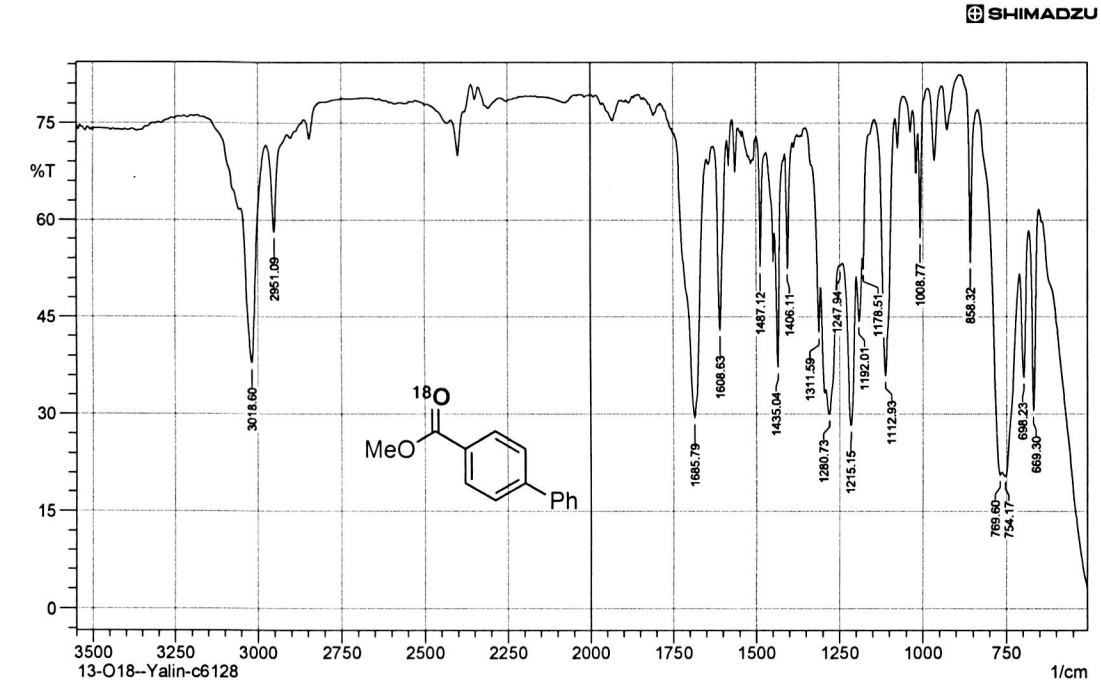
Comment;
12-Yalin-c6072

No. of Scans; 8
Resolution; 4 [1/cm]
Apodization; Happ-Genzel

Date/Time; 8/28/2014 6:35:41 PM
User; Administrator

IR Specrtum of **4.12-^{18}O**

IR 1685 (C=O) cm^{-1}



Comment;
13-O18--Yalin-c6128

No. of Scans; 8
Resolution; 4 [1/cm]
Apodization; Happ-Genzel

Date/Time; 8/28/2014 6:42:19 PM
User; Administrator

5.5 References

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