COBALT-CATALYZED REDUCTIVE DIMERIZATION OF ENONE AND MANGANESE-CATALYZED RING OPEN COUPLING OF CYCLOPROPANOLWITH ENONE ZHANG YONGHUI 2018

NANYANG TECHNOLOGICAL UNIVERSITY
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ZHANG YONGHUI

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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ZHANG YONGHUI

School of Physical and Mathematical Sciences

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Abbreviations

δ	chemical shift(ppm)
^{o}C	degree centigrade
Ac	acetyl
Ar	aryl
aq	aqueous
calcd	calculated
cm^{-1}	inverse centimeter
d	doublet
dd	doublet of doublet
dt	doublet of triplets
DMF	N,N-dimethylformide
DMSO	dimethyl sulfoxide
equiv.	equivalent(s)
Et	ethyl
g	gram
h	hour
Hz	hertz
IR	infrared
i-Pr	isopropyl
M	molar concentration

m	multiplet
m/z	mass per charge ratio
Me	methyl
MHz	mega hertz
mL	milliliter
mmol	millimole
mol%	mole percent
t-Bu	*t*-butyl
NMR	nuclear magnetic resonance
TsOH	*p*-Toluenesulfonic acid
Py	pyridine
q	quartet
s	singlet
sat	saturated
t	triplet
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin layer chromatography
UV	ultraviolet
Tol	*p*-tolyl
Bn	benzyl

Ph	phenyl
n-Bu	*n*-butyl
BDMAP	1,3-Bis(Dimethylamino)-2-Propanolato
Cp	cyclopentadienyl
acac	acetylacetone
NIS	N-Iodosuccinimide
Et	ethyl
AIBN	azobisisobutyronitrile
HMAP	hydroxymethylantipyrine
TMEDA	tetramethylethylenediamine
DEC	diethyl carbonate
BINOL	1,1-binaphthol
Cy	tricyclohexylphosphine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
BHT	butylated hydroxytoluene
IBX	2-iodoxybenzoic acid
OTf	trifluoromethanesulfonate
MS	molecular sieve

Abstract

The radical reaction has been widely applied in organic chemistry. Radical reactions, for the specific property, gained great attention. Numerous achievements have been gained in this field. The radical initiator could come from a very wild source. Typically, the illumination, trans-metal catalysts, halogen molecules, azo compounds, and organic and inorganic peroxides could all play the role of radical initiator. Among these reactions, the radical mediated C=C bond activation and C-C bond coupling reaction have taken an important position in organic synthesis.

The olefin is a kind of common organic species. The special structure and electronic property of olefin give rise to high reactivity, which leads to the wild reaction types and the various regioselective and stereoselective structure of the products. It was very common to find C=C bond structure involved in polymerization, addition, substitution oxidation and reduction reaction. Among these reactions, the coupling of olefin plays an important role in chemistry research.

The cycloalkanes generally keep stable structure in organic reaction as the C-C single bond. However, when number of carbon consisting the ring becomes less, the bond angles between C-C bond would decreases. At the same time, the ring strains would rise significantly which would lead to much higher reactivity. In most conditions, the small cycloalkane, especially cyclopropane and analogues, would undergo a ring open progress in organic reactions. The cyclopropanol contains the main properties of cyclopropane. The reaction property of cyclopropanol is to some extent similar with

enone. These characters indicate the special reactivity and potential application in organic synthesis.

Particularly, the author firstly would like to present a dimerization of enone. The C=C bond of would go through a reductive coupling progress with Cobalt(II) catalyst in mild condition. The reaction could provide dione product at good to excellent yield. Then, a ring open coupling of cyclopropanol with enone was conducted. The Manganese catalyst was selected to perform this reaction, and as a result, various dione products would be obtained at excellent yield in a simple method.

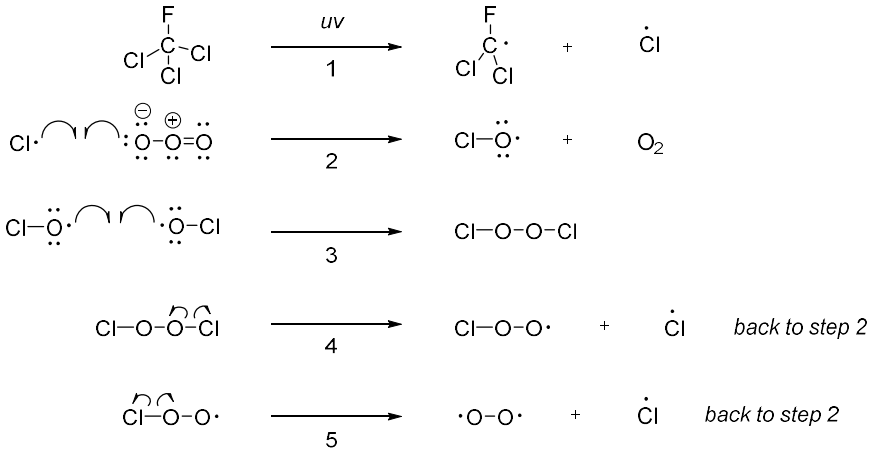
Chapter 1

Overview of Free Radical Reaction

1.1 Introduction

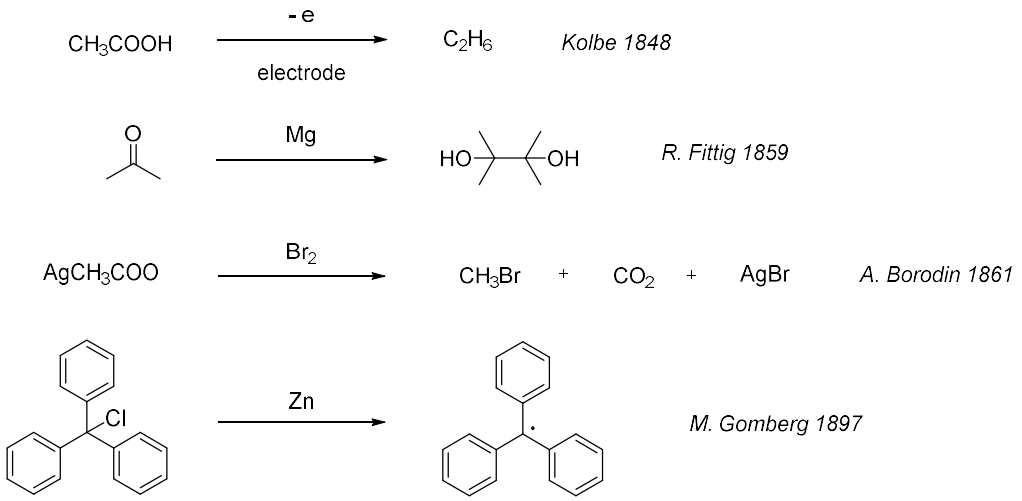
The free radical is one kind of chemical species which contains an unpaired valence electron. The radical specie could be atom, molecular, complex and ion. The unpaired electron does not contribute to the valence of the radical. Due to the singly occupied orbital, the radical has high reactivity compared with the other compounds. Sometimes the radical could follow the homocoupling or cross-coupling progress with other radicals, thus conduct the coupling reaction, dimerization and polymerization. The initiation factors of radical are common in the environment, like radiation, ultraviolet ray and high temperature. Duo to the high reactivity, the radical is quite unstable in most conditions. Thus, the radical reactions exist wildly in nature. In some medical research, the aging problem, organ damage and death would probably result from the radicals in human body and cells.[1] And the ozone depletion in the atmosphere caused by the methane, Freon and other halogen compounds is generally considered as a radical progress.[2] In organic chemistry field, the radical reaction has been drawing the attention of researchers for a long time for the reactivity. The chemists have detailly studied the mechanism of radical. And the free radical theory has been applied in organic synthesis and the mechanism study of reactions. The free radical chemistry has developed into an

important field. (Scheme 1)



Scheme 1, The chain reaction of ozone depletion

The radical chemistry has existed for a long time. From 1800s, the radical involved reactions have been reported, although the early understanding of radical would discriminate with the concept today, as well as the radial specie is hard to control and difficult to explain at that moment. In 1848 and 1849, Kolbe reported the radical electrochemistry decarbonylation.[3] The famous pinacol coupling was reported in 1859 by Fittig, which was proved to be a radical reaction.[4] The Hunsdiecher halogenation was first reported in 1861, in which the organic halides were provided from the silver salts of different carboxylic acids.[5] This reaction was performed through a radical decarbonylation progress. The modern concept of radical was proposed by Moses Gomberg in 1900s, to describe a triphenylmethyl radical, which is known as $(C_6H_5)_3C\cdot$.[6] (Scheme 2) It is the reductive product from triphenylmethyl chloride by zinc. This is the first time that a chemical reagent was described matched with the concept of modern radical species. What's more, this triphenylmethyl radical species could maintain stability at a low concentration of two percent in benzene.



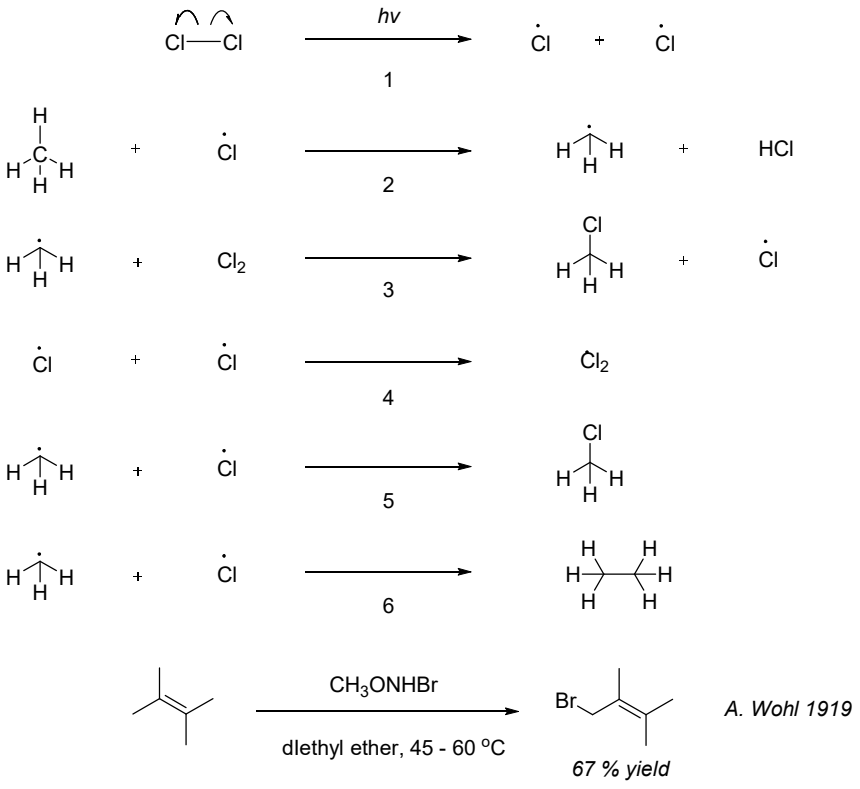
Scheme 2, The early researches in radical chemistry

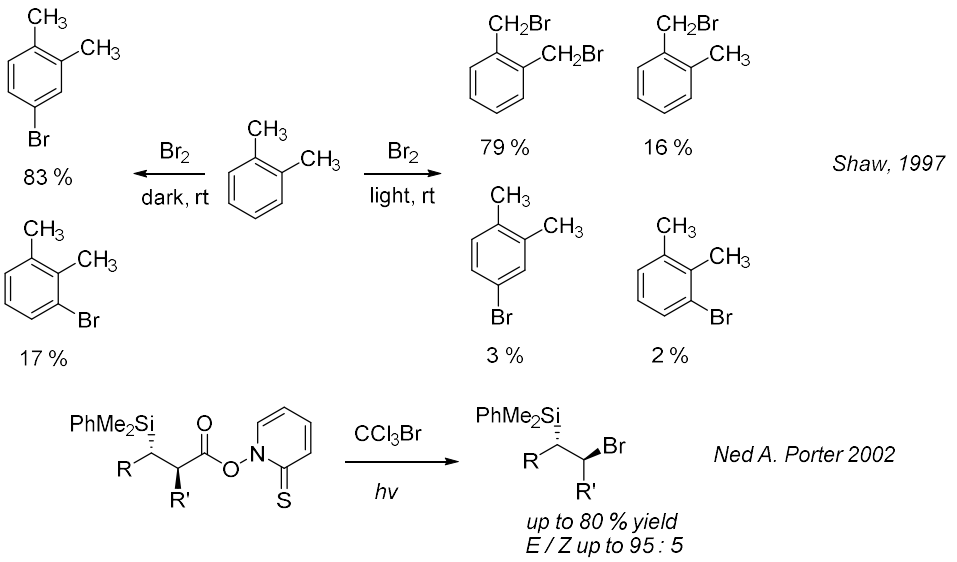
Until now, the radical and the theory of radical reaction have gained significant development and outstanding position in chemistry. In this chapter, we would like to have a concise overview about the free radical reaction, together with the examples of application in organic synthesis.

1.2 Radical Halogenation Reactions

The radical halogenation is a common method when introducing halogen atoms to organic molecule. It is widely accepted that the Fluorine and chlorine are more electrophilic and are more aggressive halogenating agents and Bromine is a weaker halogenating agent than both fluorine and chlorine, while iodine is least reactive of them all. Traditionally, the halogenation of alkane is usually considered as the photochemistry progress.[7] This kind of reaction is generally a chain reaction progress, like the industrial production of chlorinated methane.[8] (Scheme 3) However, the product would be the

mixture of single- and multi-substituted compounds, as well as the rearrangement during the reaction. The radical reaction could also be conducted by photo, heating and other methods. In 1919, the allylic bromination reaction was first reported by Wohl.[9] The purpose of bromide reagent N-bromo-O-methylhydroxylamine is similar with the N-Bromosuccinimide, which is widely applied as a bromide source at present. From then on, more and more halogenation reactions were conducted with the halogen and halogen reagents. In 1993, McMillen reported their detailed research about the photo catalyzed bromination of cyclohexene.[10] They found that the reaction was a thermodynamic progress. They also compared the ratio of substitution and addition. The outcome showed the significant advantage of NBS in substitution reaction and the reason could be attributed to the much faster speed when generating bromine radical.





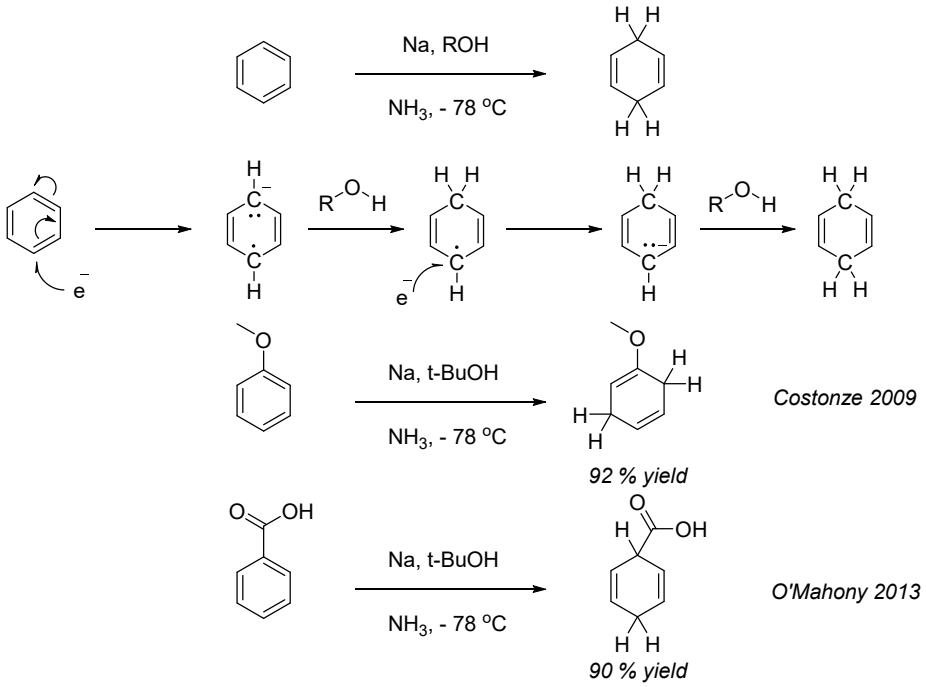
Scheme 3, Radical halogenation reactions

Beside the reactions above, there also could be selectivity among the radical halogenated reactions. In 1997, Shaw's group reported the selective bromination of organic compounds in Water. The comparing of dark reaction and photo reaction showed great difference. In 2002, the diastereoselective radical halogenation reaction was reported by Porter.[11] In the reaction, the Barton esters was decomposed and brominated with light, and the enantioselective products were obtained. (Scheme 3) The radical strategy is an important choice in the halogenation reactions.

1.3 Alkali Metal Initiated Radical Reaction

In the year 1944 to 1949, Arthur Birch published the reduction reactions of benzene and homologous compounds by dissolved alkali metals. The reaction was conducted in low temperature and the solvent was liquid NH_3. This reaction provides a new strategy to the utilization of aromatic compounds.[12] In this reaction, the metal did not react with

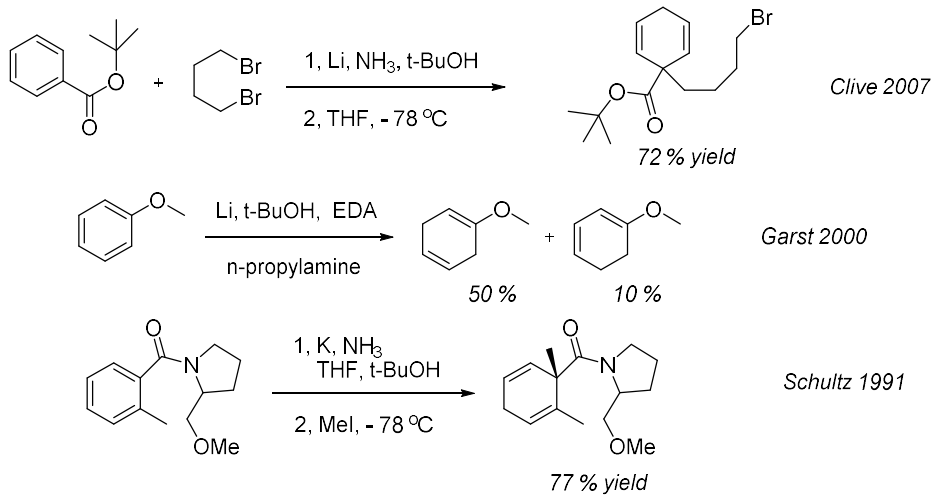
the isolated C=C bond but could reduce the more stable aryl ring. In this reaction, the benzenoid ring could be reduced to 1, 4-cyclohexadienes. The substituted group on the benzenoid ring could determine the regioselectivity of reduced position. When there is electron withdraw substituent, the reaction would occur at the 1, 4 positions.[13] The reason would be that the electron withdraw groups could stabilized the radical and when there are electron rich groups, the radical would prefer to generate at the less substituted position. Many reactions have been conducted and indicated the effect of the functional groups. In 2009 and 2013, Costonz and O'Mahony studied the different effects of substitution groups on the aryl ring. The methoxy group and acid group were not reduced by the strong alkali reductants. The high yield of single product also showed the high regioselectivity of the birch reaction.[14] (Scheme 4)



Scheme 4, Birch reaction and the mechanism

As the radical progress is involved in the Birch reduction, several routes have been

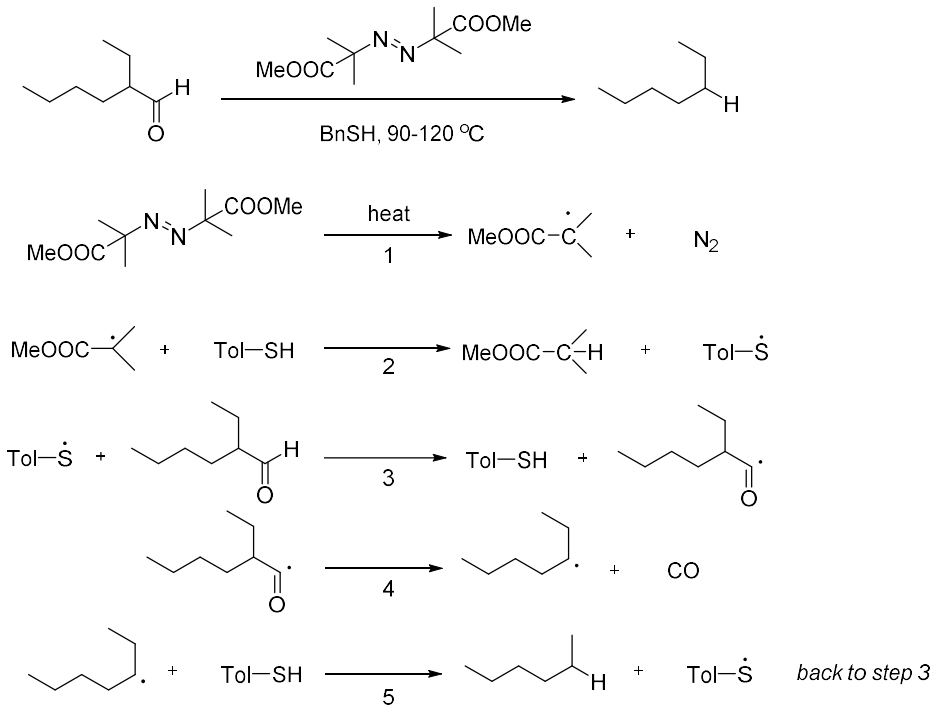
proposed to take advantage of the radical in conducting reactions. As the liquid NH_3 and the highly flammable alkalis are applied in the original Birch reactions, there would be troublesome when conducting the post-processing steps. Then some researchers modified the reaction. Common solvents like THF, n-propylamine and ethylenediamine were applied in this reaction instead of liquid NH_3, and the modifiied reactions were named as the Benkeser reaction.[15] (Scheme 5) In 2000, Garst and co-workers reported the reduction of methoxybenzene with lithium and low molecular weight amines.[16] There are also reactions utilizing the radical intermediate in Birch reaction. In 1991, Schultz reported a Benkeser reaction followed by the enantioselective coupling with alkyl halide.[17] In 2007, a reductive alkylation of benzoate compounds was reported by Clive.[18] The Birch reaction and the modified reactions are good methods in functionalization of aryl rings.



Scheme 5, Applications of Birch reactions and modification.

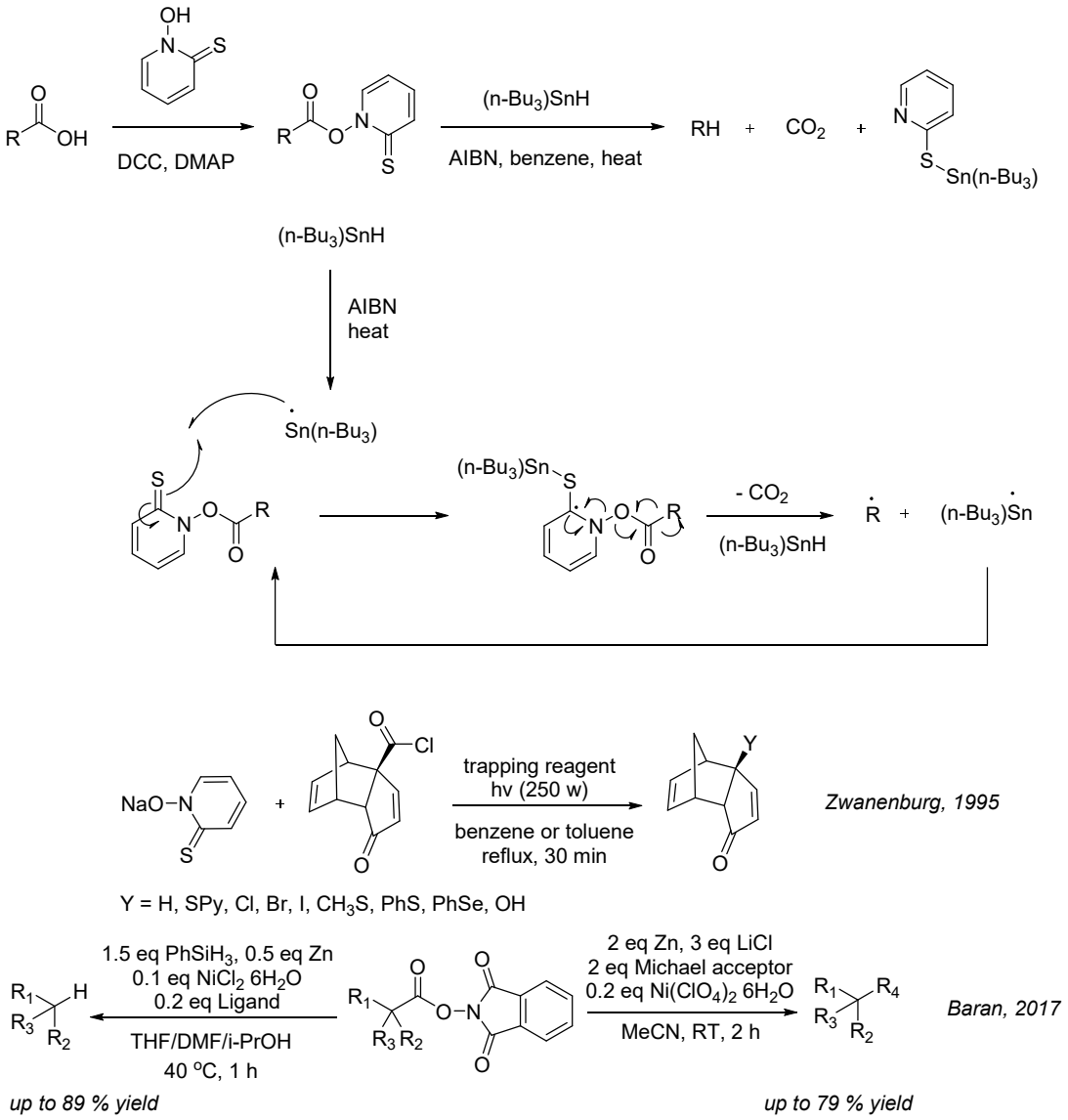
1.4 Radical Decarbonylation Reaction

In the decarbonylation reaction, the carboxyl group is removed and in most conditions the CO_2 is released. The reaction group is usually the carboxylic acid and aldehyde. The result would be the hydrodecarbonylatic reaction to C-H bond or followed by the coupling reaction to get a functionalized product. The carboxylic acid substrate is one kind of easy available, stable and cheap reagent. The decarboxylation reaction contains several potential advantages, such as high effected and high selectivity, As well as environmental friendly with releasing of nontoxic CO_2. In 1952, a decarbonylation of aldehyde reaction was reported by Waters.[19] The decarboxylation was catalyzed by benzyl thiol. In the reaction, the radical was initiated by the dimethayl-2,2'-azo-isobutyrate. Then the thiyl radical was generated from the initiator. Next the thiyl radical reacted with the aldehyde to form a carbonyl radical, followed by the decarbonylation. And the new alkyl radical reacted with the thiol to provide the product. This reaction could also work without the existence of thiol, but more catalyst was necessary. Because the crack of C-C bond requires quite high energy, which results in that this progress need a relatively high concentration of the radical. And the low efficiency of alkyl radical abstracting hydrogen is another problem in this progress. When benzyl thiol was introduced, the amount of catalyst could be reduced. The formation of carbonyl radical could be increased in the presence of thiol, together with the following decarbonylation and the trapping of alkyl radical. This reaction followed a polarity reversal catalytic progress.[20]



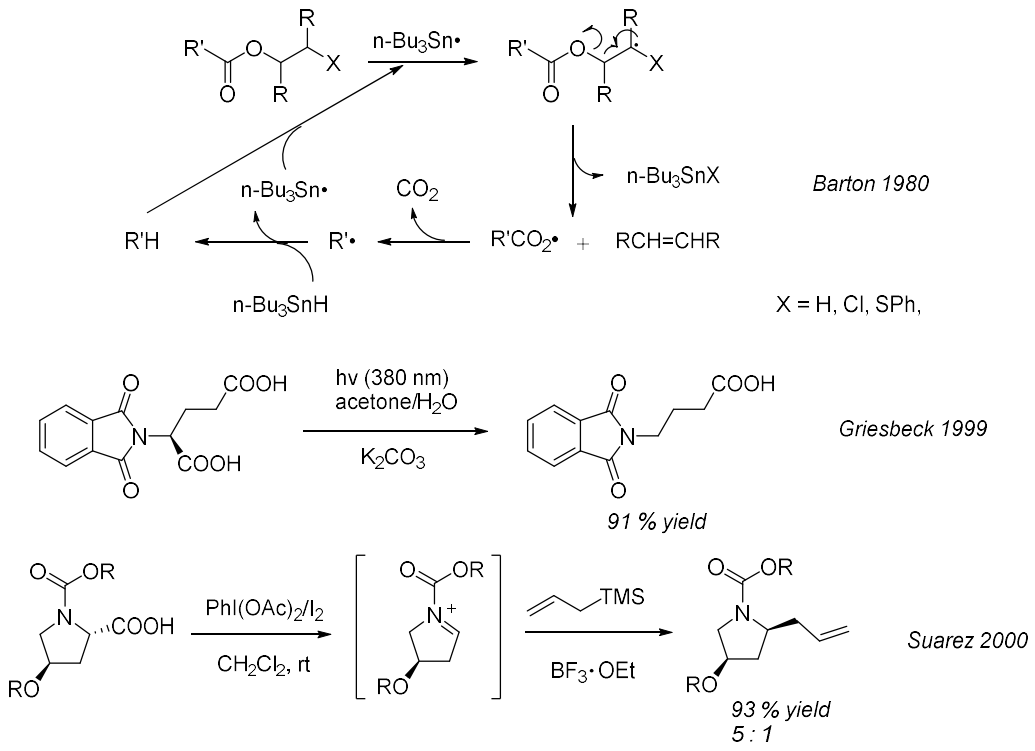
Scheme 6, The progress of thiyl radical catalyzed polarity reversal decarbonylation

When it came to 1983, Barton developed the strategy of thiohydroxmate ester decarbonylation.[21] In this method, the carboxylic acid would first react with pyrithione to get the Barton ester. Then the Barton ester would go through a radical route to the decarboxylated compounds with (n-Bu_3)Sn· as the catalyst. In the radical progress, the tributyltin radical first attacked the sulfur atom to active the compound. Then the carboxyl group underwent the decarbonylation progress after the homolysis of N-O bond, following the radical chain transfer progress. Finally, the alkyl radical was reduced by (n-Bu_3)SnH to give the desired product and the catalyst was recovered to join the next reaction cycle. In 1995, Zwanenburg's group reported the photo-initiated Barton type decarbonylation of cyclopentadienone.[22] In 2017, Baran's group reported the Ni-catalyzed Barton decarbonylation.[23]



Scheme 7, Barton decarbonylation and the mechanism.

Beside the Barton decarbonylation, there have been other types of radical decarbonylation reactions. In 1980, Barton' group reported a tri-n-butylstannane initiated thermolysis of per-esters reaction to give the decarbonylated product and the corresponding olefin.[24] In 1999, the reaction of photoinduced decarbonylation in aqueous phase was published by Griesbeck.[25] In 2000, a reaction of catalytic tandem radical decarbonylation and coupling with allylic compound was published by Suarez.[26] This reaction was conducted with iodine and Lewis acid.



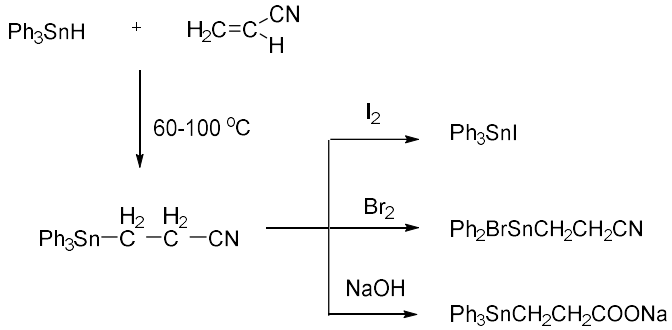
Scheme 8, radical decarbonylation reactions

1.5 Radical Reaction Involving Organotin Compound

The organotin compound is a sort of high efficient substrates in the functionalization and coupling reaction. It could function as the catalyst or the reagent. Various of organotin compounds are commercially available. Sometimes, the organotin method is irreplaceable in some specific organic synthesis. However, the organotin compounds could damage the environment. As to the human, it could do harm to the skin, eyes, the immune and reproduction system, even resulting in mutagenic. In spite of these disadvantages,[27] they are of great use in organic chemistry.

Before Van der Kerk reporting the tin-carbon bond formation reaction, most of the organic-tin compounds came from the metal-metal exchange method. One example is

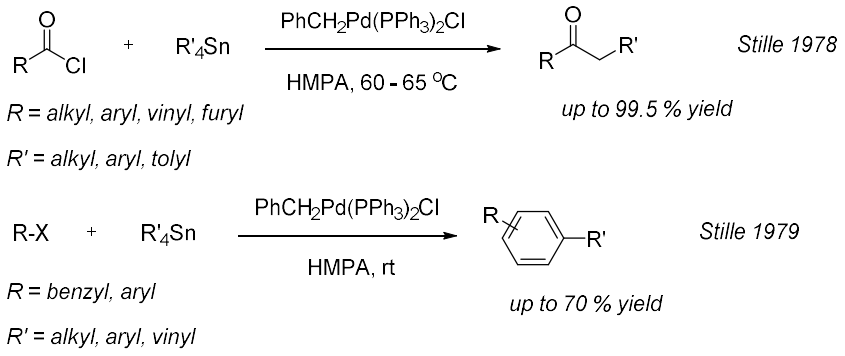
the exchange of Grignard reagent with tin salts.[28] However, this method is limited when synthesizing the organotin compound with functional groups. In 1957, the organotin hydrides reacting with the olefinic double bond was reported.[29] Utilizing the easily prepared organotin hydrides like $(n\text{-}Bu)_3SnH$ and Ph_3SnH and a wide range of olefin compounds, the target organotin compound could be acquired in a more convenient way. The scope of function groups connected with the C=C bond could be far wider than the traditional method, like -CN, -COOH, -COOR, $-NH_2$ and -OR. What's more, the product could retain the reactivity with the other compounds and at the same time keep the stability of the core Sn structure.[30] (Scheme 9)

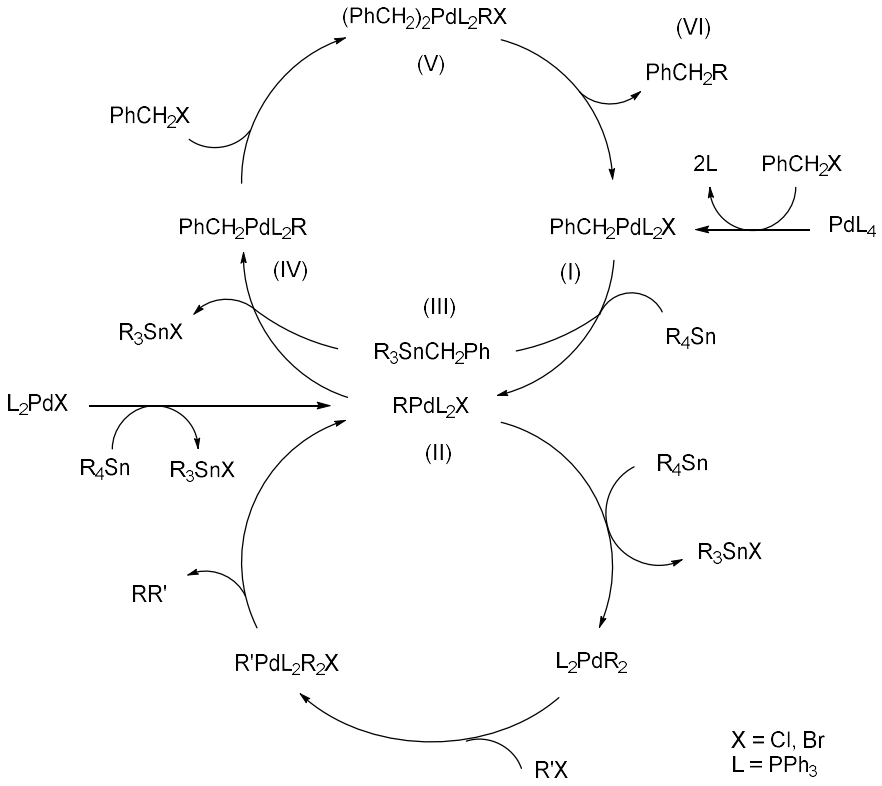


Scheme 9, functionalization of organotin reagent

With these organotin reagents, a sort of reaction has been reported and the tin-reagents were widely applied when introducing various of functional groups and different kinds of structures have been constructed. In 1978 and 1979, Stille and co-workers reported the modified palladium catalyzed coupling reactions of organotin with electrophiles. The reaction could be conducted in mild condition.[31] The scope of reagent was quite wide and with very good result. The mechanism was also studied. First, the Palladium catalyst (I) undergoes transmetalation with teraorganotin reagent. The benzyl group was replaced to form the organopalladium complex (II). Then this complex reacted with

another substituted teraorganotin compound (III) to get the diorganopalladium complex (IV). Then the diorganopalladium complex (IV) underwent the oxidative addition of another benzyl halide to form the new palladium intermediate (V). After the reductive elimination, the coupling product (VI) was formed.

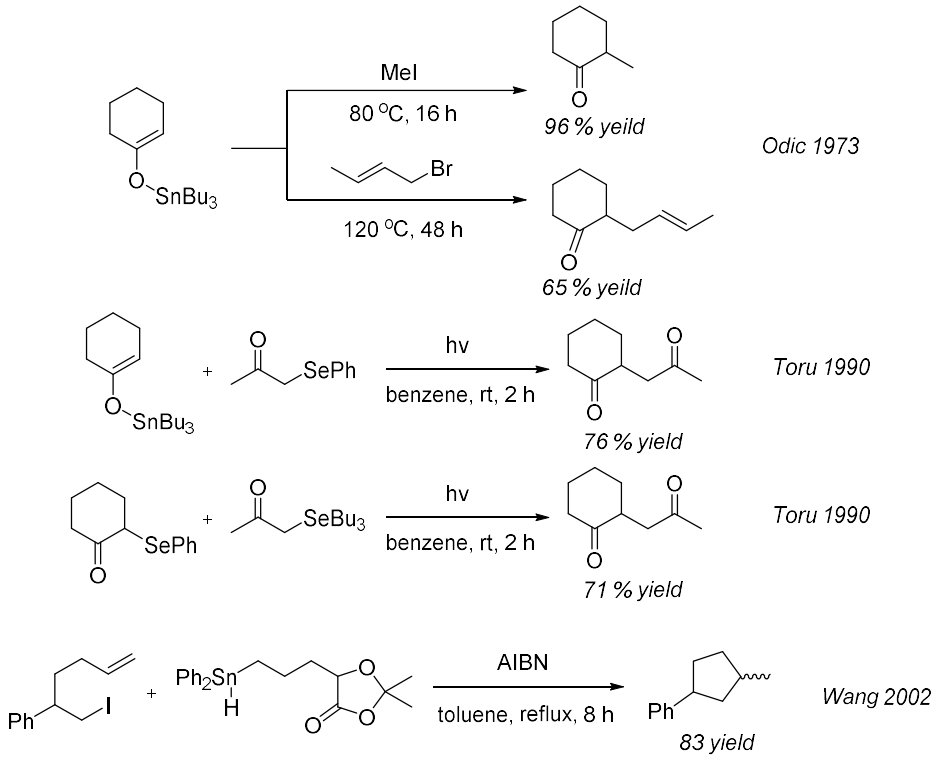




Scheme 10, The Stille reaction and mechanism

Beside the Stille reaction, other organotin reactions have also been reported. Generally, these reactions include the coupling reactions and additional reactions. In

1973, Odic reported the alkylation of organotin enolate.[32] In 1990, the Turo' group reported the coupling of organotin enolate with α-(phenylseleno) carbonyl compound.[33] The reaction was conducted under the irrigation of high pressure mercury light. In 2002, the radical cyclization by organotin hydride was reported by Wang.[34] The halogen substrate was reduced by organotin hydride to initiated the cyclization progress. (Scheme 11)

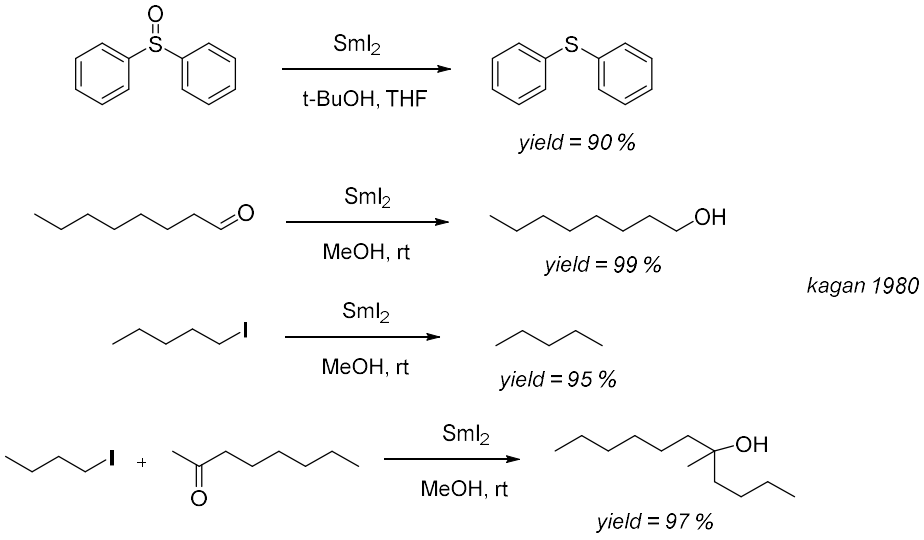


Scheme 11, coupling reactions of organotin and reductive cyclization by tin hydride.

Whatever, the organotin compound is of great toxicity to the organism and the environment. The use of organotin compounds need to be avoided if possible. We expect new reagents and reactions to replace the organotin compounds.

1.6 SmI_2 Catalyzed Radical Reaction

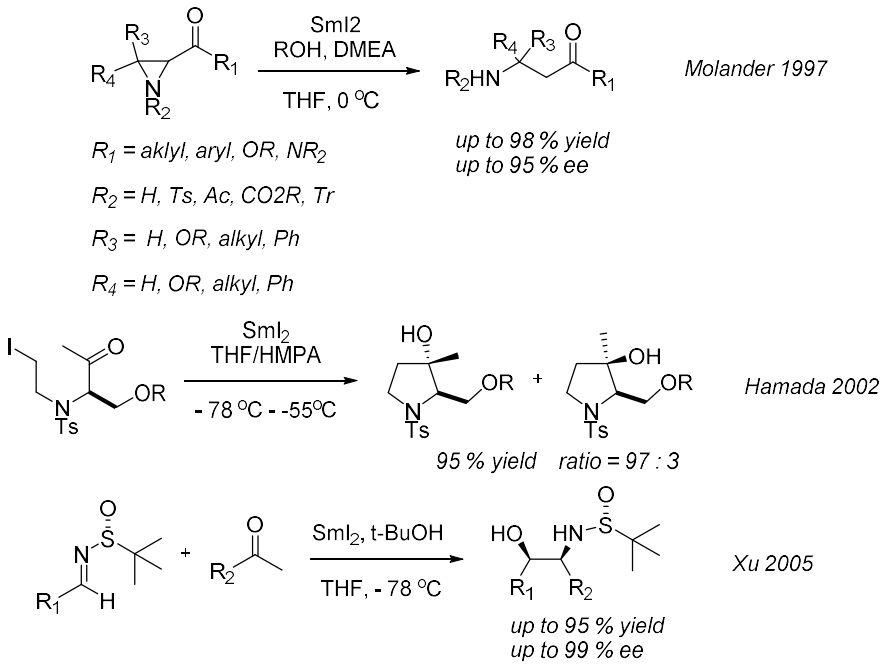
In 1979, Kagan first reported a series of organic reactions catalyzed by SmI_2.[35] The SmI_2 catalyzed radical reaction is as known as Kagan' reaction. The reaction scope could be deoxygenation, double bond reduction, halide/tosylate reduction, and ketone alkylation. (Scheme 12) Usually the reaction condition could be quite mild at room temperature and the harsh conditions are not necessary. Sometimes, the reaction is conducted with catalytic amount of NiI_2. What's more, a wide scope of function groups is tolerated in the system, like aldehyde, ketone, alkene, alkyne, acid and halide. And the reductive coupling of ketone with alkyl and functionalized halides has also been studied. In Scheme 12 are shown some radical reductions and coupling reactions catalyzed by SmI_2. The reaction is high efficient with excellent yield with concise reaction condition. From then on, the SmI_2 mediated radical reactions have developed into an important field in organic synthesis.



Scheme 12, SmI_2 catalyzed reduction and coupling reactions

Generally, the type of SmI_2 radical reactions includes functional group transformation

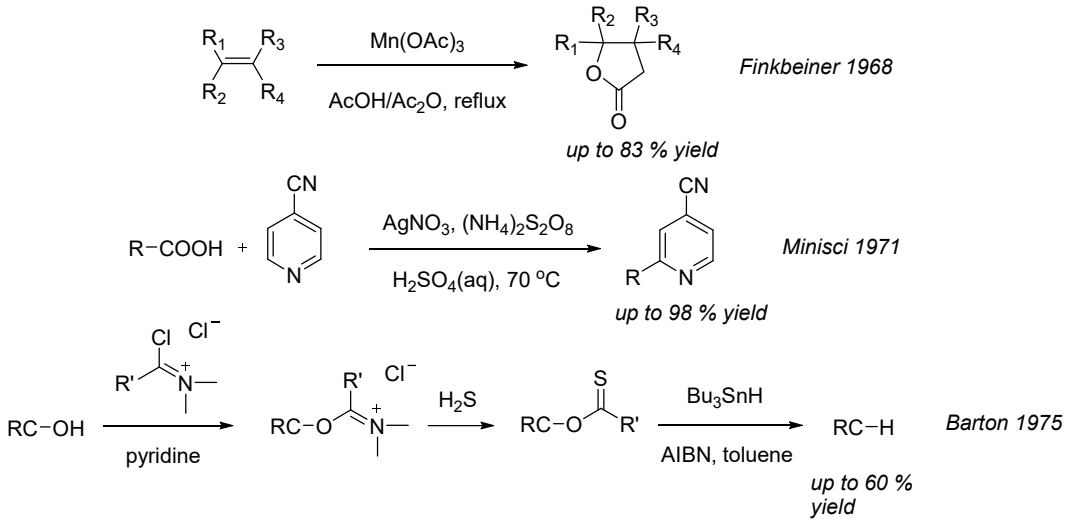
(mainly reduction reactions), coupling reaction and addition reaction. In 1992, Curran studied the mechanism of reductions of halides by SmI_2, and proposed that the co-solvent HMAP played an important role in the reduction progress.[36] In his paper, he proposed the effect of solvent in SmI_2 radical reaction. The paper indicated that the electron-donating property of HMAP or DMPU solvents helped to increase the reductive ability, for several molecules of HMPA coordinated with the SmI_2 to form the complex. In 1997, Molander reported the reduction of acylaziridines to amino carbonyl compounds with functional group selectivity and high yield.[37] In 2002, Hamada reported an intramolecular Barbier reaction catalyzed by SmI_2.[38] This reaction is proposed to be a bis-radical progress. In 2005, Xu and his group reported the cross-coupling of imine with aldehyde.[39] The high enantioselective products were obtained from this reaction.



Scheme 13, SmI_2 catalyzed reactions

1.7 Other Radical Reactions

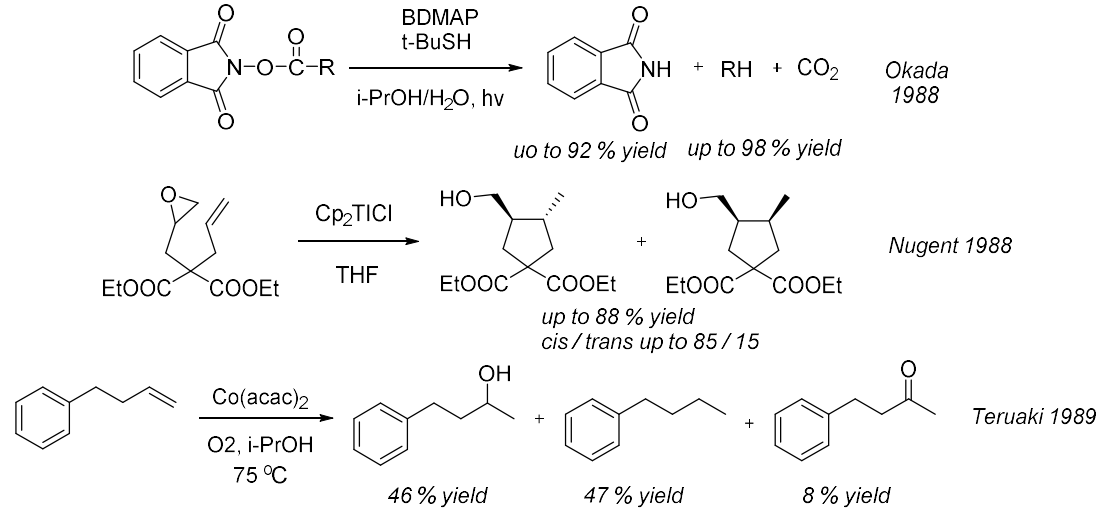
Beyond the reactions mentioned above, there are still numerous radical reactions. The reaction could be catalyzed by various transmetal catalysts. And the scope of the substrates is wide. Some examples are shown in Scheme 14. In 1968, a transmetal mediated addictive cycloaddition was reported.[40] The reaction utilizes Mn(III) acetate as catalyst and was conducted in the mixture of acetic acid and acetic anhydrous, which plays the role of solvent as well as a reactant. The author indicated that the use of acetic anhydride would promote both the conversion rate and the yield. In 1971, the silver salt catalyzed decarboxylation and electrophilic alkylation of heteroaromatic compound was reported by Minisci and co-workers.[41] With peroxydisulphate as the oxidant, the alkyl acid first went through a hemolytic progress to provide the alkyl radical under the catalysis of sliver salt. if the reactant was a non-substituted heterocyclic ring, the product could be the mixture of α, γ and the two alkylated products. When the α or γ position was occupied, the result could be a monoalkylation product. (Scheme 14)



Scheme 14, the radical cyclization, alkylation and deoxygenation reactions

In 1975, the photo initiated radical deoxygenation reaction was reported by Barton and McCombie.[42] Before the reduction, the hydroxy group is first converted to the thioester. Then the thioester was eliminated by the tributyltin radical. Through the whole progress, the alcohol was reduced to alkane. (Scheme 14)

On the other hand, the photo induced decarbonylation of organic acid via N-acyloxyphthalimide, the titanium salt induced epoxide ring opening reduction and cyclization with olefins, and the cobalt catalyzed olefin oxidation and reduction.[43] (Scheme 15) In the decarbonylation reaction reported by Okada in 1988, the alkyl radical intermediate would conduct some other radical reactions like elimination and cycloaddition, when the reductant thiol was removed from the reaction system. And the $Co(acac)_2$ catalyzed C=C bond oxidation with O_2 as oxidant to get the regioselective secondary alcohol. These reactions enriched the radical resource and provided the alternative methods in introducing new function groups and the functional group conversion.

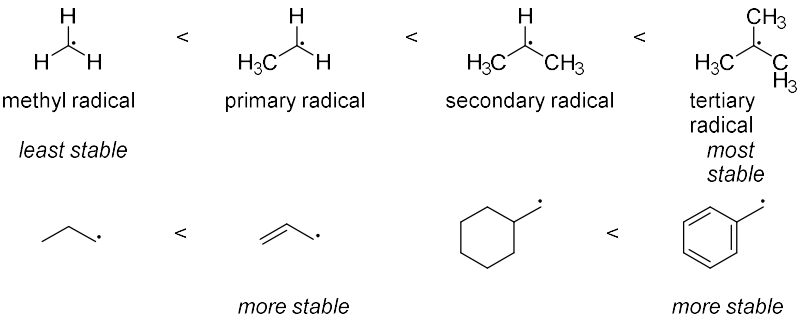


Scheme 15, Radical involved decarbonylation, cyclization and oxidation reactions.

1.8 Regioselectivity and Stereoselectivity of Radical Reaction

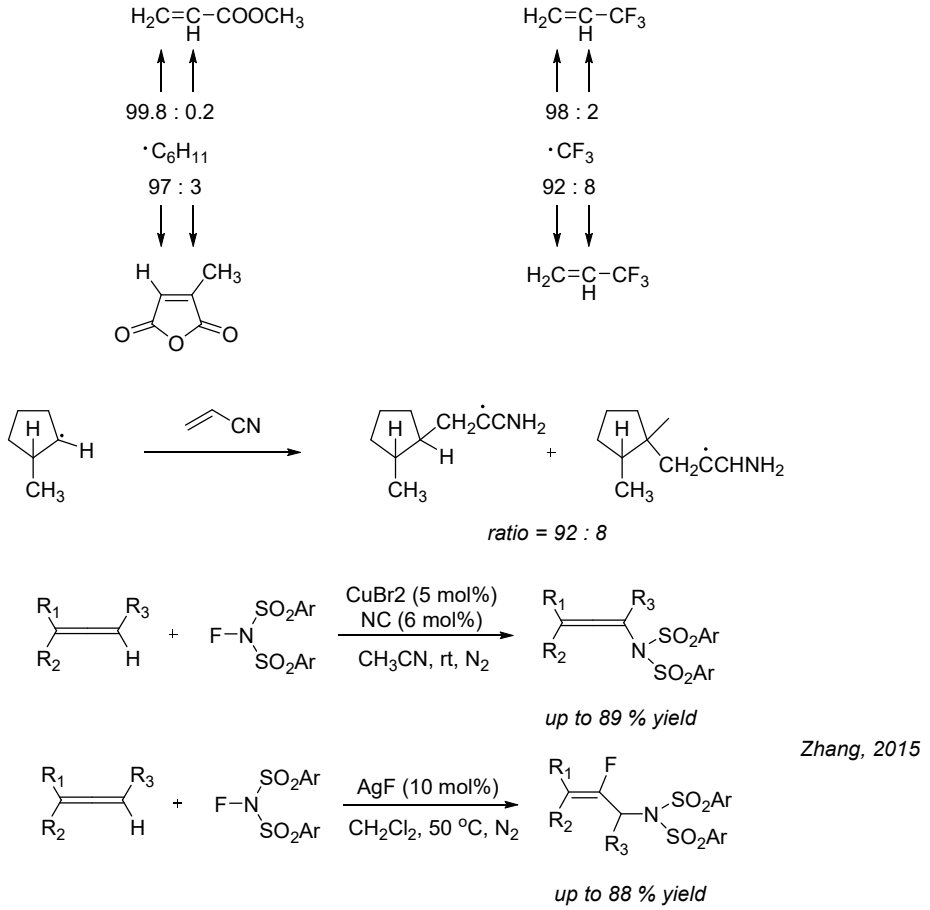
The regioselectivity and stereoselectivity are important aspects in radical reactions, which could deeply affect the application. The regioselectivity and stereoselectivity of radical reactions could be influenced from many aspects. The type and reagent of the reaction, the electronic property of the substitution group, stereo-hindrance effect and some other factors could all affect the selectivity of product. Here we would talk about several examples of radical selectivity together with the specific reactions.

Here we would mention the following few aspects. First would be the stability of radical. Generally, the radical is considered as an electron poor specie, and the electron donating substituted groups would help to stabilize the radical. Otherwise, the environment is not benefit for the radical. At the same time, the electron delocalization effect could help to stabilize the radical. (Scheme 16) In addition, the long pair electrons from atoms like oxygen and nitrogen could also stabilize the radical, even they would be electron withdraw elements. The adjacent oxygen atom could donate the long pair electron to the half-empty p orbital of the radical, thus could lead to an overall energy decrease of the radical.



Scheme 16, Factors that affect the stability of radical

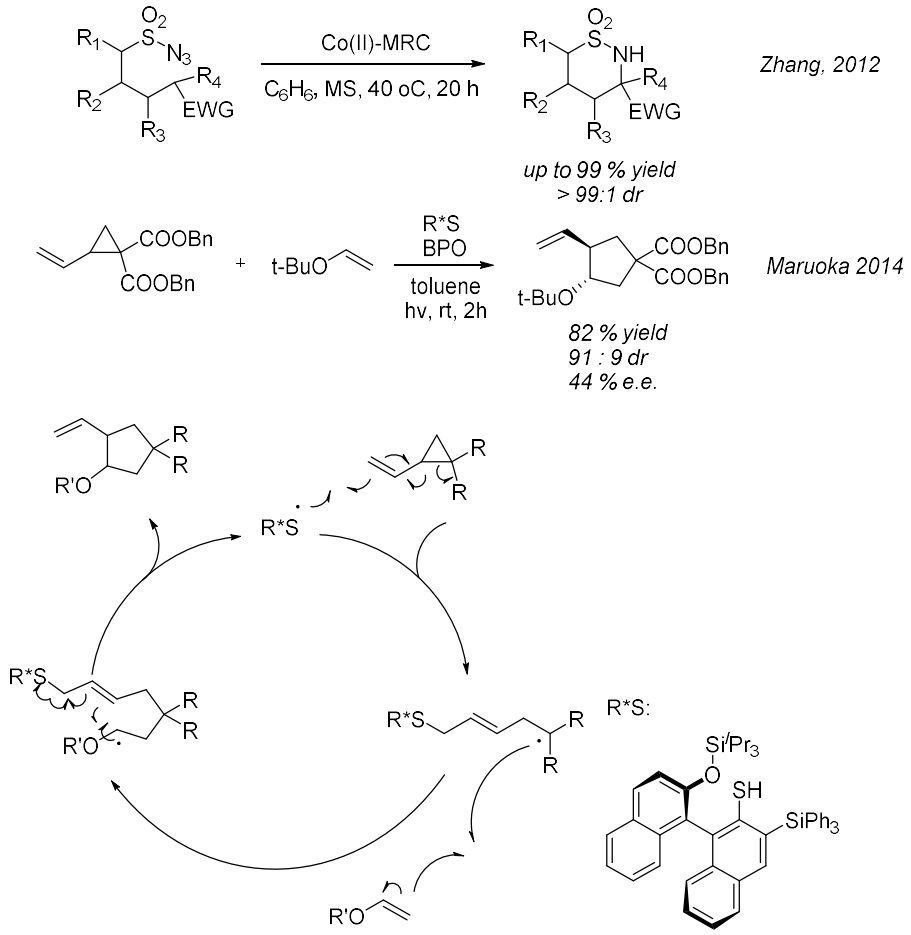
Both the regioselectivity and stereoselectivity could be the reflex of competition between low energy intermediate and the steric effect.[44] We would use examples to illustrate it. In general, the free radicals preferred to attack the less substituted carbon of alkene. However, the electronic donating group would change the ratio in different isomers. (Scheme 17) In 2015, Zhang's group reported the controllable, regioselective radical amination of allenes.[45]



Scheme 17, Regioselectivity in radical reaction

In, 2012, Zhang's group reported intramolecular amination.[46] The Co(II)-based metalloradical catalysis was applied in this reaction to obtain the high regio- and diastereoselectivity. In 2014, Maruoka reported an organic thiyl radical catalysted enantioselective cyclization of alkene and cyclopropane. The chairal cyclic product was

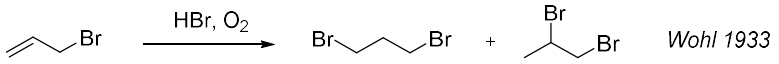
obtained and the mechanism was studied.



Scheme 17, stereoselectivity in radical reaction and catalytic cycle for the reaction of a chiral thiyl radical

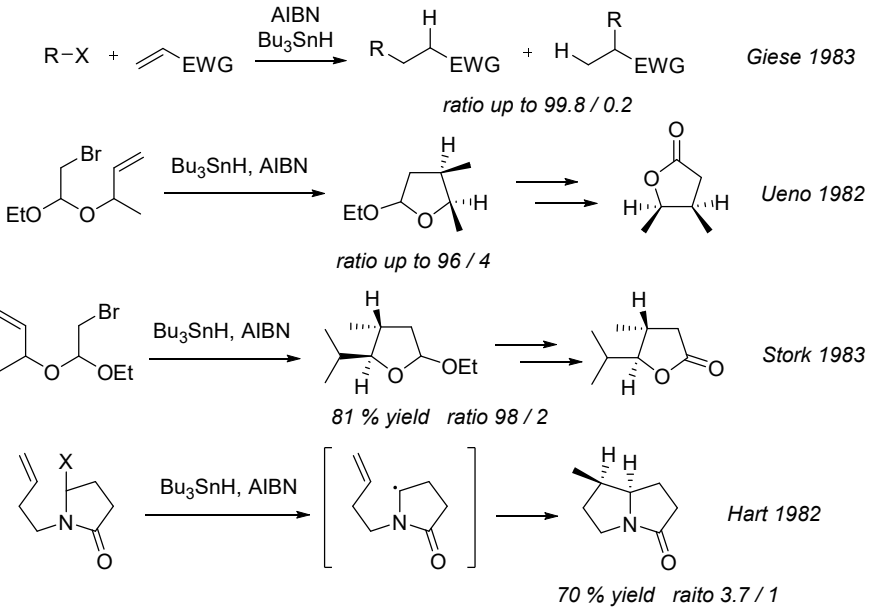
In about 1930s, one radical mechanism was proposed while reporting the additional reaction of HBr and allylic bromide,[47] which is an example of reigoselective radical reaction. (Scheme 18) The radical addiction of allylic bromide with HBr provides mainly the anti-Markovnikov product. That's because that the O_2 and other peroxides react with the HBr molecular to form the bromide radical, which initiates the radical reaction. Secondly, the bromide radical attacks the C=C bond. Then the bromide connects with the less substituted C atom to form the C-Br bond, and together with the

radical on the C atom with more substitution groups, which could be more stable than the Markovnikov intermediate. Then the radical reacts with the HBr molecular to form the product and the new bromide radical.



Scheme 18, Olefin and allylic compound bromination reactions

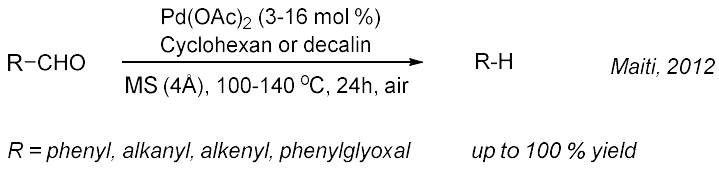
Due to the high regio- and stereoselectivity of radical reaction, it has been applied to the synthesis of multi-stereo center componds and complex natural products. In 1983, the radical addition of C=C bond was reported by Giese.[48] The reaction is a nucleophilic addition progress. The electron-deficient alkane radical coordinates with the electron rich C=C bond to form a new C-C bond. The regioselectivity of α and β position of the C=C bond is determined by the polar effect on the rate of addition but not the stability of radical intermediate. The strong withdraw group on the β position could be beneficial to the formation of β substituted product. Around 1980s, Beckwith and other researchers conducted detailed study and demonstrated the selectivity of radical chemistry.[49] The attention was paid on the steric and stereo-electronic effects. This research of radical selectivity has guidance significance and promoted the research in the mechanism study of radical reaction. The theory was soon applied to the research that Ueno-Stork and Hart separately reported their radical cyclization with a certain degree of selectivity.[50] (Scheme 19)



Scheme 19, examples of regioselectivity and stereoselectivity of radical addition

1.9 Recent Development in Free Radical Reaction

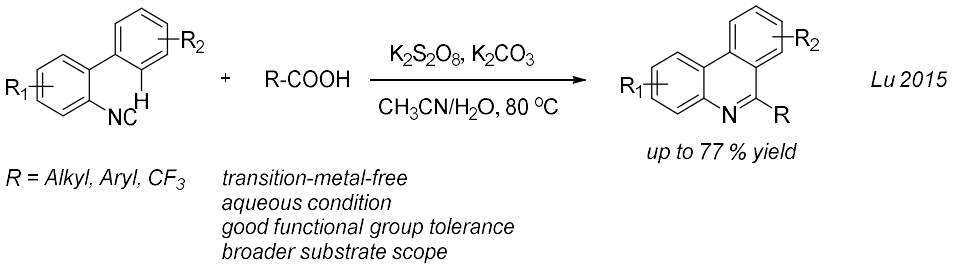
Metal mediated decarbonylation of aldehydes has drawn considerable attention over the decades.[51] In 2012, Maiti's group reported the palladium catalyzed A general and efficient aldehyde decarbonylation reaction.[52] The reaction utilized $Pd(OAc)_2$ as catalyst without using any exogenous ligand for palladium as well as CO-scavenger.



Scheme 20, Pd-catalyzed aldehyde decarbonylation reaction

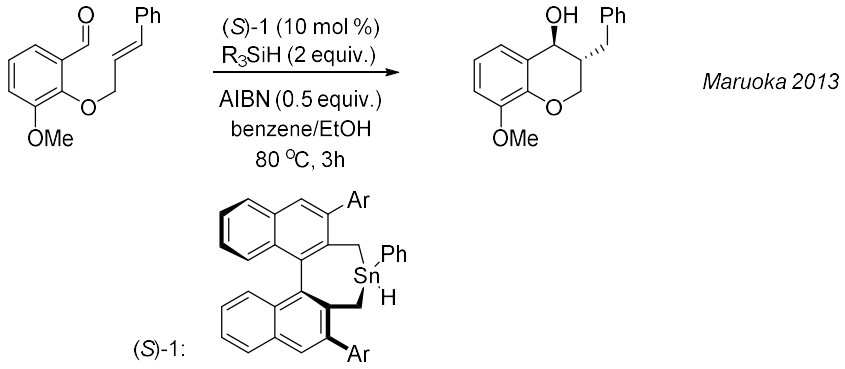
In 2015, Lu and his group reported the transition metal-free radical decarbonylation followed by cyclization with cyanide group and aryl ring.[53] The reaction was conducted in acetonitrile and water mixed solution. the radical-driven oxidative coupling

methodology was also seen as a powerful strategy for preparing phenanthridines with atom- and step-economical features. This reaction is an alternative route in construction of complex structures and introducing functional groups.



Scheme 21, transition-metal-free radical decarbonylation reaction

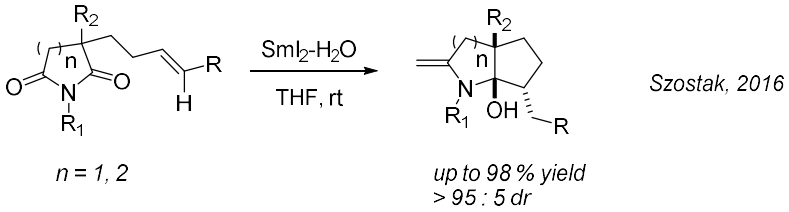
Organotin-hydride-mediated radical cyclizations are powerful tools in organic synthesis for the construction of useful carbocyclic and heterocyclic compounds. In 2013, Maruoka's group reported the enantioselective radical cyclization of aldehydes catalyzed by chiral organotin catalyst.[54] By using a catalytic amount of chiral organotin hydride, the reaction fulfilled the radical cyclization of aldehydes and C=C bond.



Scheme 22, organotin catalyzed enantioselective radical cyclization

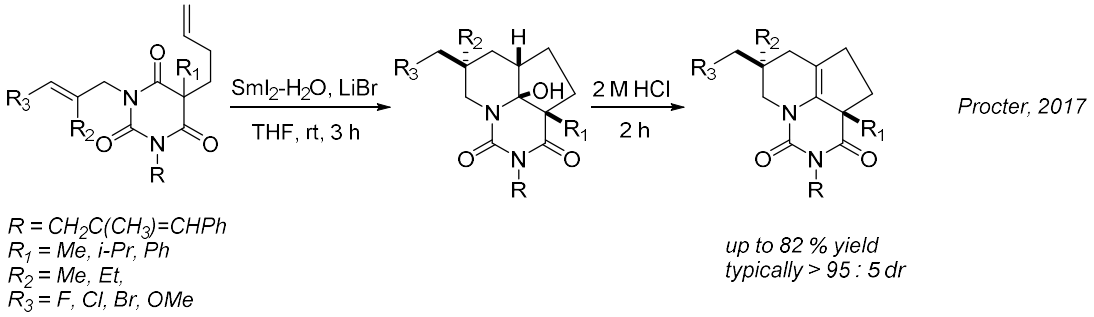
The SmI_2 catalyst has gained the position of ome of the most widely applied single-electron transfer reagent in organic synthesis for the significant advantages like user-friendly, simply operational conditions and wonderful chemoselectivity.[55] Until now, there have been two main strategies in the application of SmI_2: i) reductive manipulation

of functional groups, and ii) reductive coupling to form C-C bond. In 2016, Szostak's group reported the SmI_2-H_2O promoted reductive cyclization.[56] This reaction involved an aminoketyl radical and gave high stereoselective product.



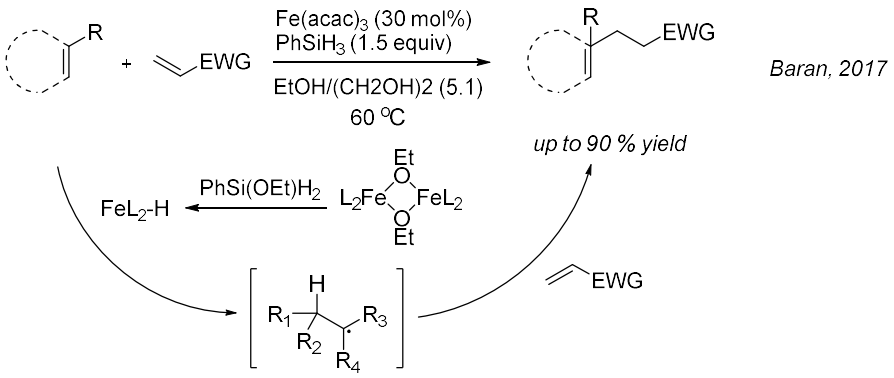
Scheme 23, SmI_2-H_2O promoted cyclization

In 2017, Procter's group reported the SmI_2-H_2O-LiBr catalyzed radical-radical Cascade cyclization.[57] This reaction was triggered by single-electron-transfer reduction of amide carbonyl. The product was formed with up to four stereocentres in good yield and with excellent diastereocontrol.



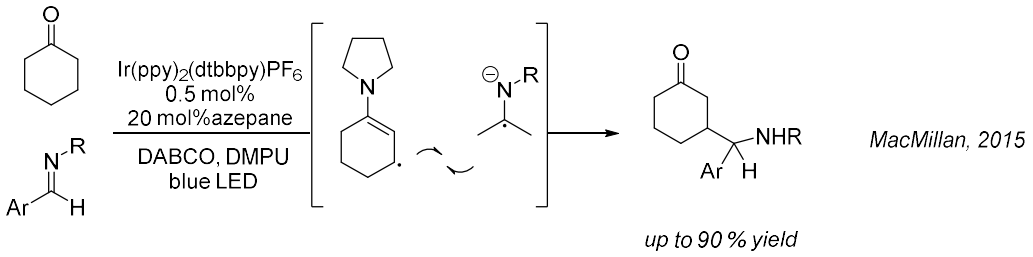
Scheme 24, SmI_2-H_2O-LiBr catalyzed cascade cyclization

In 2017, Baran's group reported the Fe(III)$acac_3$ catalyzed olefin radical coupling reaction.[58] The reaction started with the reductive initiation of donor olefin to alkyl and aryl radical species.



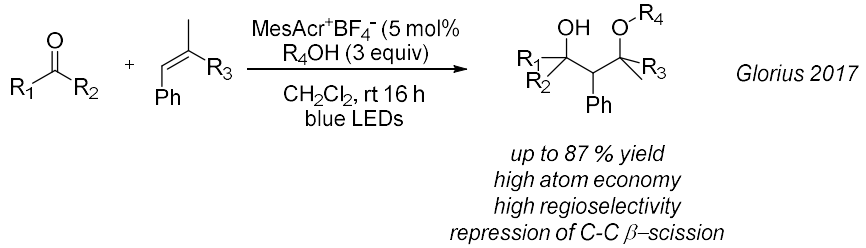
Scheme 25, Fe-Catalyzed C−C Bond construction from olefins via radicals

The photo induced radical reaction presents as a new and effective method in organic synthesis. In recent years, the photochemistry attracted more and more attention. In 2015, MacMillan's group reported the Ir-complex catalyzed cross-coupling between cyclic ketones and imines. This reaction could be conducted under mild condition with wild functional groups tolerated.



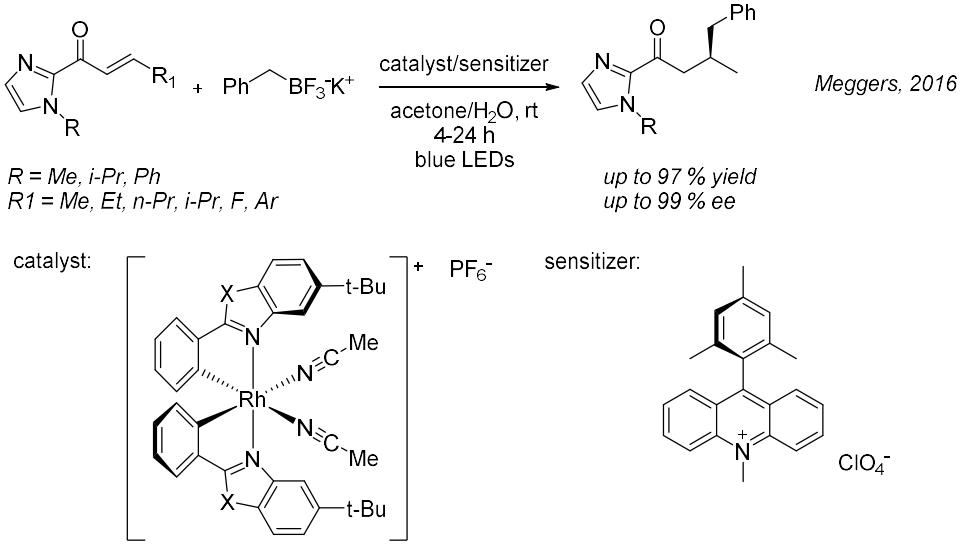
Scheme 26, photo induced direct β-coupling of cyclic ketones with imines

In 2017, Glorius's group reported the visible light photoredox initiated intermolecular radical addition to carbonyls.[59] This reaction was conducted under mild condition with high atom economy and high regioselective, together requiring no metal, ligand or other additives.



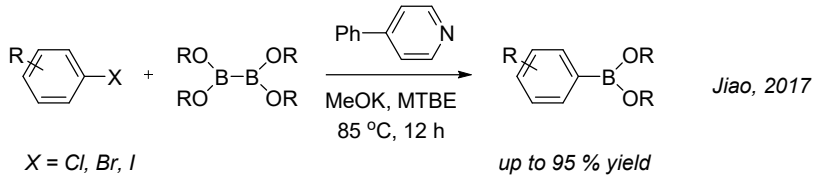
Scheme 27, intermolecular radical addition to carbonyls by visible light catalyst

In 2016, Meggers and coworkers reported the enantioselective addition of alkyl radicals to alkenes via visible-light-activated photoredox catalysts.[60] The rhodium-based Lewis acid catalyst, with low loading amount, not only provides an excellent stereocontrol, but also accelerates the involved key radical addition step.



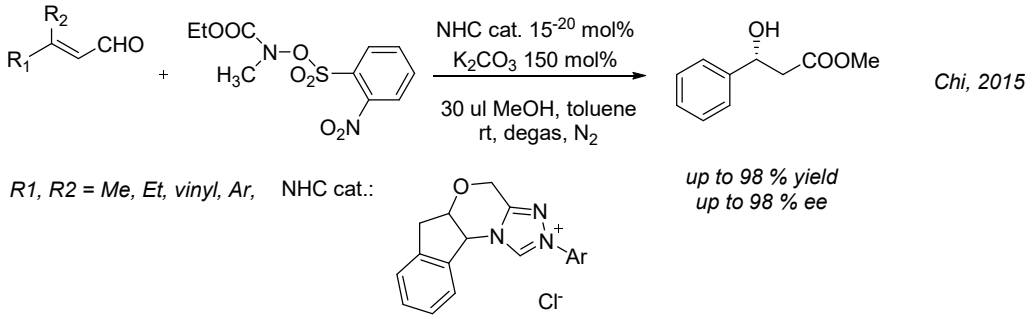
Scheme 28, enantioselective addition of alkyl radicals to alkenes

Radical strategy has also been used in the synthesize of arylboronates. In 2017, Jiao's group reported the pyridine-catalyzed radical borylation of aryl halides.[61] This reaction was a transition-metal-free one with small organic molecular as catalyst. The reaction is simple, mild and wild functional group tolerated.



Scheme 29, pyridine-catalyzed radical borylation

Carbene initiated radical progress is another hot topic in radical chemistry. In 2015, Chi and co-workers reported a reaction of an N-heterocyclic carbene-catalyzed *β*-hydroxylation of enals.[62] This reaction went through several radical intermediates and the product got high enantioselectivity and good yield.

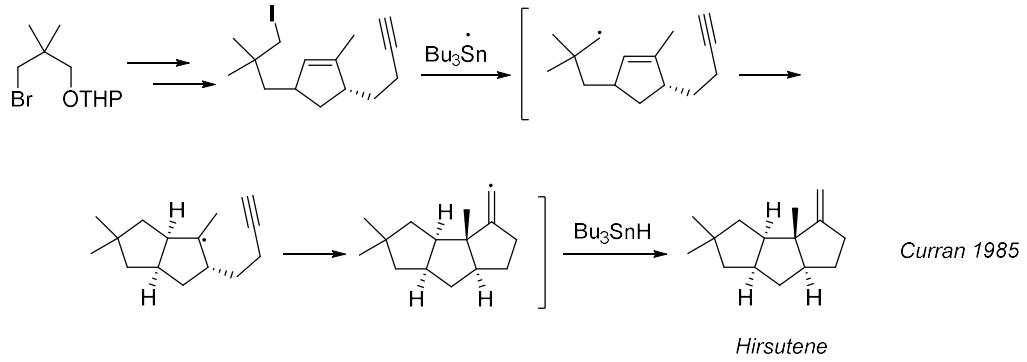


Scheme 30, NHC-catalyzed β-hydroxylation of enals

1.10 Application of Radical Reactions in Synthesis

As the radical reaction is a powerful method in conduction of organic reactions with good regioselectivity and stereoselectivity, and the scope of reaction types is wide, covering most of the organic field, the radical method is a widespread strategy in the total synthesis of natural products and other compounds. The existing theory, and long-term exploration of reaction methods lay the solid foundation for the application. In 1986, Hill reported the photo induced electron transfer to homolyzing the alkane C-H

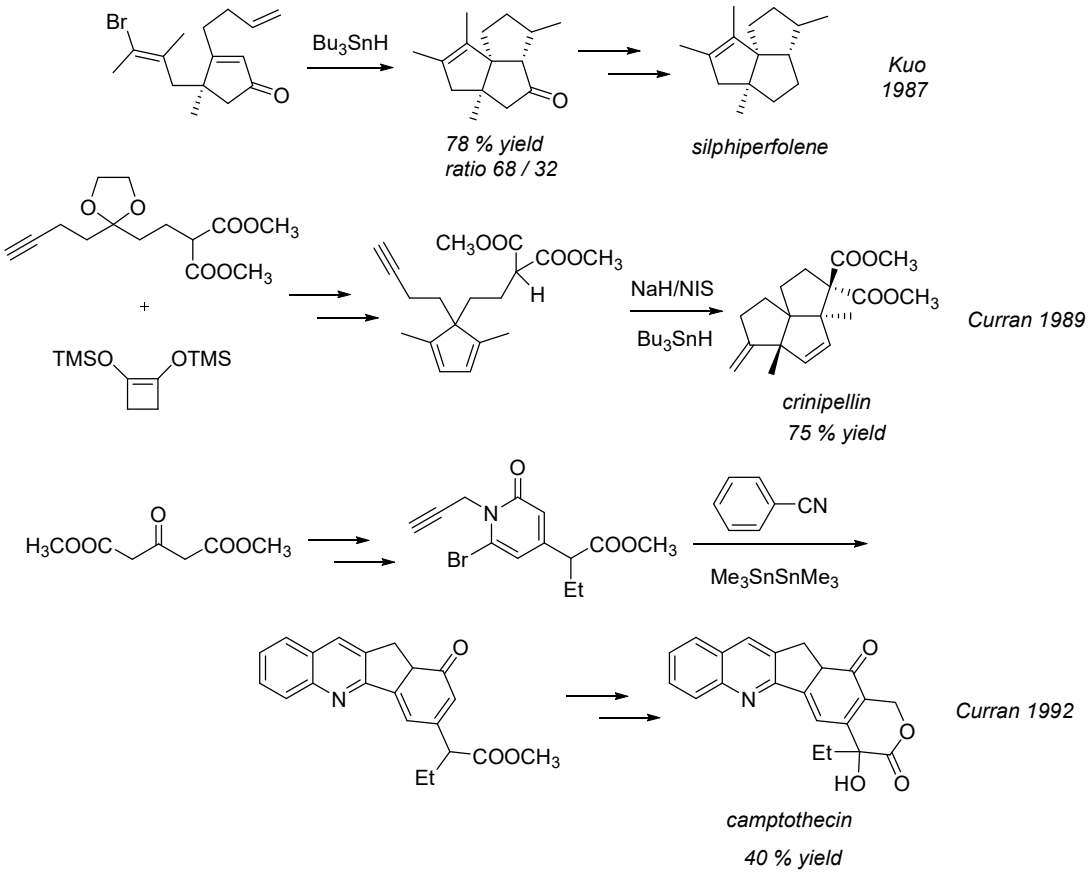
bond to form the alkane radical catalyzed by $W_{12}O_{40}$.[63] In 1985, Curran applied linear radical cyclization to the total synthesis of (±)-Hirsuene, which illustrated the possibility of radical chain reaction.[64] This chain reaction ability of radical was soon applied in the synthesis of polymer and the convenient access to the synthesis of polycyclic compounds.[65] (Scheme 30)



Scheme 30, Total synthesis of Hirsutene with chain radical strategy

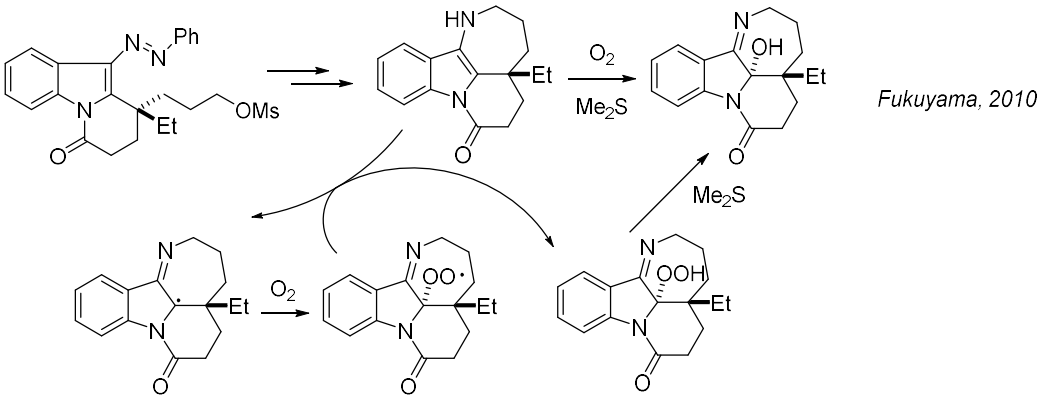
The tandem radical cyclization strategy was soon applied in the organic synthesis. The tandem radical cyclizationg strategy could synthesis one, two and more rings and stereo-centers in one step. It is a convenient way in constructing complex structures. Comparing with the traditional methods, this tandem radical cyclization could greatly shorten the steps. At the same time, the yield and selectivity could be improved significantly. In 1987, Kuo and co-workers applied the tandem radical cyclization in the synthesis of silphiperfolene.[66] This is a convenient method in building the multiple rings with good enantioselelctivity. In 1989, Curran reported an intermolecular addition of iodomalonate in the total synthesis of crimipellin.[67] In 1992, another tantem cyclization involving hetero cyclic structure was reported by Curran.[68] Compared with the traditional synthetic routes, the radical strategy would concisely shorten the steps as well

as improve the yield and selectivity. (Scheme 31)



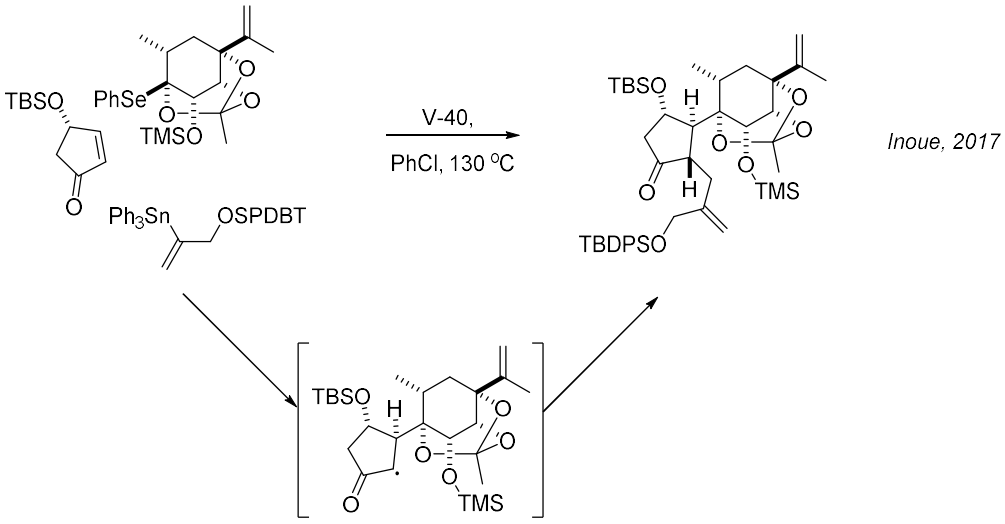
Scheme 31, Radical strategy in total synthesis

In recent years, the radical strategy has been more and more frequently applied to the synthesis of natural products and complex structures. In 2010, Fukuyama's group reported the total synthesis of (-)-Mersicarpine, which involved a peroxyl radical step.[69] This peroxyl radical was formed by the autoxidation of O_2.



Scheme 32, autoxidation by O_2 in synthesis of (-)-Mersicarpine

In 2017, Inoue and co-workers reported the total synthesis of Resiniferatoxin.[70] They developed a radical based strategy to assemble three main components of the compound. This work also demonstrated the advantage of radical reactions in linking hindered bonds without damaging the existing functional groups.



Scheme 33, radical-mediated three-component coupling strategy in total synthesis of Resiniferatoxin

1.11 Summary

After the long, continuous and steady development from the eighteenth century, the radical chemistry has blossomed out into a powerful tool and a widely applied strategy in organic and polymer synthesis. The method of radical reaction has been enriched and improved. There have been efficient and convenient methods in radical initiation and the reaction could be conducted at mild and simple condition.

Now the initiation method could be the homolytic fission of halogens, like Br_2 and halogen-succinimide, the azo compounds like AIBN, the organic and inorganic peroxides like di-t-butyl peroxide, benzoyl peroxide and cyclohexanone peroxide and the peroxydisulfate salts.[71] Beside the chemistry initiators, there are also physical methods that could initiate radical, including radiation and microwave.[72] In recent years, the photo induced photoredox catalyst has been developing rapidly.

The reactions mentioned above are the milestones in the history of radical chemistry. In the new century, the development was gained in multi directions. The pioneers work and theories laid the foundation for the various application. Since the principle of radical regioselectivity and stereoselectivity have been demonstrated, it has been the powerful tool in the introducing of specified functional group and chiral center. These foundations make it possible for the design of complex products. There have been more and more reports about the radical application in total synthesis of nature product and medicine.

The radical reaction offers an alternative in synthetic chemistry. It is a powerful tool in coupling reaction, substitution reaction, decarbonylation, and additional reaction. Due to the high reactive character of radical, the product could be the less thermodynamic stable ones. And the electronic properties of function group would affect the regioselectivity of the product. At the same time, the radical reaction would be quite high efficient and with good yield. And the radical chain reaction would be an essential tool in total synthesis, which would shorten the steps and promote the yield.

Despite these advantages, there are still some disadvantages with the radical reaction. First, the widely used Bu_3SnH radical initiator is quite toxic as the well-known organotin

compound. Second, the concertation of radical should be controlled at the low level to avoid the combination between radicals.

All in all, the radical chemistry has gained solid fundament and valid methods. The radical is widely applied in methodology research, total synthesis and polymerization. It has become a quite reliable and high efficient strategy in organic chemistry.

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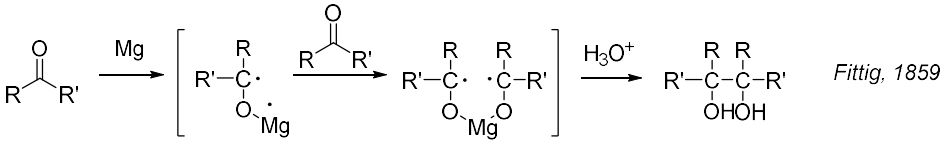
Chapter 2

Cobalt(II)-Catalyzed Reductive Dimerization of Enone

2.1 Introduction

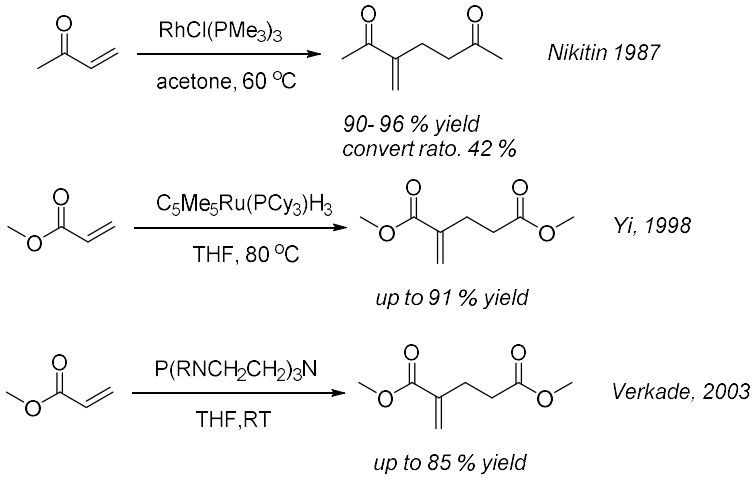
The dimerization reaction is one of the common reaction types in organic chemistry. It has been developing for a long time. The well-known pinacol coupling reaction was discovered in 1859 by Fittig.[73] After that, dimerization reactions have been reported successively. The species of reactant have become broad and various, like alkene, carbene, ketone, aldehyde and acid.[74] At the same time, the diversity of the reaction methods has been enriched, from the traditional high temperature, neat conditions with narrow scope of reactants to the transition-metal catalyzed and photo-initiated mild conditions.[75]



Scheme 1, pinacol coupling

The method of coupling between olefins is generally applied in introducing new functional groups, extending the carbon chain and formation of the cyclic structure. After the long-term research and development, the reaction could be performed with high selectivity and good yield under the selected conditions. According to the structure of the product, the reaction could be divided as both C=C bonds reserved reaction, one

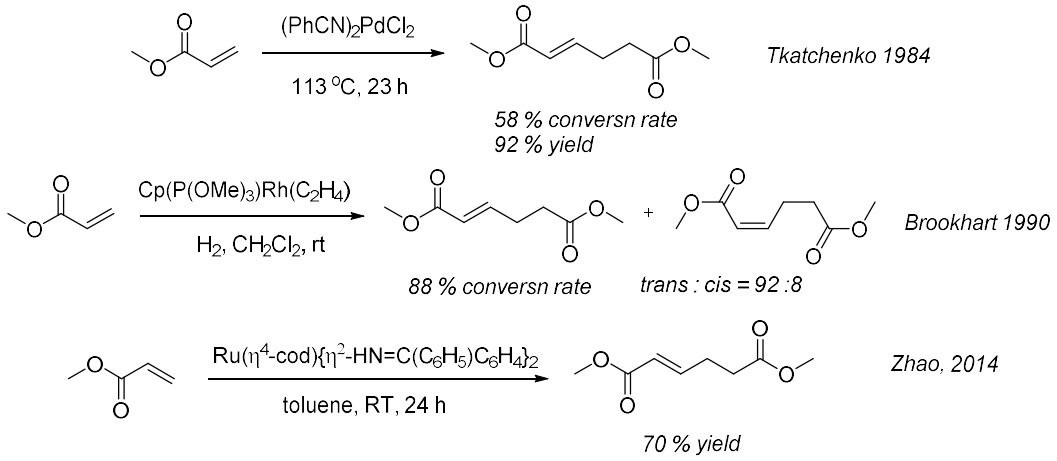
C=C bond reserved reaction, and both C=C bonds reduced reaction. On the other hand, the regioselectivity and stereoselectivity are also important aspects, which could lead to various isomers, like the E/Z selectivity and the chain/branch route competition. Specially, the coupling reaction with trans metallic catalyst could provide asymmetric selective products.[76] Specially, in 1987, Nikitin's group reported the Rh(I)-catalyzed dimerization of methyl vinyl ketone to branched 2,6-heptanedione.[77] The reaction was carried out in mild condition with good yield and regioselectivity. In 1998, Yi and co-workers reported the Ru-hydride complex catalyzed head-to-tail dimerization of acrylate. [78] In 2003, Verkade's group reported the small molecular catalyzed nonmetallic head-to-tail coupling of acrylate.[79]



Scheme 2, head-to-tail dimerization of C=C bond

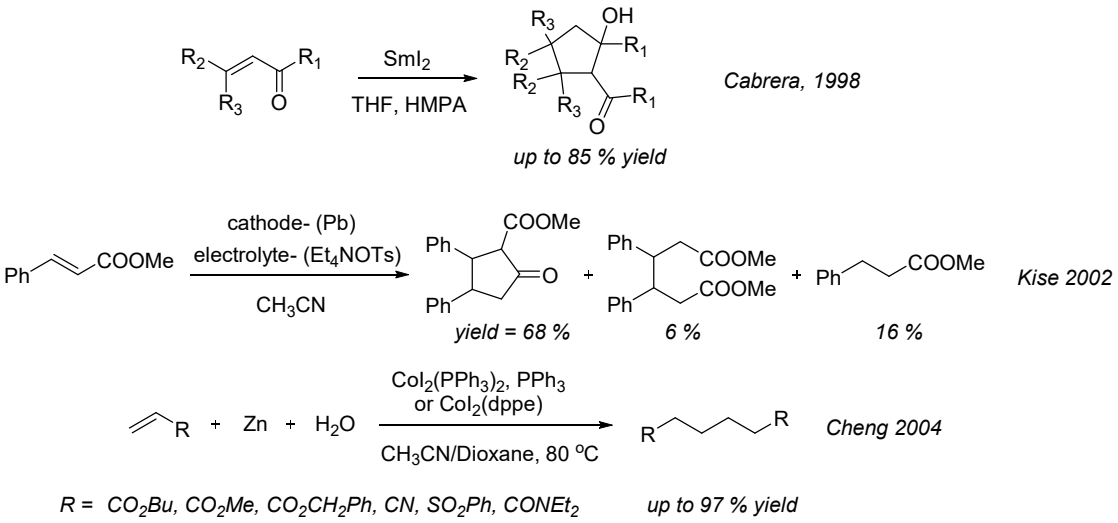
In 1984, Tkatchenko's group reported the Pd-catalyzed acrylate coupling. With the transition metal catalyst, tail-to-tail coupling product was obtained with good E/Z selectivity and high yield. In 1991, Brookhart's group reported the Rh-complex catalyzed dimerization of acrylate.[80] The reaction utilized H_2 as reductant, and the product was obtained with E/Z ratio. In 2014, Zhao's group mentioned a tail-to-tail

dimerization of acrylate when studying the coupling reaction between alkenes and alkynes.[81]



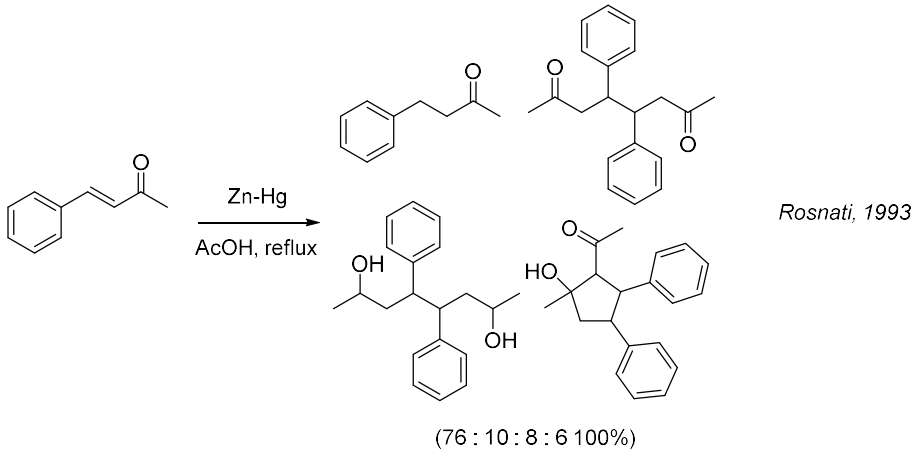
Scheme 3, acrylate tail-to-tail dimerization reactions

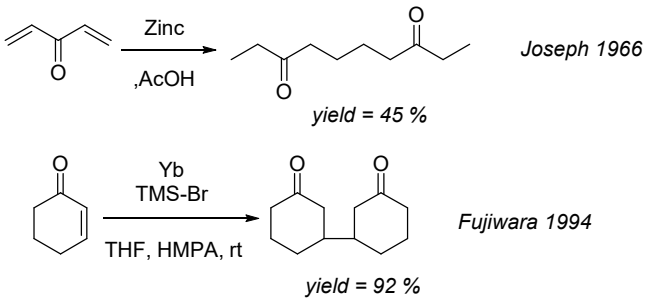
Among these acrylate coupling reactions, the type of tail-to-tail reductive coupling of substituted olefins to di-carbonyl compound is an important part, which is an alternative route to expand the liner carbon chain. For example, the adipic acid is one of the precursors in the polymerization to nylon, which is widely applied synthetic fiber,[82] and the dimerization of acrylate is an alternative route to this industry raw material. General, these reactions require a trans metallic catalyst and reductant. The reactant are usually the acrylate ester species, and the yield and selectivity were gained at quite good level.[83] In 2002, the electrochemical method was applied in the reductive dimerization of acrylate. This reaction was also reported by Armando in 1998, with SmI_2 as catalyst. Later, a dimerization reaction was reported by Wang and co-workers in 2004. The scope of reactant was wide, including acrylic ester, acrylic amide, acrylonitrile and vinyl sulfate.



Scheme 4, reductive dimerization of acrylate

But the enone was not involved in the substrate scope. Actually, there have been several reports about the hydrodimerization of vinyl ketones.[84] In 1993, Rosnati and co-workers reported the Zn-Hg mediated hydrodimerization of α,β-unsaturated ketones. In 1994, Fujiware reported the dimerization of cyclohexanone with excellent yield. This reaction was also reported by Cabreara in 1998, with SmI_2 as catalyst. (Scheme 2) In spite of the papers mentioned above, other report about the hydrodimerization of enone reactant is still rare. Among these reactions, most of the results are not good enough. Some reactions involved heavy metal, which is not preferred.





Scheme 5, Examples of tail to tail hydrodimerization of enones

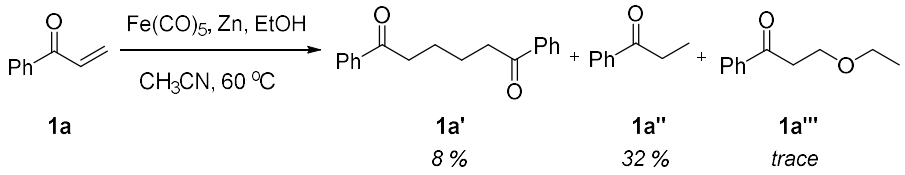
In this chapter, we would like to present an alternative method to the tail to tail reductive dimerization of enones. With the trans-metal catalyst, we could get various dione products in mild condition.

2.2 Result and Discussion

According to the literatures we reviewed, most of this kind of reactions use trans-metal salts or complexes as catalyst. In our proposal, we would first follow their experience and screen from various trans metal catalysts. A simple enone reactant is necessary when preparing the reactant, to test the common applicability of our method, at the same time it is convenient to identify the product, and the possible byproduct and isomers. As our target is to get the reductive product, there should be reductant in the reaction system. With these factors in mind, we started our reaction.

First, the phenyl vinyl ketone is selected as the reactant to screen the conditions. As the phenyl vinyl ketone is first easy to prepare, only two steps from the basic material benzaldehyde (find in experiment section). Secondly, the phenyl vinyl ketone contains an aryl group, which is easy to spot under ultraviolet ray. Moreover, this material has a

relatively high boiling point which is easier to deal with than the low boiling point alkyl ketones, like methyl vinyl ketone. The next is the catalyst. In the literatures, the trans-metal catalysts involved in this kind of dimerization reaction generally could be Pd, Ru, Rh, Co, Ni, Fe and so on, and good results were obtained in their reaction. We would follow their steps and consider to screen from these catalysts. There is one more thing need attention that the photochemistry is widely studied and applied in this field.[85] We would also try to introduce photochemistry to our reaction. Then it comes to the reductant. The commonly applied reductant in organic reaction could be alcohols, boranes, silanes, inorganic salts and metal powders. We could consider to consult from them. Then we tried this reaction with these assumed proposals with $Fe(CO)_5$ catalyst.[86] (Scheme 3)



Scheme 6, the origin attempts of proposed reaction

As the first attempt of this reaction, 0.5 mmol of **1a** was loaded as the reactant. Then 0.05 mmol (0.1 equiv.) of $Fe(CO)_5$ was applied as catalyst. The catalyst was chosen inspired by the literature published in 1970 by Nagoya and coworkers.[87] The zinc power was added as reductant at excessive amount of 2 mmol (4.0 equiv.). And the ethanol (8.0 equiv.) was proposed to be the proton source. we used acetonitrile as the solvent because it is a commonly used polar solvent which works quite well in Wang's work as well as other relevant reactions.[88] The reaction was performed in sealed tube and was stirred in

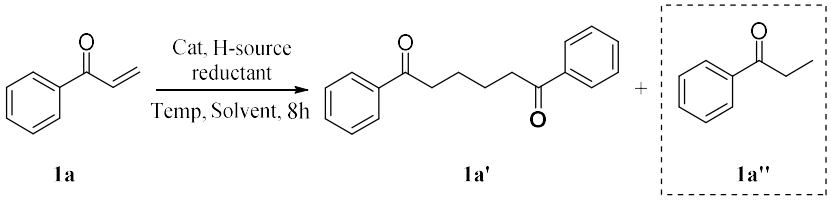
oil bath for 8 h.

From the origin reaction showed in scheme 3, the desired dimerization product **1a'** was obtained, even the yield was as low as 8 %. The reduced product **1a"** was the main byproduct. There is also trace amount of the additional byproduct **1a"'**. In spite of the low yield, this origin reaction shows the possibility of dimerization. The next would be the screening conditions to modify this reaction, which was desired to increase the yield and control the side reactions.

The modification would focus on the catalyst, reductant, solvent and temperature. We screened different kinds of trans metal catalysts, mainly the iron salts and cobalt salts. We also tried several different reductants. The manganese power, magnesium power and zinc power were all tried in the reaction. In addition, we tried different alcohols as the proton source. At last, the solvent could also affect this reaction, and the common organic solvents were all added to this reaction to see the best one. In the following modifications, we would gradually screen different components and find the best reaction conditions.

First, we applied this reaction with different conditions together with several iron catalysts. (Table 1) We tried different kind of iron salts in this reaction, as well as the modification of the solvent and reductant. At the very beginning, we proposed to do a photochemistry. But while screening conditions, we found that this reaction could also perform well with common reaction conditions.

Table 1, Reaction with Iron salts as catalyst



Entry	Catalyst	Reductant	H-Source	Solvent	Temp(°C)	**1a'** Yield(%)[b]
1[c]	$Fe(CO)_5$	Mn	H_2O	CH_3CN	110	23
2[c]	$Fe(CO)_5$	Mg	H_2O	CH_3CN	110	trace
3[c]	$Fe(CO)_5$	Zn	H_2O	CH_3CN	110	15
4[c]	$Fe(CO)_5$	Zn	t-BuOH	CH_3CN	110	55
5[c]	$Fe(CO)_5$	Fe	t-BuOH	CH_3CN	110	20
6[c]	$Fe(CO)_5$	Cu	t-BuOH	CH_3CN	110	17
7	$Fe(CF_3SO_3)_2$	Zn	t-BuOH	CH_3CN	110	50
6	$FeBr_2$	Zn	t-BuOH	CH_3CN	110	32
7	$FeCl_3$	Zn	t-BuOH	CH_3CN	110	trace
8	$FeCl_2$	Zn	t-BuOH	CH_3CN	110	8
9	FeI_2	Zn	t-BuOH	CH_3CN	110	23
10	$Fe(OAc)_2$	Zn	t-BuOH	CH_3CN	110	28
11	FeF_2	Zn	t-BuOH	CH_3CN	110	trace

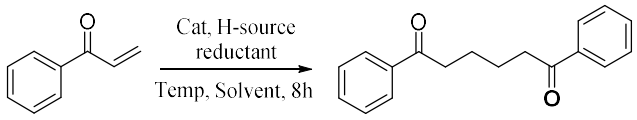
[a] Condition: Substrate **1a** (67 mg, 0.5 mmol 1 eq), Catalyst (0.1 eq), H-source (2 eq), Reductant (2 eq), Solvent (2 mL) was added to a 10-mL sealed tube. The reaction time is 8 h. [b] isolated yield [c] under uv (350 nm)

According to the result shown in table 1, with $Fe(CO)_5$ as catalyst, the groups with Zinc reductant and t-BuOH proton source provides the highest 55 % yield (Table 1, Entry 4). The Mn, Mg, Fe and Cu powders were all tried, but the results were not improved. As the byproduct **1b"** (scheme 3) comes from the addition reaction of alcohol to the C=C bond, we tried H_2O and the multi substituted t-BuOH as the proton source. it is significant that sterically hindered t-BuOH would be the better H-source (comparing Table 1, Entry 3 and 4,). Likewise, the other iron salts were screened, but yield is not good enough in the end, no matter how to modify the conditions. Although the results were not ideal, we found the effect of Zinc and t-BuOH in promoting the reaction. From

then on, we hypothesized the Zinc and t-BuOH as the reductant and H-source.

Based on this result, we expanded the scope of catalyst to the cobalt species. (Table 2) Although the reaction with $CoBr_2$ as catalyst instead of $Fe(CO)_5$ could provide moderate yield (Table 2, Entry 5 and 11), it is still not good enough. We tried to apply our reaction in different polar solvents, like DMSO, DMF, Dioxane, and CF_3CH_2OH.

Table 2, screening condition with Co catalyst



1a **1a'**

Entry	Catalyst	Reductant	H-Source	Solvent	Temp(°C)	**1a'** Yield(%)[b]
1	$CoCp_2$	Zn	t-BuOH	CH_3CN	110	trace
2	$Co(OAc)_2$	Zn	t-BuOH	CH_3CN	110	trace
3	$Co(acac)_2$	Zn	t-BuOH	CH_3CN	110	trace
4	$CoCl_2$	Zn	t-BuOH	CH_3CN	110	45
5	$CoBr_2$	Zn	t-BuOH	CH_3CN	110	50
6	$CoBr_2$	Zn	t-BuOH	DMSO	110	10
7	$CoBr_2$	Zn	t-BuOH	Dioxane	110	17
6	$CoBr_2$	Zn	t-BuOH	H_2O	110	27
7	$CoBr_2$	Zn	t-BuOH	DMF	110	27
8	$CoBr_2$	Zn	t-BuOH	CF_3CH_2OH	110	trace
9[c]	$CoBr_2$	Zn	t-BuOH	CH_3CN	110	trace
10[d]	$CoBr_2$	Zn	t-BuOH	CH_3CN	110	trace
11	$CoBr_2$	Zn	t-BuOH	CH_3CH_2CN	110	60
12[e]	$CoCl_2(PPh_3)_2$	Zn	H_2O/PPh_3	CH_3CN	80	trace

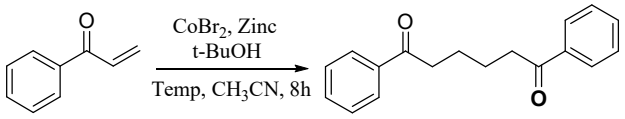
[a] Condition: Substrate **1a** (67 mg, 0.5 mmol 1 eq), Catalyst (0.1 eq), H-source (2 eq), Reductant (2 eq), Solvent (2 mL) was added to a 10-mL sealed tube. The reaction time is 8 h. [b] isolated yield [c] with PPh_3 (1 eq) [d] with $P(Cy)_3$ (1 eq) [e] reaction time 24 hour

At last, the modification of solvent shows that the acetonitrile and propionitrile perform well in the reaction. and the solvent is not the obstacle when improving the

yield. We tried to add some ligand to the reaction, but the reactions with ligands obtained no good result (Table 2, Entry 9 and 10).

Since the propionitrile as solvent could improve the yield slightly than the acetonitrile, we paid out attention on this aspect. As a solvent, the main different of propionitrile and acetonitrile would be the boiling point. The boiling point of propionitrile is 97 ºC, while the boiling point of acetonitrile is lower at 82 ºC. Since we used the sealed tube as the reaction container, and set the reaction temperature at 110 ºC, the solvent would be boiling when conducting the reaction. This was supposed to affect the reaction.

Table 3, Temperature modification



1a **1a'**

Entry	Temp(ºC)	**1a'** yield(%)[b]
1	110	50
2	100	75
3	80	68
4	60	85
5	RT	10
6	0	trace

[a] Condition: Substrate **1a** (67 mg, 0.5 mmol 1 eq), Catalyst (0.1 eq), H-source (2 eq), Reductant (2 eq), Solvent (2 mL) was added to a 10-mL sealed tube. The reaction time is 8 h. [b] isolated yield

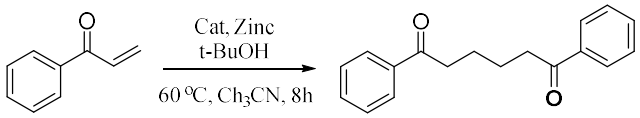
At the same time, the vinyl reactant is easy to conduct polymerization, and the rate would increase with the rising of temperature. Therefore, to test the effect of temperature, we conducted the reaction with a temperature gradient. (table 3)

As shown in Table 3, with lowering the temperature, the yield increased significantly,

and the best yield reached 85 % at 60 ºC. (Table 3, Entry 4) This result demonstrated our hypothesis that the temperature affects the reaction to some extent, and the relatively low temperature could benefit this reaction.

According to the reactions mentioned in the introduction of this chapter, there exists the condition that the ratio of catalyst and reactant varied with different reaction. At last, we conducted the reaction with different amount of catalyst to explore the best ratio to see if it could further improve the yield. (Table 4) We tried different ratio of catalyst from 1.0 equive to 0.05 equive. The result shows that either higher ratio or lower ratio could reduce the yield, and 0.1 equiv. of catalyst could improve the yield to the best.

Table 4, the influence about the amount of catalyst



1a **1a'**

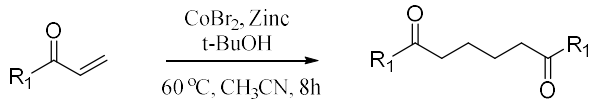
Entry	Catalyst	**1a'** Yield (%)[b]
1	$CoBr_2$(1.0 eq)	11
2	$CoBr_2$(0.5 eq)	45
3	$CoBr_2$(0.3 eq)	55
4	$CoBr_2$(0.2 eq)	60
5	$CoBr_2$(0.1 eq)	85
6	$CoBr_2$(0.05 eq)	5

[a] Condition: Substrate **1a** (67 mg, 0.5 mmol 1 eq), Catalyst (0.1 eq), H-source (2 eq), Reductant (2 eq), Solvent (2 mL) was added to a 10-mL sealed tube. The reaction time is 8 h. [b] isolated yield

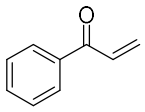
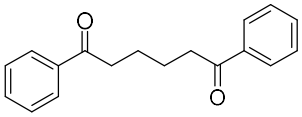
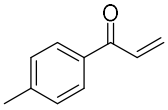
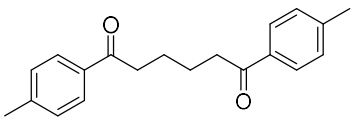
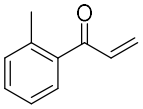
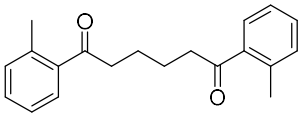
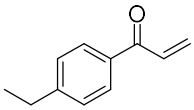
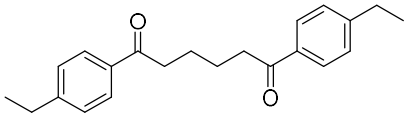
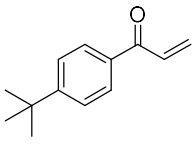
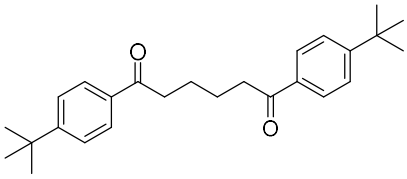
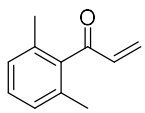
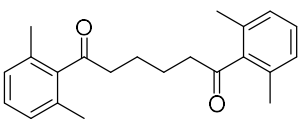
Until now we have screened the catalyst, solvent, reductant, proton source and temperature. Among the various condition groups, the reaction with $CoBr_2$ as catalyst, the Zinc as reactant and t-BuOH as proton source, the reaction could get the desired product in acetonitrile at 60 ºC with the yield as high as 85 %.

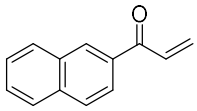
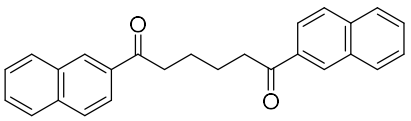
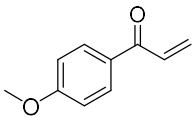
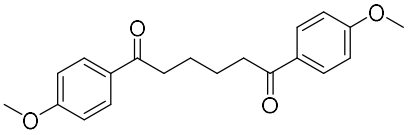
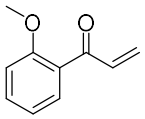
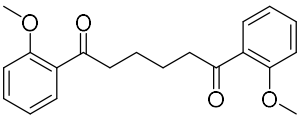
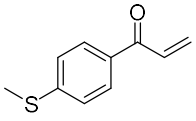
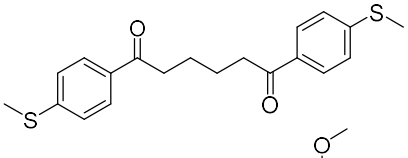
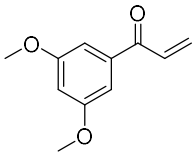
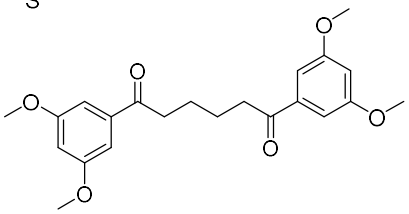
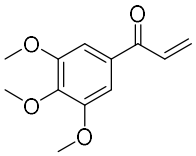
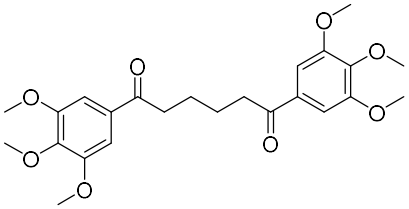
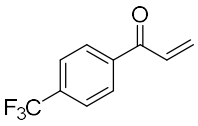
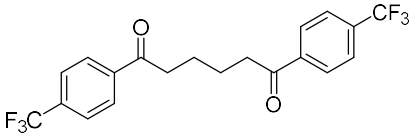
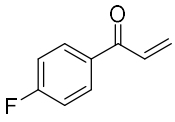
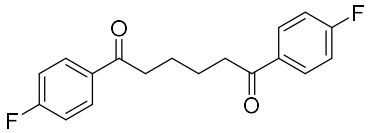
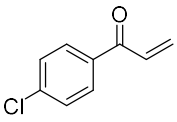
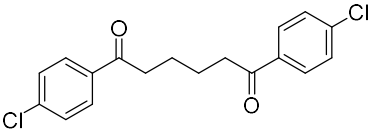
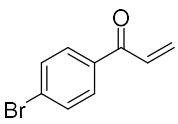
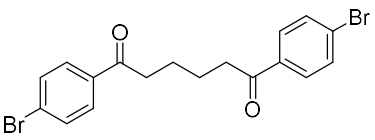
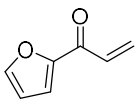
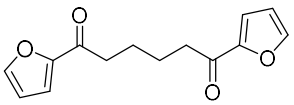
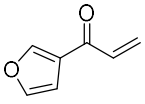
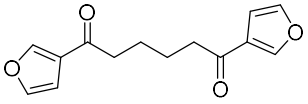
With the screened condition mentioned above, we started to screen among different substrates. Various of aryl vinyl ketones and alkyl vinyl ketones were applied in the reaction. At the same time, we also tried several organohalide substrates, different founctional groups substituted groups and heterocyclic substrates in this reaction. Most substrates could perform smoothly in this reaction and the dimerization products were obtained in moderate to good yield. the result was shown in the table below. (Table 5)

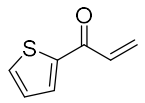
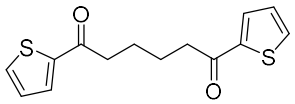
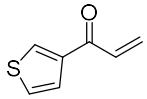
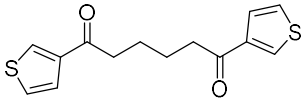
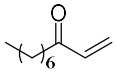
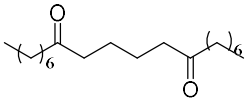
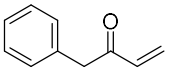
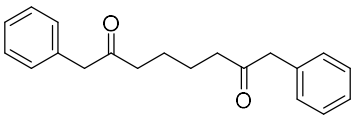
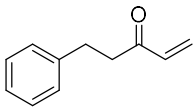
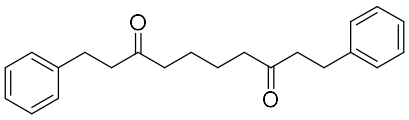
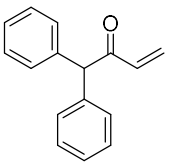
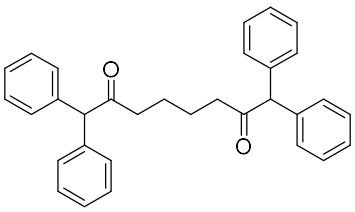
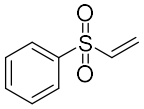
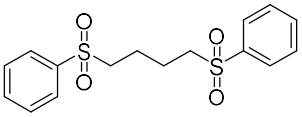
Table 5, $CoBr_2$-catalyzed dimerization of different enones



1a **1a'**

Entry	Substrate		Product		Yield (%)[b]
1		**1a**		**1a'**	85
2		**1b**		**1b'**	53
3		**1c**		**1c'**	66
4		**1d**		**1d'**	73
5		**1e**		**1e'**	75
6		**1f**		**1f'**	18

7		**1g**		**1g'**	49
8		**1h**		**1h'**	67
9		**1i**		**1i'**	30
10		**1j**		**1j'**	27
11		**1k**		**1k'**	78
12		**1l**		**1l'**	65
13		**1m**		**1m'**	62
14		**1n**		**1n'**	35
15		**1o**		**1o'**	25
16		**1p**		**1p'**	53
17		**1q**		**1q'**	55
18		**1r**		**1r'**	55

19		**1s**		**1s'**	44
20		**1t**		**1t'**	55
21		**1u**		**1u'**	73
22		**1v**		**1v'**	50
23		**1w**		**1w'**	47
24		**1x**		**1x'**	48
25		**1y**		**1y'**	27

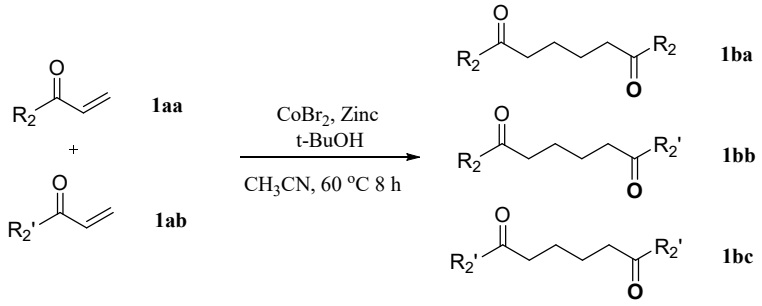
[a] Condition: Substrate **1a** (67 mg, 0.5 mmol 1 eq), Catalyst (0.1 eq), H-source (2 eq), Reductant (2 eq), Solvent (2 mL) was added to a 10-mL sealed tube. The reaction time is 8 h. [b] isolated yield

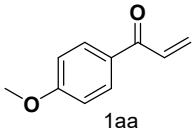
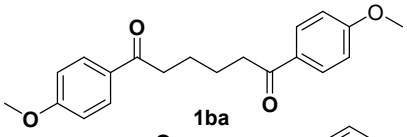
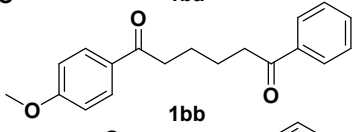
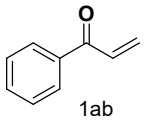
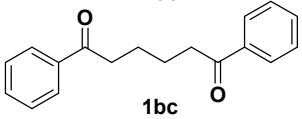
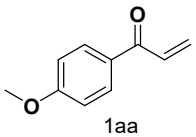
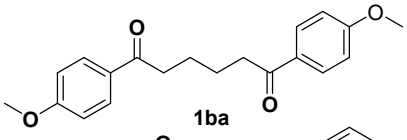
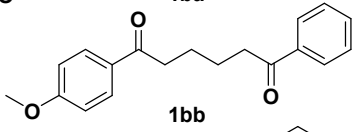
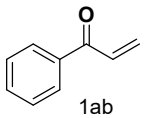
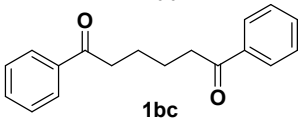
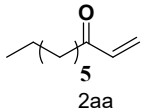
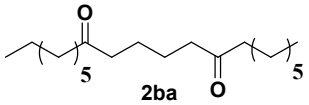
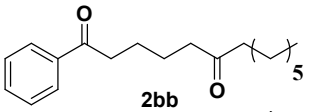
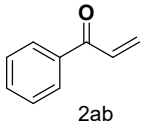
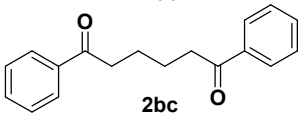
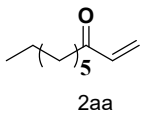
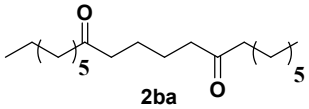
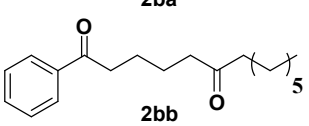
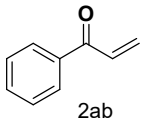
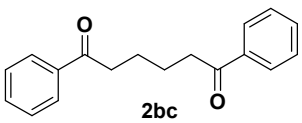
From the result above, we could find that the reactions of various substrates could give the hydrodimerized products at medium to excellent yield. And the byproducts were mostly reduced ones like **1a"** and the polymerized ones, for the substrates were all very easy to polymerize. When alcohol like ethanol was applied instead of t-BuOH, the would be by product like **1a"'**, but the t-BuOH as H-source could greatly reduce this kind of by product. Specially, when R_1 is alkyl groups and alkyl substituted phenyl

groups, the yield is better than the halogen substituted species. We proposed that the reaction is a radical progress, and the electron-donating groups could help to stabilize the intermediate. And this could be proved from the result that the yield of **1p'** is better than the **1n'** and **1o'**. But this electron effect is not for sure. And by comparing the yield of **1h'** and **1i'**, it is easy to find that the stereochemistry plays an important role in this reaction. The more the adjacent position is substituted, the lower the yield would be. What's more, the heterocyclic substrate, like **1q'-1t'**, could also obtain relatively good yield in this reaction. And such cases also appear when the substituted groups are alkyl species. In addition, the sulfonyl substrate **1y'** could give the corresponding product, although the yield is not quite good. From these results, we could say that the scope of this substrates is quite wide.

Beside the homo dimerization, we also proposed to do the cross-coupling reaction between different enones with this method. We tried to load the mixture of different enones. Although the cross-coupling product could be obtained, the selectivity is not controllable. To test the ability of cross-coupling, we applied different ratios of substrates, and kept one substrate excess than the other one. The product was a mixture of homocoupling products and the cross-coupling product. That may be ascribed as the properties of our enones are similar and there is no significant selectivity between the homocoupling and the cross-coupling. (table 6)

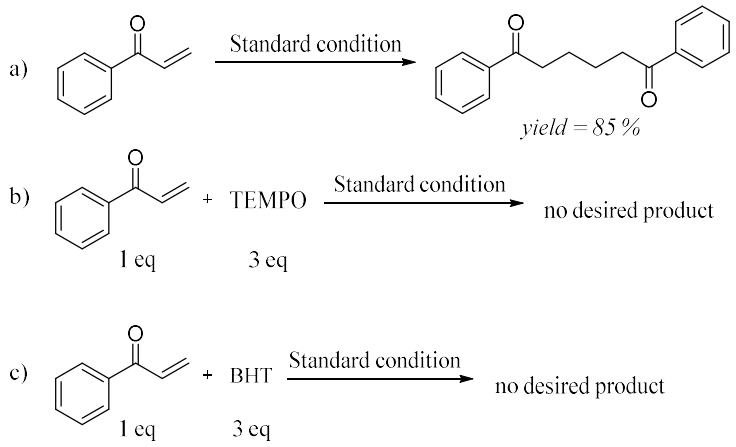
Table 6, the Attempts of cross-coupling reactions



Entry	Substrate		Product	yield(%)[b]
1	 1aa	3 eq	 1ba	56
			 1bb	45
	 1ab	1 eq	 1bc	trace
2	 1aa	1 eq	 1ba	trace
			 1bb	50
	 1ab	3 eq	 1bc	56
3	 2aa	3 eq	 2ba	50
			 2bb	35
	 2ab	1 eq	 2bc	14
4	 2aa	1 eq	 2ba	trace
			 2bb	30
	 2ab	3 eq	 2bc	60

[a] Condition: Substrate **1aa** and **1ab** (0.5 mmol = 1 eq), $CoBr_2$ (0.1 eq), t-BuOH (4 eq), zinc power (4 eq), CH_3CN (4 mL) was added to a 10-mL sealed tube. The reaction time is 8 h. [b] isolated yield

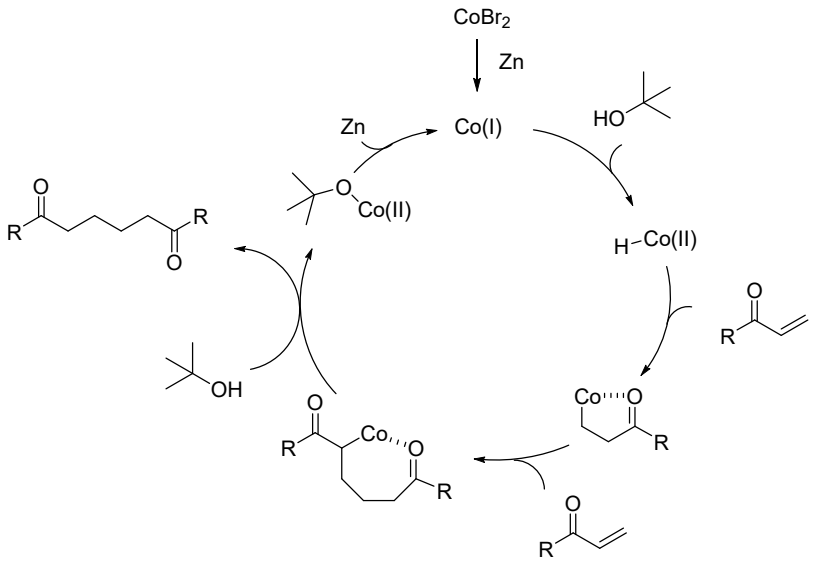
In the introduction part mentioned above, many of the olefin coupling reactions are radical progress.[89] In our reaction, many conditions show the character of radical reaction. For example, the origin reaction that when using $Fe(CO)_5$ as catalyst, the ultraviolet ray could help to improve the yield. As shown in many of the literature, the ultraviolet ray is an important radical initiator.[90] We supposed our reaction to be a radical mechanism. To verify our proposal, we did the controlled trial. We did the reactions with the normal condition, and the ones with addition of TEMPO and BHT in the control groups. The TEMPO and BHT are widely used to detect radicals. Finally, the control groups gave no desired product. The result showed that this reaction was a radical progress.



Scheme 7, controlled reactions

When referring to the literature, the similar pathway of hydrodimerization by Rh and Co-complex have been studied and reported.[91] Based on these studies, we proposed the possible mechanism for our reaction. (Scheme 8) First, the Cobalt (II) salt was reduced

to Co(I)-H complex. Then the complex coordinated with the C=C bond to form the intermediate. Then there would be a coupling progress of the intermediate with another enone. In the end, the coupling product was formed with intermediate was hydrogenated by alcohol and the catalyst was reduced by zinc to continue the new catalytic cycle.



Scheme 8, The controlled reactions and the proposed mechanism.

2.3 Conclusion

Through the transmetal-catalytic reaction, we have developed a simple, mild and high efficient dimerization method of enones. When using $CoBr_2$ as catalyst, with zinc power and t-BuOH as reductant and proton source, the reaction could provide the desired product with various of substrates. The reaction could also work smoothly when containing halogen atoms. It is even applied to the vinyl sulfate compound.

2.4 Experiment Section

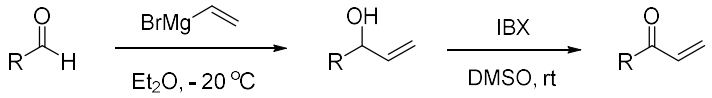
General Information

Unless specially mentioned, the common solvents and reagents were obtained from the commercial sources and applied to the experiment directly. The dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained from the solvent purification machine. Except for the reactant preparation, the reactions were conducted in the sealed tube which is available as a commercial product. Before the reaction, all of the reaction containers were dried in the 110 ºC oven for overnight and cooled down. The reactions were monitored by the thin layer chromatography (TLC), and were detected by ultraviolet ray radiation (wave length = 254 nm) and the potassium permanganate ($KMnO_4$) stain solution. Flash chromatography was conducted with silica gel from Merck and distilled solvents.

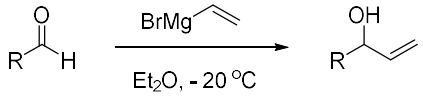
The proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) were performed on Bruker AV-300, AV-500 and BBFO-400 instruments. The chemical shift of ^{1}H NMR spectra was calibrated as δ in the unite of parts per million (ppm). The NMR sample was prepared using chloroform-d with $SiMe_4$ (δ = 0.0). The ^{1}H NMR multiplicities were described as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet) and br (broad). The number of proton is shown as nH. Carbon nuclear magnetic resonance spectras (^{13}C NMR) are calibrated as δ in the unite of parts per million (ppm). The NMR sample was prepared using chloroform-d with $SiMe_4$ (δ = 0.0). The mass data was obtained by high-resolution

mass spectral analysis (HRMS) form Q-Tof permier mass spectrometer.

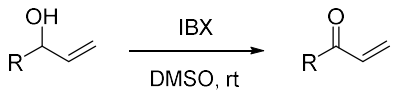
Experiment procedure and data of products



Enone generation.



Step1: To an oven dried round bottom flask (100 mL) equipped with a magnetic stir bar, aldehyde (10 mmol) was dissolved in dry diethyl ether (30 mL). The solution was stirred at - 20 ºC for 10 min. Keeping at - 20 ºC, vinylmagnesium bromide (11 mL, 1.1 eq., 1M in THF) was add dropwise to the solution. The mixture was stirred for 4 h, followed by warming up to RT. Then the reaction was quenched by gently addition of saturated NH_4Cl solution. After extracting with diethyl ether (3 × 30 mL), the combined organic phase was washed with saturated brine, and dried with $MgSO_4$. The dry solution was filtered and concentrated *in vacuo.* The crude was purified by flash column chromatography on silica gel (hexane/EtOAc mixture) to provide the enol product.



Step 2: A round bottom flask (100 mL) was equipped with a magnetic stir bar. The enol (10 mmol, yield from step 1) and dimethyl sulfoxide (20 mL) were added and stirred for 2 min. Then IBX (12 mmol, 1.2 eq) was add in two portions in 5 min. The

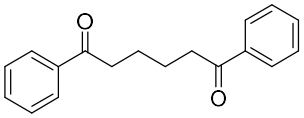
mixture was stirred at room temperature. After stirring for 2 h, water (20 mL) and diethyl ether (20 mL) was added to the solution. The mixture was filtered with a Buchner funnel. The solid residue was rinsed with diethyl ether (3×20 mL). the liquid was collected and extracted with diethyl ether (3×20 mL). the combined organic layer was washed with brine (2×30 mL), dried by Na_2SO_4. The solution was filtered and concentrated under reduced pressure to give the crude product. After purified by flash column chromatography on silica get (hexane/EtOAc mixture), the enone product was obtained.

The general procedure for dimerization of enones

1a **1b**

To an oven dried sealed tube equipped with a magnetic stir bar, the enone (0.5 mmol), $CoBr_2$ (0.05 mmol), zinc power (2 mmol) and t-BuOH (2 mmol) in 2 mL of CH_3CN was added. The mixture was stirred and heated at 60 ºC for 8 h. the mixture was filtered and washed with ethyl ester (5 mL) for 3 times. The combined organic solution was concentrated under reduced pressure followed by going through flash column chromatography on silica get (Hexane/EtOAc mixture) to provide the product.

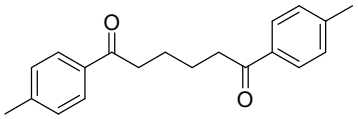
1,6-diphenylhexane-1,6-dione (1a')



White solid; $C_{18}H_{18}O_2$; yield: 85 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.85-1.90 (m, 4H), 3.05-3.10 (m, 4H), 7.45-7.49 (m, 4H), 7.55-7.61 (m, 2H), 7.96-8.02 (m, 4H); ^{13}C NMR (100M $CDCl_3$): δ 23.91, 38.42, 128.04, 128.60, 133.00, 136.97, 200.03. HRMS (ESI): m/z $[M+H]^+$ for $C_{18}H_{18}O_2$: exact mass calcd. 267.1385, found 267.1387.

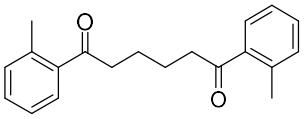
1,6-di-p-tolylhexane-1,6-dione (1b')



White solid; $C_{20}H_{22}O_2$; yield: 53 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.82-1.88 (m, 4H), 2.43 (s, 6H), 3.00-3.06 (m, 4H), 7.28 (d, *J* = 8.0 Hz, 4H), 7.89 (d, *J* = 7.8 Hz, 4H); ^{13}C NMR (100M $CDCl_3$): δ 21.63, 24.07, 38.32, 128.18, 129.27, 134.52, 143.72, 199.77. HRMS (ESI): m/z $[M+H]^+$ for $C_{20}H_{22}O_2$: exact mass calcd. 295.1698, found 295.1695.

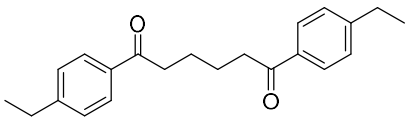
1,6-di-o-tolylhexane-1,6-dione (1c')



White solid; $C_{20}H_{22}O_2$; yield: 66 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.79-1.83 (m, 4H), 2.52 (s, 6H), 2.94-2.99 (m, 4H), 7.25-7.29 (m, 4H), 7.35-7.40 (m, 2H), 7.63-7.66 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100M $CDCl_3$): δ 21.23, 24.01, 36.64, 41.41, 125.67, 128.32, 131.15, 131.93, 137.90, 138.12, 204.29. HRMS (ESI): m/z $[M+H]^+$ for $C_{20}H_{22}O_2$: exact mass calcd. 295.1698, found 295.1693.

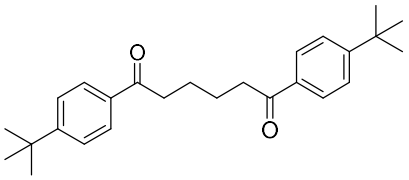
1,6-bis(4-ethylphenyl)hexane-1,6-dione (1d')



White solid; $C_{22}H_{26}O_2$; yield: 73 %;

^{1}H NMR (500M, $CDCl_3$): δ 1.28 (t, *J* = 7.6 Hz, 6H), 1.83-1.87 (m, 4H), 2.73 (q, *J* = 7.5 Hz, 4H), 3.02-3.07 (m, 4H), 7.29-7.33 (d, *J* = 8.0 Hz, 4H), 7.89-7.93 (d, *J* = 8.2 Hz, 4H); ^{13}C NMR (125M $CDCl_3$): δ 15.22, 24.09, 28.93, 38.34, 128.09, 128.29, 134.79, 149.09, 199.78. HRMS (ESI): m/z $[M+H]^+$ for $C_{22}H_{26}O_2$: exact mass calcd. 323.2011, found 323.2015.

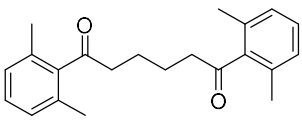
1,6-bis(4-(tert-butyl)phenyl)hexane-1,6-dione (1e')



White solid; $C_{26}H_{34}O_2$; yield: 75 %;

^{1}H NMR (500M, $CDCl_3$): δ 1.38 (s, 18H), 1.86-1.88 (m, 4H), 3.03-3.07 (m, 4H), 7.50 (d, *J* = 8.2 Hz, 4H), 7.93 (d, *J* = 8.2 Hz, 4H); ^{13}C NMR (125M $CDCl_3$): δ 24.11, 31.11, 35.10, 38.34, 125.53, 128.04, 134.43, 156.67, 199.80. HRMS (ESI): m/z $[M+H]^+$ for $C_{26}H_{34}O_2$: exact mass calcd. 379.2637, found 379.2639.

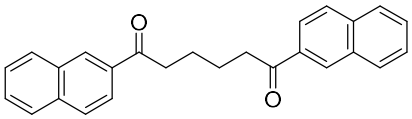
1,6-bis(2,6-dimethylphenyl)hexane-1,6-dione (1f')



White solid; $C_{22}H_{26}O_2$; yield: 18 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.82-1.85 (m, 4H), 2.25 (s, 12H), 2.78-2.81 (m, 4H), 7.04 (d, *J* = 7.5 Hz, 4H) 7.19 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (400M $CDCl_3$): δ 19.13, 22.89, 44.54, 127.28, 128.53, 132.37, 142.36, 210.13. HRMS (ESI): m/z $[M+H]^+$ for $C_{22}H_{26}O_2$: exact mass calcd. 323.2011, found 323.2017.

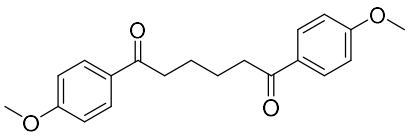
1,6-di(naphthalen-2-yl)hexane-1,6-dione (1g')



White solid; $C_{26}H_{22}O_2$; yield: 49 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.95-1.99 (m, 4H), 3.21-3.24 (m, 4H), 7.56-7.63 (m, 4H), 7.89-8.08 (m, 8H), 8.52 (s, 2H); ^{13}C NMR (100M $CDCl_3$): δ 24.15, 38.52, 123.91, 126.76, 127.78, 128.40, 128.46, 129.58, 129.68, 132.57, 134.33, 135.58, 200.03. HRMS (ESI): m/z $[M+H]^+$ for $C_{26}H_{22}O_2$: exact mass calcd. 367.1698, found 367.1695.

1,6-bis(4-methoxyphenyl)hexane-1,6-dione (1h')

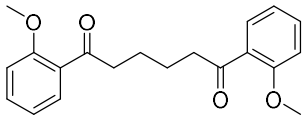


White solid; $C_{20}H_{22}O_4$; yield: 67 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.82-1.86 (m, 4H), 2.98-3.02 (m, 4H), 3.89 (s, 6H), 6.96 (d, *J* = 8.5 Hz, 4H), 7.97 (d, *J* = 8.1 Hz, 4H); ^{13}C NMR (100M $CDCl_3$): δ 24.24, 38.10, 55.46, 113.71, 130.11, 130.31, 163.39, 198.72. HRMS (ESI): m/z $[M+H]^+$ for $C_{20}H_{22}O_4$:

exact mass calcd. 327.1596, found 327.1599.

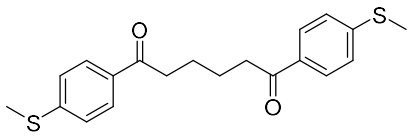
1,6-bis(2-methoxyphenyl)hexane-1,6-dione (1i')



White solid; $C_{20}H_{22}O_4$; yield: 30 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.75-1.78 (m, 4H), 2.98-3.03 (m, 4H), 3.91 (s, 6H), 6.96-7.01 (m, 4H), 7.45-7.49 (m, 2H), 7.67 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100M $CDCl_3$): δ 24.19, 43.70, 55.48, 111.50, 120.63, 130.18, 133.17, 158.41, 202.87. HRMS (ESI): m/z $[M+H]^+$ for $C_{20}H_{22}O_4$: exact mass calcd. 327.1596, found 327.1597.

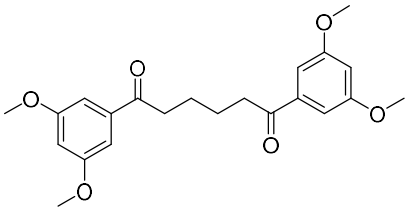
1,6-bis(4-(methylthio)phenyl)hexane-1,6-dione (1j')



White solid; $C_{20}H_{22}S_2O_2$; yield: 27 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.83-1.86 (m, 4H), 2.55 (s, 6H), 3.02-3.05 (m, 4H), 7.29 (d, *J* = 8.4 Hz, 4H), 7.89 (d, *J* = 8.5 Hz, 4H); ^{13}C NMR (100M $CDCl_3$): δ 14.80, 24.05, 38.20, 125.05, 128.48, 133.29, 145.69, 199.06. HRMS (ESI): m/z $[M+H]^+$ for $C_{20}H_{22}S_2O_2$: exact mass calcd. 359.1139, found 359.1141.

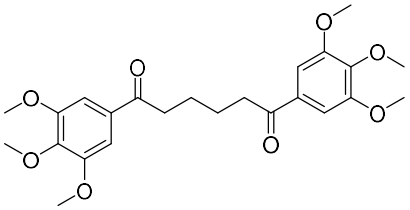
1,6-bis(3,5-dimethoxyphenyl)hexane-1,6-dione (1k')



White solid; $C_{22}H_{26}O_6$; yield: 78 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.77-1.79 (m, 4H), 2.99-3.02 (m, 4H), 3.89 (s, 12H), 7.02-7.13 (m, 6H); ^{13}C NMR (100M $CDCl_3$): δ 23.92, 43.25, 56.00, 61.50, 115.36, 120.57, 124.10, 134.29, 147.90, 152.95, 203.30. HRMS (ESI): m/z $[M+H]^+$ for $C_{22}H_{26}O_6$: exact mass calcd. 387.1808, found 387.1810.

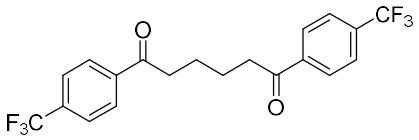
1,6-bis(3,4,5-trimethoxyphenyl)hexane-1,6-dione (1l')



White solid; $C_{24}H_{30}O_8$; yield: 65 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.85-1.88 (m, 4H), 3.01-3.05 (m, 4H), 3.96-3.98 (m, 18H), 7.24 (s, 4H); ^{13}C NMR (100M $CDCl_3$): δ 24.10, 38.18, 56.33, 60.95, 105.58, 132.25, 153.09, 196.78. HRMS (ESI): m/z $[M+H]^+$ for $C_{24}H_{30}O_8$: exact mass calcd. 447.2019, found 447.2015.

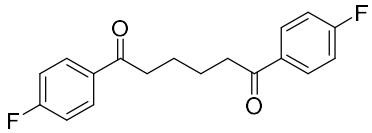
1,6-bis(4-(trifluoromethyl)phenyl)hexane-1,6-dione (1m')



White solid; $C_{20}H_{16}F_6O_2$; yield: 62 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.86-1.90 (m, 4H), 3.07-3.10 (m, 4H), 7.77 (d, J = 8.2 Hz, 4H), 8.11 (d, J = 8.0 Hz, 4H); ^{13}C NMR (100M $CDCl_3$): δ 24.64, 38.47, 125.66 (q, $J_{C\text{-}F}$ = 270.4 Hz), 125.68 (q, $J_{C\text{-}F}$ = 3.7 Hz), 129.42, 134.42 (q, $J_{C\text{-}F}$ = 31.8 Hz), 139.65, 198.92. HRMS (ESI): m/z $[M+H]^+$ for $C_{20}H_{16}F_6O_2$: exact mass calcd. 403.1133, found 403.1135.

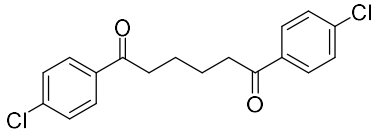
1,6-bis(4-fluorophenyl)hexane-1,6-dione (1n')



White solid; $C_{18}H_{16}F_2O_2$; yield: 35 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.83-1.87 (m, 4H), 3.04-3.06 (m, 4H), 7.19 (m, 4H), 8.13 (m, 4H); ^{13}C NMR (100M $CDCl_3$): δ 23.54, 38.65, 115.86 (d, $J_{C\text{-}F}$ = 21.5 Hz), 130.61 (d, $J_{C\text{-}F}$ = 9.1 Hz), 133.81 (d, $J_{C\text{-}F}$ = 2.8 Hz), 167.86 (d, $J_{C\text{-}F}$ = 253.1 Hz), 198.72. HRMS (ESI): m/z $[M+H]^+$ for $C_{18}H_{16}F_2O_2$: exact mass calcd. 303.1197, found 303.1194.

1,6-bis(4-chlorophenyl)hexane-1,6-dione (1o')

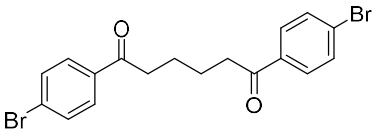


White solid; $C_{18}H_{16}Cl_2O_2$; yield: 25 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.71-1.74 (m, 4H), 3.00-3.05 (m, 4H), 7.39 (d, J = 8.2 Hz,

4H), 7.87 (d, J = 8.2 Hz, 4H); ^{13}C NMR (100M $CDCl_3$): δ 23.49, 38.27, 128.00, 129.44, 134.85, 139.36, 198.65. HRMS (ESI): m/z $[M+H]^+$ for $C_{18}H_{16}Cl_2O_2$: exact mass calcd. 335.0606, found 335.0609.

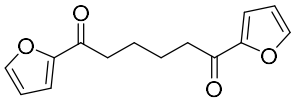
1,6-bis(4-bromophenyl)hexane-1,6-dione (1p')



White solid; $C_{18}H_{16}Br_2O_2$; yield: 24 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.82-1.86 (m, 4H), 3.01-3.05 (m, 4H), 7.64 (d, J = 8.4 Hz, 4H), 7.83 (d, J = 8.4 Hz, 4H); ^{13}C NMR (100M $CDCl_3$): δ 23.49, 38.22, 128.11, 129.56, 131.86, 135.61, 198.79. HRMS (ESI): m/z $[M+H]^+$ for $C_{18}H_{16}Br_2O_2$: exact mass calcd. 422.9595, found 422.9592.

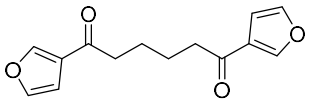
1,6-di(furan-2-yl)hexane-1,6-dione (1q')



White solid; $C_{14}H_{14}O_4$; yield: 55 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.79-1.82 (m, 4H), 2.85-2.89 (m, 4H), 6.52 (dd, J = 3.4 Hz, 2H) 7.19 (d, J = 3.5 Hz, 2H), 7.58 (d, J = 3.5 Hz, 2H); ^{13}C NMR (100M $CDCl_3$): δ 23.82, 38.23, 112.21, 116.94, 146.26, 152.75, 189.24. HRMS (ESI): m/z $[M+H]^+$ for $C_{14}H_{14}O_4$: exact mass calcd. 247.0970, found 247.0973.

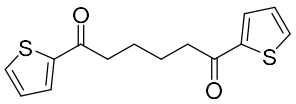
1,6-di(furan-3-yl)hexane-1,6-dione (1r')



White solid; $C_{14}H_{14}O_4$; yield: 55 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.77-1.81 (m, 4H), 2.78-2.81 (m, 4H), 6.78 (d, *J* = 3.5 Hz, 2H) 7.43 (d, *J* = 3.5 Hz, 2H), 8.03 (s, 2H); ^{13}C NMR (100M $CDCl_3$): δ 23.87, 39.15, 107.69, 127.96, 144.73, 146.35, 194.46. HRMS (ESI): m/z $[M+H]^+$ for $C_{14}H_{14}O_4$: exact mass calcd. 247.0970, found 247.0971.

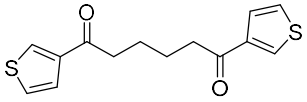
1,6-di(thiophen-2-yl)hexane-1,6-dione (1s')



White solid; $C_{14}H_{14}S_2O_2$; yield: 44 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.84-1.88 (m, 4H), 2.96-2.99 (m, 4H), 7.13 (dd, *J* = 3.7 Hz, 2H) 7.65 (d, *J* = 4.8 Hz, 2H), 7.73 (d, *J* = 3.8 Hz, 2H); ^{13}C NMR (100M $CDCl_3$): δ 23.78, 37.76, 127.84, 132.52, 133.57, 140.86, 192.59. HRMS (ESI): m/z $[M+H]^+$ for $C_{14}H_{14}S_2O_2$: exact mass calcd. 279.0513, found 279.0517.

1,6-di(thiophen-3-yl)hexane-1,6-dione (1t')

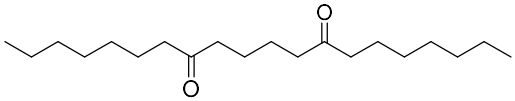


White solid; $C_{14}H_{14}S_2O_2$; yield: 55 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.80-1.83 (m, 4H), 2.92-2.96 (m, 4H), 7.32 (d, *J* = 3.8 Hz,

2H) 7.55 (d, J = 3.8 Hz, 2H), 8.06 (s, 2H); ^{13}C NMR (100M $CDCl_3$): δ 24.4, 38.52, 126.94, 127.06, 132.25, 142.88, 195.21. HRMS (ESI): m/z $[M+H]^+$ for $C_{14}H_{14}S_2O_2$: exact mass calcd. 279.0513, found 279.0516.

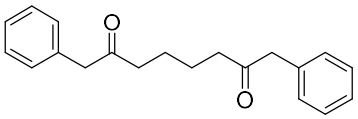
icosane-8,13-dione (1u')



White solid; $C_{20}H_{38}O_2$; yield: 73 %;

^{1}H NMR (400M, $CDCl_3$): δ 0.89-0.93 (t, J = 6.7 Hz, 6H), 1.25-1.37 (m, 16H), 1.56-1.61 (m, 8H) 2.39-2.45 (m, 8H); ^{13}C NMR (100M $CDCl_3$): δ 14.1, 22.6, 23.07, 23.51, 29.12, 29.17, 31.74, 42.8, 42.64, 211.75. HRMS (ESI): m/z $[M+H]^+$ for $C_{20}H_{38}O_2$: exact mass calcd. 311.2950, found 311.2955.

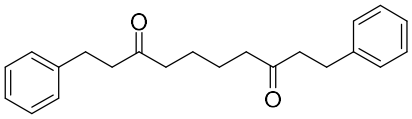
1,8-diphenyloctane-2,7-dione (1v')



White solid; $C_{20}H_{22}O_2$; yield: 50 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.48-1.52 (m, 4H), 2.51-2.54 (m, 4H), 3.69 (s, 4H) 7.20 (m, 4H), 7.24-7.37 (m, 6H); ^{13}C NMR (100M $CDCl_3$): δ 23.00, 41.57, 50.17, 127.02, 128.74, 129.39, 134.25, 208.07. HRMS (ESI): m/z $[M+H]^+$ for $C_{20}H_{22}O_2$: exact mass calcd. 295.1698, found 295.1694.

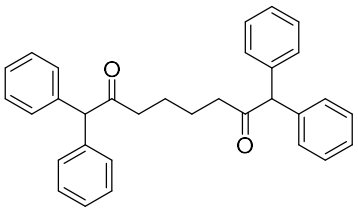
1,10-diphenyldecane-3,8-dione (1w')



White solid; $C_{22}H_{26}O_2$; yield: 47 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.52-1.56 (m, 4H), 2.38-2.43 (m, 4H), 2.73 (t, *J* = 7.6 Hz, 4H), 2.91 (t, *J* = 7.6 Hz, 4H), 7.19-7.31 (m, 10H); ^{13}C NMR (100M $CDCl_3$): δ 23.14, 29.78, 42.70, 44.27, 126.11, 128.33, 128.50, 141.07, 209.77. HRMS (ESI): m/z $[M+H]^+$ for $C_{22}H_{26}O_2$: exact mass calcd. 323.2011, found 323.2010.

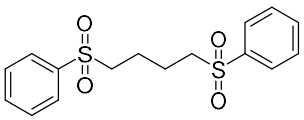
1,1,8,8-tetraphenyloctane-2,7-dione (1x')



White solid; $C_{32}H_{30}O_2$; yield: 48 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.56-1.59 (m, 4H), 2.52-2.55 (m, 4H), 5.12 (s, 2H), 7.25-7.39 (m, 20H); ^{13}C NMR (100M $CDCl_3$): δ 23.62, 42.82, 64.18, 127.27, 128.75, 129.03, 138.54, 208.39. HRMS (ESI): m/z $[M+H]^+$ for $C_{32}H_{30}O_2$: exact mass calcd. 447.2324, found 447.2327.

1,4-bis(phenylsulfonyl)butane (1y')

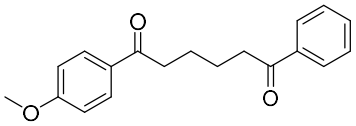


White solid; $C_{16}H_{18}S_2O_4$; yield: 27 %;

^{1}H NMR (400M, $CDCl_3$): δ 1.85-1.88 (m, 4H), 3.09-3.13 (m, 4H), 7.57-7.69 (m, 6H),

7.90-9.94 (m, 4H); ^{13}C NMR (100M $CDCl_3$): δ 22.19, 56.02, 128.14, 129.30, 133.72, 139.00. HRMS (ESI): m/z $[M+H]^+$ for $C_{16}H_{18}S_2O_4$: exact mass calcd. 339.0725, found 339.0725.

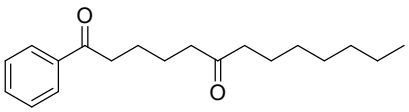
1-(4-methoxyphenyl)-6-phenylhexane-1,6-dione (1bb)



White solid; $C_{19}H_{20}O_3$; yield: refer to Table 6;

^{1}H NMR (400M, $CDCl_3$): δ 1.79-1.85 (m, 4H), 2.98-3.04 (m, 4H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.44-7.55 (m, 5H), 7.99 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100M $CDCl_3$): δ 24.05, 38.32, 55.47, 113.72, 128.05, 128.61, 130.10, 130.28, 133.02, 136.99, 163.40, 198.74, 200.01. HRMS (ESI): m/z $[M+H]^+$ for $C_{19}H_{20}O_3$: exact mass calcd. 297.1491, found 297.1496.

1-phenyltridecane-1,6-dione (2bb)



White solid; $C_{19}H_{28}O_2$; yield: refer to Table 6;

^{1}H NMR (400M, $CDCl_3$): δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.22-1.34 (m, 8H), 1.53-1.77 (m, 6H), 2.38-2.47 (m, 4H), 2.97-3.01 (t, *J* = 6.9 Hz, 2H), 7.46-7.59 (m, 3H), 7.93-7.97 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100M $CDCl_3$): δ 14.05, 22.59, 23.45, 23.79, 23.87, 29.06, 29.21, 31.66, 38.34, 42.53, 42.88, 128.01, 128.58, 132.97, 136.96, 199.99, 211.12. HRMS (ESI): m/z $[M+H]^+$ for $C_{19}H_{28}O_2$: exact mass calcd. 289.1268, found 289.1266.

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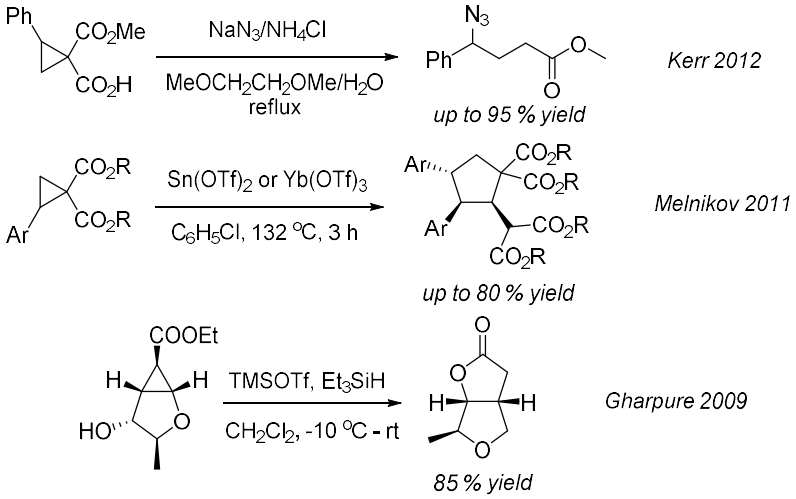
Chapter 3

Mn-Catalyzed Ring Open Coupling Reaction of Cyclopropanol with Enone.

3.1 Introduction

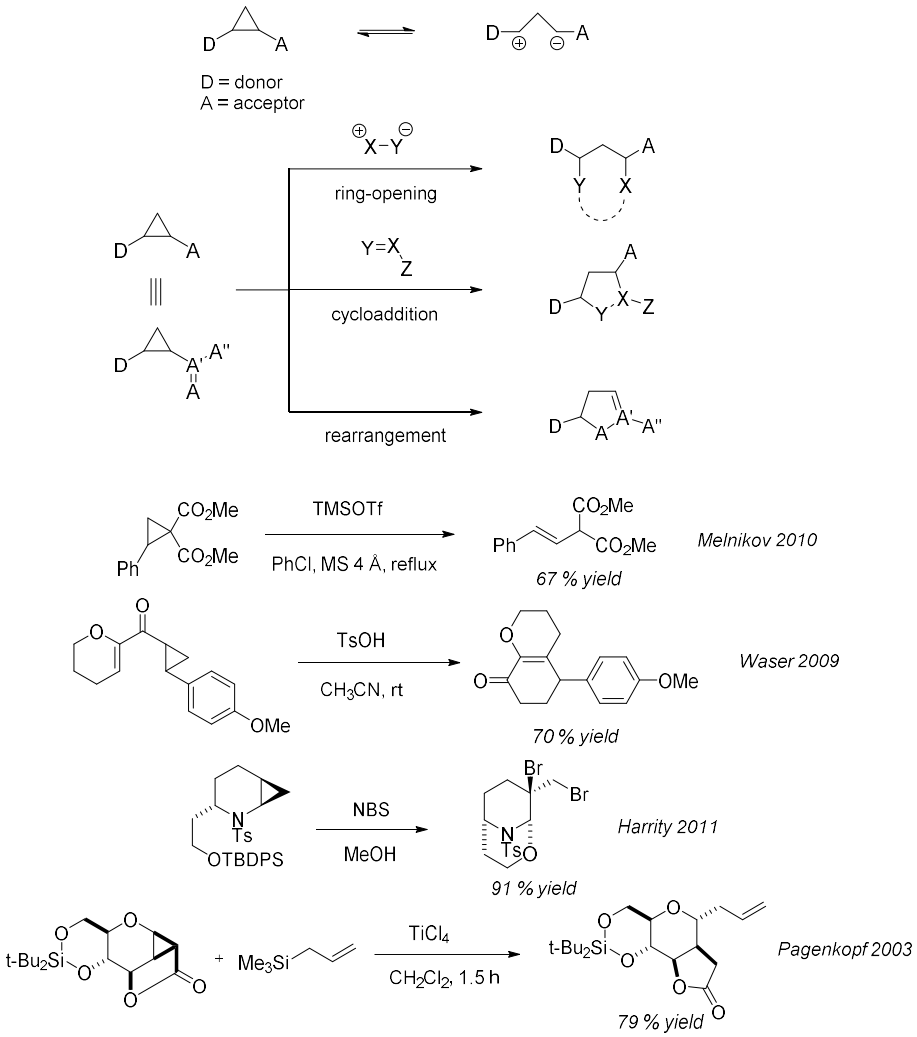
The cyclic structure is very common in organic compounds and natural product. Cyclopropane is the smallest and simplest structure of cycloalkane. As the bond angle is 60 degrees, which is much smaller than the chain alkane (109.5 degree), there exists quite strong ring strain in cyclopropane. The strong ring strain leads to the weakened C-C bond. Thus, it would be more difficult when synthesizing the ring and on the other hand, the cyclopropane ring is more reactive than the other cycloalkanes and chain alkanes. Compared with the highly stable chain alkanes, the cyclopropane is similar to the C=C double bond to some extent. The cyclopropane and derivates could undergo the ring-opening reaction, cycloaddition and rearrangement reactions.[92] The ring-opening reaction is generally catalyzed by Brönsted acid or Lewis acid. The cyclopropane species has been applied as reactant in various organic synthesis, and some of reactions has been emerged as the methodology in total synthesis of natural products.[93] In 2011, Melnikov and co-workers reported the Lewis acid catalyzed homoaddition of substituted cyclopropanes. In 2009, Gharpure reported the cyclopropane rearrangement reaction with esters. (Scheme 1) These methods are commonly high efficient with good

selectivity.



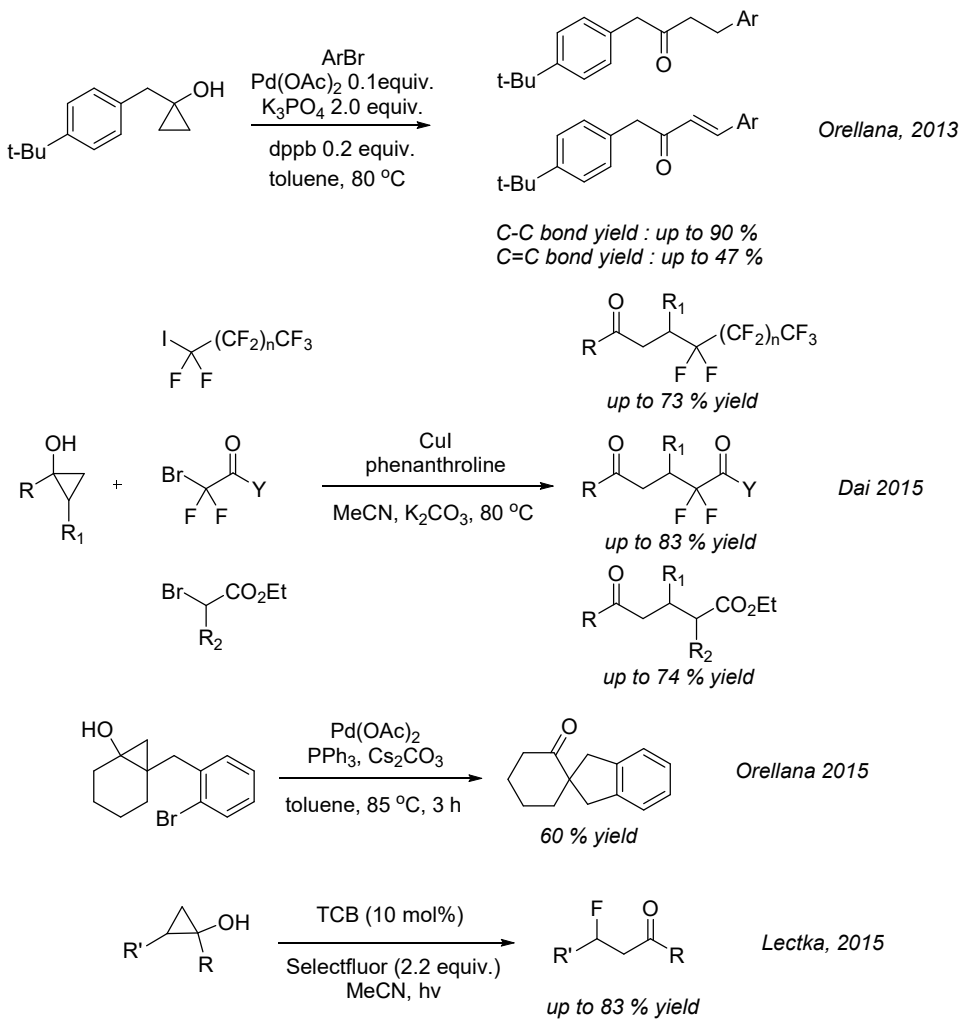
Scheme 1, The rearrangement of cyclopropane

Among these cyclopropane reactions, the Donor-Acceptor cyclopropane is the basic and fundamental reaction form. Generally, the cyclopropane is substituted by electrophilic and nucleophilic groups, which is called Donor-Acceptor cyclopropane. It could transform into a chain molecule by the ring-opening reaction and the following additional reaction. In the cycloaddition reaction, there could be high regioselectivity, due to the polarity of the cyclopropane ring and the electron density distribution. Such reactions required Lewis acid catalysts. The additional reagent could be either nucleophile or electrophile. When conduction the reaction, the Lewis acid coordinates to the acceptor group and further activates the cyclopropane. It could cause the nucleophile to attack on the donor-substituted carbon.[94] This is the main progress in cyclopropane reaction. These principles have been well studied.[95] The procedure of Donor-Accepter cyclopropane reaction and some examples were shown in Scheme 2.



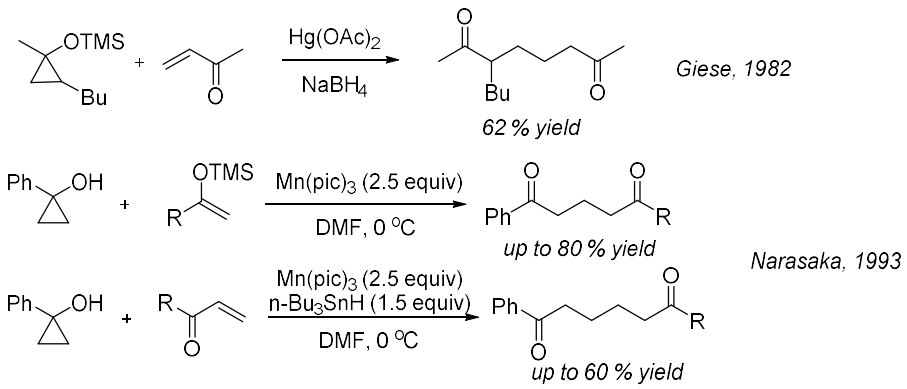
Scheme 2, The concise procedure and applications of Donor-Acceptor cyclopropanes

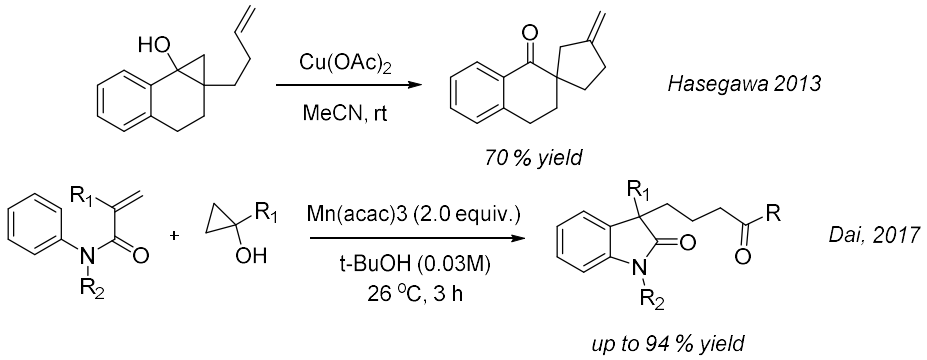
The cyclopropanol, as a derivate of cyclopropane, follows the main principles of cyclopropane. At the same time, as there is a hydroxy group on the ring, it is identified as the carbocyclic homologues of enol, not only according to the molecular formula but also the chemical property. Due to the unique structure, the hydroxy substituted cyclopropane is specially studied.[96] The reaction of cyclopropanol has coherence with alkyl cyclopropane but contains some particular routes and methods in synthetic strategy.[97] These reactions in Scheme 3 indicated the addition ability of cyclopropanol with C=C bond and halogenated groups.



Scheme 3, Ring-opening and addition of cyclopropanol with halogenated compounds.

There have been several reports about the addition of cyclopropanol with C=C bond.[98] In some conditions, the TMSO- group was applied instead of hydroxy group.





Scheme 4, cyclopropanol addition with C=C bond

The cyclopropanol reaction involves hydroxyl group displacement and the C-C bond cleavage. For the hydroxy group substitution, it is preferred if there is a nucleophile substituted on the carbon together with the hydroxy group. And for the C-C bond cleavage, as there is hydroxy group attached to the ring, it is favorable to conduct ring-opening and ring-expansion when attacked by nucleophilic substrate. At the same time, the hydroxy group also help to stabilize the intermediate.

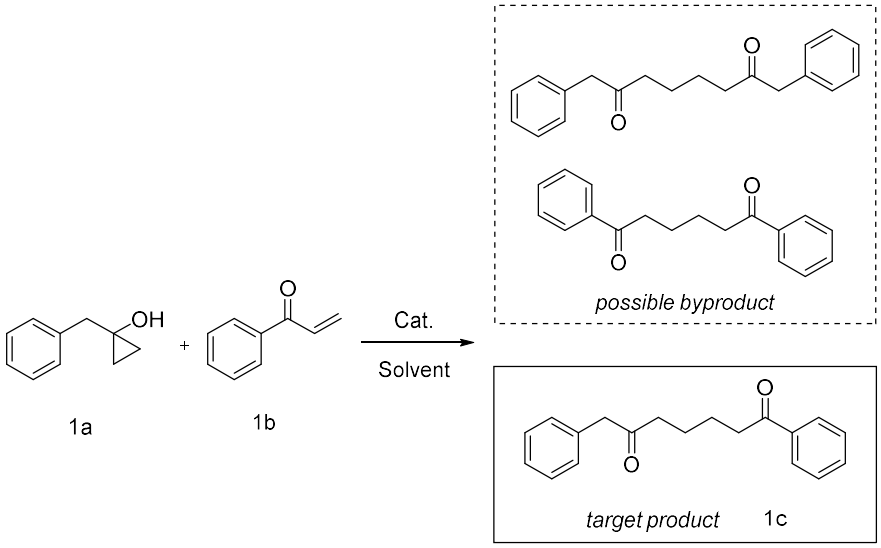
Herein, we would present a cyclopropanol ring-opening coupling with enone reaction. compared with the reactions of similar type, this reaction was conducted in mild condition, as well as high efficient. This reaction is concise and easy handled. The atom economy is also good.

3.2 Result and Discussion

In chapter 3, we introduced a homo dimerization of enone to 1,6-dione. At the end, we tried the cross-coupling reaction, but the selectivity and specificity are not good. Then we turned to try other routes to achieve this aim. Since the property of

cyclopropanol species is similar with enone to some extent, we proposed to try the coupling of cyclopropanol with enone. To our literature review, there have been few report on the cyclopropanol ring opening reaction.[99] However, these reactions either involve the heavy metal or need considerable additives. On the other hand, the result of the reaction is not good. In our proposal, we planned to conduct a concise and high-efficient reaction to fulfill our target.

First, we designed the substrates. The enone substrate was vinyl ketone. As the target product would be the 1,6-dione species, we need to distinguish from the byproducts. There would be the homo-coupling product of enone and the theoretical possible ring-opening homo-coupling product of cyclopropanol or other possible ones. As our target product has the similar structure with the possible by-products, we intended to design the unique structure of products, which would be easily distinguished in spectrum. Besides, the structure of substrate need to be concise and easily detected. For these reasons, we intended to use benzyl cyclopropanol (Scheme 4, 1a) as the substrate.

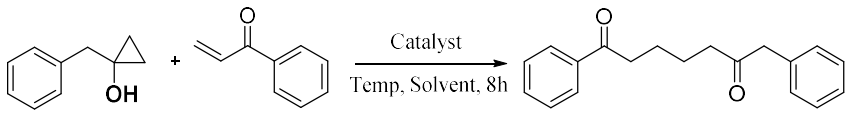


Scheme 5, The proposed original reaction

According to the literature review, the catalysts for ring-opening reaction of cyclopropanol could be Lewis acid, like palladium, copper, iron, Manganese and titanium. Inspired by these reactions, we first screened the catalysts from various metal catalyst. In our proposal, the cyclopropanol would be oxidized and the enone was reduced. As the valences of the target product (Scheme 4, 1c) is the result of comproportionation, reductant or oxidant was not necessary in this reaction. Due to the same reason, the utilization ratio of atoms would be 100 perecent.

With these proposals in mind, we started to screen the reaction conditions. The focus would be on the catalysts and temperature. Most of the solvents screened were not shown in the table, for the low reactivity. Part of the screened conditions were shown in the following Table 1.

Table 1, Condition screening.[a]



1a **2a'** **3aa'**

Entry	Catalyst	Solvent	Temp(°C)	1cYield(%)[b]
1	$CoBr_2$	CH_3CN	60	trace
2	$Co(OAc)_2$	CH_3CN	60	trace
3	$InCl_3$	CH_3CN	60	30
4	$Fe(acac)_3$	CH_3CN	60	trace
5	$FeCl_3$	CH_3CN	60	53
6	Iron Triflate	CH_3CN	60	45
7	$PdCl_2$	CH_3CN	60	trace
8	$Pd(OAc)_2$	CH_3CN	60	trace
9	$NiCl_2$	CH_3CN	60	trace
10	$[Rh(C_5Me_5)_2]_2$	CH_3CN	60	trace
11	$RhCl(PPh_3)_3$	CH_3CN	60	trace
12	$MnBr_2$	CH_3CN	60	trace

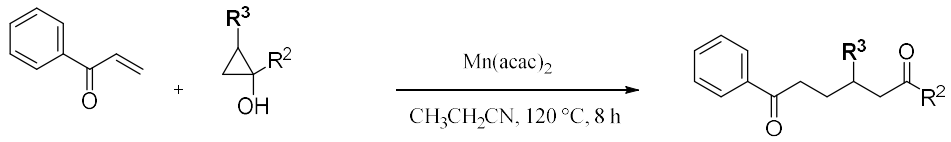
13	$Mn(OAc)_2$	CH_3CN	60	trace
14	$Mn(acac)_2$	CH_3CN	60	66
15	$Mn(acac)_2$	CH_3CH_2CN	80	70
16	$Mn(acac)_2$	CH_3CH_2CN	100	88
17	$Mn(acac)_2$	CH_3CH_2CN	120	90
18	$Mn(acac)_2$	CH_3CH_2CN	140	88

[a] Reaction condition: Substrate **1a** (74 mg, 0.5 mmol, 1 eq), **2a'** (67 mg, 0.5 mmol, 1 eq), Catalyst (0.1 eq), Solvent (2 mL) was added to a 10-mL sealed tube, stirred and heated in oil bath. The reaction time is 8 h. [b] isolated yield

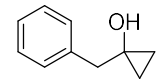
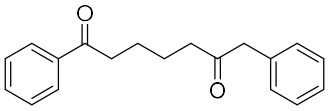
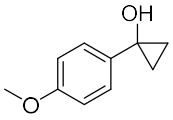
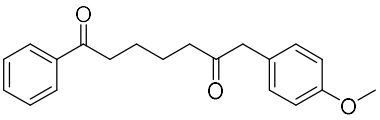
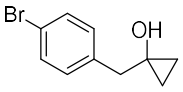
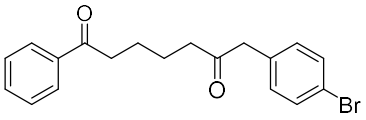
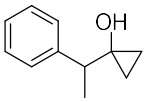
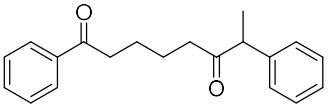
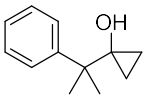
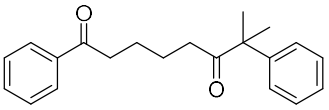
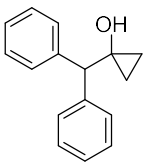
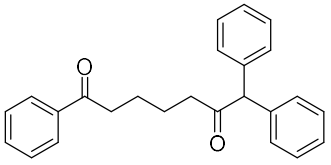
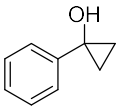
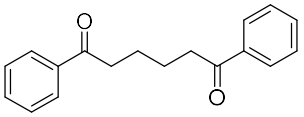
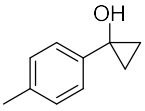
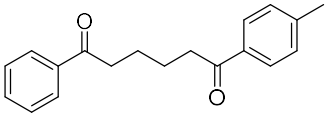
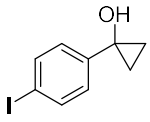
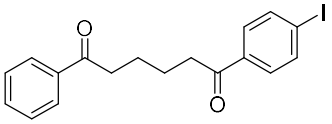
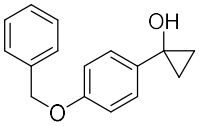
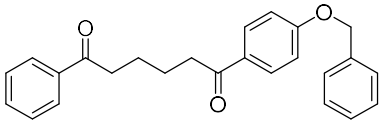
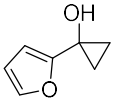
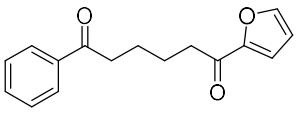
We tested various of trans metal catalyst. The iron salts, indium salts and manganese salts provided the desired product, and the $Mn(acac)_2$ gave the best yield of 90 %. Other transmetal catalysts like palladium and nickel salts were tried in the reaction, however there was no desired product. In the beginning, we use acetonitrile as solvent. But with the raising of temperature, the solvent turned to propionitrile. The butyronitrile was also tested, but the yield was not improved. We also tried other solvent like alcohol, ketone, EA, dioxane, DMF, DMSO and toluene. But the results were not good enough, comparing with the propionitrile solvent. The yield of the reaction would be improved along with the rising of temperature. And the most suitable temperature was found at 120 ºC.

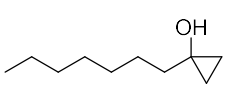
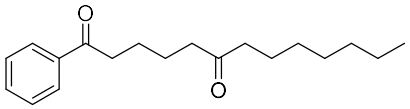
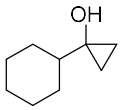
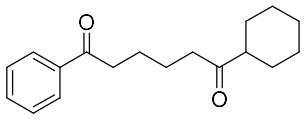
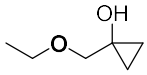
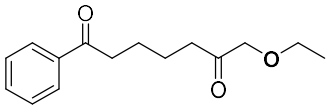
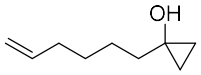
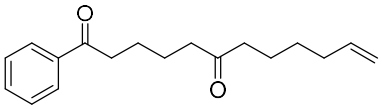
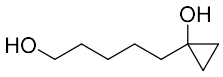
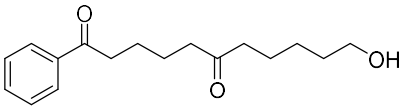
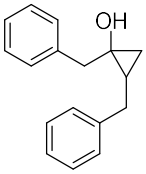
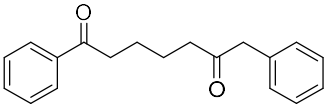
So far, we have got the optimum reaction condition. This condition is simple as well as high efficient. Next, we would apply our reaction to different scopes of substrates. The scopes would be divided into two species: the cyclopropanols and the enones. The results were shown in Table 2 and Table 3.

Table 2, substrate scope of cyclopropanols.[a]



1a **2a'-2q'** **3aa'-3aq'**

Entry	Substrate		Product		Yield (%)[b]
1		**2a'**		**3aa'**	90
2		**2b'**		**3ab'**	68
3		**2c'**		**3ac'**	76
4		**2d'**		**3ad'**	67
5		**2e'**		**3ae'**	52
6		**2f'**		**3af'**	64
7		**2g'**		**3ag'**	80
8		**2h'**		**3ah'**	35
9		**2i'**		**3ai'**	45
10		**2j'**		**3aj'**	75
11		**2k'**		**3ak'**	57

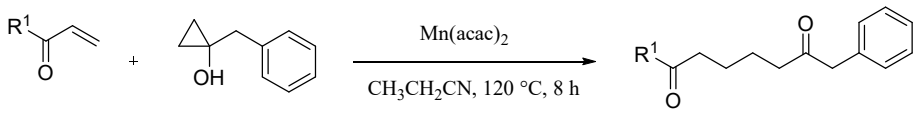
12		2l'		3al'	75
13		2m'		2am'	45
14		2n'		3an'	75
15		2o'		3ao'	47
16		2p'		3ap'	75
17		2q'		3aq'	65

[a] Reaction condition: Substrate **1a** (74 mg, 0.5 mmol, 1 eq), **2a'** (67 mg, 0.5 mmol, 1 eq), $Mn(acac)_2$ (0.1 eq), CH_3CN (2 mL) was added to a 10-mL sealed tube, stirred and heated in oil bath. The reaction time is 8 h. [b] isolated yield

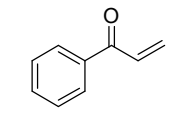
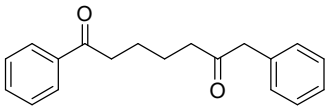
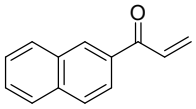
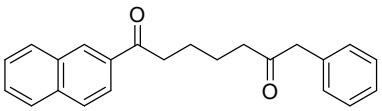
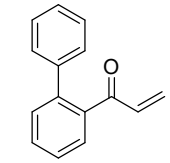
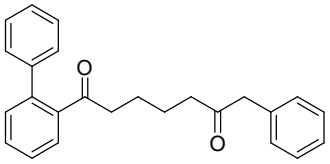
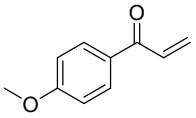
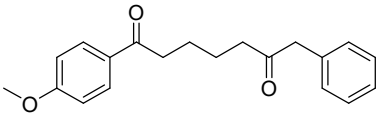
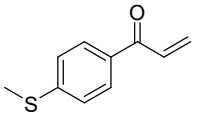
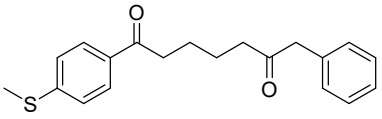
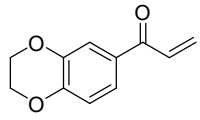
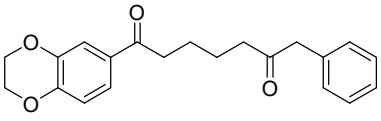
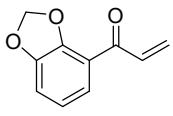
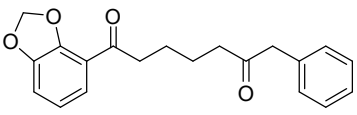
As shown in Table 2, various of cyclopropanols were applied in this reaction and the results were summarized. A variety of benzyl-substituents cyclopropanols were examined. To our delight, the substituents on phenyl ring and benzylic position did not lead to obvious negative effect on the reaction, giving **3aa'-3af'** in moderated to good yields. A plethora of cyclopropanols bearing aromatic substituents could also react with enone **1a** smoothly to furnish the desired products **3ag'-3ak'** in synthetic useful yields, also noteworthy was the excellent compatibility of heterocyclic furan moiety. Gratifyingly, aliphatic substituted cyclo-propanols could also uneventfully participated in the transformation to give **3al'-3an'** without deteriorating the reaction efficiency.

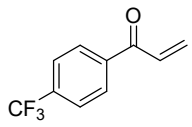
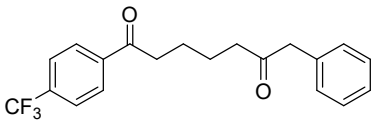
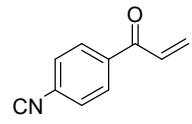
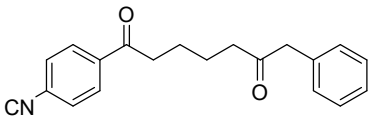
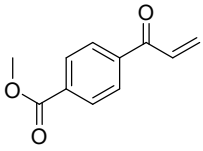
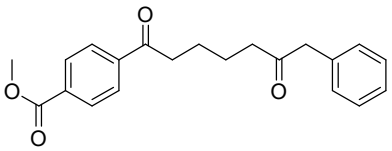
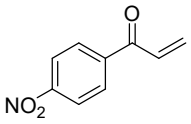
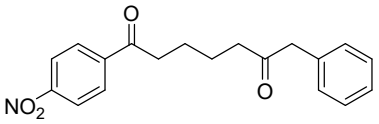
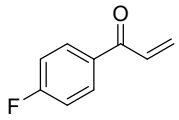
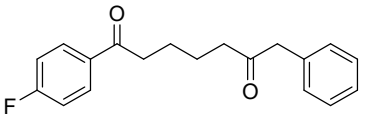
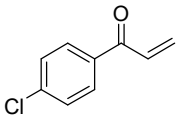
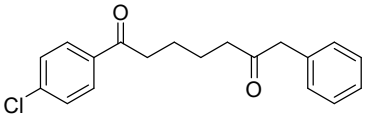
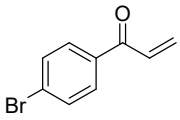
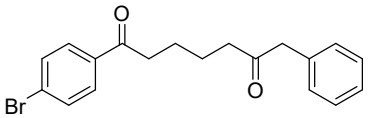
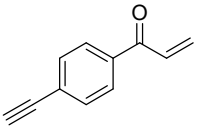
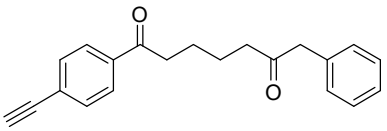
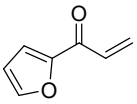
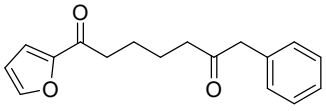
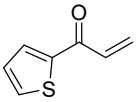
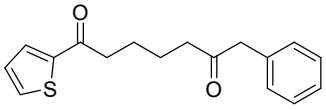
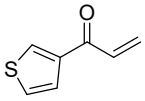
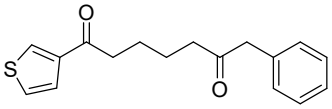
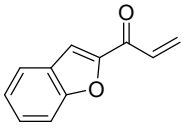
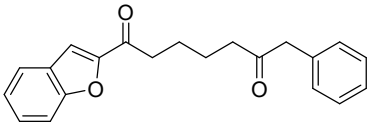
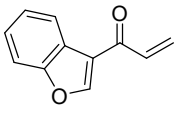
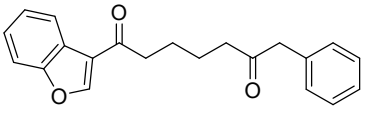
Notably, the presence of relatively sensitive functional groups such as alkene moiety hydroxyl group did not compromise the reaction efficiency, thus giving rise to synthetically useful products **3ao'** and **3ap'** in one-step without resorting to the protection and deprotec-tion steps. It is notable that the multisubstituted cyclopropanol proved to be suitable substrate for this transformation, affording **3aq'** in 65% yield.

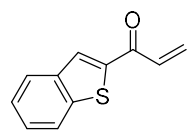
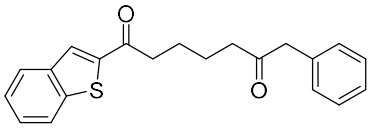
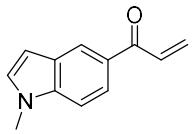
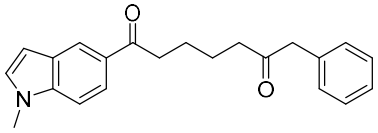
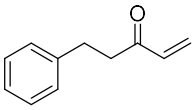
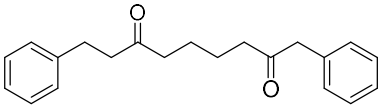
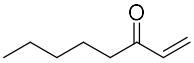
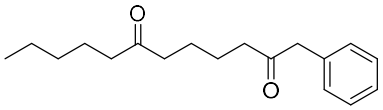
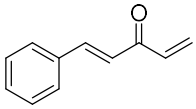
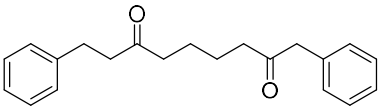
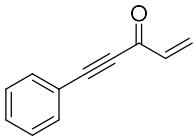
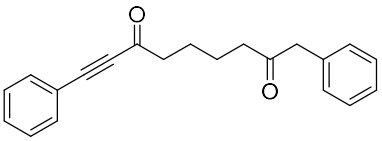
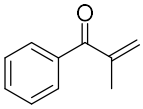
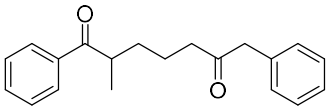
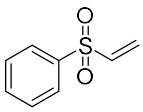
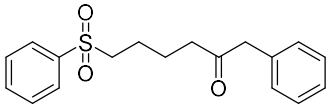
Table 3, Substrate scope of enones.[a]



1a-1b' **2a'** **3aa'-3b'a'**

Entry	Substrate		Product		Yield (%)[b]
1		**1a**		**3aa'**	90
2		**1b**		**3ba'**	73
3		**1c**		**3ca'**	67
4		**1d**		**3da'**	84
4		**1d**		**3da'**	66
6		**1f**		**3fa'**	71
7		**1g**		**3ga'**	62

8		**1h**		**3ha'**	57
9		**1i**		**3ia'**	63
10		**1j**		**3ja'**	74
11		**1k**		**3ka'**	32
12		**1l**		**3la'**	71
13		**1m**		**3ma'**	68
14		**1n**		**3na'**	77
15		**1o**		**3oa'**	56
16		**1p**		**3pa'**	90
17		**1q**		**3qa'**	72
18		**1r**		**3ra'**	93
19		**1s**		**3sa'**	53
20		**1t**		**3ta'**	56

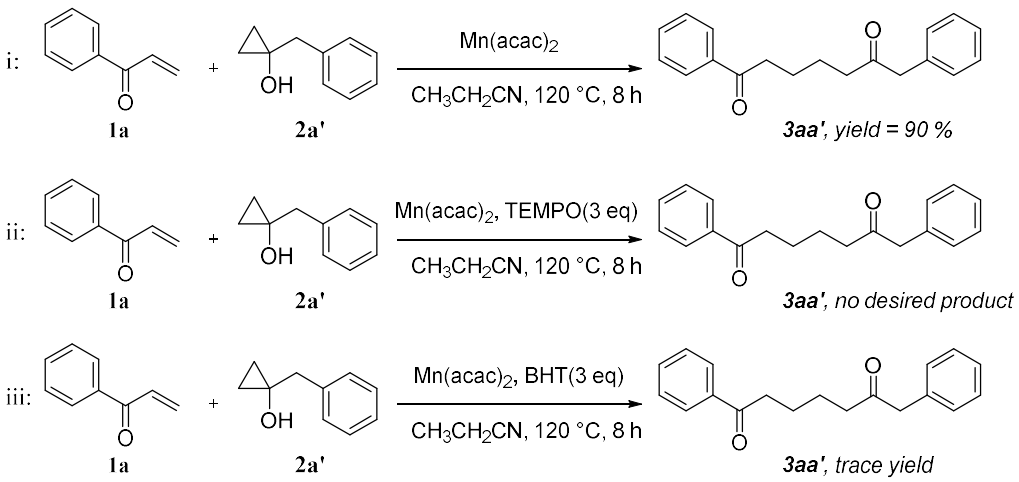
21		1u		3ua'	75
22		1v		3va'	82
23		1w		3wa'	80
24		1x		3xa'	88
25		1y		3ya'	90
26		1z		3za'	57
27		1a'		3a'a'	40
28		1b'		3b'a'	26

[a] Reaction condition: Substrate **1a** (74 mg, 0.5 mmol, 1 eq), **1a'** (67 mg, 0.5 mmol, 1 eq), $Mn(acac)_2$ (0.1 eq), CH_3CN (2 mL) was added to a 10-mL sealed tube, stirred and heated in oil bath. The reaction time is 8 h. [b] isolated yield

We also investigated the substrate scope of enones, the results are summarized in Table 3. In general, the enones bearing electron-donating groups **3a-3g** reacted with 1-benzylcyclopropan-1-ol **2a'** smoothly to give the desired products **3aa'-3ga'** in good to excellent yields. The substrates with electron-withdrawing substituents were also compatible with the reaction conditions to give **3ha'-3na'** in considerable yields. It is

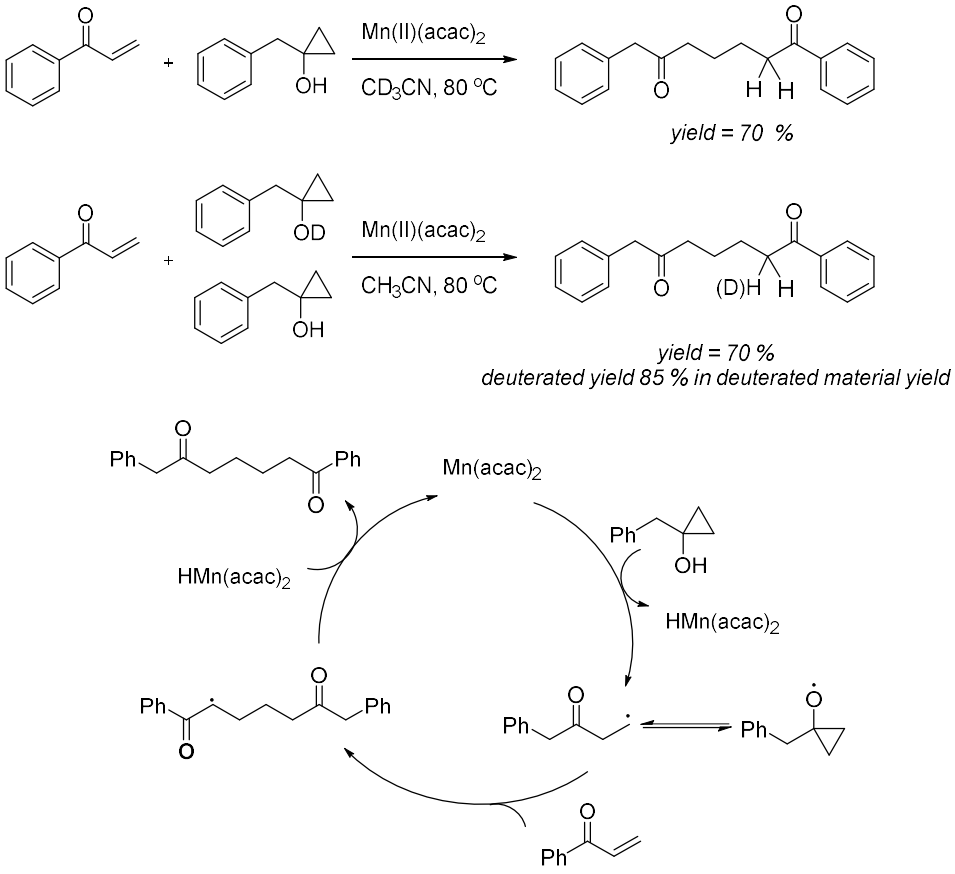
notable that a variety of synthetically important functional groups such as CF_3, CN, CO_2Me, NO_2 and alkyne moiety were well tolerated to afford the target products in moderate to good yields, respectively. The 1,6-diketones bearing a chloride or bromide substituents were also successfully obtained in considerable yields, which made them amenable to further functionalization through well-established cross-coupling reactions. Gratifyingly, a plethora of enones bearing heterocycles could reaction smoothly with **2a'** to furnish the desired 1,6-diketones without deteriorating the yields. Moreover, aliphatic enones were also amenable to this transformation to give **3wa'-3xa'** in excellent yields. The unsaturated alkene and alkyne substituents did not result in deleterious effect on the reaction, thus give **3ya'-3za'** in considerable yields. Enone bearing a beta-methyl substituent could also react with **2a'** smoothly to give **3a'a'**, albeit with a slight decrease of the yields. In addition, the unsaturated sulfone was also compatible to the current reaction conditions to give the desired product **3b'a'** in 27% yield.

Besides the substrates, the mechanism study was also conducted. Due to the literature review, the ring-opening of cyclopropanol could be conducted via a radical progress. From this, we proposed our reaction to be a radical progress. Then we conducted a series of reactions to test it. First of all, the controlled reactions were performed. Excess amount of TEMPO and BHT to the controlled groups. The result showed that the reactions were interrupted with little desired product detected. This could be an evidence that the reaction was supposed to be a radical progress.



Scheme 6, controlled reactions with radical inhibitors

Referred to the literature review, we've found that the β-carbonyl radical presented as the necessary intermediate in the transformation progress.[100] a reasonable mechanism was proposed. (Scheme 6) We conducted the deuterated reaction to study the mechanism. First, we used deuterated acetonitrile as solvent to conduct this reaction and found that there is no deuterated product found in the spectrum. Then, we prepared the deuterated cyclopropanol material and applied it to the reaction. The result showed that 85% of the product was deuterated product was formed. According to these results, we proposed the following procedure of this reaction. With the Mn-catalyst present, the cyclopropanol went through a ring-opening progress together with the radical and hydrogen-metal complex was formed. Then the enone reacted with the radical to generate the coupling intermediate. At last the hydrogen-metal complex provide H to give the product and the metal catalyst was recovered to join a new catalytic circulation.



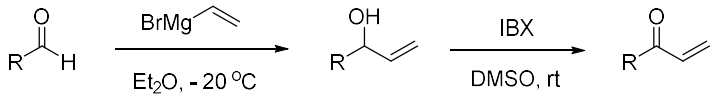
Scheme 7, The proposed mechanism

3.3 Conclusion

In this chapter, we have developed a concise and efficient method to the coupling of cyclopropanol with enone. The reaction was catalyzed by $Mn(acac)_2$ in CH_3CH_2CN. The reaction could provide a series of 1,6-dione products at good to excellent yield. The scope of substrates is wide. This reaction is proved to be a radical progress and a reasonable mechanism was proposed. Compared with the previous literature, this reaction is simple and convenient, as well as high atom economy.

3.4 Experiment Section

Experiment procedure and data of products

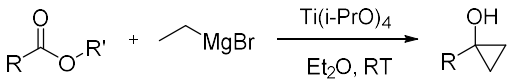


Enone generation.

Step1: To an oven dried round bottom flask (100 mL) equipped with a magnetic stir bar, aldehyde (10 mmol) was dissolved in dry diethyl ether (30 mL). The solution was stirred at – 20 ºC for 10 min. Keeping at – 20 ºC, vinylmagnesium bromide (11 mL, 1.1 eq., 1M in THF) was added dropwise to the solution. The mixture was stirred for 4 h, followed by warming up to RT. Then the reaction was quenched by gently addition of saturated NH_4Cl solution. After extracting with diethyl ether (3 × 30 mL), the combined organic phase was washed with saturated brine, and dried with $MgSO_4$. The dry solution was filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography on silica gel (hexane/EtOAc mixture) to provide the enol product.

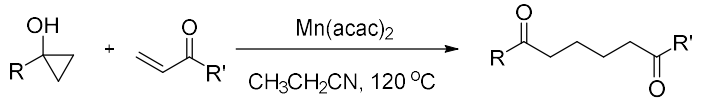
Step 2: A round bottom flask (100 mL) was equipped with a magnetic stir bar. The enol (10 mmol, yield from step 1) and dimethyl sulfoxide (20 mL) were added and stirred for 2 min. Then IBX (12 mmol, 1.2 eq) was add in two portions in 5 min. The mixture was stirred at room temperature. After stirring for 2 h, water (20 mL) and diethyl ether (20 mL) was added to the solution. The mixture was filtered with a Buchner funnel. The solid residue was rinsed with diethyl ether (3×20 mL). the liquid was collected and extracted with diethyl ether (3×20 mL). the combined organic layer was washed with brine (2×30 mL), dried by Na_2SO_4. The solution was filtered and concentrated under

reduced pressure to give the crude product. After purified by flash column chromatography on silica get (hexane/EtOAc mixture), the desired enone product was obtained.



Cyclopropanol generation.

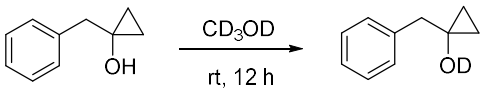
To an oven dried round bottom flask (100 mL) equipped with a magnetic stir bar, the ester (10 mmol) was dissolved in dry Diethyl Ester (30 mL). The $Ti(i\text{-}PrO)_4$ (14mmol, 1.4 eq) was added to the solution and stirred for 2 min. Then the ethylmagnesuim bromide (28 mmol, 28 mL, 1.0mol/L in THF) was added dropwise to the solution. The solution generally turned dark green. After stirring at room temperature for 8 h, sulfuric acid solution (2 mol/L) was added and stirred until all the solid dissolved to give a clear two-phase liquid. The liquid was separated and the aqueous solution was extracted with diethyl ether (3×30 mL). The organic layer was collected, washed by brine, and dried over Na_2SO_4. The organic solution was filtered and concentrated by vacuo. The residue was purified by flash column chromatography on silica gel (Hexane/EtOAc mixture) to provide the cyclopropanol product.



The general procedure for the coupling of cyclopropanol with enone.

To an oven dried sealed tube equipped with a magnetic stir bar, the cyclopropanol

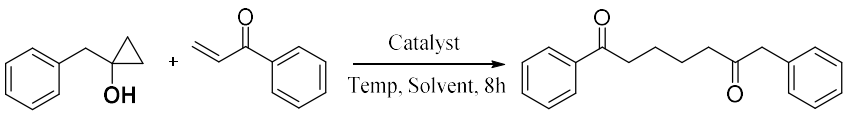
(0.5 mmol) and enone (0.5 mmol), $Mn(acac)_2$ (0.05 mmol) and CH_3CH_2CN (2 mmol) was added. The mixture was stirred at 120 °C (oil bath) for 8 h. After cooling down, the mixture was filtered and washed with ethyl ester (3×5 mL). the organic solution was collected and concentrated over vacuo. After flash column chromatography on silica gel (Hexane/EtOAc mixture), the purified product was obtained.



Preparation of deuterated material:

To an oven dried RBF (10 mL), the cyclopropanol (500 mg, 3.38 mmol) was add to CD_3CD (1 mL). the solution was stirred for 12 h at room temperature under N_2 atmosphere. Then the solution was concentrated under vacuum to get the mixture of deuterated product and normal cyclopropanol. This mixture was applied to the reaction immediately.

Part of the optimization condition of solvents are shown as below.



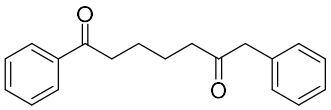
1a **2a'** **3aa'**

Entry	Catalyst	Solvent	Temp(°C)	3aa'Yield(%)[b]
1	$Mn(acac)_2$	EA	60	35
2	$Mn(acac)_2$	H_2O	60	5
3	$Mn(acac)_2$	Dioxane	60	12

4	$Mn(acac)_2$	DMSO	60	trace
5	$Mn(acac)_2$	DMF	60	trace
6	$Mn(acac)_2$	Toluene	60	45
7	$Mn(acac)_2$	Acetone	60	trace
8	$Mn(acac)_2$	THF	60	trace
9	$Mn(acac)_2$	CCl_4	60	8
10	$Mn(acac)_2$	Hexane	60	trace
11	$Mn(acac)_2$	Et_2O	60	48
12	$Mn(acac)_2$	neat	60	trace

[a] Reaction condition: Substrate **1a** (74 mg, 0.5 mmol, 1 eq), **2a'** (67 mg, 0.5 mmol, 1 eq), Catalyst (0.1 eq), Solvent (2 mL) was added to a 10-mL sealed tube, stirred and heated in oil bath. The reaction time is 8 h. [b] isolated yield

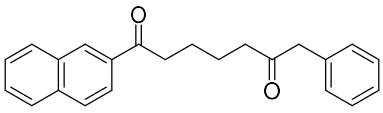
1,7-diphenylheptane-1,6-dione (3aa')



White solid; $C_{19}H_{20}O_2$; melting point 56.5 oC; yield: 90 %

1H NMR (400M, $CDCl_3$): δ 1.64-1.74 (m, 4H), 2.53 (t, *J* = 8.0 Hz, 2H), 2.93-2.97 (t, *J* = 8.0 Hz, 2H), 3.71 (s, 2H), 7.21-7.36 (m, 5H), 7.44-7.49 (m, 2H), 7.57 (m, 1H), 7.94 (d, *J* = 8.0, 2H); 13C NMR (100M $CDCl_3$): δ 23.30, 23.59, 38.24, 41.73, 50.18, 127.02, 128.02, 128.60, 128.75, 129.43, 133.00, 134.31, 136.93, 199.94, 208.11. HRMS (ESI): m/z [M+H]+ for $C_{19}H_{20}O_2$: exact mass calcd. 281.1542, found 281.1543.

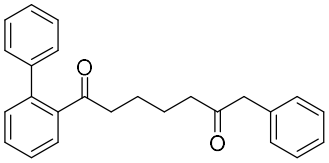
1-(naphthalen-2-yl)-7-phenylheptane-1,6-dione (3ba')



White solid; $C_{23}H_{22}O_2$; melting point 85.2 oC; yield: 73 %

1H NMR (500M, $CDCl_3$): δ 1.70-1.82 (m, 4H), 2.56 (t, J = 7.0 Hz, 2H), 3.08 (t, J = 7.0 Hz, 2H), 3.74 (s, 2H), 7.24-7.37 (m, 5H), 7.58-7.65 (m, 2H), 7.88-7.93 (m, 2H), 7.98 (d, J = 8.0 Hz, 1 H), 8.03 (d, J = 8.6 Hz, 1H), 8.48 (s, 1H); 13C NMR (125M $CDCl_3$): δ 23.37, 23.78, 38.32, 41.76, 50.21, 123.88, 126.77, 127.03, 127.78, 128.44, 128.75, 129.43, 129.57, 129.63, 132.56, 134.28, 135.57. HRMS (ESI): m/z [M+H]+ for $C_{23}H_{22}O_2$: exact mass calcd. 331.1698, found 331.1706.

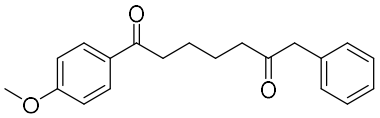
1-([1,1'-biphenyl]-2-yl)-7-phenylheptane-1,6-dione (3ca')



White solid; $C_{25}H_{24}O_2$; melting point ; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.31-1.44 (m, 4H), 2.22-2.31 (m, 4H), 3.63 (s, 2H), 7.16-7.20 (m, 2H), 7.25-7.54 (m, 12H); 13C NMR (75M $CDCl_3$): δ 22.93, 23.79, 41.53, 42.50, 50.09, 126.99, 127.49, 127.60, 127.85, 128.70, 128.84, 129.36, 130.13, 130.44, 134.25, 140.01, 140.62, 141.03, 207.61, 208.01. HRMS (ESI): m/z [M+H]+ for $C_{25}H_{24}O_2$: exact mass calcd. 357.1855, found 357.1849.

1-(4-methoxyphenyl)-7-phenylheptane-1,6-dione (3da')

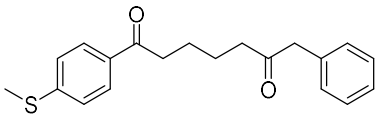


White solid; $C_{20}H_{22}O_3$; melting point ; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.62-1.72 (m, 4H), 2.51 (t, J = 6.0 Hz, 2H), 2.88 (t, J = 6.2

Hz, 2H), 3.72 (s, 2H), 3.84 (s, 3H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.25-7.36 (m, 5H), 7.92 (d, *J* = 8.4 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 23.37, 23.63, 37.89, 41.76, 50.15, 53.48, 55.45, 113.70, 126.99, 128.72, 129.41, 130.04, 130.27, 134.31, 163.39, 198.55, 208.15. HRMS (ESI): m/z [M+H]+ for $C_{20}H_{22}O_3$: exact mass calcd. 311.1647, found 311.1642.

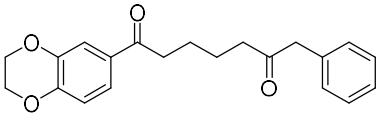
1-(4-(methylthio)phenyl)-7-phenylheptane-1,6-dione (3ea')



White solid; $C_{20}H_{22}O_2S$; melting point 87.3 oC; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.60-1.70 (m, 4H), 2.53 (m, 5H), 2.89 (t, *J* = 6.8 Hz, 2H), 3.70 (s, 2H), 7.20-7.33 (m, 7H), 7.84 (d, *J* = 8.6 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 14.78, 23.37, 23.71, 38.03, 41.72, 50.18, 125.02, 127.01, 128.44, 128.73, 129.40, 133.25, 134.29, 145.69, 198.95, 208.10. HRMS (ESI): m/z [M+H]+ for $C_{20}H_{22}O_2S$: exact mass calcd. 327.1419, found 327.1415.

1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-7-phenylheptane-1,6-dione (3fa')

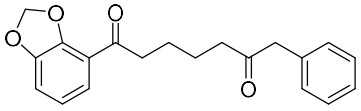


White solid; $C_{21}H_{22}O_4$; melting point ; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.60-1.69 (m, 4H), 2.51 (t, *J* = 6.5, 2H), 2.85 (t, *J* = 6.6 Hz, 2H), 3.70 (s, 2H), 4.25-4.34 (m, 4H), 6.90 (d, *J* = 8.7 Hz, 1H), 7.19- 7.35 (m, 5H), 7.45-7.49 (m, 2H); 13C NMR (75M $CDCl_3$): δ 23.34, 23.81, 37.90, 41.74, 50.16, 64.12, 64.67, 117.18, 117.54, 122.12, 127.00, 128.72, 129.41, 130.83, 134.29, 140.30, 147.91, 198.44,

208.17. HRMS (ESI): m/z [M+H]+ for $C_{21}H_{22}O_4$: exact mass calcd. 339.1596, found 339.1595.

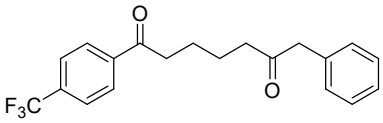
1-(benzo[d][1,3]dioxol-5-yl)-7-phenylheptane-1,6-dione (3ga')



White solid; $C_{20}H_{20}O_4$; melting point ; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.63-1.68 (m, 4H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.93 (t, *J* = 6.5 Hz, 2H), 3.70 (s, 2H), 6.07 (s, 2H), 6.88 (m, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 7.19-7.42 (m, 6H); 13C NMR (75M $CDCl_3$): δ23.27. 23.34, 41.80, 42.07, 50.15, 101.48, 112.36, 121.18, 121.49, 126.98, 128.71, 129.10, 129.41, 134.32, 147.69, 148.56, 197.47, 208.20. HRMS (ESI): m/z [M+H]+ for $C_{20}H_{20}O_4$: exact mass calcd. 325.1440, found 325.1439.

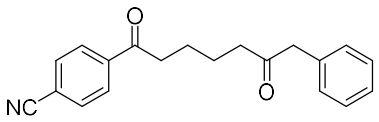
7-phenyl-1-(4-(trifluoromethyl)phenyl)heptane-1,6-dione (3ha')



White solid; $C_{20}H_{19}F_3O_2$; melting point 58.8 oC; yield: 57 %

1H NMR (400M, $CDCl_3$): δ 1.64-1.74 (m, 4H), 2.54 (t, *J* = 6.7 Hz, 2H), 2.97 (t, *J* = 6.7 Hz, 2H), 3.71 (s, 2H), 7.22-7.37 (m, 5H), 7.73 (d, *J* = 8.2 Hz, 2H), 8.03 (d, *J* = 8.1 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.13, 23.34, 38.55, 41.60, 50.21, 123.63 (q, $J_{C\text{-}F}$ = 272.0 Hz), 125.66 (q, $J_{C\text{-}F}$ = 3.7 Hz), 127.04, 128.34, 128.75, 129.40, 134.25 (q, $J_{C\text{-}F}$ = 32.4 Hz), 134.25, 139.55, 198.87, 208.01. HRMS (ESI): m/z [M+H]+ for $C_{20}H_{19}F_3O_2$: exact mass calcd. 349.1415, found 349.1412.

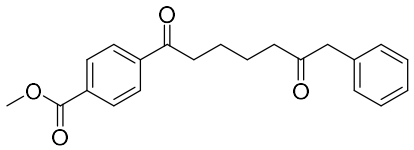
4-(6-oxo-7-phenylheptanoyl)benzonitrile (3ia')



White solid; $C_{20}H_{19}O_2N$; melting point ; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.62-1.71 (m, 4H), 2.53 (t, *J* = 6.5, 2H), 2.94 (t, *J* = 6.6 Hz, 2H), 3.70 (s, 2H), 7.18- 7.33 (m, 5H), 7.76 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 8.3 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 23.06, 23.25, 38.57, 41.55, 50.20, 116.24, 117.96, 127.05, 128.42, 128.75, 129.39, 132.51, 134.21, 139.81, 198.47, 207.96. HRMS (ESI): m/z [M+H]+ for $C_{20}H_{19}O_2N$: exact mass calcd. 306.1494, found 306.1492.

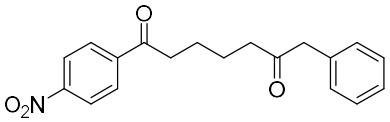
methyl 4-(6-oxo-7-phenylheptanoyl)benzoate (3ja')



White solid; $C_{21}H_{22}O_4$; melting point 88.0 oC; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.60-1.72 (m, 4H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.95 (t, *J* = 6.8 Hz, 2H), 3.69 (s, 2H), 3.95 (s, 3H), 7.18-7.43 (m, 5H), 7.96 (d, *J* = 8.3 Hz, 2H), 8.10 (d, *J* = 8.2 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 23.16, 23.37, 38.59, 41.62, 50.19, 52.44, 127.02, 127.90, 128.73, 129.39, 129.81, 133.77, 124.26, 140.11, 166.21, 199.36, 207.99. HRMS (ESI): m/z [M+H]+ for $C_{21}H_{22}O_4$: exact mass calcd. 339.1596, found 339.1596.

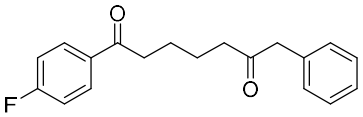
1-(4-nitrophenyl)-7-phenylheptane-1,6-dione (3ka')



White solid; $C_{19}H_{19}NO_4$; melting point 63.7 oC; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.56-1.77 (m, 4H), 2.54 (t, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 6.4 Hz, 2H), 3.70 (s, 2H), 7.19-7.46 (m, 5H), 8.07 (d, *J* = 8.7 Hz, 2H), 8.31 (d, *J* = 8.7 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 23.04, 23.24, 38.82, 41.53, 50.23, 123.84, 127.06, 128.76, 129.00, 129.38, 134.20, 141.31, 198.24, 207.92. HRMS (ESI): m/z [M+H]+ for $C_{19}H_{19}NO_4$: exact mass calcd. 326.1392, found 326.1397.

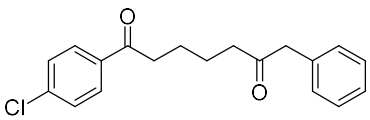
1-(4-fluorophenyl)-7-phenylheptane-1,6-dione (3la')



White solid; $C_{19}H_{19}FO_2$; melting point ; yield: 71 %

1H NMR (400M, $CDCl_3$): δ 1.63-1.72 (m, 4H), 2.53 (t, *J* = 6.7 Hz, 2H), 2.91 (t, *J* = 6.6 Hz, 2H), 3.71 (s, 2H), 7.12-7.16(m, 2H), 7.20-7.37 (m, 5H), 7.95-7.99 (m, 2H); 13C NMR (100M $CDCl_3$): δ 23.24, 23.55, 38.17, 41.67, 50.20, 115.60 (d, $J_{C\text{-}F}$ = 21.7 Hz), 127.03, 128.75, 129.41, 130.63 (d, $J_{C\text{-}F}$ = 9.2 Hz), 133.34 (d, $J_{C\text{-}F}$ = 2.8 Hz), 134.27, 165.7 (d, $J_{C\text{-}F}$ = 252.9 Hz), 198.30, 208.09. HRMS (ESI): m/z [M+H]+ for $C_{19}H_{19}FO_2$: exact mass calcd. 299.1447, found 299.1444.

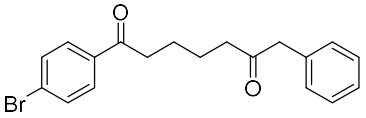
1-(4-chlorophenyl)-7-phenylheptane-1,6-dione (3ma')



White solid; $C_{19}H_{19}ClO_2$; melting point ; yield: 68 %

1H NMR (400M, $CDCl_3$): δ 1.63-1.72 (m, 4H), 2.53 (t, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 6.6 Hz, 2H), 3.72 (s, 2H), 7.23-7.46 (m, 5H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.87(d, *J* = 8.4 Hz, 2H); 13C NMR (400M $CDCl_3$): δ 23.20, 23.49, 38.23, 41.65, 50.21, 127.04, 128.75, 128.89, 129.41, 129.44, 134.25, 135.22, 139.40, 198.67, 208.07. HRMS (ESI): m/z [M+H]+ for $C_{19}H_{19}ClO_2$: exact mass calcd. 315.1152, found 315.1154.

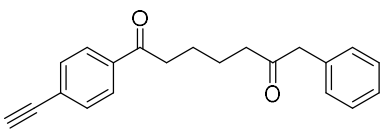
1-(4-bromophenyl)-7-phenylheptane-1,6-dione (3na')



White solid; $C_{19}H_{19}BrO_2$; melting point ; yield: 77 %

1H NMR (400M, $CDCl_3$): δ 1.62-1.74 (m, 4H), 2.53 (t, *J* = 6.8 Hz, 2H), 2.90 (t, *J* = 6.9 Hz, 2H), 3.70 (s, 2H), 7.22-7.38 (m, 5H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.9 (d, *J* = 8.6 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.21, 23.48, 38.21, 41.66, 50.20, 127.04, 128.11, 128.76, 129.42, 129.57, 131.89, 134.28, 135.63, 198.83, 208.02. HRMS (ESI): m/z [M+H]+ for $C_{19}H_{19}BrO_2$: exact mass calcd. 359.0647, found 359.0648.

1-(4-ethynylphenyl)-7-phenylheptane-1,6-dione (3oa')

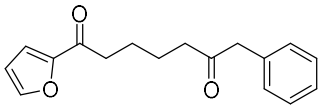


White solid; $C_{21}H_{20}O_2$; melting point 66.4 oC; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.57-1.74 (m, 4H), 2.52 (t, *J* = 6.7 Hz, 2H), 2.92 (t, *J* = 6.8

Hz, 2H), 3.26 (s, 1H), 3.70 (s, 2H), 7.16-7.38 (m, 5H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.5 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 23.22, 23.50, 37.24, 38.31, 50.21, 80.29, 82.78, 126.79, 127.03, 127.89, 128.74, 129.39, 132.29, 134.25, 136.60, 199.08, 208.03. HRMS (ESI): m/z [M+H]+ for $C_{21}H_{20}O_2$: exact mass calcd. 305.1542, found 305.1539.

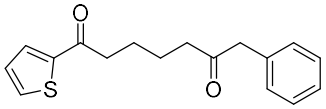
1-(furan-2-yl)-7-phenylheptane-1,6-dione (3pa')



White solid; $C_{17}H_{18}O_3$; melting point ; yield: 90 %

1H NMR (300M, $CDCl_3$): δ 1.59-1.76 (m, 4H), 2.51 (t, *J* = 6.4 Hz, 2H), 2.80 (t, *J* = 6.5 Hz, 2H), 3.71 (s, 2H) 6.53 (dd, *J* =3.5, 1.8 Hz, 1H), 7.19-7.37 (m, 6H), 7.58 (d, *J* = 3.6 Hz, 1H); 13C NMR (75M $CDCl_3$): δ 23.26, 23.51, 38.09, 41.62, 50.17, 112.16, 116.91, 127.01, 128.73, 129.39, 134.26, 146.24, 152.71, 189.18, 208.05. HRMS (ESI): m/z [M+H]+ for $C_{17}H_{18}O_3$: exact mass calcd. 271.1334, found 271.1337.

7-phenyl-1-(thiophen-2-yl)heptane-1,6-dione (3qa')

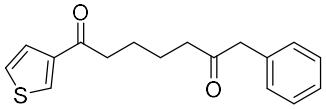


White solid; $C_{17}H_{18}O_2S$; melting point ; yield: 84 %

1H NMR (400M, $CDCl_3$): δ 1.62-1.73 (m, 4H), 2.53 (t, *J* = 6.9, 2H), 2.89 (t, *J* = 7.0 Hz, 2H), 3.71 (s, 2H), 7.23-7.15 (m, 1H), 7.22-7.37 (m, 5H), 7.64 (d, *J* = 4.8 Hz, 1H), 7.69 (d, *J* = 3.8 Hz, 1H); 13C NMR (100M $CDCl_3$): δ 23.26, 23.95, 39.01, 41.62, 50.18, 127.02, 128.08, 128.76, 129.40, 131.78, 133.47, 134.26, 144.30, 192.91, 208.06. HRMS

(ESI): m/z [M+H]+ for $C_{17}H_{18}O_2S$: exact mass calcd. 287.1106, found 287.1104.

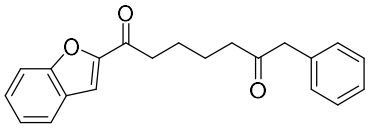
7-phenyl-1-(thiophen-3-yl)heptane-1,6-dione (3ra')



White solid; $C_{17}H_{18}O_2S$; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.63-1.75 (m, 4H), 2.52 (t, *J* = 6.6 Hz, 2H), 2.85 (t, J = 6.7 Hz, 2H), 3.70 (s, 2H), 7.19-7.45 (m, 5H), 7.53 (d, *J* = 5.1 Hz, 2H), 8.02 (d, *J* = 2.8 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 23.28, 23.61, 39.52, 41.67, 50.19, 126.32, 126.92, 127.02, 128.74, 129.40, 131.78, 134.27, 142.28, 194.31, 208.08. HRMS (ESI): m/z [M+H]+ for $C_{21}H_{22}O_4$: exact mass calcd. 287.1106, found 287.1110.

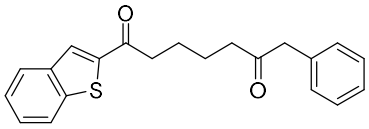
1-(benzofuran-2-yl)-7-phenylheptane-1,6-dione (3sa')



White solid; $C_{21}H_{20}O_3$; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.63-1.78 (m, 4H), 2.53 (t, *J* = 6.8 Hz, 2H), 2.74 (t, *J* = 7.0 Hz, 2H), 3.71 (s, 2H), 7.21-7.32 (m, 6H), 7.46-7.51 (m, 2H), 7.57-7.61 (m, 1H), 7.71 (d, *J* = 7.8 Hz, 1H); 13C NMR (75M $CDCl_3$): δ 23.23, 23.49, 38.58, 41.60, 50.19, 112.44, 112.68, 123.29, 123.90, 127.03, 128.20, 128.74, 129.40, 134.25, 152.52, 155.58, 191.06, 208.03. HRMS (ESI): m/z [M+H]+ for $C_{21}H20O_3$: exact mass calcd. 321.0491, found 321.1489.

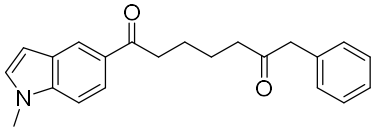
1-(benzo[b]thiophen-2-yl)-7-phenylheptane-1,6-dione (3ua')



White solid; $C_{21}H_{20}O_2S$; melting point 74.5 oC; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.64-1.78 (m, 4H), 2.54 (t, *J* = 6.7, 2H), 2.99 (t, *J* = 6.8 Hz, 2H), 3.71 (s, 2H), 7.21-7.36 (m, 5H), 7.38-7.50 (m, 2H), 7.88-7.92 (m, 3H); 13C NMR (75M $CDCl_3$): δ 23.25, 23.95, 38.91, 41.61, 50.20, 122.99, 125.00, 125.92, 127.04, 127.38, 128.75, 128.91, 129.41, 134.26, 139.15, 142.44, 143.68, 194.41, 209.04. HRMS (ESI): m/z [M+H]+ for $C_{21}H_{20}O_2S$: exact mass calcd. 337.1262, found 337.1262.

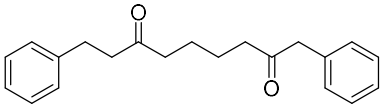
1-(1-methyl-1H-indol-5-yl)-7-phenylheptane-1,6-dione (3va')



White solid; $C_{22}H_{23}O_2N$; melting point ; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.65-1.76 (m, 4H), 2.54 (t, *J* = 6.8, 2H), 3.03 (t, *J* = 6.9 Hz, 2H), 3.71 (s, 2H), 3.86 (s, 3 H), 6.62 (d, *J* = 3 Hz, 1H), 7.13 (d, *J* = 3.2 Hz, 1H), 7.22-7.35 (m, 6H), 7.90 (d, *J* = 8.7 Hz, 1H), 8.29 (s, 1H); 13C NMR (75M $CDCl_3$): δ 23.51, 24.19, 33.02, 38.11, 41.86, 50.15, 102.98, 109.11, 121.72, 122.74, 126.98, 127.93, 128.72, 129.16, 129.43, 130.39, 134.34, 139.12, 200.09, 208.27. HRMS (ESI): m/z [M+H]+ for $C_{22}H_{23}O_2N$: exact mass calcd. 334.1817, found 334.1810.

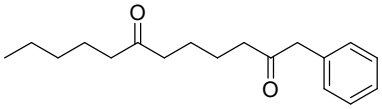
1,9-diphenylnonane-2,7-dione (3wa')



White solid; $C_{21}H_{24}O_2$; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.51-1.60 (m, 4H), 2.36 (t, *J* = 6.4 Hz, 2H), 2.46 (t, *J* = 6.4 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.9 (t, *J* = 7.6 Hz, 2H), 3.68 (s, 2H)7.19-7.32 (m, 10H); 13C NMR (75M $CDCl_3$): δ 23.05, 23.11, 29.78, 41.59, 42.64, 44.23, 50.19, 126.11, 127.03, 128.32, 128.50, 128.75, 129.41, 134.28, 141.08, 208.05, 209.75. HRMS (ESI): m/z [M+H]+ for $C_{21}H_{24}O_2$: exact mass calcd. 309.1855, found 309.1854.

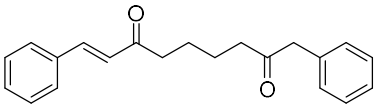
1-phenyldodecane-2,7-dione (3xa')



White solid; $C_{18}H_{26}O_2$; yield: 88 %

1H NMR (300M, $CDCl_3$): δ 0.86-0.93 (t, *J* = 6.7 Hz, 3H), 1.22-1.38 (m, 5H), 1.47-1.61 (m, 6H), 2.33-2.51 (m, 6H), 3.68 (s, 2H), 7.29-7.38 (m, 5H); 13C NMR (75M $CDCl_3$): δ 13.90, 22.44, 23.14, 23.17, 23.52, 31.41, 41.64, 42.37, 42.80, 50.19, 127.01, 128.72, 129.38, 134.27, 208.08, 211.04. HRMS (ESI): m/z [M+H]+ for $C_{18}H_{26}O_2$: exact mass calcd. 275.2011, found 275.2011.

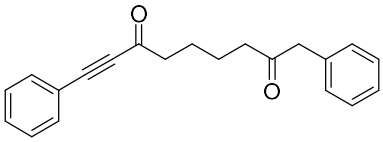
(E)-1,9-diphenylnon-8-ene-2,7-dione (3ya')



White solid; $C_{21}H_{22}O_2$; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.59-1.64 (m, 4H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.85 (t, *J* = 6.6 Hz, 2H), 3.70 (s, 2H), 6.73 (d, *J* = 16.2 Hz, 1H), 7.21-7.52 (m, 8H), 7.51-7.58 (m, 3H); 13C NMR (75M $CDCl_3$): δ 23.28, 23.61, 40.52, 41.68, 50.19, 126.15, 127.01, 128.27, 128.74, 128.95, 129.41, 130.45, 134.29, 134.52, 142.49, 199.97, 208.07. HRMS (ESI): m/z [M+H]+ for $C_{21}H_{22}O_2$: exact mass calcd. 307.1698, found 307.1696.

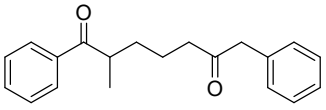
1,9-diphenylnon-8-yne-2,7-dione (3za')



White solid; $C_{21}H_{20}O_2$; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.59-1.71 (m, 4H), 2.51 (t, *J* = 6.7 Hz, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 3.70 (s, 2H), 7.19-7.49 (m, 7H), 7.58 (d, *J* = 7.0 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 22.97, 23.42, 41.46, 45.18, 50.20, 87.78, 90.80, 119.95, 127.04, 128.64, 128.75, 129.40, 130.72, 133.04, 134.24, 187.52, 207.83. HRMS (ESI): m/z [M+H]+ for $C_{21}H_{20}O_2$: exact mass calcd. 305.1541, found 305.1542.

2-methyl-1,7-diphenylheptane-1,6-dione (3a'a')

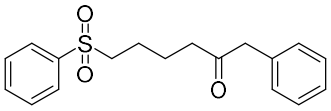


White solid; $C_{20}H_{22}O_2$; yield: 84 %

1H NMR (300M, $CDCl_3$): δ 1.19 (d, *J* = 6.9 Hz, 3H), 1.36-1.47 (m, 1H), 1.48-1.66 (m,

2H), 1.67-1.80 (m, 1H), 2.46 (t, *J* = 7.1 Hz, 2H), 3.44 (m, 1H), 3.67 (s, 2H), 7.18-7.35 (m, 5H), 7.43-7.58 (m, 3H), 7.94 (d, *J* = 7.8 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 17.47, 21.60, 32.87, 40.55, 41.88, 50.15, 127.00, 128.25, 128.66, 128.72, 129.38, 132.93, 134.26, 136.54, 204.04, 208.01. HRMS (ESI): m/z [M+H]+ for $C_{20}H_{22}O_2$: exact mass calcd. 295.1698, found 295.1701.

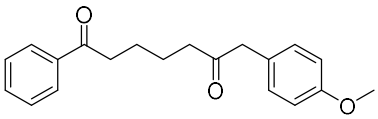
1-phenyl-6-(phenylsulfonyl)hexan-2-one (3b'a')



White solid; $C_{18}H_{20}SO_3$; yield: 26 %

1H NMR (400M, $CDCl_3$): δ 1.59-1.71 (m, 4H), 2.47 (t, *J* = 6.4 Hz, 2H), 3.04 (t, *J* = 7.4 Hz, 2H), 3.68 (s, 2H), 7.19 (d, *J* = 7.1 Hz, 2H), 7.27-7.36 (m, 3H), 7.57-7.70 (m, 3H), 7.89 (d, *J* = 8.2 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 22.11, 22.15, 40.85, 50.26, 55.98, 127.15, 128.02, 128.82, 129.29, 129.32, 133.69, 134.00, 139.10, 207.25. HRMS (ESI): m/z [M+H]+ for $C_{18}H_{20}SO_3$: exact mass calcd. 317.1211, found 317.1207.

7-(4-methoxyphenyl)-1-phenylheptane-1,6-dione (3ab')

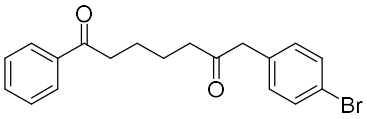


White solid; $C_{20}H_{22}O_3$; yield: 68 %

1H NMR (400M, $CDCl_3$): δ 1.65-1.73 (m, 4H), 2.51 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H), 3.51 (s, 2H), 3.80 (s, 3H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.44-7.58 (m, 3H), 7.93 (d, *J* = 7.2 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.32, 23.60,

38.24, 41.52, 49.28, 55.24, 114.17, 126.33, 128.01, 128.59, 130.42, 132.99, 136.93, 158.65, 199.95, 208.55. HRMS (ESI): m/z [M+H]+ for $C_{20}H_{22}O_3$: exact mass calcd. 311.1647, found 311.1649.

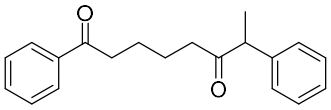
7-(4-bromophenyl)-1-phenylheptane-1,6-dione (3ac')



White solid; $C_{19}H_{19}BrO_2$; yield: 76 %

1H NMR (400M, $CDCl_3$): δ 1.64-1.74 (m, 4H), 2.52 (t, *J* = 6.6 Hz, 2H), 2.96 (t, *J* = 6.6 Hz, 2H), 3.67 (s, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.43-7.58 (m, 5H), 7.94 (d, *J* = 7.2 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.29, 23.55, 38.21, 42.01, 49.21, 121.04, 128.00, 128.62, 131.19, 131.77, 133.04, 133.20, 136.90. HRMS (ESI): m/z [M+H]+ for $C_{19}H_{19}BrO_2$: exact mass calcd. 359.0648, found 359.0647.

1,7-diphenyloctane-1,6-dione (3ad')

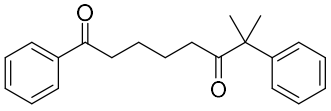


White solid; $C_{20}H_{22}O_2$; yield: 76 %

1H NMR (400M, $CDCl_3$): δ 1.41 (d, *J* = 7.0 Hz, 3H), 1.59-1.66 (m, 4H), 2.43 (t, *J* = 6.7 Hz, 2H), 2.89 (t, *J* = 6.8 Hz, 2H), 3.78 (q, *J* = 7.0 Hz, 1H), 7.23-7.36 (m, 5H), 7.45-7.58 (m, 3H), 7.92 (d, *J* = 7.2 Hz, 2H); 13C NMR (400M $CDCl_3$): δ 17.40, 23.42, 23.56, 38.20, 40.74, 53.20, 127.16, 127.88, 128.01, 128.56, 128.93, 132.95, 136.95, 140.65, 199.96, 210.55. HRMS (ESI): m/z [M+H]+ for $C_{20}H_{22}O_2$: exact mass calcd. 295.1698,

found 295.1699.

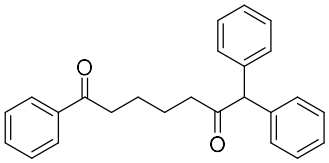
7-methyl-1,7-diphenyloctane-1,6-dione (3ae')



White solid; $C_{21}H_{24}O_2$; yield: 52 %

1H NMR (400M, $CDCl_3$): δ 1.52 (s, 6H), 1.56-1.59 (m, 4H), 2.29 (t, *J* = 6.8 Hz, 2H), 2.86 (t, *J* = 7.1 Hz, 2H), 7.23-7.37 (m, 5H), 7.44-7.58 (m, 3H), 7.92 (d, *J* = 7.1 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.45, 23.61, 25.16, 36.98, 38.27, 58.32, 127.19, 127,92, 128.18, 128.59, 132.97, 136.98, 142.86, 200.1, 210.05. HRMS (ESI): m/z [M+H]+ for $C_{21}H_{24}O_2$: exact mass calcd. 309.1855, found 309.1857.

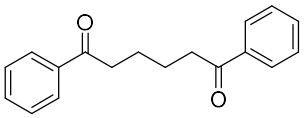
1,7,7-triphenylheptane-1,6-dione (3af')



White solid; $C_{25}H_{24}O_2$; yield: 64 %

1H NMR (400M, $CDCl_3$): δ 1.72-1.76 (m, 4H), 2.66 (t, *J* = 6.7 Hz, 2H), 2.95 (t, *J* = 6.9 Hz, 2H), 5.20 (s, 1H), 7.30-7.39 (m, 10H), 7.47-7.61 (m, 3H), 7.96 (d, *J* = 7.2 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.58, 23.60, 38.25, 42.68, 64.17, 127.26, 128.05, 128.62, 128.75, 129.00, 133.02, 136.97, 136.47, 199.95, 208.30. HRMS (ESI): m/z [M+H]+ for $C_{25}H_{24}O_2$: exact mass calcd. 357.1855, found 357.1854.

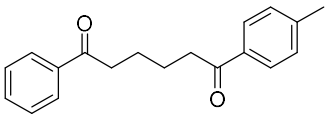
1,6-diphenylhexane-1,6-dione (3ag')



White solid; $C_{18}H_{18}O_2$; melting point 105.4 oC; yield: 80 %

1H NMR (400M, $CDCl_3$): δ 1.85-1.90 (m, 4H), 3.05-3.10 (m, 4H), 7.45-7.49 (m, 4H), 7.55-7.61 (m, 2H), 7.98 (d, J = 7.7 Hz, 4H); 13C NMR (100M $CDCl_3$): δ 23.91, 38.42, 128.04, 128.60, 133.00, 136.97, 200.03. HRMS (ESI): m/z [M+H]+ for $C_{18}H_{18}O_2$: exact mass calcd. 267.1385, found 267.1387.

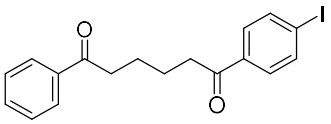
1-phenyl-6-(p-tolyl)hexane-1,6-dione (3ah')



White solid; $C_{19}H_{20}O_2$; melting point 120.5 oC; yield: 35 %

1H NMR (400M, $CDCl_3$): δ 1.83-1.88 (m, 4H), 2.44 (s, 3H), 3.01-3.07 (m, 4H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.47-7.62 (m, 3H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 7.7 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 21.63, 23.96, 24.03, 38.31, 38.44, 128.05, 128.18, 128.59, 132.98, 134.52, 136.99, 143.74, 199.74, 200.08. HRMS (ESI): m/z [M+H]+ for $C_{19}H_{20}O_2$: exact mass calcd. 281.1542, found 281.1544.

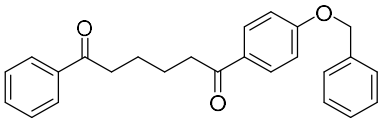
1-(4-iodophenyl)-6-phenylhexane-1,6-dione (3ai')



White solid; $C_{18}H_{17}IO_2$; melting point 126.0 ºC; yield: 45 %

1H NMR (400M, $CDCl_3$): δ 1.84-1.89 (m, 4H), 3.00-3.07 (m, 4H), 7.48-7.51 (m, 3H), 7.68 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 7.3 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.80, 23.82, 38.35, 100.91, 128.04, 128.62, 129.48, 133.03, 136.20, 136.95, 137.92, 199.25, 199.95. HRMS (ESI): m/z [M+H]+ for $C_{18}H_{17}IO_2$: exact mass calcd. 393.0352, found 393.0351.

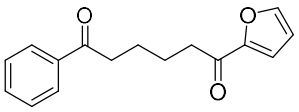
1-(4-(benzyloxy)phenyl)-6-phenylhexane-1,6-dione (3aj')



White solid; $C_{25}H_{24}O_3$; melting point ; yield: 75 %

1H NMR (400M, $CDCl_3$): δ 1.84-1.89 (m, 4H), 2.98-3.09 (m, 4H), 5.16 (s, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 7.36-7.61 (m, 8H), 7.96-8.02 (m, 4H); 13C NMR (100M $CDCl_3$): δ 24.00, 24.15, 38.09, 38.44, 70.14, 114.58, 127.48, 128.05, 128.24, 128.59, 128.71, 130.29, 130.33, 132.98, 136.22, 137.00, 162.55, 198.63, 200.09. HRMS (ESI): m/z [M+H]+ for $C_{25}H_{24}O_3$: exact mass calcd. 373.1782, found 373.1785.

1-(furan-2-yl)-6-phenylhexane-1,6-dione (3ak')

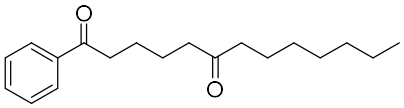


White solid; $C_{16}H_{16}O_3$; yield: 57 %

1H NMR (400M, $CDCl_3$): δ 1.82-1.87 (m, 4H), 2.91 (t, *J* = 8.0, 2H), 3.04 (t, *J* = 8.0, 2H), 6.55 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.20 (d, J = 3.6, 1H), 7.45-7.61 (m, 4H), 7.97 (d, *J* = 7.4, 2H); 13C NMR (100M $CDCl_3$): δ 23.84, 23.87, 38.25, 38.31, 112.19, 116.96,

128.03, 128.60, 133.00, 136.95, 146.28, 152.75, 189.27, 199.97. HRMS (ESI): m/z [M+H]+ for $C_{16}H_{16}O_3$: exact mass calcd. 257.1178, found 257.1177.

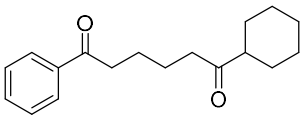
1-phenyltridecane-1,6-dione (3al')



White solid; $C_{19}H_{28}O_2$; yield: 75 %

1H NMR (300M, $CDCl_3$): δ 0.89 (t, *J* = 6.5 Hz, 3H), 1.23-1.37 (m, 8H), 1.52-1.81 (m, 6H), 2.40-2.52 (m, 4H), 2.97-3.03 (t, *J* = 6.9 Hz, 2H), 7.45-7.59 (m, 3H), 7.96 (d, *J* = 7.2 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 14.05, 22.60, 23.46, 23.79, 23.87, 29.06, 29.21, 31.67, 38.34, 42.54, 42.88, 128.01, 128.58, 132.97, 136.69, 199.99, 211.12. HRMS (ESI): m/z [M+H]+ for $C_{19}H_{20}O_3$: exact mass calcd. 286.1268, found 289.1266.

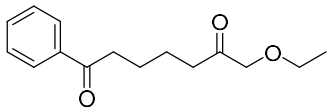
1-cyclohexyl-6-phenylhexane-1,6-dione (3am')



White solid; $C_{18}H_{24}O_2$; yield: 45 %

1H NMR (400M, $CDCl_3$): δ 1.23-1.35 (m, 6H), 1.63-1.85 (m, 10H), 2.31-2.37 (m, 1H), 2.51 (t, *J* = 7.0 Hz, 2H), 2.99 (t, *J* = 7.0 Hz, 2H), 7.46-7.59 (m, 3H), 7.96 (d, *J* = 7.3 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.36, 23.88, 25.68, 25.86, 28.51, 38.42, 40.41, 50.84, 128.02, 128.58, 132.97, 136.96, 200.05, 213.93. HRMS (ESI): m/z [M+H]+ for $C_{18}H_{24}O_2$: exact mass calcd. 273.1855, found 273.1856.

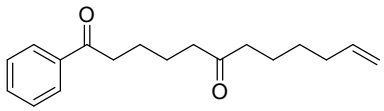
7-ethoxy-1-phenylheptane-1,6-dione (3an')



White solid; $C_{15}H_{20}O_3$; yield: 34 %

1H NMR (300M, $CDCl_3$): δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.67-1.84 (m, 4H), 2.54 (t, *J* = 6.8 Hz, 2H), 3.01 (t, J = 6.8 Hz, 2H), 3.56 (q, *J* = 7.0 Hz, 2H), 7.42-7.62 (m, 3H), 7.96 (d, *J* = 7.5 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 15.01, 22.96, 23.74, 67.16, 75.84, 128.01, 128.59, 132.99, 136.96, 199.92, 208.94. HRMS (ESI): m/z [M+H]+ for $C_{19}H_{20}O_2$: exact mass calcd. 249.1491, found 249.1490.

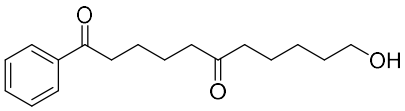
1-phenyldodec-11-ene-1,6-dione (3ao')



White solid; $C_{18}H_{24}O_2$; yield: 47 %

1H NMR (400M, $CDCl_3$): δ 1.36-1.43 (m, 2H), 1.57-1.78 (m, 6H), 2.06-2.12 (m, 2H), 2.41-2.51 (m, 4H), 3.00 (t, *J* = 7.0 Hz, 2H), 4.95-5.05 (m, 2H), 5.77-5.86 (m, 1H), 7.47-7.60 (m, 3H), 7.97 (d, J = 7.3 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.29, 23.45, 23.77, 28.46, 33.51, 38.34, 42.58, 42.65, 114.65, 128.02, 128.59, 133.00, 136.95, 138.49, 199.99, 210.86. HRMS (ESI): m/z [M+H]+ for $C_{18}H_{24}O_2$: exact mass calcd. 273.1855, found 273.1854.

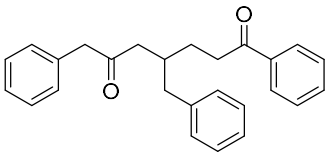
11-hydroxy-1-phenylundecane-1,6-dione (3ap')



White solid; $C_{17}H_{24}O_3$; yield: 75 %

1H NMR (400M, $CDCl_3$): δ 1.34-1.41 (m, 2H), 1.57-1.77 (m, 8H), 2.41-2.50 (m, 4H), 3.0 (t, *J* = 7.1 Hz, 2H), 3.66 (t, *J* = 6.5 Hz, 2H), 7.45-7.60 (m, 3H), 7.96 (d, *J* = 7.7 Hz, 2H); 13C NMR (100M $CDCl_3$): δ 23.42, 23.45, 23.74, 25.34, 32.41, 38.32, 42.62, 42.66, 62.62, 128.02, 128.60, 133.02, 136.93, 200.05, 210.99. HRMS (ESI): m/z [M+H]+ for $C_{17}H_{24}O_3$: exact mass calcd. 277.1804, found 277.1805.

4-benzyl-1,7-diphenylheptane-1,6-dione (3aq')



White solid; $C_{26}H_{26}O_2$; yield: 65 %

1H NMR (300M, $CDCl_3$): δ 1.67-1.82 (m, 2H), 2.35-2.73 (m, 5H), 2.90 (t, *J* = 7.7 Hz, 2H), 3.71 (s, 2H) 7.10-7.36 (m, 10H), 7.40-7.61 (m, 3H), 7.88 (d, *J* = 7.4 Hz, 2H); 13C NMR (75M $CDCl_3$): δ 28.43, 35.29, 36.21, 40.55, 45.97, 50.54, 126.18, 127.03, 128.04, 128.57, 129.26, 129.43, 132.99, 134.09, 136.84, 139.99, 200.00, 207.79. HRMS (ESI): m/z [M+H]+ for $C_{26}H_{26}O_2$: exact mass calcd. 371.2011, found 371.2011.

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