NANYANG TECHNOLOGICAL UNIVERSITY

OXIDATIVE OR METAL-MEDIATED CYCLIZATION APPROACHES TO CARBOCYCLES AND HETEROCYCLES

HE XINYAO

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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A thesis submitted to the Nanyang Technological University in fulfillment of the requirement for the degree of Doctor of Philosophy

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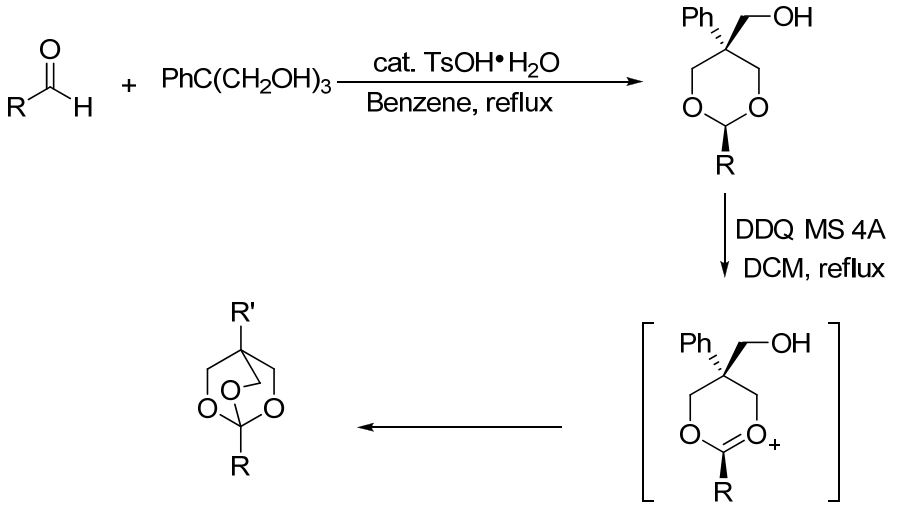
ABSTRACT

Cyclic organic compounds especially heterocyclic compounds occupy an important position in organic chemistry. They are widely used in synthetic chemistry, fine chemical industry, biological chemistry and material science. The synthesis of carbo/heterocycles has been extensively studied and a huge number of strategies have been demonstrated. Considering the tremendous demand of various carbo/heterocycles, it is still highly desirable to develop novel and efficient methodologies. The author aimed to develop new reactions for the construction of carbocylces and heterocycles. Oxidative cyclization and metal-mediated cyclization to carbo(hetero)cycles are two useful strategies to construct them. Two parts are covered in this thesis: **Part I** (chapters 1 and 2) contains oxidative generation of acyl cation equivalent and application to the synthesis of aromatic orthoesters and ketones. **Part II** (chapter 3) contains $W(CO)_6$-mediated 7-*endo* cyclization to heterocycles.

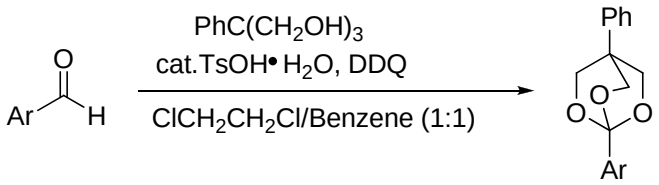
Part I (chapter 1 and 2): Oxidative cyclization approach to heterocycles and carbocycles

Intramolecular oxidative cyclization reaction is very useful method for the synthesis of carbocycles and heterocycles such as DDQ-mediated oxidative cyclization reactions. We are interested in synthesizing useful and valuable targets using this method. As well known, orthoesters are important building blocks in organic synthesis and have been widely used as masked carboxylic acids and esters. Traditionally, orthoesters were prepared from nitriles, imino esters, or by orthoester exchange. However, there are still some limitations in the conventional synthetic methods of orthoesters, for example, harsh reaction conditions, low yields, together with side reactions. Based on the

above-mentioned remarks, more efficient and convenient methods for preparation of orthoesters are highly desirable. Thus, the author started the research on the synthesis of orthoesters. Until now, there is no report for preparation of orthoesters directly by reaction of carboxylic acids or esters with alcohols under acid catalysis, although it seems to be a direct and easy way. The author described DDQ-mediated oxidative preparation of bicyclic aromatic orthocarboxylates from aldehydes in chapter 1.



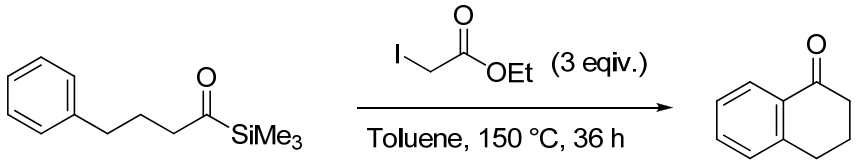
This method provides a convenient access to bicyclic orthoesters. Aromatic orthoesters could be readily prepared from the corresponding aldehydes in high yield, and various functional groups were well tolerated under these conditions. Moreover, one-pot synthesis of aromatic orthoesters from aldehydes was also achieved without isolation of the intermediate hydroxyl acetal, and good yields were obtained.



In chapter 2, α-halo ester-mediated oxidative cyclization to carbocycles was described. Selective and efficient functionalization of the unactive aromatic C–H bonds of

organic molecules into ketone is a challenging work in organic chemistry, which has been paid huge attention recently.

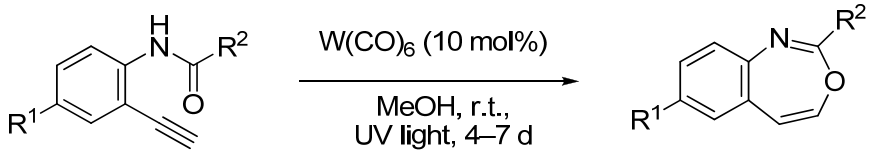
Interestingly, the author found the α-tetralone could also be produced in the presence of ethyl α-haloacetate.



This oxidative cyclization method provides a simple, facile access to carbocycles, α-tetralone could be oxidatively synthesized from the corresponding acylsilane with ethyl iodoacetate. The reaction which the author found is carbon-carbon bond formation with activation of both carbon-hydrogen bond and carbon-silicon bond. It is noteworthy because there is no report on a coupling reaction between C–H compound and organometallic reagents. Additionally, the reaction proceed without any strong Lewis acid or transition-metal which are necessary in the classical Friedel-Craft acylation reactions and transition-metal catalyzed acylation reactions.

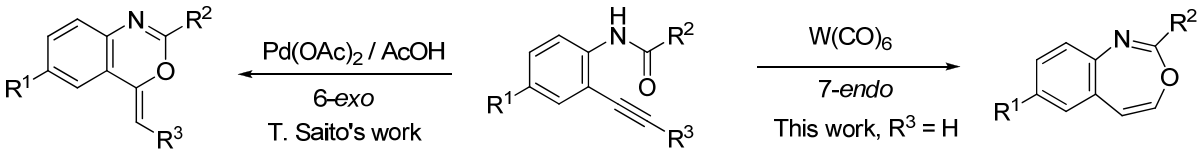
Part II (chapter 3): Metal-mediated cyclization approach to heterocycles

Metal-mediated cyclization reaction is one of the important methods to synthesis heterocycles. In chapter 3, the author described a $W(CO)_6$-mediated intramolecular cyclization reaction from *o*-alkynylphenyl derivatives to afford 7-membered nitrogen-containing heterocyclic compound 3,1-benzoxazepines, which are of great importances in biological and medicinal chemistry due to their unique bioactivity.



R^1 = alkyl, alkoxyl, halide, nitrile
R^2 = aryl, alkyl, benzyl

In this work, 6-membered ring products were not detected, and the highly regioselective 7-membered ring cyclic products were obtained in high yield, which exhibit interesting biological reactivities. A variety of substrates were well tolerated under the mild reaction conditions and gave the corresponding 3,1-benzoxazepines derivatives in moderate to good yields. In other word, this method provided a simple way to construct 7-membered heterocycles efficiently and regioselectively via tungsten-mediated cyclization reaction.



Keywords: orthoester, oxidation, DDQ, acetal, aldehyde, one-pot reaction, acylsilane, cyclization.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

δ	chemical shift
°C	degree centigrade
Ac	acetyl
Ar	Aryl
AcCl	acetyl chloride
AcOH	acetic acid
aq.	aqueous
Ar	aryl
Bn	benzyl
Cat.	catalytic
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichoromethane
CCl_4	Carbon tetrachloride
cm^{-1}	inverse centimeter
DCM	dichloromethane
d	doublet
DCE	dichloromethane
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
FG	Functional group
FTIR	Fourier Transform Infrared Spectrometry
g	gram
h or hrs	hour(s)
H	hydrogen
Hex	hexane
HF	hydrogen fluoride
HRMS	high resolution mass spectrometry
Hz	Hertz

i-Pr	Isopropyl
IR	infrared
J	coupling constants
kg	kilogram
L	ligand
LA	Lewis acid
m	multiplet
m/z	mass per charge ratio
M	concentration (mol/dm^{-3})
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	mega hertz
min	minute(s)
mL	millilitres
mmol	millimole
mol%	mole percent
N.R.	no reaction
Ph	phenyl
ppm	parts per million
q	quartet
rt.	room temperature
s	singlet
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

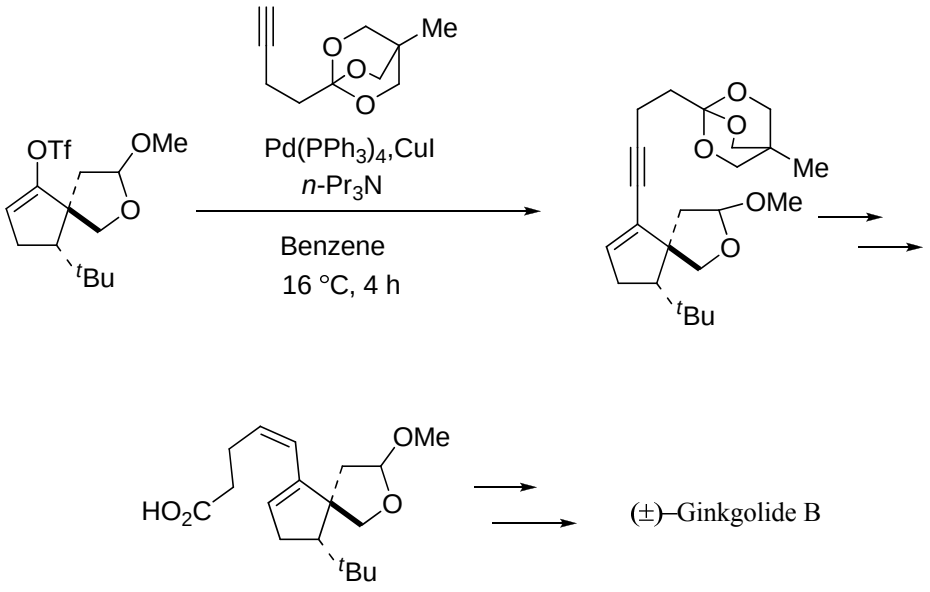
PART I

CHAPTER 1

Oxidative Preparation of Orthoester

1.1 Introduction

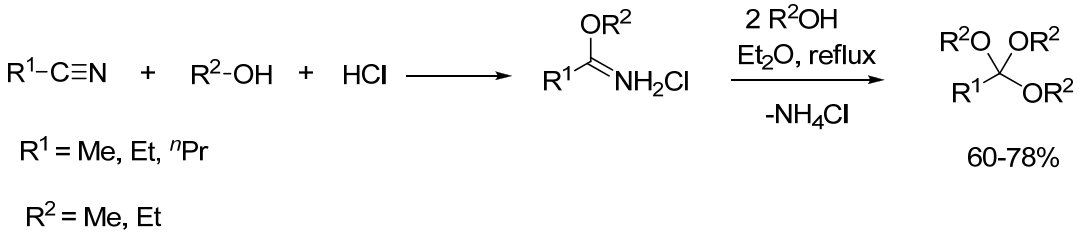
Orthoesters with the formula $RC(OR')_3$ are substances containing three alkoxy groups attached to one carbon atom. Due to its stability towards nucleophiles and strong bases and easiness for the conversion into carboxylic acid derivatives by acidic solvolysis,[1] orthoesters have been widely used as masked carboxylic acids and esters.[2] Meanwhile, they are important building blocks in organic synthesis.[3] Amongst orthoesters, bicyclic orthoesters are especially useful and widely used as masked carboxylic acid in total synthesis, due to their chromatographic stability when comparig with acyclic orthoesters. For example, total synthesis of (±) Grinkgolide B was developed by Elias James Corey (Scheme 1-1),[4] acetylenic OBO orthoester was introduced as the protecting group for carboxylic acid in the base condition during the course of synthesis, considering that it is base stable and easy to be cleaved under mild conditions.



Scheme 1-1. Total synthesis of (±)-Ginkgolide B

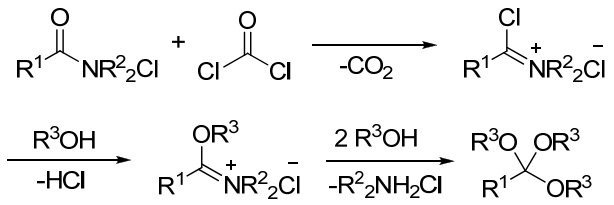
Recently some bicyclo orthoesters have been found to be highly potent insecticides.[5] In addition, it was found that some bicyclic orthoesters can be used for polymeric materials,[6] which can offer environmentally-friendly recycling systems.

Traditionally, orthoesters are prepared from nitriles,[7] imino esters,[8] or by orthoester exchange.[9] As shown in Scheme 1-2, orthoesters can be prepared through the reaction of nitriles with alcohols and anhydrous hydrogen chloride, involving alcoholysis of the iminoester hydrochloride. However, orthoesters were generally obtained in low yields under harsh reaction conditions using this method. Moreover, its major disadvantage is that the intermediates of iminoester hydrochlorides are easily decomposed to amides and alkylhalides.



Scheme 1-2. Synthesis of orthoesters from nitriles and alcohols

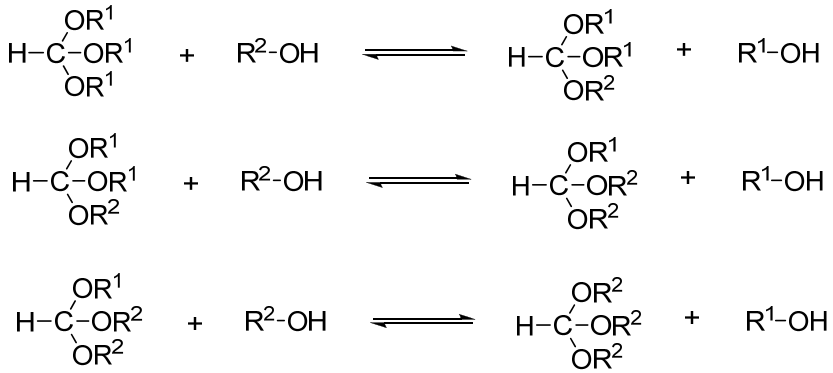
Orthoesters can also be prepared from *N*,*N*-disubstitutedcarboxamides, as presented in Scheme 1-3. Similarly, the intermediates of iminoester hydrochlorides also tend to decompose to amides and alkyl halides.



Scheme 1-3. Synthesis of orthoesters from amides and alcohols

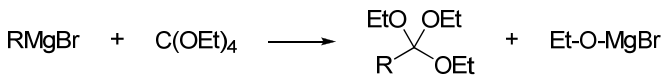
Orthoester exchange is also a generally practical method for the preparation of orthoester, as shown in Scheme 1-4. It is a good way to prepare orthoesters from most primary alcohols in the presence of hydrogen chloride or sulfuric acid. However,

Orthoester exchange involving secondary and tertiary alcohols will probably be influenced by steric hindrance, resulting in a decrease of the scope of this method.



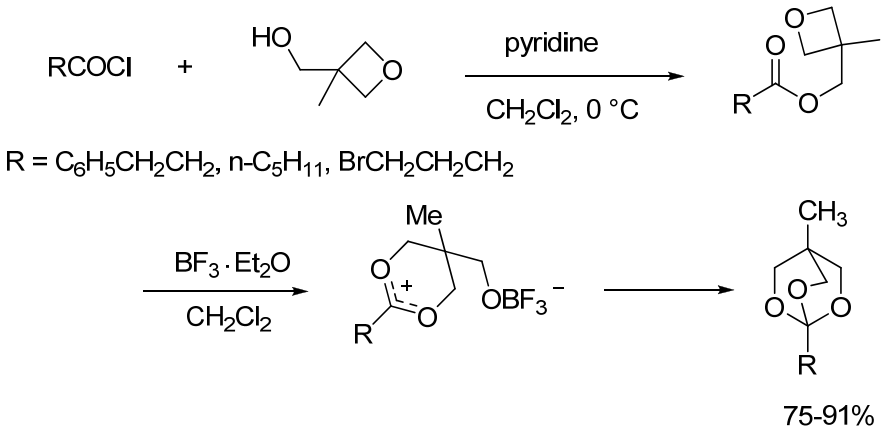
Scheme 1-4. Synthesis of orthoesters by ester exchange

As depicted in Scheme 1-5, the reaction of orthocarbonates with Grignard reagents is also one of the conventional methods for preparing orthoesters. Generally, Grignard reagent can't be prepared from the organohalides, which bear reactive functional groups or acidic protons. In this case, the limitation of preparation for Grignard reagents reduces the scope of this protocol.



Scheme 1-5. Synthesis of orthoesters from orthocarbonates and Grignard reagents

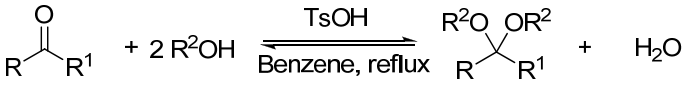
Previously, bicyclic orthoesters have been prepared by an ester interchange reaction involving a triol and a noncyclic ortho ester.[10] However, its preparation is limited to the ones from reactive carboxylic acid derivatives. In 1983, E. J. Corey and N. Raju developed a practical synthetic method for preparation of orthoesters from carboxylic acids by the esterification of carboxylic acids and 3-hydroxymethyl-2-methyloxetane and successive nucleophilic attack on the ester carbonyl on the oxetane ring by a Lewis acid catalyst (Scheme 1-6),[11] which has been widely used as protected carboxylic acid equivalents, especially for natural product synthesis.[12]



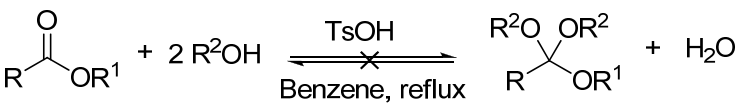
Scheme 1-6. Synthesis of orthoesters from carboxylic acids

Based on the above-mentioned remarks, more efficient and convenient methods for preparation of orthoesters are highly desirable, since that there are still some limitations in the conventional systems, such as low yields, undesirable side reactions, limited substrate scope and relatively harsh reaction conditions.

It's well known that carbonyl group of a ketone can be easily protected via its reaction with two equivalents of alcohols to form an acetal (Scheme 1-7). However, it is impossible to protect carboxylic acid ester as an orthoester in similar way (Scheme 1-8). Up to now, there is no report on the synthesis of an orthoester from carboxylic acids or esters with alcohols using the method employed for acetal formation. So we are interested in finding a new strategy for preparation of orthoester based upon the study of this case.



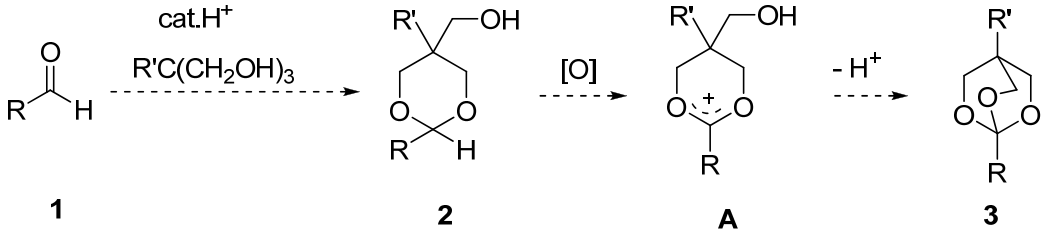
Scheme 1-7. Synthesis of acetal from ketone and alcohol



Scheme 1-8. Synthesis of orthoester from ester and alcohol

As mentioned above, orthoesters cannot be prepared from the corresponding carboxylic esters and alcohols by the acid-catalyzed strategy used for acetal synthesis. However, if the corresponding aldehyde was used instead of the ester under an oxidative condition, followed by the nucleophilic attack of an alcohol to the carbocation, which gave an orthoester from the corresponding aldehyde and alcohol directly.

With the above idea, the conversion of an aldehyde into a bicyclic orthoester **3** was supposed to proceed through acetal formation, oxidation and nucleophilic substitution (Scheme1-9),[13] the key step is to generate the intermediate **A** by the oxidation of hydroxyacetal **2**, which could be easily prepared from an aldehyde and a triol under acid-catalyzed azeotropic conditions.



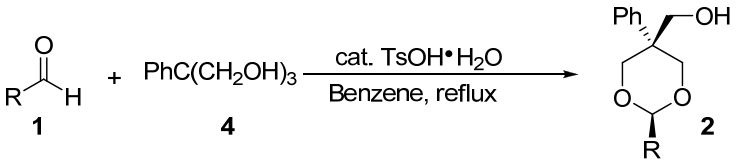
Scheme 1-9. Transformation of aldehyde into bicyclic orthoester

1.2 Results and Discussion

1.2.1 Synthesis of hydroxyacetals

To confirm the hypothesis of the conversion of hydroxyacetals **2** into orthoesters **3**, hydroxyacetals **2** were prepared from the corresponding aldehydes and a triol **4**[14] in good yields as a mixture of diastereoisomers in 10:1 to 7:1 ratio (Table 1-1). The major isomers were isolated by silica gel column chromatography (hexane:EtOAc = 4:1) followed by recrystallization (hexane –EtOAc).

Table 1-1. Preparation of Hydroxy Acetal**2**[a]



Entry	R	Product	Yield (%)[b, c]
1	naphthalen-2-yl **(1a)**	**2a**	72
2	4-$Me_2NC_6H_4$ **(1b)**	**2b**	81
3	4-$MeOC_6H_4$ **(1c)**	**2c**	79
4	4-MeC_6H_4 **(1d)**	**2d**	73
5	Ph **(1e)**	**2e**	80
6	4-BrC_6H_4 **(1f)**	**2f**	69
7	4-$MeO_2CC_6H_4$ **(1g)**	**2g**	71

[a] Reaction conditions: aldehyde 1 (10 mmol), triol 4 (12.5 mmol), $TsOH \cdot H_2O$ (0.2 mmol), benzene (40 mL), reflux. [b] Isolated yield of a major diastereoisomer separated by column chromatography and recrystallization (hexane – EtOAc). [c] The relative stereochemistry of the major product was determined by NOESY analysis.

The relative stereochemistry of the major product was determined by NOESY analysis (Figure 1-1). The key hydrogen at the 2-position in benzene ring provides clear evidence of the relative stereochemistry of the ring substituent. An axial orientation of the hydrogen at 2-position in minor product generates unfavourable steric interaction, NOE spectroscopy for minor product gave no correlations between the 2-position proton and Ha, the result revealed that the 1,3-dioxane moiety faced the benzene ring.

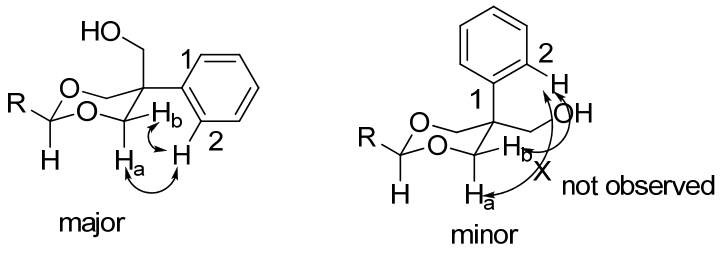
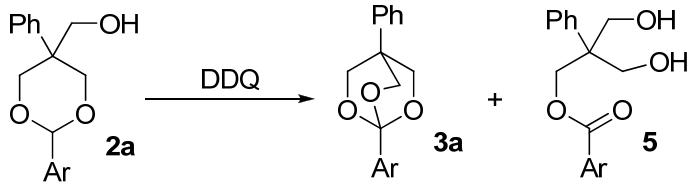


Figure 1-1. Determination of stereochemistry for hydroxyester

1.2.2 Optimization of the Reaction Conditions

Then, the oxidation of the isolated hydroxyacetals **2** was examined to convert to bicyclic orthoesters. Herein, various oxidants were examined, such as *N*-bromosuccinimide (NBS),[15] cerium ammonium nitrate (CAN)[16] and $Pd(OAc)_2/O_2$.[17] Finally dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was found to be the best choice for this purpose.[18] Investigations of solvents and reaction temperatures in the reactions of hydroxyacetal **2a** with DDQ were summarized in Table 1-2. When acetonitrile was used as solvent, no products were observed, and the hydroxyacetal **2a** was recovered in 88% yield (entry 1). When toluene was used, dihydroxy ester **5** was isolated in 30% yield, along with 58% of recovery of the starting material **2a** (entry 2). When the oxidation was performed in halogenated solvents, the desired orthoester **3a** could be produced along with dihydroxy ester **5**. For example, the orthoester **3a** could be obtained in 20% yield in dichloromethane at room temperature, however, with 41% yield of **5** and 21% of the starting material **2a** (entry 3). At higher temperature, the yield of desired product **3a** was improved dramatically (entries 4-7). Finally, we found the oxidation in refluxing 1,2-dichloroethane solvent in the presence of MS4A gave the orthoester **3a** in 94% yield.

Table 1-2. Optimization of Oxidative Preparation of Orthoester **3a**[a]



Ar = Naphthalen-2-yl

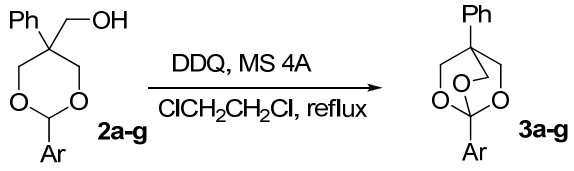
Entry	Solvent	Temp. (bp)[b]	Time (h)	Orthoester **3a** (%)	Ester **5** (%)	Recovery **(2a)** (%)[c]
1	CH_3CN	r.t.	14	0	0	88
2	Toluene	r.t.	20	0	30	58

3	CH_2Cl_2	r.t.	10	20	41	21
4	CH_2Cl_2	reflux(40 °C)	8	62	24	7
5	CCl_4	reflux(77 °C)	12	72	14	0
6	CCl_4[d]	reflux(77 °C)	4	87	12	0
7	$ClCH_2CH_2Cl$[d]	reflux(84 °C)	5	94	6	0

[a] Reaction conditions: hydroxyl acetal **2a** (0.2 mmol), DDQ (0.24 mmol), solvent (5 mL). [b] Boiling point of the solvent. [c] Numbers in parentheses show recovery of the starting material **2a**. [d] 4 Å MS added (100 mg/0.2 mmol of **2a**).

With these information in hand, the transformation of various aromatic hydroxyacetals to the corresponding orthoesters was examined under the above optimized reaction conditions (Table 1-3). In the cases of electron rich aromatic acetals, the reactions were proceeded smoothly and the desired orthoesters were obtained in high yields (entries 2-4). Notablely, hydroxyl acetal **2b** having a p-dimethylaminophenyl group, was consumed rapidly at room temperature to give the desired orthoester **3b** in 93% yield (entry 2). On the other hand, electron deficient arylacetals **2e** and **2f** required longer reaction times to prepare orthoesters **3**, together with lower yields. Even in such cases, high yields were achieved by the use of excess amounts of DDQ (entries 5 and 6). Hydroxyacetal **2g** (entry 7), having a *p*-MeO_2C group, however, was not easily oxidized even by excess of DDQ and resulted in only a 14% yield of orthoester **3g**. Not only aromatic substrates, hydroxyacetal **2h** derived from an alkenyl aldehyde also gave the corresponding orthoester **3h** in high yield (entry 8).

Table 1-3. Preparation of Orthoester from HydroxyAcetal[a]



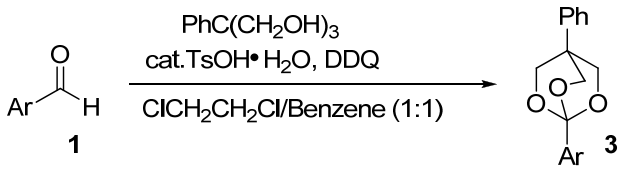
Entry	HydroxyAcetal **2** Ar	DDQ[b]	Time (h)	Orthoester **3** (%)[d]
1	naphthalen-2-yl **(2a)**	1.2	5	94 **(3a)**
2[c]	*p*-$Me_2NC_6H_4$ **(2b)**[c]	1.2	0.5	93 **(3b)**
3	*p*-$MeOC_6H_4$ **(2c)**	1.2	7	92 **(3c)**
4	*p*-MeC_6H_4 **(2d)**	2.0	20	78 **(3d)**
5	C_6H_5 **(2e)**	10.0	7	79 **(3e)**
6	*p*-BrC_6H_4 **(2f)**	10.0	11	89 **(3f)**
7	*p*-$MeO_2CC_6H_4$ **(2g)**	10.0	10	14 **(3g)**
8	2-Phenylethen-1-yl **(2h)**	1.2	0.2	93 **(3h)**

[a] Reaction conditions: hydroxyl acetal **2** (0.2 mmol), DDQ (0.24-2.0 mmol), 4 Å MS (100 mg), DCE (5 mL). [b] Numbers show the molar amounts of DDQ. [c] Reaction was performed at r.t. [d] Isolated yield

From the above experiments, it is noted that hydroxyacetals **2** can be easily prepared from aromatic aldehydes with a triol in the presence of a catalytic amount of protic acid. And they are easily converted into orthoesters by the treatment with DDQ in dichloroethane. For the aim of a simple operation, an in situ method was expected to be tested. Based on this consideration, one-pot preparation was attempted to prepare orthoester from aldehydes without the isolation hydroxyacetals.

When naphthalenecarbaldehyde **1a** was treated with triol **4** and a catalytic amount of toluenesulfonic acid hydrate ($TsOH \cdot H_2O$) in the presence of 1.2 equivalents of DDQ and then heated at reflux temperature in a mixed solvent of dichloroethane/benzene (1:1), orthoester **3a** was obtained in 92% yield (Table 1-4, entry 1). However, *p*-dimethylaminobenzaldehyde **1b** and cinnamaldehyde **1h** were found to be easily oxidized by DDQ before the acetalization and gave complex mixtures. When DDQ was added after the complete acetalyzation of these aldehydes, the desired orthoesters **3b** and **3h** were obtained in good yields (entries 2 and 5)

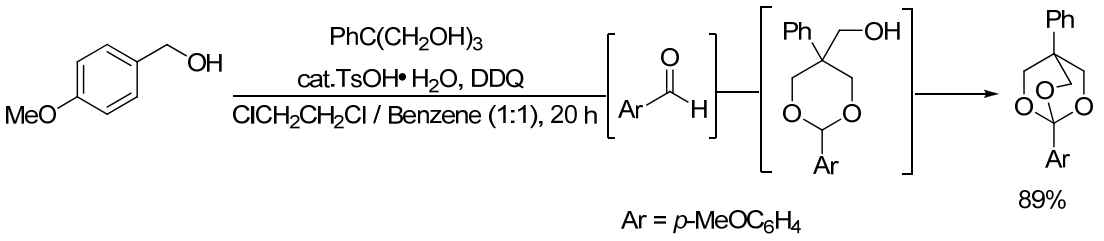
Table 1-4. One-Pot Preparation of Aromatic Orthoester from Aldehyde[a]



Entry	Ar	Time (h)	Orthoester **3** Yield (%)
1	Naphthalen-2-yl (**1a**)	20	92 (**3a**)
2[b]	*p*-$Me_2NC_6H_4$ (**1b**)	10[c]	92 (**3b**)
3	*p*-$MeOC_6H_4$ (**1c**)	24	90 (**3c**)
4	*p*-MeC_6H_4 (**1d**)	24	87 (**3d**)
5[b]	2-Phenylethen-1-yl (**1h**)	20	99 (**3h**[c])

[a] Reaction conditions: aldehyde **1** (0.5 mmol), triol **4** (0.55 mmol), DDQ (0.55 mmol), $TsOH·H_2O$ (0.055 mmol) with Soxhlet filled with 4 Å MS. [b] DDQ was added after the confirmation of complete consumption of aldehyde. [c] The reaction time after the addition of DDQ.

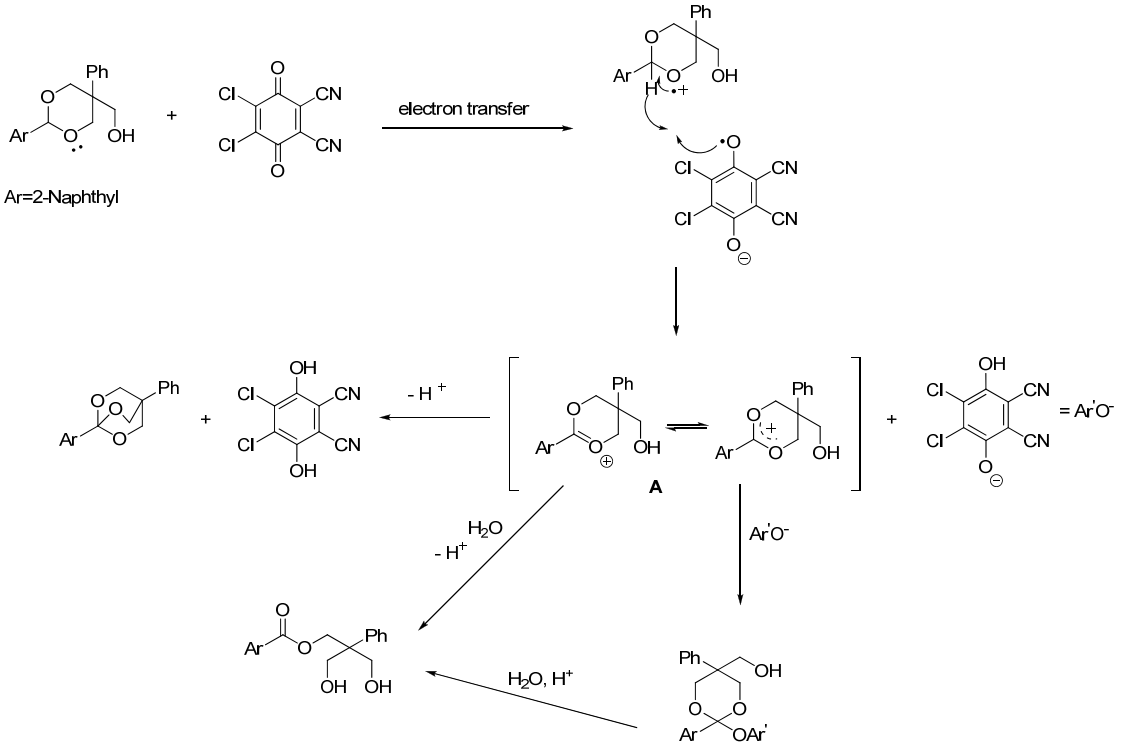
Finally, orthoesters were expected to be prepared from the benzyl alcohols instead of aldehydes, expecting that such alcohols would be oxidized to aldehydes by DDQ. As DDQ is known as the deprotection reagent for *p*-methoxybenzyl (PMB) ether,[19] we attempted the conversion of *p*-methoxybenzyl alcohol to bicyclic acetal **2c** (Scheme 1-10). When *p*-methoxybenzyl alcohol was treated with triol **4**, DDQ, and a catalytic amount of $TsOH·H_2O$ in a mixed solvent of 1,2-dichloroethane and benzene (1:1), the corresponding orthoester **3c** was obtained in 89% yield.



Scheme 1-10. One-pot preparation of aromatic orthoester from alcohol

1.2.3 Proposed mechanism

As mentioned above, orthoester **3a** and dihydroxy ester **5** were formed at room temperature in the presence of DDQ from hydroxyacetal **2a**. A possible mechanism for the formation of orthoester and dihydroxy ester is proposed in Scheme 1-11. A single electron transfer from the hydroxyacetal to DDQ generates a radical cation and a DDQ radical anion. Then the radical oxygen of the DDQ radical anion abstracts a H-atom from the radical cation and generates a hydroxyacetal cation, and the anionic oxygen of DDQ radical anion. Finally, intramolecular nucleophilic cyclization generates the desired orthoester product. There are two possible mechanisms for the formation of dihydroxy ester, one is produced by the attack of water in the reaction system to intermediate **A**, follow by deprotonation. Another is that oxonium intermediate was firstly trapped by dihydroquinone generated by the oxidation and then hydrolysed in the workup process.

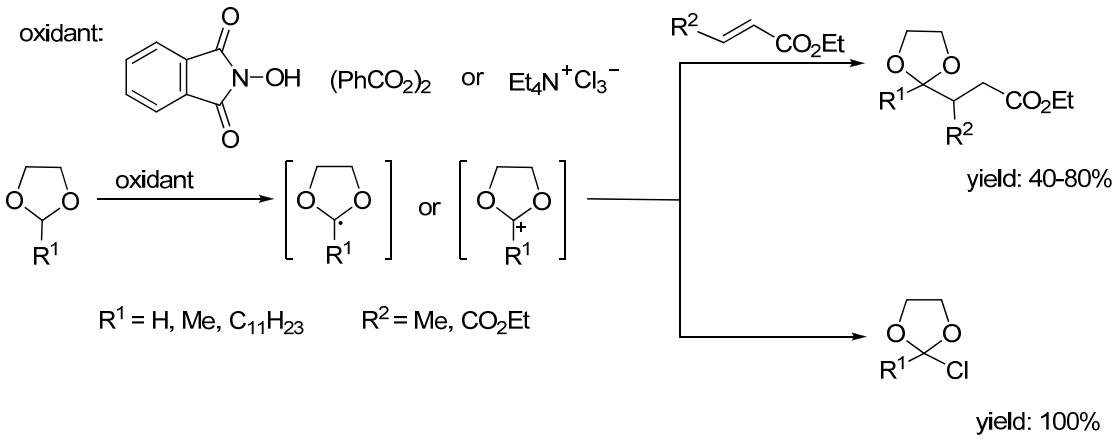


Scheme 1-11. Proposed mechanism for the formation of orthoester and dihydroxy ester

1.3 Conclusion and Future work

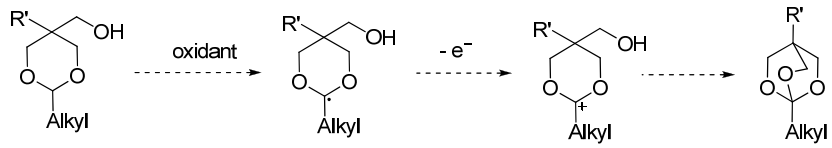
An oxidative method to prepare orthoesters from aldehydes was developed. By means of the in situ method, an efficient and convenient one-pot synthesis of orthoesters from aldehydes was realized in this work. Further attempts to synthesize orthoesters via direct C–H bond activation will be investigated.

Thus the practical method was developed to synthesize orthoesters from aromatic aldehydes by using DDQ as the oxidant. However, this oxidative method has a drawback, that is, it is only applicable for the synthesis of aromatic orthoesters. Aliphatic orthoesters can't be formed because acetals derived from aliphatic aldehydes are not easily oxidized by DDQ. We considered that aliphatic orthoesters would be prepared by choosing the appropriate oxidizing reagent. It is known that the combination of *N*-hydroxyphthalimide and benzoylperoxide generates 2-dioxolanyl radicals from acetals derived from aliphatic aldehydes, which in turn can react with electron deficient alkenes.[20] (Scheme 1-12). Similarly, the functionalization of 2-position of 2-alkyl-substituted dioxolane is possible by using tetraethylammoniumtrichloride[21] (Scheme 1-12). These results indicate that appropriate oxidizing reagents may realize the formation of aliphatic orthoesters from the hydroxyacetals (Scheme 1-13).



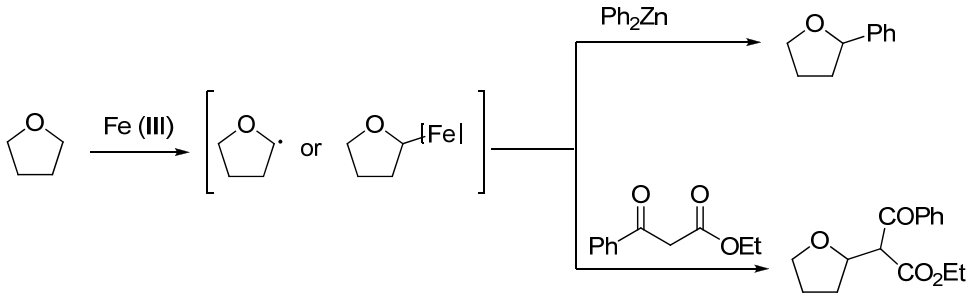
Scheme 1-12. Functionalization of acetals

Future work:



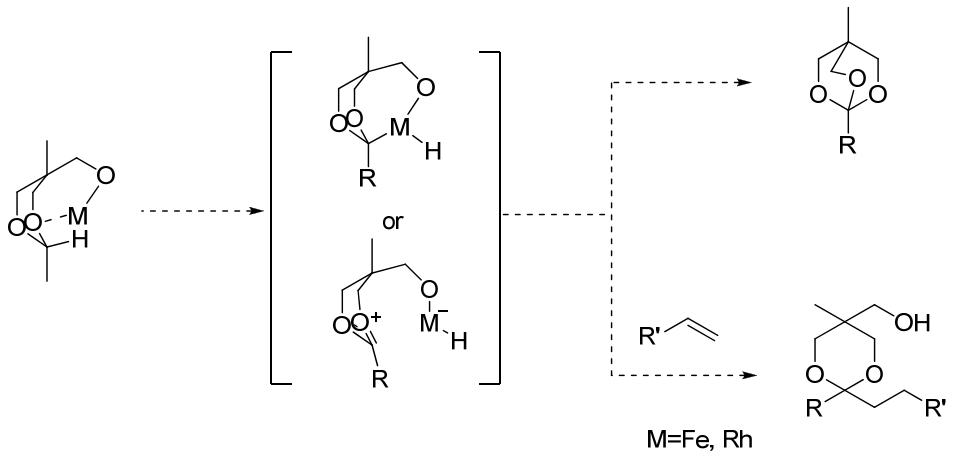
Scheme 1-13. Oxidative preparation of aliphatic orthoester

We are also interested in the possible transition-metal-catalyzed reaction using the hydroxy group in hydroxyacetals as the directing group. It is known that the C–H bond adjacent to an oxygen atom can be activated by iron, rhodium or copper catalysts.[22] The activation is used for functionalization of ethers (Scheme 1-14). If the hydroxy group in the hydroxyacetals can be used as a directing group, the functionalization of acetals would be achieved under milder reaction conditions. This methodology would provide not only the preparation for orthoesters but also the methods to introduce protected carbonyl groups to various organic compounds such as alkenes and alkynes (Scheme 1-15).



Scheme 1-14. Transition metal-catalyzed α-functionalization of cyclic ether

Future work:



Scheme 1-15. Hydroxy-directed functionalization of acetals

PART I

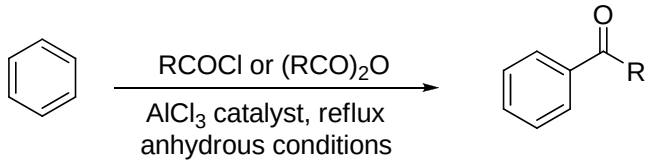
CHAPTER 2

Oxidative Cyclization of 4-Phenylbutanoylsilane to Prepare α-Tetralone

2.1 Introduction

Functionalization of unactive aromatic C–H bonds of organic molecules is a challenging work in organic chemistry. Selectivity and efficiency are most important topics to achieve useful functionalized molecules, which have attracted huge attention recently. Many progress has been achieved in this area in the past decades.[23]

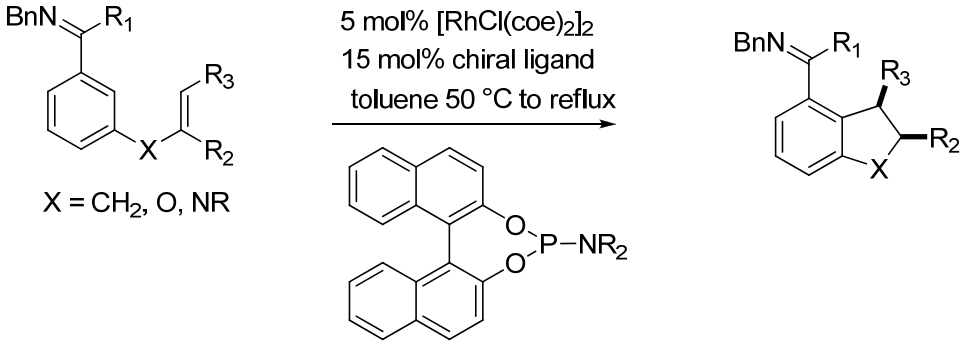
Classic conversion of aromatic C–H bonds into C=O bonds relies on Friedel-Crafts reaction, which generally requires a stoichiometric amount of the Lewis acids and absence of moisture. The general Friedel-Crafts reaction is shown as below (Scheme 2-1).



Scheme 2-1. Friedel-Crafts reaction

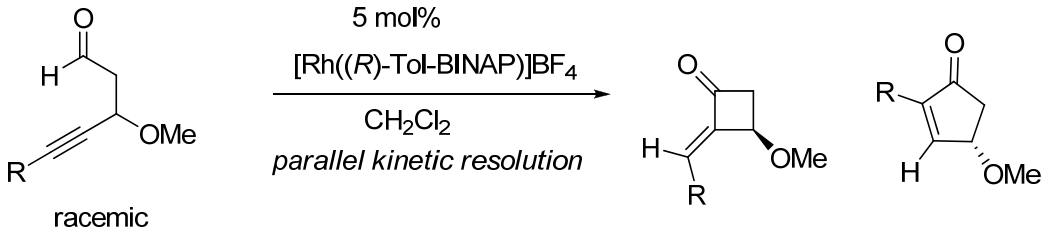
Transition-metal catalyzed functionalization of aromatic C–H bonds has been developed within recent years, which has been regarded as one of the most valuable synthetic methods for C–C formation. Among many processes in C–H activation, rhodium catalysts have been reported as a powerful tool. However, only a handful amount of reports described aromatic C–H bonds were activated by rhodium catalyst for the new C–C bonds formation.

Bergman and Ellman reported intramolecular C–H bond activation and cyclization reactions with Rhodium catalyst in 2004 (Scheme 2-2).[24] They developed a highly intramolecular hydroarylation of alkenes via directly C–H bond activation using a Rh/chiral phosphoramidite catalyst system. In this C–H bond activation reaction, the variety of enantioselectivity is still under challenge.



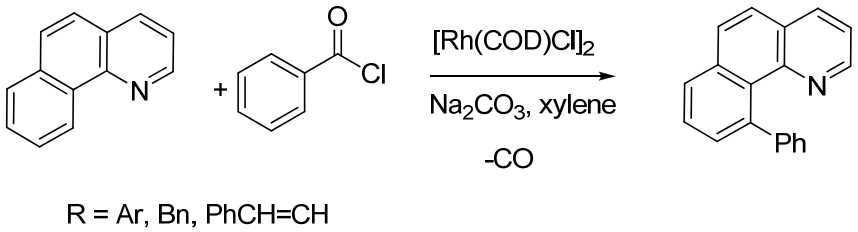
Scheme 2-2. Rhodium catalyzed intramolecular cyclization of alkenes

In 2007, a versatile catalytic method for the synthesis of cyclopentenones was reported by Fu and co-workers with a new catalytic system.[25] The cyclopentenones were synthesized from 4-alkynals through intramolecular hydroacylation. The substrate scope was expended greatly which represented a versatile method for the synthesis of cyclo pentenones. Later, the same group reported Rh(I)/(Tol-BINAP)-catalyzed cyclization of 4-alkynals, which can furnish enantioenriched cyclobutanones and cyclopentenones (Scheme 2-3).[26]



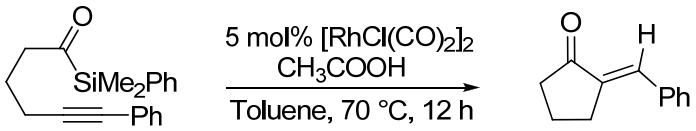
Scheme 2-3. Rhodium-catalyzed formation of cyclobutanones and cyclopentenones

In 2008, Yu and co-workers reported an efficient Rh-catalyzed functionalization of aromatic C–H bonds reaction using acid chlorides as the coupling partners under phosphine-free condition (Scheme 2-4).[27] In this work, the ionic rhodium(I) salt $Rh(COD)_2BF_4$ and Wilkinson's catalyst showed poor catalytic activity. Moreover, a phosphine ligand, which presented in the reaction system such as PPh_3, retarded the coupling reaction.



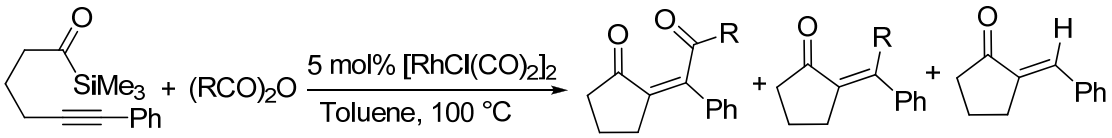
Scheme 2-4. C–H functionalization via decarbonylation and C–H bond activation

In 2001, our group reported a rhodium(I)-catalyzed desilylative cyclization of 5-alkynoylsilanes reaction (Scheme 2-5). In the presence of acetic acid and a catalytic amount of $[RhCl(CO)_2]_2$, 5-alkynoylsilanes were converted into α-alkylidenecyclopentanone derivatives. The reaction proceeded with acylsilanes bearing a dimethylphenylsilyl group and without any functionalizations on the silicon atom nor addition of expensive activation reagents such as fluoride salts, which is significant to achieve conventional palladium-catalyzed coupling reaction of organosilicon compounds with organic halide.



Scheme 2-5. Rhodium-catalyzed acylation of alkyne with acysilane

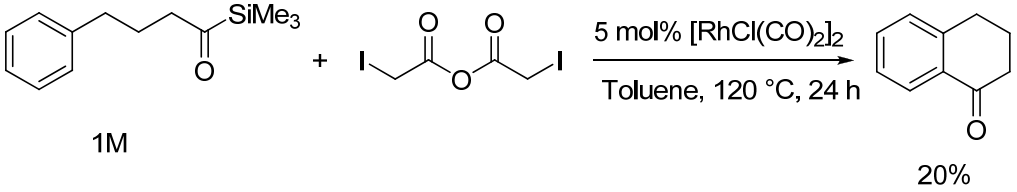
Recently, cross-coupling reactions between alkynoylsilanes and various anhydrides have been explored in our group using $[RhCl(CO)_2]_2$ catalyst (Scheme 2-6). Acid anhydrides provided double acylation to the alkyne part of alkynoylsilane to give three different cyclopentanes.



Scheme 2-6. Rhodium-catalyzed acylation between alkynoylsilane and acid anhydride

Altogether, functionalization of inert aromatic C-H bonds has been a competed area and the development of new capable approach to catalytically transform the inert aromatic C–H bonds into more useful functional group is still challenging. Our further aim is to synthesis more useful molecules, such as functionalized carbocycles, through direct C–H activation.

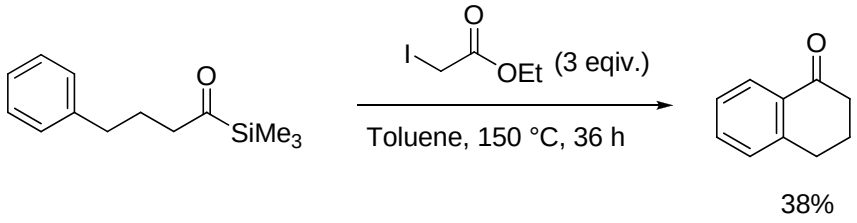
As part of our ongoing research on the development of efficient methods to construct the C–C bonds, we became interested in the direct cross-coupling of acylsilane with simple arenes. Recently, an interesting C–H activation reaction was found accidently during the course of development the transition metal-catalyzed reaction of acylsilanes with various anhydrides in our group. *α*-Tetralone was obtained from treatment of 4-phenylbutanoylsilane with 2-iodoacetic anhydride in the presence of rhodium catalyst (Scheme 2-7). This is a new kind of cross-coupling of acylsilane with non-functionalized arenes without any report previously. We dedicated our further efforts to explore more suitable condition details.



Scheme 2-7. Intramolecular annulation of acylsilane catalyzed by rhodium

Interestingly, we found that the α-tetralone could be produced even without rhodium catalyst during the course of our studies of rhodium-catalyzed C–H acylation with acylsilane (Scheme 2-8). This provided one of more facile and efficient accesses to carbocycles, *α*-tetralone could be oxidatively synthesized from the corresponding acylsilane with ethyl iodoacetate. The reaction which we found is C–C bond formation with activation of both carbon-hydrogen bond and carbon-silicon bond. It is

noteworthy because there is no report on a coupling reaction between C–H compound and organometallic reagents.

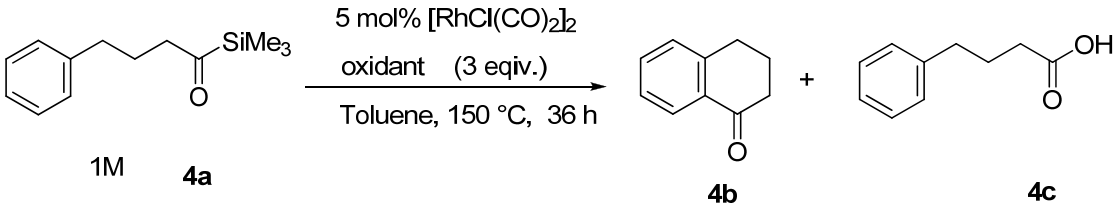


Scheme 2-8. Intramolecular cyclization of acylsilane with α-haloester

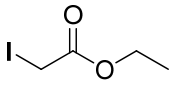
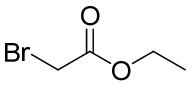
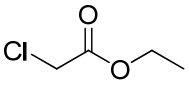
2.2. Results and Discussion

To initiate our study, acylsilane **4a** was employed as the model substrate, which could be prepared according to the reported procedure. As summarized in Table 2-1, the combination of 1 equiv of **4a** with 3 equiv of ethyl iodoacetate in the presence of 5 mol% $[RhCl(CO)_2]_2$ in a sealed tube in toluene at 150 °C for 36 h, the desired product **4b** was produced in 60% yield along with carboxylic acid **4c** in 25% yield. At the same time, an unidentified compound was also obtained; further efforts are needed to clarify the structure of this unknown compound (Table 2-1, entry 1). Other different oxidants were also examined at 150 °C in toluene solvent (entries 2-6). All the other α-halo esters were found to be ineffective, since no desired product **4b** was obtained in these cases (entries 2-4). This may suggest that the α-chloro and α-bromo esters might be unreactive enough to promote such cyclization reaction. When inorganic salt such as copper chloride was employed as an oxidant, carboxylic acid **4c** was obtained in 40% isolated yield instead of the desired product **4b**, suggesting inorganic salts were not suitable for the C–H activation of acylsilane (entries 5 and 6).

Table 2-1 Screening the oxidant[a]



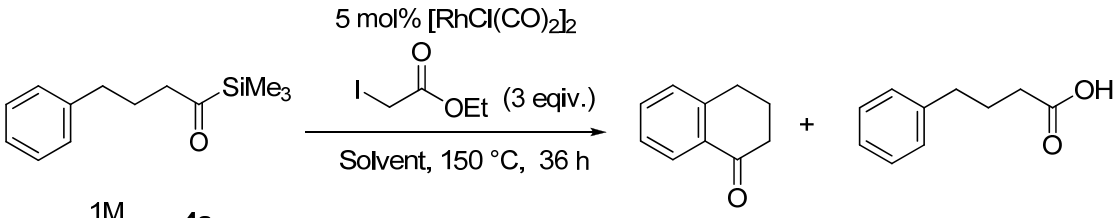
1M **4a** **4b** **4c**

Entry	Oxidant	Yield of **4b** (%)[b]	Recovery of **4a** (%)[b]	Yield of **4c** (%)[c]
1		60	0	25
2		0	0	0
3		0	78	0
4	CCl_3COCCl_3	0	0	0
5	$CuCl_2$	15	0	40
6	$CuCl_2/O_2$	15	0	40

[a] The reaction concentrations are in 1 mol/L. [b] the isolated yield. [c] The yields were NMR calculated using 1,1,2,2-tetrachloroethane as the internal standard.

Solvents were screened before we did further studies. 1,4-dioxane and octane gave trace amount of product **4b**, while DMSO gave no reaction (entries 1-3). Among all solvents tested, aromatic organic solvent such as toluene, mesitylene, chlorobenzene gave good results. At this stage, toluene was proved to be the best choice in terms of reaction efficiency.

Table 2-2. Screening the different solvents[a]

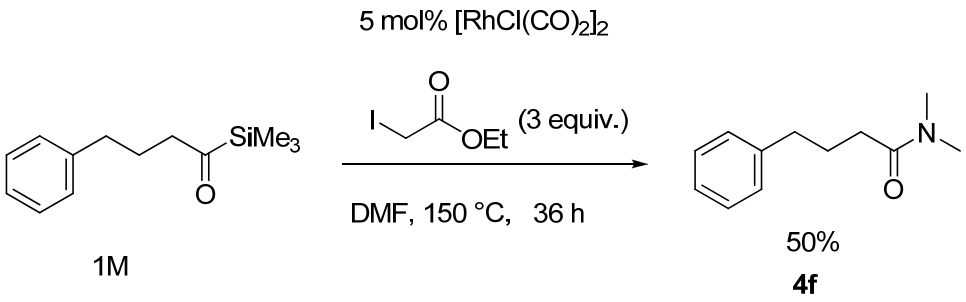


1M **4a** **4b** **4c**

Entry	Solvent	Yield of **4b** (%)[b]	Recovery of **4a** (%)	Yield of **4c** (%)[c]
1	DMSO	0	0	0
2	Octane	trace	0	10%
3	1,4-dioxane	trace	0	0
4	*o*-xylene	38	0	0
5	Chlorobenzene	31	0	18
6	Mesitylene	36	0	15

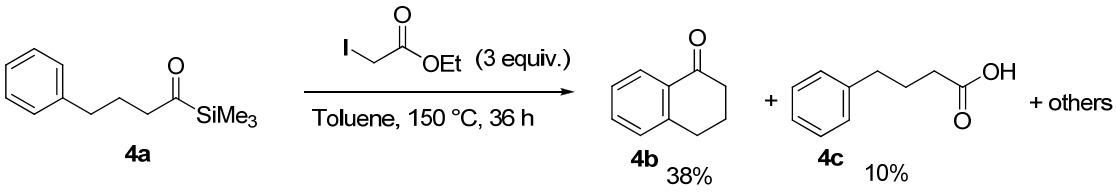
[a] The reaction concentrations are in 1 mol/L. [b] the isolated yield. [c] The yields were NMR calculated using 1,1,2,2-tetrachloroethane as the internal standard.

When DMF was used as the solvent, *N*,*N*-Dimethyl-4-phenylbutanamide **4f** was produced in 50% isolated yield using (Scheme 2-9).



Scheme 2-9. Intramolecular cyclization of acylsilane with ethyl iodoacetate in DMF

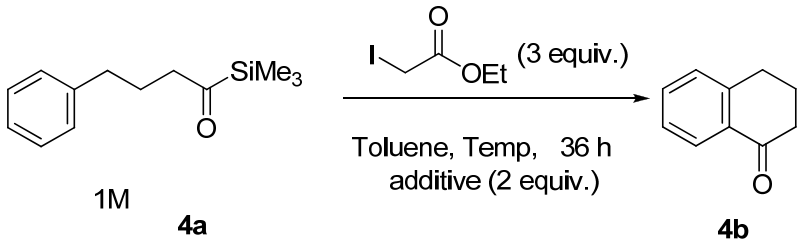
When a toluent solution containing **4a** and ethyl iodoacetate was heated at 150 °C without rhodium catalyst for 36 h, surprisingly, the reaction could also proceed and gave the cyclization product α-tetralone **4b** in 38% yield (Scheme 2-10), side product **4c** was also isolated in 10% yield. It was an interesting finding, which provided a new method to construct new C–C bonds via C–H functionalization without metal. This unexpected result encouraged us to study the reaction conditions further.



Scheme 2-10. Intramolecular cyclization of acylsilane with ethyl iodoacetate

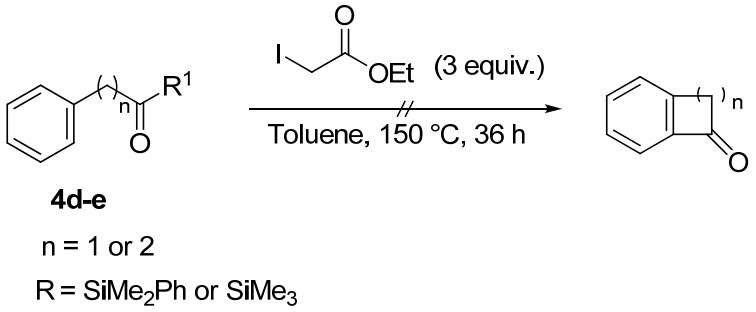
We proceeded the experiments in different aromatic solvent without rhodium catalyst again, no significant difference was observed comparing previous result. In all the cases, the starting material **4a** consumed completely. We assumed that HI may be produced and then decomposed the **4a**, so different bases were added. The result was shown in Table 2-3, the reaction did not occur in the presence of base or inorganic oxide (entries 1-4). The temperature was also investigated in toluene. The ideal temperature should be 150 °C for the reaction system as it gave the best yield in 38% compared to 90 °C and 110 °C (entries 5-7).

Table 2-3. Screening the additives without rhodium catalyst



Entry	Additive	Temp (°C).	Recovery **4a** (%)	Yield **4b**(%)
1	Na_2CO_3	150	82	0
2	Et_3N	150	46	0
3	CuO	150	98	0
4	Ag_2O	150	79	0
5	-	90	92	0
6	-	120	78	15
7	-	150	0	38

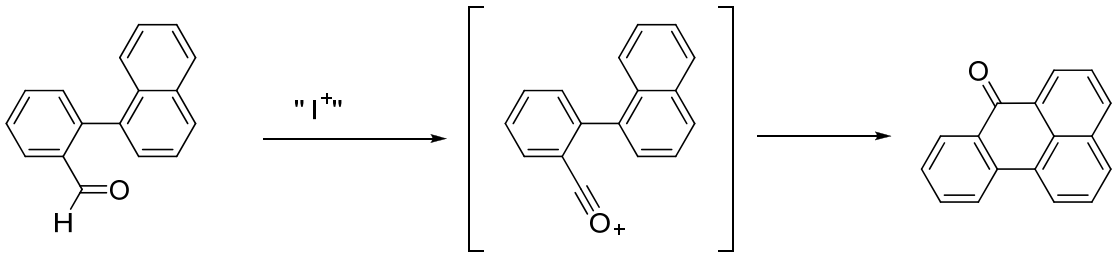
Next, the scope of acylsilane substrates was explored. In an initial study, treatment of 1-(dimethyl(phenyl)silyl)-3-phenylpropan-1-one **(4d)** or 2-(2-methylphenyl)-1-(trimethylsilyl)ethan-1-one (**4e**) with 3 equiv ethyl iodoacetate at 150 °C did not give the desired four- or five-membered ring product (Scheme 2-11). Continued substrates extension and mechanism studies are underway.



Scheme 2-11. Intramolecular cyclization of acylsilane without transition metal

2.3 Proposed mechanism

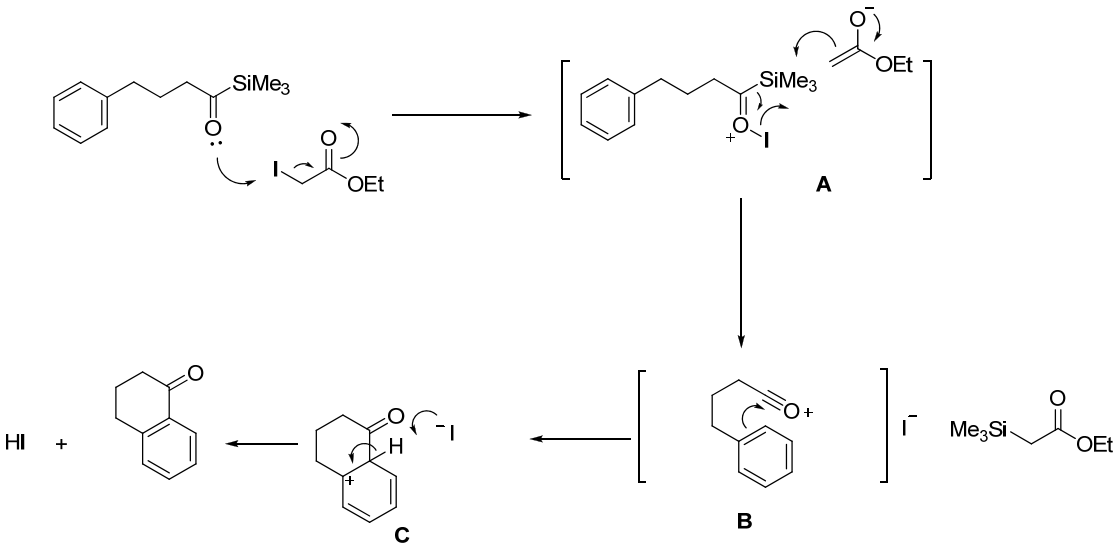
In 2006, Barluenga *et. al.* exploited a novel intramolecular approach to the preparation of benzocyclic ketones (Scheme 2-12),[28] they proposed a cationic pathway of their cyclization reaction. It might also be possible that our reaction conditions follow similar mechanism.



Scheme 2-12 Intramolecualr approach to benzocyclic ketone through a cationic pathway

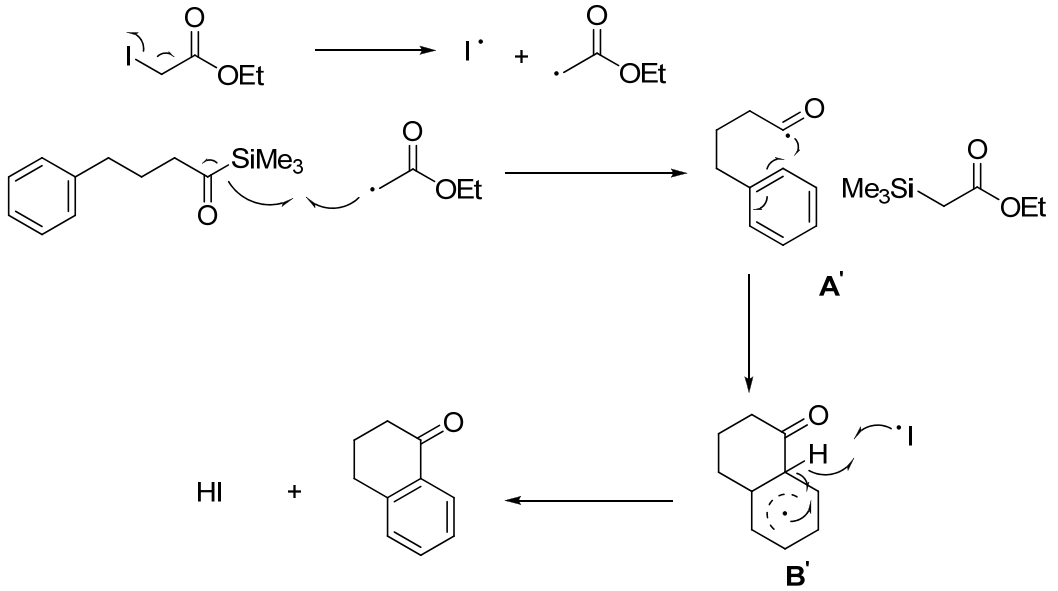
An ionic mechanism was proposed to account for the formation of α-tetralone (Scheme 2-13). First, nucleophilic attack of acylsilane to the iodine atom of ethyl iodoacetate gave species **A**, such a complex could then further react to yield acylium

intermediate **B**, follow by carbocation attack of benzene ring to form intermediate **C**, finally, loss of HI to give the desired product.



Scheme 2-13. Proposed ionic mechanism

Radical mechanism was also proposed for this reaction. Initially, ethyl iodoacetate was homolysed by heating to give ethoxycarbonylmethyl radical and iodine radical, and then reacted with the acylsilane to give radical intermediate **A'**. Intermediate **A'** underwent an intramolecular radical addition to give the intermediate **B'**, which was dehydrogenated by iodine radical to give the desired product and HI.



Scheme 2-14. Proposed radical mechanism

To understand the mechanism of the cyclization, we attempted the experiment in presence of radical scavengers, TEMPO and Galvinoxy. For both cases, radical intermediates were not trapped. At present, we cannot draw a conclusion whether the reaction proceeds in radical or cationic paths.

2.4 Conclusion

In summary, we discovered an intramolecular oxidative cyclization approach to synthesis of carbocycles by a simple procedure. Moreover, direct acylation of aromatic ring with acylsilane was achieved in the absence of Lewis acid or transition-metal, which are necessary in the classical Fredical-Craft acylation reactions and transition-metal catalyzed acylation reactions. This oxidative cyclization method provides a new pathway for the synthesis of functionalized carbocycles via aromatic C–H bond activation efficiently and straightforward. Furthermore, it indicates a wide field for the application of acylsilanes in organic chemistry. Until now, this intramolecular cyclization of acylsilane is still at the early stage, further investigation and experiments are required to understand and determine the true mechanism of this cyclization process. In addition, substrate scope screening should be done to determine if this reaction could be used as a general method to obtain derivatives, further application is expected to form 5- or 7-membered rings compounds.

PART II

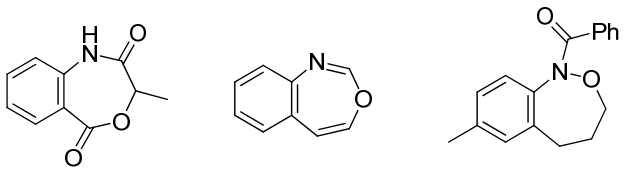
CHAPTER 3

$W(CO)_6$-Mediated 7-endo Cyclization of N-Acyl-o-alkynylanilines

3.1 Introduction

Heterocycles are ubiquitous motif in many biologically active natural or non-natural compounds. The synthesis of various heterocycles was thus attracted attention over a century. Many strategies for synthesis heterocycles have been established. with the growing demand of variety hetrocycles in medicinal and material chemistry, development of efficient and economical synthetic routes for heterocycles is still of great interest.[29]

In particular, the synthesis of nitrogen containing heterocyclic system has caused great interest, because these kinds of compounds have been widely presented in biological and pharmaceutical active reagents. During the past two decades, these compounds have been extensively studied, especially 5- and 6-membered heterocyclic compounds. That's because they are not only exhibiting attractive biological activities, but also belonging highly useful synthetic intermediates for many kinds of alkaloids.[30] However, less attention was paid to the 7-membered nitrogen-containing heterocyclic compounds. The later kind of structure have been found in many natural products and biologically active substances such as benzo[e][1,4]oxazepine(A), benzo[d][3,1]oxazepine(B) and benzo[c][1,2]oxazepine(C) (Figure 3-1), which have been attracting more and more pharmaceutical interests.[31] For example, benzoxazepine derivatives are important scaffolds in medicinal chemistry with various biological activities.[32] The 3,1-Benzoxazepines derivatives have been reported to possess important biological activities and used as fungicidal, anti-inflammatory, anticonvulsant drugs,[33] human leukocyte elastase (HLE) inhibitors,[34] potent progesterone-receptor agonists, and DNA binding antitumor agents.[35]



A B C

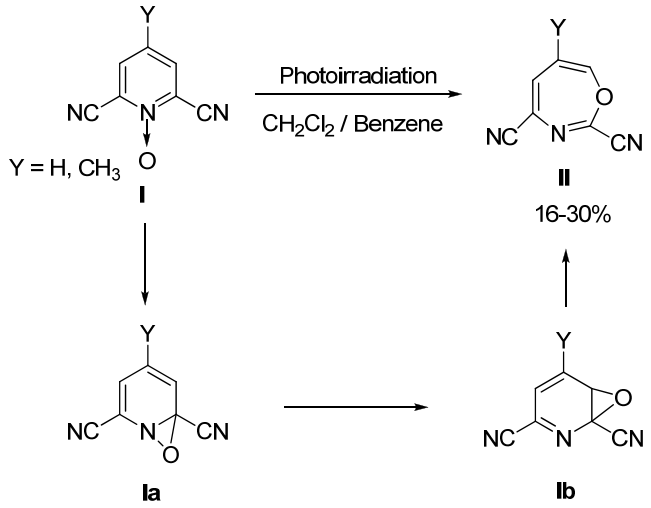
Figure 3-1. Examples of benzoxazepines derivatives

Diversity of synthesis methods to 7-membered nitrogen-containing heterocyclic compounds have been reported including intramolecular cycloamination using palladium as catalyst,[36] intramolecular cyclization of *N*-progargyl-*β*-hydroxylmethyl enamide,[37] cyclization of aminophenols derivatives by thermolysis,[38] intramolecular Michael addition of ethyl 4-(2-hydroxyphenylamino)-4-oxobut-2-enoate derivative,[32b] and photolysis of 2,6-dicyanopyridine 1-oxides.[39]

However, few methods have been reported for the synthesis of 3,1-benzoxazepine derivatives, such as the photolysis of quinolone *N*-oxides,[40] and thermal rearrangements of heterocyclic azides[41] to afford the corresponding 3,1-benzoxazepines. The preparation of 3,1-benzoxazepines has been summarized below.

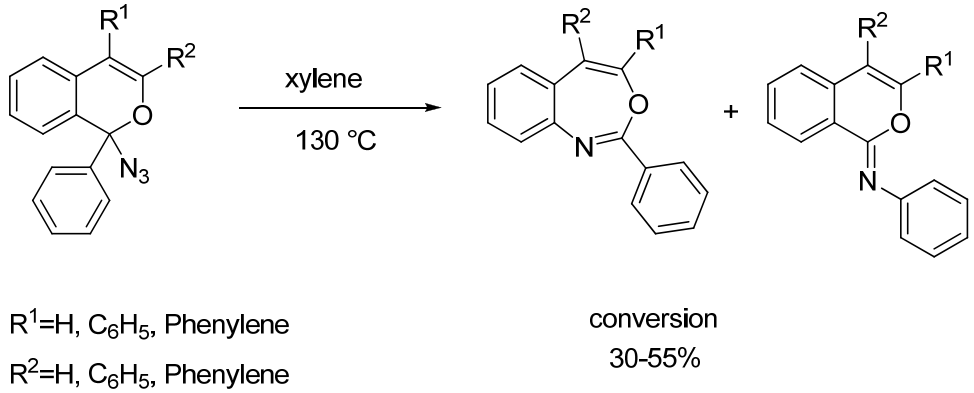
In 1969, Ishikawa's group reported a synthesis of 3,1-benzoxazepine and benzoxadiazepines through photochemical isomerization of 2,6-dicyanopyridine-1-oxides **(I)**. In the photochemical isomerization of 2,6-dicyanopyridine-1-oxides **(I)** to 1,3-oxazepines derivative **(II)**, the following pathway was proposed (Scheme 3-1), which was confirmed by UV and NMR spectra. Irradiation of **I** in dichloromethane and benzene under high-pressure mercury lamp, the intermediate 1,2-epoxypyridines **(Ia)** was formed first, which valence-tautomerizes partly to give 1,2-oxazepines, while the rest are converted to 1,3-epoxypyridines (**Ib**) to give 1,3-oxazepine in low yields of 16-30%. Although this method could afford 1,3-oxazepines in fairly simple synthetic procedures, the yields obtained are poor to modest. Moreover, one important limitation of this method is that the starting material

required a symmetrical arrangement of the substituents to the N-O axis to minimize the formation of other side products, which limited the substrate scope.



Scheme 3-1. Photolysis of 2,6-dicyanopyridine-1-oxides

In 1981, Jean-Pierre developed a method to synthesize 3,l-benzoxazepines via the rearrangement of heterocyclic azides (Scheme 3-2). In their work, 3,l-benzoxazepines were achieved by thermal rearrangements of azides at 130 °C in xylene in moderate yields of 30-55%. From a synthetic point of view, the yields to formation of benzoxazepines were not satisfactory although the reaction procedure was simple.

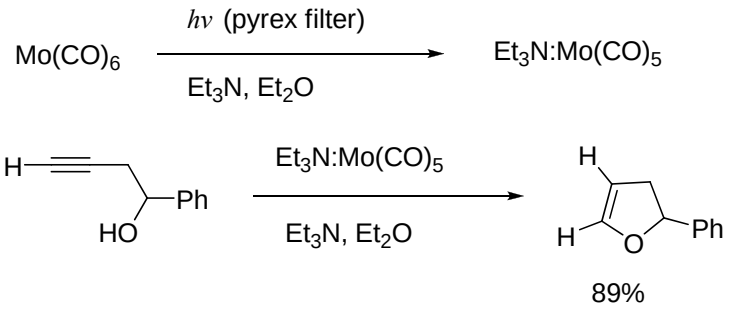


Scheme 3-2. Preparation of 3,1-benzoxazepines by thermal rearrangement

Since the 7-membered nitrogen containing heterocycles become more and more importance in biological and medicinal chemistry, we have been prompted to investigate it further. We focused on the group VI metal carbonyl complexes mediated

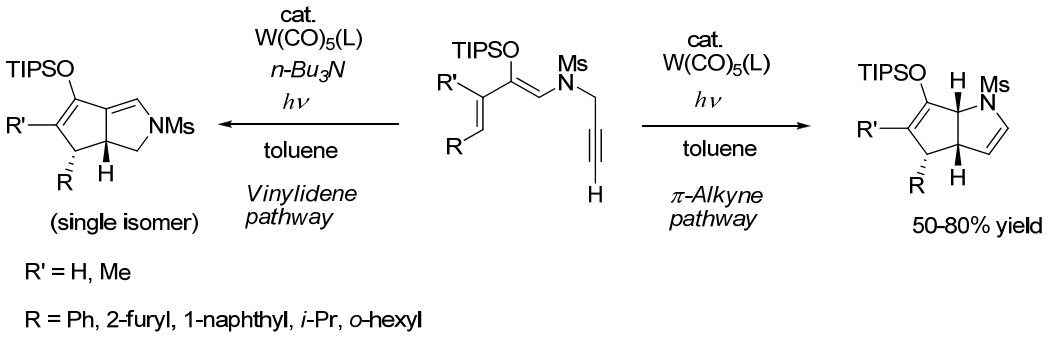
carbomoylation reactions. It was also reported that group VI metal carbonyl complexes could activate alkyne for nucleophilic addition reactions to construct useful cyclic carbon skeletons.[42]

McDonald and co-workers developed the molybdenum-catalyzed cyclization of terminal alkynes tethered to oxygen or nitrogen nucleophiles (Scheme 3-3).[43] In their work, $Mo(CO)_5$:(Et_3N) was used as a catalyst to promote the cyclization of alkynyl alcohols.



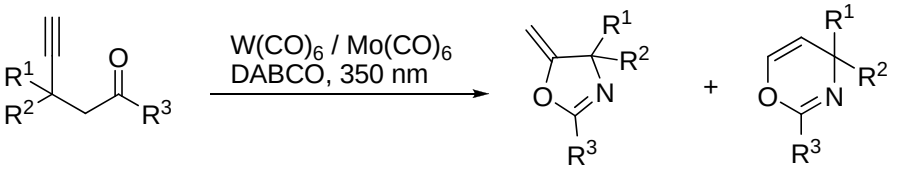
Scheme 3-3. $Mo(CO)_6$ cyclized 1-alkyn-4-ol to the isomeric 2,3-dihydrofurans

Iwasawa *et al*. reported a series of $W(CO)_5$(L)-catalyzed cyclization of various acetylenic silyl enol ethers, the mechanism for this kind of cyclization reactions was also investigated (Scheme 3-4).[44] For example, $W(CO)_5$(L) and amine catalyzed cyclization of 2-aza- and 3-azabicyclo[3.3.0]octane skeletons in moderate to good yields .



Scheme 3-4. $W(CO)_5$(L)-catalyzed reaction of dienol silyl ethers

Recently, Kim *et al*. reported tungsten and molybdenum carbonyl as catalysts to promote the cyclization of *N*-propargylic amides for the preparation of the corresponding oxazolines or oxazines via 5-*exo*-dig or 6-*endo*-dig mode in good to excellent yield (Scheme 3-5).[45] The ratio of oxazines and oxazolines depended on the nature of the catalysts and the structure of the substrates.



R^1 = Ph, 2-MeOPh, 2-BrPh, *n*-C_7H_{15}, 4-NO_2Ph R^2 = H	80-91%	0
R^1 = Ph, Bn, 2-BrPh, n-C_7H_{15} R^2 = Me	20-75%	20-75%

Scheme 3-5. $Mo(CO)_6$-catalyzed cyclization of propargyl amide

The intramolecular cyclization of alkynes possessing nucleophiles, which is close to the C≡C triple bond, provide a series of heterocyclic compounds in an efficient way, the nucleophile can be oxygen-, sulfur-, nitrogen containing functional groups. This is an important strategy to construct heterocycles, especially, cyclization of *o*-alkynylphenyl derivatives for construction of heteroaromatic compounds has become a useful method for the preparation of compounds such as indoles, benzofurans, isoquinolines and so on (Figure 3-2).

Heterocyclic ring systems can be readily prepared through this strategy. Many research work have focused on this aspect, vast of reports have detailed on the basis of this strategy. A variety of transition-metal catalysts such as copper,[46] silver,[47] mercury,[48] palladium,[46a, 49] gold,[49b] tungsten[43d, 44b, 44e, 45] have been introduced for this purpose. And various natural products were prepared with this synthesis method. [46b, 49d, 49l]

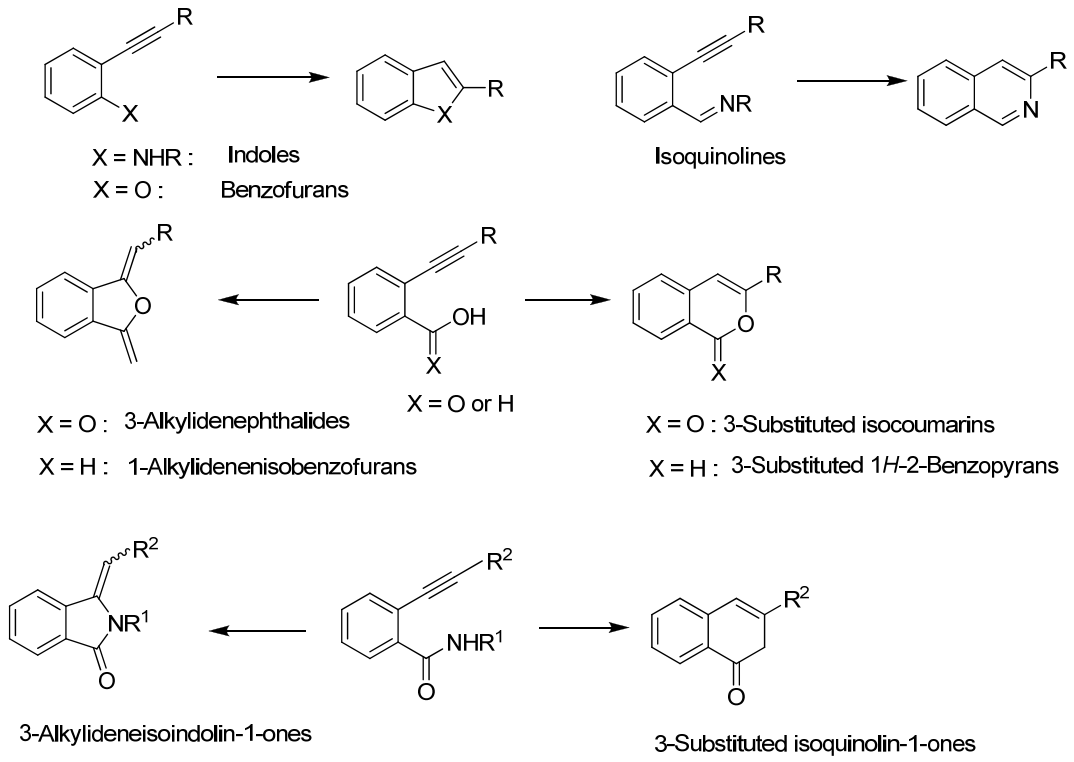
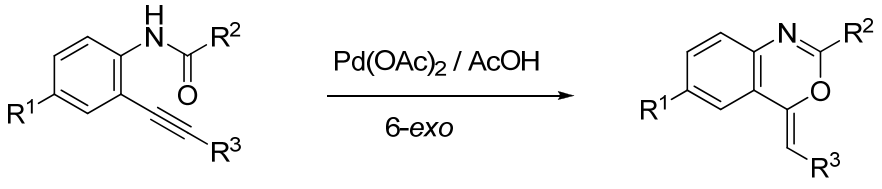


Figure 3-2. Examples of various heteroaromatic compounds

Very recently, T. Saito *et al.* reported a palladium-catalyzed 6-*exo*-dig cyclization of *N*-acyl-*o*-alkynylanilines to synthesize 4-alkylidene-4*H*-3,1-benzoxazines (Scheme 3-6).[49n]



R^1 = H, Me,Cl

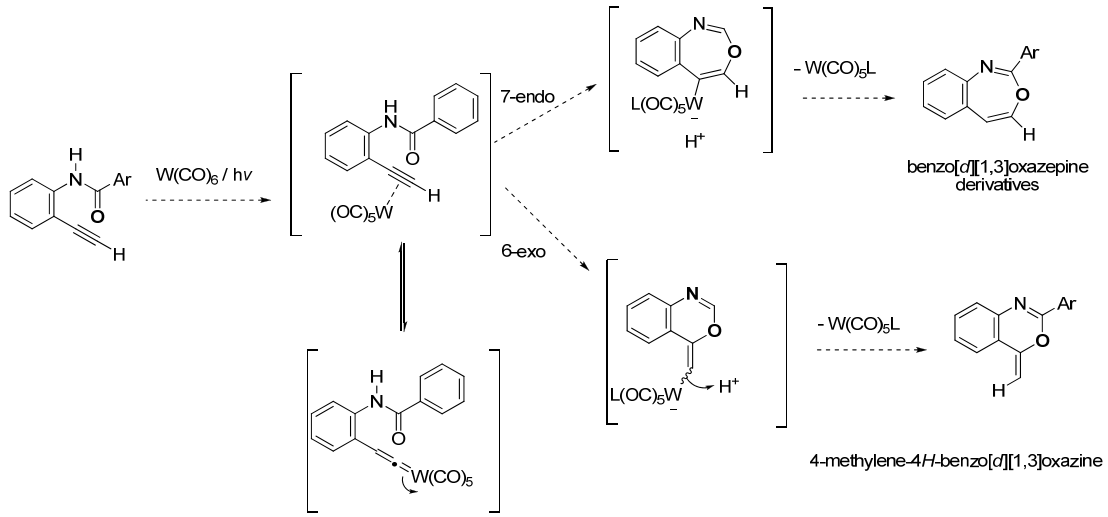
R2 = Me, ^{t}Bu, Ph, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$

R^3 = Me, ^{t}Bu, ^{n}Pr, H, Ph, *p*-$MeOC_6H_4$

Scheme 3-6. Palladium-catalyzed cyclization of *N*-Acyl-*o*-alkynylanilines

Driven by our interests in the synthesis of nitrogen heterocycles, we investigated the $W(CO)_6$-catalyzed cyclization of *N*-Acyl-*o*-alkynylanilines. Under basic conditions, 6- or 7-membered heterocyclic could be formed via π-alkyne complex or vinylidene

complex (Scheme 3-7). It is noteworthy that both of these two kinds of compounds possess potential biological activities.[50]



Scheme 3-7. Potential of $W(CO)_6$-catalyzed cyclization of terminal alkyne

Generally, there are two possible mechanisms for group VI metal carbonyl complex catalyzed cyclization of terminal alkynes bearing a nucleophile, the π-alkyne- and vinylidene-complex pathways (Scheme 3-8).[44c]

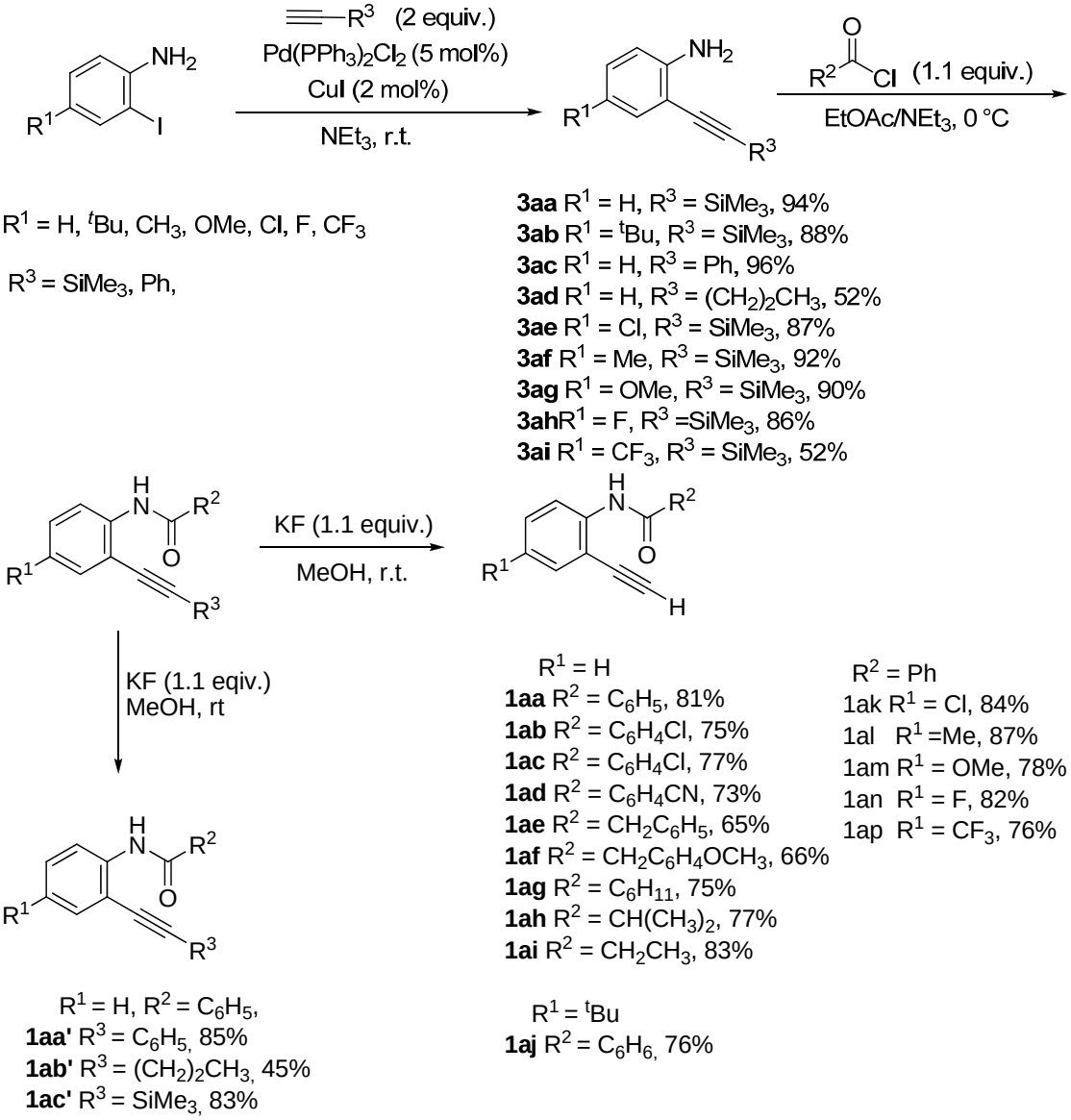
Scheme 3-8. Two possible pathways of group VI metal carbonyl complex

3.2 Results and Discussion

3.2.1 Synthesis of *N*-(2-ethynylphenyl) amide derivatives

The *N*-(2-ethynylphenyl) amide derivatives (**1aa-aj**) were prepared in 3 steps from the corresponding iodoaniline according to the known procedures, which includes Cassar-Sonogashira coupling of commercial available aryliodide with trimethylsilylacetylene, followed by amide formation with acid chloride, and

deprotection with KF (Scheme 3-9).[51] The desired compounds (**1aa–ap**) were acquired in moderate to good overall yields (45-87%).

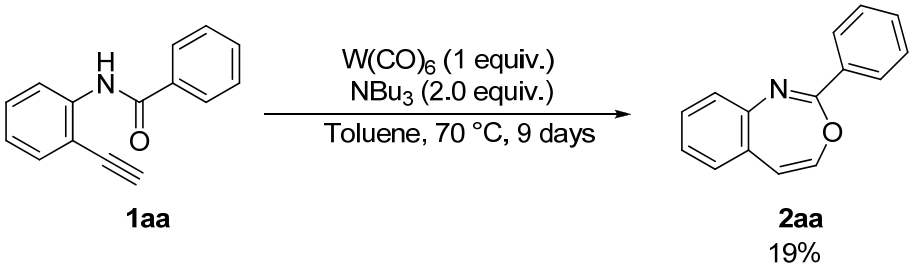


Scheme 3-9. Synthesis of *N*-(2-ethynylphenyl) derivatives

3.2.2 $W(CO)_6$-catalyzed cyclization of *N*-(2-ethynylphenyl) benzamide

Initially, *N*-(2-ethynylphenyl) benzamide **(1aa)** was used as model substrate to investigate the cyclization reaction (Scheme 3-10). A toluene solution of 1 equivalent of **1aa**, 1 equivalent of $W(CO)_6$, 2 equivalents of additives and NBu_3 were heated at 70 °C for 9 days, 2-phenylbenzo[1,3]oxazepine **2aa** was obtained in 19% yield as expected with the recovery of starting material **1aa** in 51% yield (Scheme 3-10).

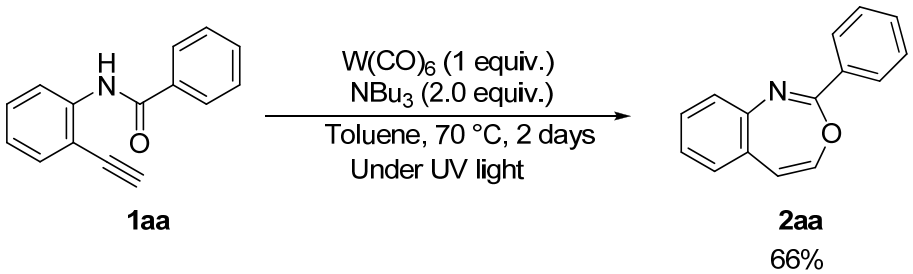
However, the reaction time required for this reaction was long. Hence, methods to accelerate the reaction and enhance the yields of the reaction were investigated.



1aa **2aa** 19%

Scheme 3-10. The first attempt of the $W(CO)_6$-catalyzed cyclization of benzamide

As mentioned above, it is known that irradiation of $W(CO)_6$ in THF by a high-pressure Hg lamp can produce $W(CO)_5$**:**THF complex in situ.[44e] This tungsten-complex could activate the alkyne moiety efficiently towards the nucleophilic attack of ω-acetylenic silyl enol ethers. Hence, we tested the reaction in the presence of UV light (Scheme 3-11).



1aa **2aa** 66%

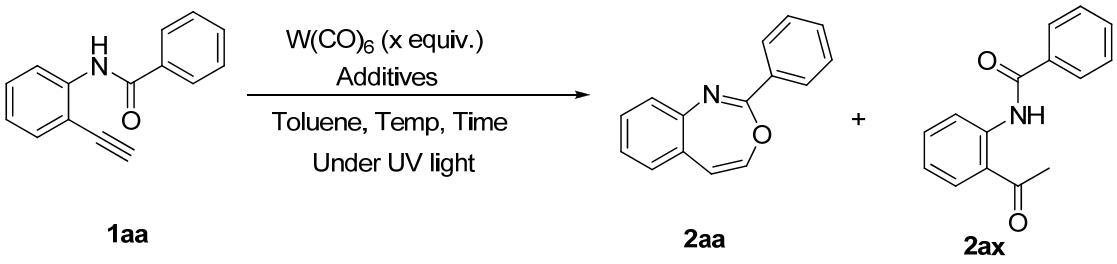
Scheme 3-11. $W(CO)_6$-catalyzed cyclization of benzamide under UV light

We performed the cyclization of **1aa** under direct irradiation with a UV lamp. Interestingly, the reaction time was shortened to 2 days with higher yield (66%) desired product (Scheme 3-11). Photo-irradiation was proved indeed crucial for the reaction. The yield of the desired product **2aa** obtained using UV light was three times higher than that of under heating conditions. It is important to note the reaction time required was significantly shortened to 2 days. Next, we proceeded with the optimization of the reaction conditions. The solvents, temperature, amount of catalyst and additive were screened respectively.

3.2.2.1 Effects of temperature and additive on the $W(CO)_6$-mediated 7-*endo* cyclization of *N*-(2-ethynylphenyl) benzamide

In order to investigate the effects of temperature and additive for the reaction, all other conditions were kept constant. Temperature of 25 °C, 70 °C and 110 °C were chosen for investigation and the equivalents of additive, i.e. NBu_3 were varied. The mixture was stirred under UV light for the indicated time. Results were summarized in Table 3-1. Without the additives (Table 3-1, entry 2), the reaction proceeded with excellent isolated yield of 83% of the desired product (**2aa**), along with trace amount of starting material and trace amount of *N*-(2-acetylphenyl) benzamide (**2ax**). It indicated that the additive was not essential for the reaction. An excellent yield of 83% for the desired product (**2aa**) was also obtained by changing the temperature to 25 °C (Table 3-1, entry 3). Comparison with the experiment results in Table 3-1, the conditions depicted as entry 3 were used as the optimal conditions for further modifications.

Table 3-1. Effects of temperature and additive on the $W(CO)_6$-mediated cyclization reaction[a]



1aa **2aa** **2ax**

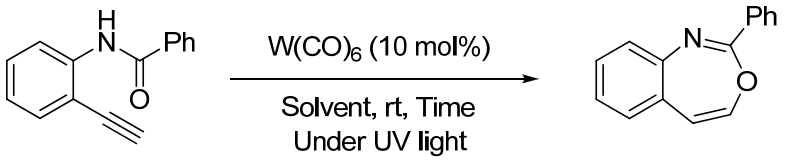
Entry	Temp./ °C [b]	Additives	Time/days	Yield **2aa**/%	Recovery of **1aa**/%	Yield **2ax**
1	70	NBu_3/0.5 equiv.	3	83	3	trace
2	70	-	1	82 (83)[c]	trace	trace
3	25	-	3	83	1	trace
4	110	-	2	48	15	trace

[a] The reaction concentrations are in 0.1 mol/L. [b] Temperature of the oil bath. [c] The number in parathesis is the isolated yield. The yields were NMR calculated using 1,1,2,2-tetrachloroethane as the internal standard.

3.2.2.2 Effects of solvent on the $W(CO)_6$-mediated 7-*endo* cyclization of *N*-(2-ethynylphenyl)benzamide

As discussed and summarized in previous table (Table 3-1), the conditions of room temperature without additives were applied as the optimal result for further optimizations (Table 3-1, entry 3). Then modification of appropriate solvents was also carried out. A series of solvents such as acetonitrile (MeCN), dimethylformamide (DMF), tetrahydrofuran (THF), hexane, methanol (MeOH), toluene and acetone were screened under the following reaction conditions: 0.1mol/L of **1aa** in solvent, 1 equivalent of $W(CO)_6$, room temperature, under UV light for 2 days. The results were summarized in Table 3-2. It was found that the solvent such as dichloromethane (DCM), MeCN, DMF, THF and hexane are extremely poor solvents for this reaction (Table 3-2, entries 1-5), which gave very low yields of desired product (**2aa**). In these reaction mediums, large amount of the starting materials (**1aa**) were recovered, whereas methanol and acetone afforded desired product (**2aa**) in 98% and 80% yields, respectively (Table 3-2, entries 6 and 7). Finally, methanol was concluded to be the appropriate solvent for this reaction.

Table.3-2 Effects of solvent on the $W(CO)_6$-mediated cyclization of *N*-(2-ethynylphenyl)benzamide [a]



1aa **2aa**

Entry	Solvent	Time/day	Yield / **2aa**	Recovery / **1aa**
1	DCM	4	19	77
2	MeCN	4	0	99
3	DMF	4	0	99
4	THF	4	22	60
5	Hexane	4	8	84
6	Acetone	4	80	17
7	MeOH	4	98	0
8[b]	MeOH	10	64	27
9[c]	MeOH	5	87	4

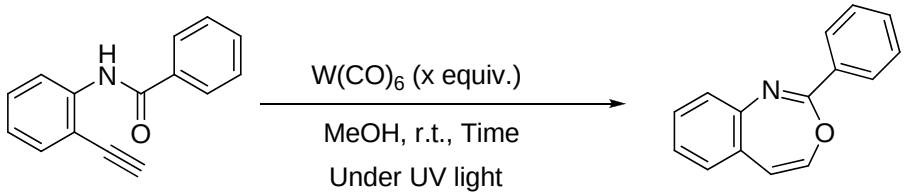
[a] The yield was NMR calculated yield using the 1,1,2,2-tetrachloroethane as the internal standard. [b] Without UV light irradiation. [c] The loading of $W(CO)_6$ is 5 mol%.

3.2.2.3 Modification of the amounts of the metal on the $W(CO)_6$-mediated 7-*endo* cyclization of *N*-(2-ethynylphenyl)benzamide

Since the present reaction conditions gave the desired product in a very high yield when 1 equivalent of $W(CO)_6$ were used in methanol, the author decided to investigate the catalytic amounts of $W(CO)_6$ for this reaction. The results were summarized in Table 3-3. Initially, the reaction was carried out with 20 mol% of $W(CO)_6$ under UV for 3 days. Surprisingly, an 89% yield of **2aa** was obtained, and no starting materials (**1aa**) were observed (Table 3-3, entry 1), which suggests that only catalytic amounts of $W(CO)_6$ is required for this reaction. Further optimization was done by reducing the equivalents of catalyst to 10 mol% (Table 3-3, entry 2). The result showed that 10 mol% of $W(CO)_6$ would slightly increase the yield to 91% at a longer reaction time. At last, the author concluded that the optimal conditions for this reaction is described as

following: 1 equiv. of **1aa**, methanol as solvent, catalytic amounts (10 mol%) of $W(CO)_6$, room temperature, and UV light.

Table 3-3. Modification of the amounts of the metal required in the $W(CO)_6$-mediated cyclization reaction[a]



1aa **2aa**

Entry	$W(CO)_6$/equiv.	Time/days	Yield **2aa**/%[b]	Recovery of **1aa**/%
1	0.2	3	89	0
2	0.1	4	91	0

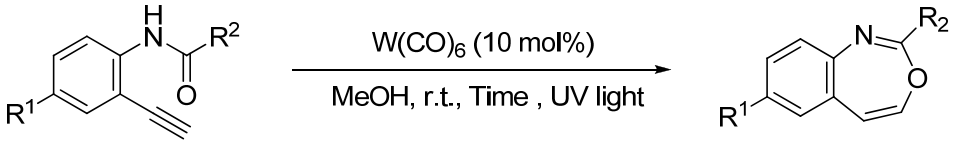
[a] The concentration for all entries are in 0.1 mol/L. [b] The yield was NMR calculated yield using the 1,1,2,2-tetrachloroethane as the internal standard.

3.2.3 Investigation of the substrate scope

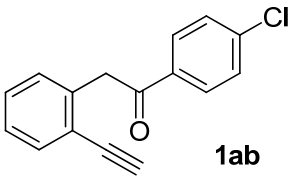
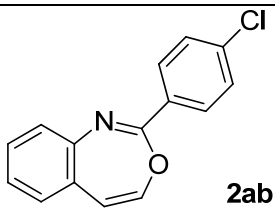
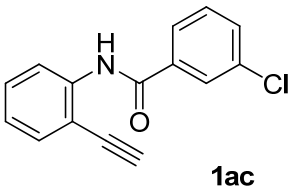
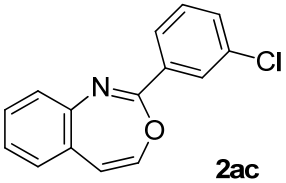
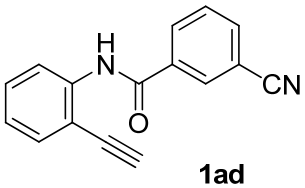
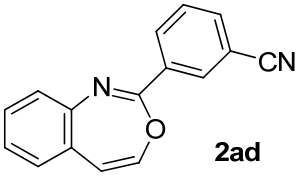
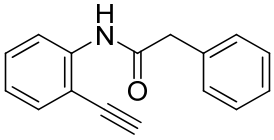
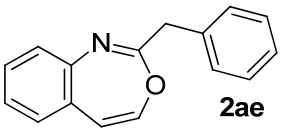
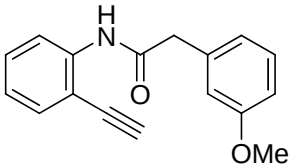
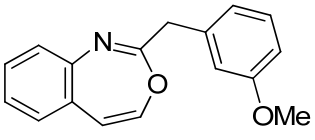
With the optimized reaction conditions in hand, the scope and limitation of this reaction were investigated by using *N*-(2-ethynylphenyl) bearing various substituents (R^1 and R^2) as the starting materials (Table 3-4). A mixture of 1 equivalent of *N*-(2-ethynylphenyl) amide derivatives together with 10 mol% of $W(CO)_6$ in methanol was stirred at room temperature under UV light. All reactions were conducted at a concentration of 0.1 mol/L. The results were summarized in Table 3-4. In all cases, the desired products were obtained in moderate to good yields (Table 3-4, entries 3-14,). It was found that the R^2 can be aryl or alkyl substituents, the cyclization reaction could smoothly proceed to give the corresponding 3,1-benzoxazepines with excellent yields. In the case of the substrate bearing a strong electron-withdrawing group (R^2), such as CN (Table 3-4, entry 3), the reaction cannot be finished after 8 days and afforded the

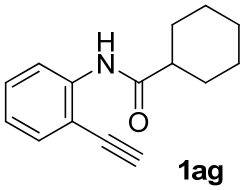
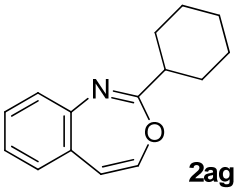
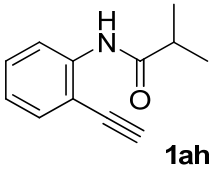
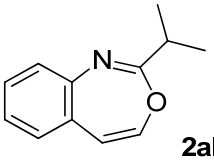
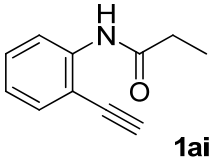
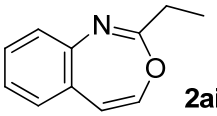
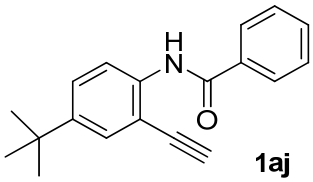
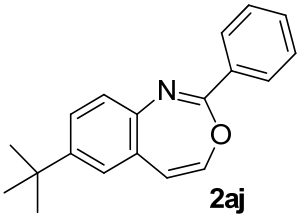
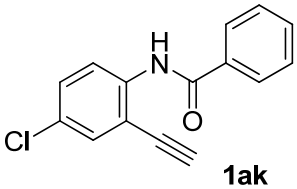
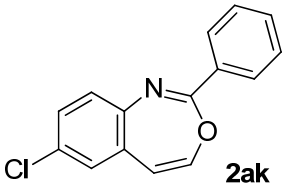
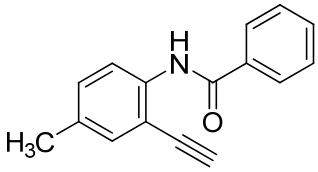
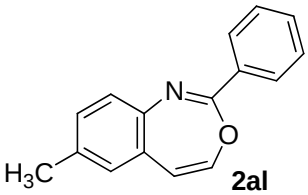
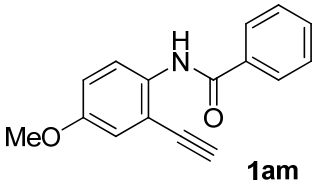
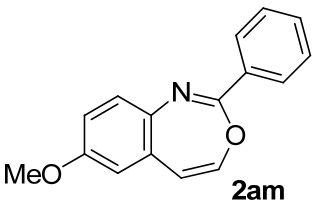
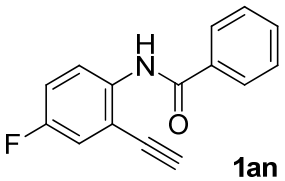
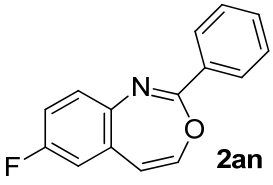
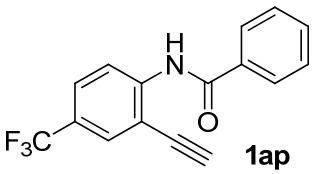
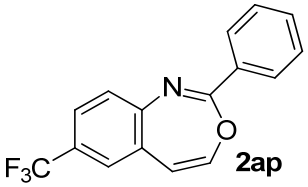
desired product **2ad** in moderate yield of 50%. The tolerance of the substituent R^1 was also investigated, alkyl, halide and alkoxyl groups were tolerated under this reaction conditions to give the corresponding product in excellent yields (Table 3-4, entries 9-14).

Table 3-4 Screening of *N*-(2-ethynylphenyl)amide derivatives for the $W(CO)_6$-mediated cyclization reaction.[a]



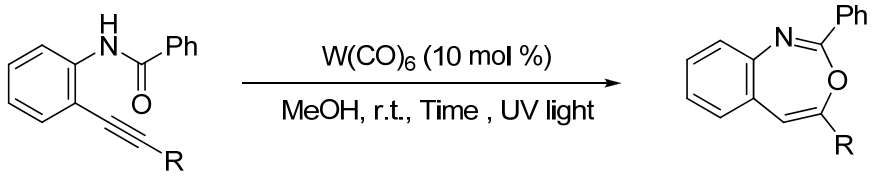
1aa-ap **2aa-ap**

Entry	**(1)**	Time (days)	Product **(2)**	Yield (%)
1	 **1ab**	5	 **2ab**	98
2	 **1ac**	6	 **2ac**	97
3	 **1ad**	8	 **2ad**	50(36)[b]
4	 **1ae**	7	 **2ae**	95
5	 **1af**	7	 **2af**	96

6	 **1ag**	4	 **2ag**	85
7	 **1ah**	5	 **2ah**	95
8	 **1ai**	6	 **2ai**	83
9	 **1aj**	5	 **2aj**	88
10	 **1ak**	4	 **2ak**	88
11	 **1al**	4	 **2al**	90
12	 **1am**	4	 **2am**	92
13	 **1an**	4	 **2an**	89
14	 **1ap**	4	 **2ap**	88

[a] All reactions were carried out with **1** (0.30 mmol), $W(CO)_6$ (0.03 mmol) in methanol (3.0 mL) under N_2 at 25 °C under irradiation of normal UV light unless otherwise stated. [b] The starting material recovery by 1H NMR analysis.

When the substrates of *N*-acyl-o-alkynylaniline was not a terminal alkyne, there is no cyclization reactions observed even after 5 days (Scheme 3-12), the starting material was recovered almost totally (from 70% - 93% by ^{1}H NMR analysis). This result indicates that substitution of the triple bonds suppresses the nucleophilic attack of carbonyl oxygen to alkyne, the tungsten carbonyl may activate the alkyne through a vinylidene complex intermediate.



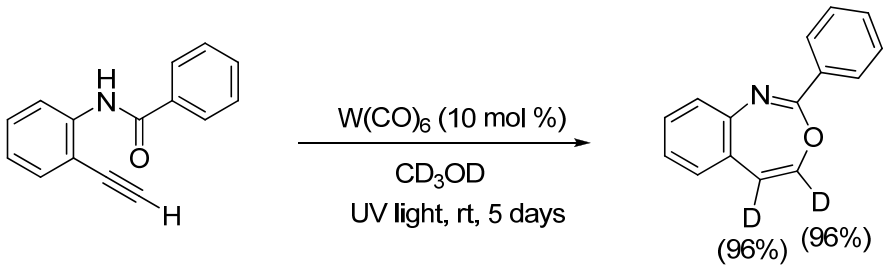
R = Ph	5 days	n.d.
R = $SiMe_3$	5 days	n.d.

Scheme 3-12. The attempt of cyclization of *N*-acyl-*o*-alkynylanilines with disubstituted alkyne

In addition, molybdenum carbonyl and chromium carbonyl were also tested as catalyst under the same reaction conditions, no desired products were observed.

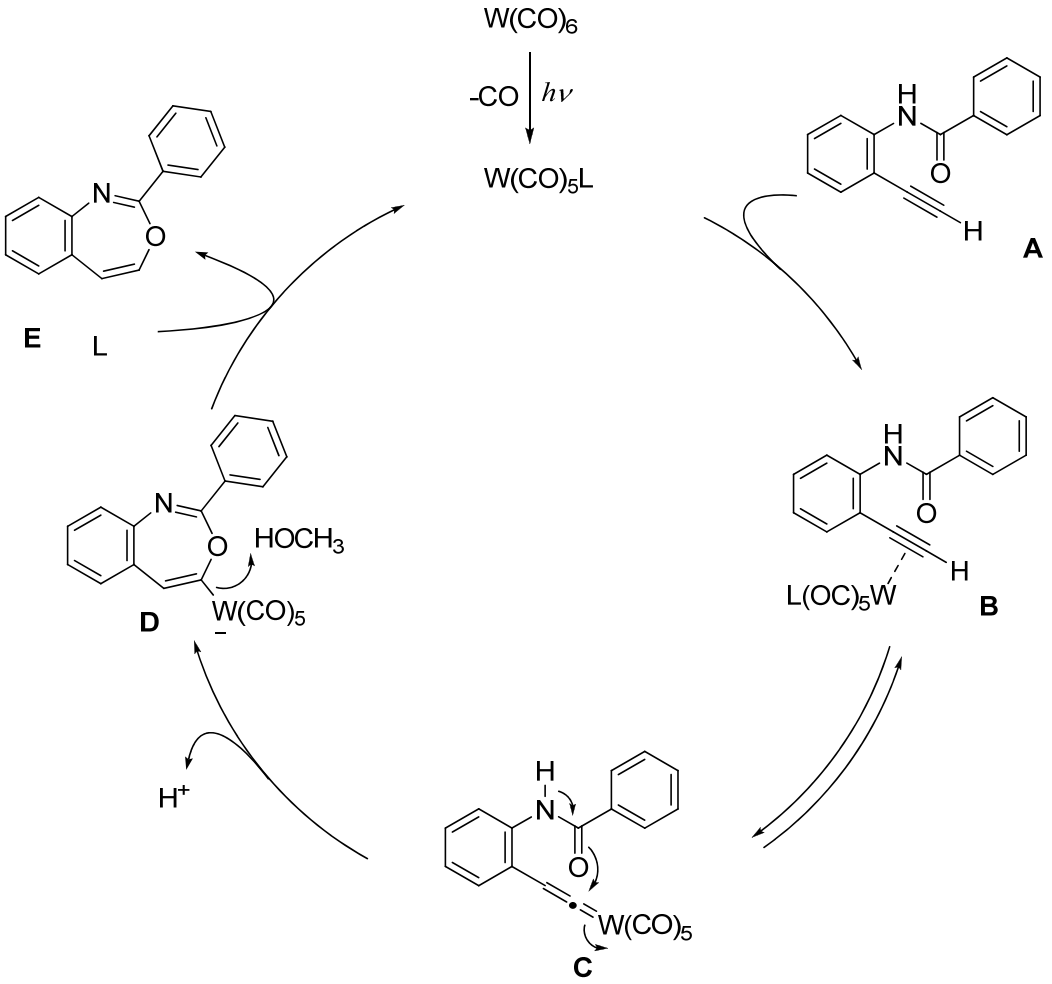
3.2.4 Proposed mechanism

In order to investigate the reaction mechanism and identify the hydrogen source, the cyclization reaction was carried out in deuterated solvent. The solution of 1 equivalent of *N*-(2-ethynylphenyl) amide (**1aa**) and 10 mol% of $W(CO)_6$ in deuterated methanol was stirred at room temperature under UV light for 5 days. We found that the two deuterium atoms in the product were both approximately 96% deuterium incorporated (Scheme 3-13). With these information, we proposed that the cyclization should proceed through a vinylidene tungsten intermediate.[52]



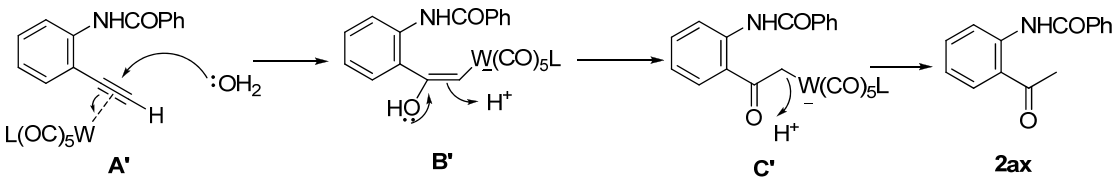
Scheme 3-13. The cyclization reaction of *N*-acyl-*o*-alkynylanilines conducted in deuterated methanol

Based on the above experimental results and literatures, a plausible mechanism has been proposed to account for the formation of 3,1-benzoxazepine (Scheme 3-14). At first, the UV light produces $W(CO)_5L$ complex in situ from $W(CO)_6$.[53] Upon addition of *N*-(2-ethynylphenyl) amide derivatives, the triple bond of the terminal alkyne will coordinate to $W(CO)_5L$ **A**, which leads to an activated π-alkyne complex **B**. The activated π-alkyne complex **B** will be in equilibrium with the vinylidene complex **C**. Then the intramolecular nucleophilic attack of the amide on the activated terminal alkyne results in the cyclization of *N*-(2-ethynylphenyl) benzamide to give vinylmetalic intermediate **D**. Finally the tungsten complex leaves and protonation occurs to form the desired product, 3,1-benzoxazepine derivative **E** and regenerate the catalyst.



Scheme 3-14. The proposed pathway of 3,1-benzoxazepine derivatives formation

The proposed mechanism for the formation of *N*-(2-acetylphenyl) benzamide, (**2ax**) was outlined in Scheme 3-15. H_2O attacking the π-alkyne complex, resulting in the intermediate **B'.** Intermediate **B'** was protonated, resulting in the formation of intermediate **C'**. In the final step, the $W(CO)_5L$ complex left and the resulting *N*-(2-acetylphenyl)amide benzamide (**2ax**) was formed.



Scheme 3-15. The proposed mechanism for the formation of *N*-(2-acetylphenyl) benzamide

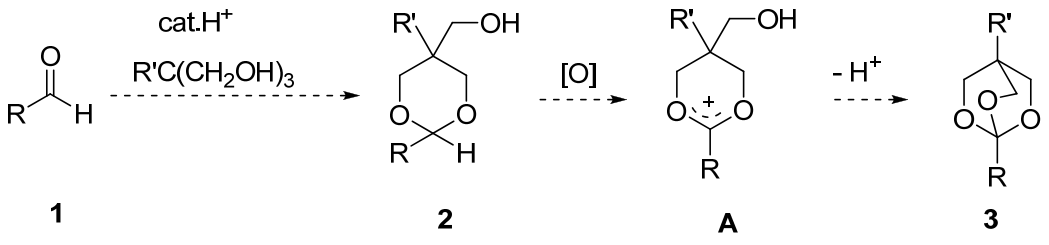
3.3 Conclusion

In summary, an efficient method for the preparation of 3,1-benzoxazepine derivatives under mild reaction conditions was developed. The highly regioselective 7-*endo*-dig cyclization of *N*-acyl-o-alkynylanilines have been proceeded to afford 3,1-benzoxazepines in high yields by using $W(CO)_6$ as the catalyst under normal UV light irradiation at room temperature. In addition, a plausible mechanism for this reaction has been proposed. This reaction would be very useful and practical in synthesis of 7-membered heterocyclic compounds, especially for the pharmaceutical interests.

CHAPTER 4 Summary

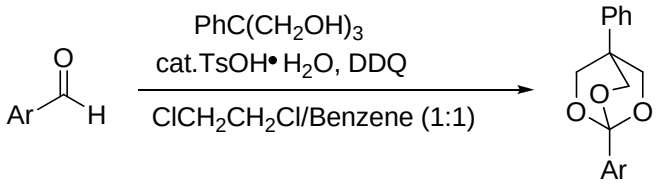
Carbocycles and heterocycles are basic skeletons of many biologically active natural products. Oxidative cyclization and metal-mediated cyclization reactions are two useful strategies to construct them. This thesis has presented the new development of these two methods for the synthesis of carbocylces and heterocycles.

DDQ-mediated oxidative cyclization reaction is very useful method for the synthesis of carbocycles and heterocycles. We are interested in synthesis of useful and valuable targets using this method. Orthoesters are important building blocks in organic synthesis and have received much attention as masked carboxylic acids and esters. Traditionally, orthoesters were prepared from nitriles, imino esters, or by orthoester exchange. However, there are still some limitations in the conventional synthesis methods of orthoesters, for example, harsh reaction conditions, low yields, together with side reactions. Based on the above-mentioned remarks, more efficient and convenient methods for preparation of orthoesters are highly desired. After reviewing the literature, no report for the synthesis of orthoesters directly by reaction of carboxylic acids or esters with alcohols under acid catalysis was found, the conditions commonly used in the equivalent acetal formation. Thus, the author designed an oxidative preparation of bicyclic aromatic orthocarboxylates from aldehydes. Various oxidants were examined, at last the author found DDQ was the best choice to realize this transformation (Scheme 4-1).



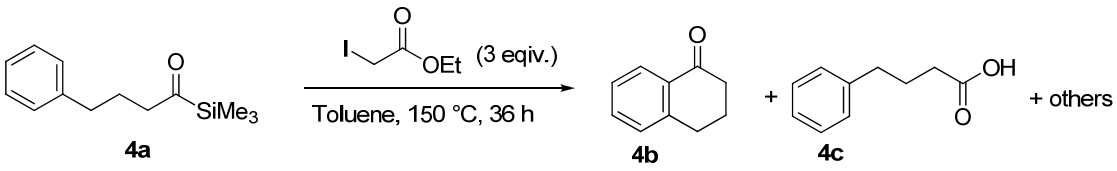
Scheme 4-1. Our design for the transformation of aldehyde into bicyclic orthoester

In summary, an oxidative method to prepare orthoesters from aldehydes was developed in chapter 1. By means of the in situ method, a simple one-pot synthesis of orthoesters from aldehyde was realized in this work (Scheme 4-2).



Scheme 4-2. One-pot preparation of aromatic arthoester from aldehyde

In chapter 2, the author continued the study of synthesis of carbocycles and heterocycles. Aryl-acylsilane was selected to construct carbocycles, expecting that rhodium catalyzed aromatic C–H bond activation could achieve this process. Various oxidants were examined, ethyl iodoacetate was selected as the appropriate oxidant at present. Interestingly, the author found the α-tetralone could also be produced without rhodium catalyst during the course of our studies of rhodium-catalyzed C–H acylation with acylsilane (Scheme 4-3).



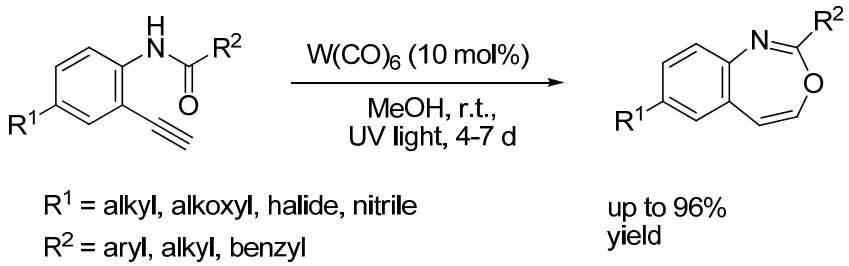
Scheme 4-3. Intramolecular cyclization of acylsilane with iodo ethyl acetate

This oxidative cyclization method provides a simple, facile access to carbocycles, α-tetralone could be oxidatively synthesized from the corresponding acylsilane with the iodo ethylacetate. Moreover, intramolecular acylation of aromatic ring with acylsilane was achieved in the absence of strong Lewis acid or transition-metal which are necessary in the classical Friedel-Craft acylation reactions and transition-metal

catalyzed acylation reactions. The investigation of this topic is in an early stage. Further optimization is still in progress to form 6-membered ring and further application is expected to form 5- or 7-membered rings compounds.

Heterocycles are ubiquitous motif of a vast number of biologically active natural and non-natural compounds. Thus, synthesis of various heterocycles has attracted much attention for over a century and a variety of synthetic strategies for heterocycles have been established. Transition metal-mediated cyclization reaction is also one of the important methods to prepare heterocycles.

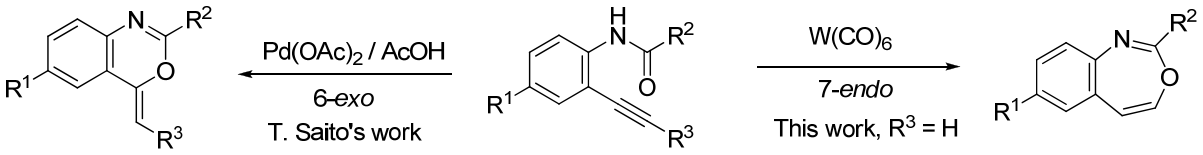
7-membered nitrogen containing heterocycles have attracted more interests of the chemists. An efficient method for the preparation of 3,1-benzoxazepine derivatives under mild reaction conditions has been developed in chapter 3. The highly regioselective 7-*endo*-dig carbonylative cyclization of *N*-acyl-*o*-alkynylanilines proceeds to afford 3,1-benzoxazepines in high yields by using $W(CO)_6$ as the catalyst under normal UV light irradiation at room temperature.



Scheme 4-4. $W(CO)_6$-mediated cyclization to heterocycles

In this work, 6-membered ring products were not detected, the highly regioselective 7-membered ring cyclic products were obtained in high yield, which are attractive compounds of growing pharmaceutical interests as reported by many publications. A variety of substrates were well tolerated under the mild reaction conditions and gave

the corresponding substituted 3,1-benzoxazepines product in moderate to good yields. Thus, this method provided a simple and efficient way to construct 7-membered heterocycles via tungsten-mediated cyclization reaction.



Scheme 4-5. Different cyclization modes of *N*-acyl-*o*-alkynylanilines

In conclusion, three new synthetic methods have been described in Chapters 1, 2 and 3 of this thesis, however some insufficiencies still exist, such as relatively low yield, limited substrates scope. Thus, more efforts should be done in the future to improve the yield and scope.

EXPERIMENTAL

Commercial solvents and reagents were used without further purification with the following exceptions: hexane and ethyl acetate were fractionally distilled. THF, Toluene and dichloromethane (CH_2Cl_2) were taken from a solvent purification system. Ethanol (EtOH) was distilled from sodium and stored over MS4Å. N,N-Dimethylformamide (DMF) was distilled from CaH_2 and stored over MS 4Å.

^1H NMR (500, 400 and 300 MHz) spectra were recorded on Bruker AVANCE 500, 400 and 300 in $CDCl_3$. Spectra were calibrated using the residual ^1H chemical shift in $CDCl_3$ (7.26 ppm), which was used as internal reference standards for ^1H NMR. ^{13}C NMR (125, 100 and 75 MHz) spectra were recorded on Bruker AVANCE 500, 400 and 300 in $CDCl_3$. Spectra were calibrated using $CDCl_3$ (77.0 ppm) for ^{13}C NMR spectra. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = double of doublets, dt = double triplet, m = multiplet. Melting points were uncorrected. IR spectra were recorded on Shimazu IR Prestige-21 FT-IR Spectrometer. High-resolution mass (HRMS) spectra were obtained with JEOL MS-700P mass spectrometer and Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation) and Q-Tof Premier. Flash column chromatography was performed using Merck silica gel 60 with distilled solvents, and preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F.

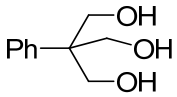
Chapter 1 Oxidative Preparation of Orthoester

General procedure to synthesis triol 4

A solution of phenylacetaldehyde 10.75 g (90mmol), paraformaldehyde 16.8 g (560 mmol) and $Ca(OH)_2$ 5.2 g (700 mmol) in THF (50 mL) was stirred at 60-65 °C for about 5 days. After cooling to room temperature, the mixture was filtered through

celite and the solvent was evaporated under vacuum. The residual oil was dissolved in hot ethyl acetate. The product crystallized as a white solid.

2-(hydroxymethyl)-2-phenylpropane-1,3-diol (4):[14, 54]



Yield: 35%; White solid;

IR (KBr) 3335, 1218, 1036, 1012, 915, 840, 771 cm^{-1};

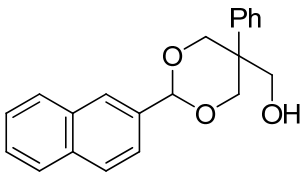
^{1}H NMR (400 MHz, DMSO-d_6) δ 3.92 (s, 6H), 4.39-4.41 (m, 3H), 7.12-7.16 (m, 1H), 7.23-7.27 (m, 2H), 7.45-7.47 (m, 2H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 45.2, 63.4, 125.2, 127.4, 127.5, 142.9.

General procedure for preparation of hydroxyacetals 2a-h

Compound **2a-h** were prepared according to the literature[14]: A mixture of 2-naphthaldehyde **(1a)** 3.12 g (20 mmol) and triol **4** 4.37 g (24 mmol) with 50 mg (0.27 mmol) *p*-toluenesulfonic acid and 50 mL of benzene was refluxed for 5-24 hours., using an azeotrotropic head to remove water as it was formed. After the completion of the reaction (monitored by TLC), 30 mL saturated sodium bicarbonate was added, 20 mL ethyl ether extracted twice, the combined organic layer was washed with sodium sulfate. The major isomers were isolated pure by silica gel column chromatography (hexane–EtOAc=4:1) followed by recrystallization (Hexane–EtOAc).

(2-(naphthalene-2-yl)-5-phenyl-1,3-dioxan-5-yl)methanol (2a)



Yield: 72%; White solid;

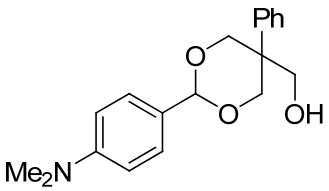
IR (KBr) 2965, 1174, 1105, 1027, 858, 687, 509 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (br, 1H), 4.15 (d, J = 11.2 Hz, 2H), 4.30 (m, 2H), 4.64 (d, J = 11.2 Hz, 2H), 5.67 (s, 1H), 7.25-7.27 (m, 2H), 7.32-7.34 (m, 1H), 7.40-7.42 (m, 2H), 7.44-7.48 (m, 2H), 7.64-7.66 (m, 1H), 7.78-7.89 (m, 3H), 8.10 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 41.3, 65.4, 71.6, 102.0, 123.7, 125.6, 126.2, 126.4, 127.5, 127.7, 128.2, 128.4, 129.0, 133.0, 133.7, 135.4;

ESIHRMS: Found: m/z 321.1482. Calcd for: $C_{21}H_{21}O_3$: $(M+H)^+$ 321.1491.

(2-(4-(dimethylamino)cyclohexa-1,5-dienyl)-5-phenyl-1,3-dioxan-5-yl)methanol (2b)



Yield: 81%; White solid;

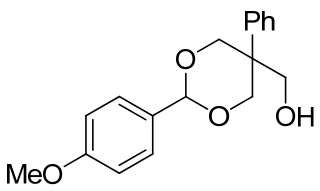
IR (KBr) 3473, 2854, 1616, 1527, 1353, 971, 757, 698 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 6H), 4.06 (d, J = 11.7 Hz, 2H), 4.24-4.25 (2H, m), 4.55 (d, J = 11.7 Hz, 2H), 5.47 (s, 1H), 7.18-7.26 (m, 4H), 7.30-7.32 (m, 1H), 7.37-7.42 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 40.6, 41.2, 71.5, 102.2, 112.1, 125.5, 126.1, 126.8, 127.2, 128.8, 139.7, 151.0;

ESIHRMS: Found: m/z 314.1774. Calcd for: $C_{18}H_{20}O_3$: $(M+H)^+$ 314.1782.

(2-(4-methoxycyclohexa-1,5-dienyl)-5-phenyl-1,3-dioxan-5-yl)methanol (2c):



Yield: 79%; White solid;

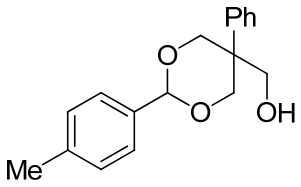
IR (KBr) 3477, 2856, 1614, 1389, 1246, 1169, 1101, 1020 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 1.44-1.48 (m, 1H), 3.81 (s, 3H), 4.08 (d, J = 11.6 Hz, 2H), 4.24 (m, 2H), 4.56 (d, J = 11.6 Hz, 2H), 5.47 (s, 1H), 6.89-6.93 (m, 2H), 7.21-7.25 (m, 2H), 7.30-7.32 (m, 1H), 7.43-7.47 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 41.2, 55.3, 65.4, 71.5, 101.8, 113.6, 125.5, 127.3, 127.4, 128.9, 130.4, 139.5, 160.0;

ESIHRMS: Found: m/z 300.1370. Calcd for: $C_{18}H_{20}O_4$: $(M+H)^+$ 300.1362..

(2-(4-methylcyclohexa-1,5-dienyl)-5-phenyl-1,3-dioxan-5-yl)methanol (2d):



Yield: 73%; White solid;

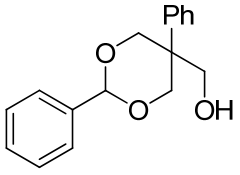
IR (KBr) 3446, 2859, 1388, 1174, 1105, 1020, 975, 813, 671 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 1.40-1.43 (1H, m), 2.36 (3H,s), 4.08 (2H, d, J = 11.7 Hz), 4.24-4.26 (2H, m), 4.57 (2H, d, J = 11.7 Hz), 5.47 (1H, s), 7.18-7.24 (4H, m),7.30-7.32 (1H, m), 7.38-7.42 (4H, m);

^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 30.9, 65.4, 71.5, 71.9, 101.9, 125.4, 125.5, 125.9, 127.3, 128.8, 128.9, 135.1, 138.7;

ESIHRMS: Found: m/z. 285.1477. Calcd for: $C_{18}H_{20}O_3$: $(M+H)^+$ 285.1485.

(2-(cyclohexa-1,5-dienyl)-5-phenyl-1,3-dioxan-5-yl)methanol (2e):



Yield: 80%; White solid;

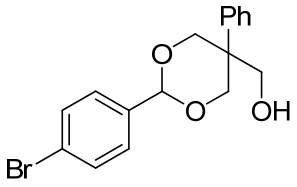
IR (KBr) 3452, 2858, 1498, 1454, 1389, 1105, 1018, 971, 771 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 1.38-1.41 (1H, m), 4.09 (2H, d, J = 11.7 Hz), 4.25-4.27 (2H, m), 4.59 (2H, d, J = 11.7 Hz), 5.50 (1H, s), 7.22-7.24 (2H, m),7.31-7.35 (1H, m), 7.37-7.41 (5H, m), 7.52-7.54 (2H, m);

^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 41.2, 65.2, 71.5, 101.8, 125.5, 126.0, 127.2, 128.2, 128.8, 128.9, 137.9, 139.6;

ESIHRMS: Found: m/z. 271.1316. Calcd for: $C_{18}H_{20}O_3$: $(M+H)^+$ 271.1334.

(2-(4-bromocyclohexa-1,5-dienyl)-5-phenyl-1,3-dioxan-5-yl)methanol (2f):



Yield: 69%; White solid;

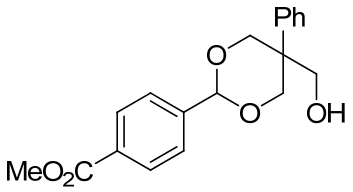
IR (KBr) 3453, 2856, 1597, 1489, 1385, 1173, 1109, 1011, 812, 773, 698 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 1.42-1.45 (1H, m), 4.06 (2H, d, J = 11.7 Hz), 4.20-4.21 (2H, m), 4.58 (2H, d, J = 11.7 Hz), 5.45 (1H, s), 7.20-7.25 (2H, m),7.31-7.34 (1H, m), 7.41-7.42 (4H, m), 7.51-7.53 (2H, m);

^{13}C NMR (100 MHz, $CDCl_3$) δ 41.2, 65.3, 71.5, 101.0.123.0, 125.5, 127.5, 127.8, 128.9, 131.4, 136.9, 139.3;

ESIHRMS: Found: m/z 350.0214 Calcd for: $C_{17}H_{17}BrO_3$: $(M+H)^+$ 349.0417.

Methyl4-(5-(hydroxymethyl)-5-phenyl-1,3-dioxan-2-yl)cyclohexa-2,4-dienecarboxylate (2g):



Yield: 71%; White solid;

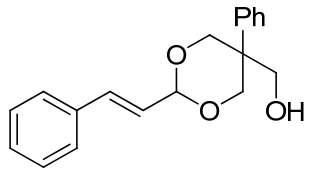
IR (KBr) 3486, 2859, 1716, 1386, 1278, 1176, 1106, 1018, 663 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (1H, br), 3.92 (3H, s), 4.10 (2H, d, J = 11.5 Hz), 4.22-4.23 (2H, m), 4.60 (2H, d, J = 11.5 Hz), 5.54 (1H, s), 7.22-7.24 (2H, m),7.29-7.33 (1H, m), 7.40-7.42 (2H, m), 7.59-7.61 (2H, m), 8.05-8.08 (2H, m);

^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 30.9, 41.3, 52.2, 71.5, 101.0, 125.5, 126.1, 127.4, 128.9, 129.5, 139.3, 166.6, 206.7;

ESIHRMS: Found: m/z. 329.1397. Calcd for: $C_{19}H_{20}O_5$: $(M+H)^+$329.1378

(*E*)-(5-phenyl-2-styryl-1,3-dioxan-5-yl)methanol (2h):



Yield: 77%; White solid

IR (KBr) 3494, 2858, 1496, 1386, 1137, 1093, 964, 727, 690 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (1H, br), 4.01 (2H, d, J = 11.7 Hz), 4.20-4.21 (2H, m), 4.53 (2H, d, J = 11.7 Hz), 5.15 (1H, d, J = 4.6 Hz), 6.23-6.28 (1H, dd, J = 16.4, 4.6 Hz),6.83 (1H, d, J = 16.4 Hz), 7.20-7.22 (2H, m), 7.28-7.34 (4H, m), 7.37-7.43 (4H, m);

^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 41.2, 65.1, 71.2, 100.9, 125.0, 125.5, 126.8, 127.3, 128.2, 128.5, 128.8, 133.7;

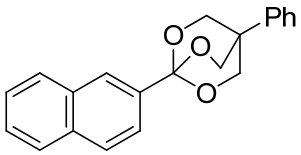
ESIHRMS: Found: m/z 297.1479. Calcd for: $C_{19}H_{20}O_3$: $(M+H)^+$ 297.1497.

Preparation of bicycle orthoester 3a-h from hydroxyacetals 2a-h

A mixture of aromatic hydroxyacetals **(2a)** 162 mg (0.5 mmol) and 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) 140 mg (0.6 mmol) with 100 mg

4A MS and 10 mL of 1,2-dichloroethane was refluxed for 5-20 hours (referring to the Table 1-3). After the completion of the reaction (monitored by TLC), evaporated the solvent under reduce pressure and purified by column chromatography on florisil (Hexane–EtOAc=2:1).

1-(naphthalen-2-yl)-4-phenyl-2,6,7-trioxabicyclo[2.2.2]octane (3a):



Yield: 94%; White solid;

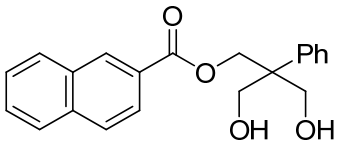
IR (KBr) 3054, 1326, 1268, 1132, 1022, 970, 900, 858, 694 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 4.55 (6H, s), 7.20-7.22 (2H, m), 7.33-7.34 (1H, m), 7.37-7.41 (2H, m), 7.46-7.50 (2H, m), 7.76-7.78 (1H, m), 7.82-7.89 (3H, m), 8.19 (1H, s);

^{13}C NMR (100 MHz, $CDCl_3$) δ 37.0, 72.2, 108.2, 123.2, 125.1, 125.2, 126.0, 126.4, 127.5, 127.9, 128.0, 128.6, 129.1, 132.7, 133.6, 134.4, 135.8;

ESIHRMS: Found: m/z 319.1385. Calcd for: $C_{19}H_{20}O_3$: $(M+H)^+$ 319.1378.

3-hydroxy-2-(hydroxymethyl)-2-phenylpropyl-2-naphthoate (5):



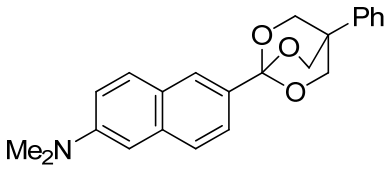
IR (KBr) 3388, 2890, 1700, 1225, 1196, 1039, 1020, 698 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (1H, br), 2.82 (t, J = 6.1Hz, 2H), 4.00-4.04 (m, 2H), 4.12-4.16 (m, 2H), 4.89 (s, 1H), 7.29-7.30 (m, 1H), 7.38-7.40 (m, 2H), 7.47-7.52 (m, 2H). 7.52-7.53 (m, 1H), 7.56-7.57 (m, 1H), 7.81-7.83 (m, 2H), 7.85-7.88 (m, 1H), 7.93-7.94 (m, 1H), 8.48 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 48.8, 65.4, 66.3, 125.0, 126.7, 126.8, 127.3, 127.7, 128.3, 128.5, 128.9, 129.4, 131.4, 132.4, 135.6, 139.0, 167.4;

ESIHRMS: Found: m/z 337.1443. Calcd for: $C_{19}H_{20}O_3$: $(M+H)^+$ 338.1440.

_N,N_-dimethyl-6-(4-phenyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)naphthalen-2-amin e (3b):



Yield: 93%; White solid;

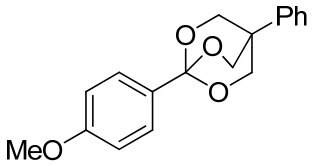
IR (KBr) 2947, 2883, 1614, 1525, 1340, 1219, 1127, 1111, 1012, 814 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 6H), 4.51 (s, 6H), 6.68-6.69 (m, 2H), 7.19-7.21 (m, 2H), 7.30-7.34 (m, 1H), 7.37-7.41 (m, 2H), 7.51-7.53 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 40.6, 72.0, 111.7, 125.2, 125.3, 126.3, 126.4, 127.9, 129.0, 136.2, 151.0;

ESIHRMS: Found: m/z 362.1771. Calcd for: $C_{19}H_{20}O_3$: $(M+H)^+$362.1776.

1-(4-methoxyphenyl)-4-phenyl-2,6,7-trioxabicyclo[2.2.2]octane (3c):



Yield: 92%; White solid;

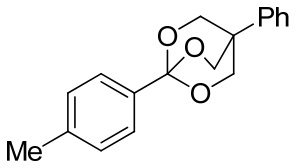
IR (KBr) 2898, 1612, 1515, 1338, 1219, 1109, 1009, 980, 829, 712 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.49 (s, 6H), 6.88-6.90 (m, 2H), 7.19-7.21 (m, 2H), 7.31-7.34 (m, 1H), 7.35-7.41 (m, 2H), 7.59-7.61 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 55.3, 72.1, 108.0, 113.3, 125.2, 127.0, 128.0, 129.1, 129.7, 135.9, 160.1;

ESIHRMS: Found: m/z. 299.1288. Calcd for: $C_{19}H_{20}O_3$: $(M+H)^+$ 299.1283.

4-phenyl-1-p-tolyl-2,6,7-trioxabicyclo[2.2.2]octane (3d):



Yield: 78%; White solid;

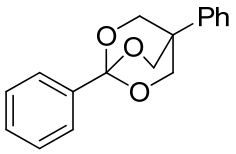
IR (KBr) 3383, 1705, 1635, 1610, 1274, 1218, 1020, 956 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 4.49 (s, 6H), 7.16-7.26 (m, 4H), 7.31-7.33 (m, 1H), 7.38-7.41 (m, 2H), 7.54-7.56 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 36.9, 72.1, 108.1, 125.2, 125.4, 128.0, 128.6, 129.1, 134.3, 136.0, 139.0;

ESIHRMS: Found: m/z. 283.1320. Calcd for: $C_{18}H_{19}O_3$: $(M+H)^+$ 283.1334.

1,4-diphenyl-2,6,7-trioxabicyclo[2.2.2]octane (3e):[55]



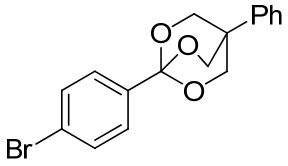
Yield: 79%; White solid;

IR (KBr) 2964, 1498, 1450, 1338, 1118, 1011, 972, 912, 758 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (s, 6H), 7.21-7.23 (m, 2H), 7.33-7.43 (m, 6H), 7.68-7.70 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 72.1, 108.0, 125.3, 125.6, 128.0, 128.1, 128.2, 129.2, 129.3, 136.0, 137.2;

1-(4-bromophenyl)-4-phenyl-2,6,7-trioxabicyclo[2.2.2]octane (3f):



Yield: 89%; White solid;

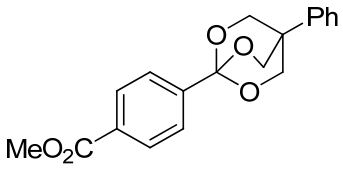
IR (KBr) 2965, 1338, 1270, 1218, 1027, 914, 771, 698 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (s, 6H), 7.19-7.21 (m, 2H), 7.34-7.36 (m, 1H), 7.39-7.42 (m, 2H), 7.49-7.56 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 72.1, 107.7, 123.5, 125.2, 127.5, 128.1, 129.1, 131.1, 135.6, 136.2;

ESIHRMS: Found: m/z 347.0292. Calcd for: $C_{18}H_{19}O_3$: $(M+H)^+$ 347.0298.

methyl 4-(4-phenyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)benzoate (3g):



Yield: 14%; White solid;

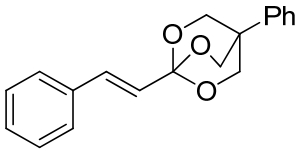
IR (KBr) 2989, 2856, 1740, 1385, 1218, 1099, 1014, 964, 912, 771 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 4.51 (s, 6H), 7.20-7.22 (m, 2H), 7.34-7.36 (m, 1H), 7.39-7.42 (m, 2H), 7.74-7.76 (m, 2H), 8.04-8.06 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 52.2, 72.1, 108.2, 125.2, 125.5, 128.0, 129.5, 139.2, 144.3, 152.1, 166.9, 169.7.

ESIHRMS: Found: m/z 327.1266. Calcd for: $C_{18}H_{19}O_3$: $(M+H)^+$ 327.1274.

(E)-4-phenyl-1-styryl-2,6,7-trioxabicyclo[2.2.2]octane (3h)



Yield: 93%; White solid;

IR (KBr) 2965, 2929, 1340, 1218, 1099, 1014, 962, 912, 701 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$): δ 4.42 (s, 6H), 6.18 (d, J = 16.1 Hz, 1H), 7.03 (d, J = 16.1 Hz, 1H), 7.17-7.19 (m, 2H), 7.25-7.34 (m, 4H), 7.37-7.42 (m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 71.9, 107.1, 123.4, 125.2, 127.0, 128.0, 128.3, 128.4, 129.1, 133.6, 135.6, 135.8;

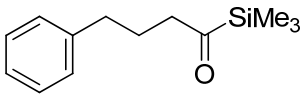
ESIHRMS: Found: m/z 295.1382. Calcd for: $C_{19}H_{18}O_3$: $(M+H)^+$ 295.1374.

General Procedure for the One-Pot Preparation of Orthocarboxylic Ester 3a-3h

To a 30 mL three-neck round-bottom flask equipped with a Soxhlet condenser containing 4 Å MS, a solution of aldehyde (0.5 mmol), triol (0.55 mmol), and PTSA·H_2O (0.055 mmol) in a mixture of DCE (5 mL) and benzene (5 mL) was added. After heating for the period described in the text, the reaction mixture was filtered through a pad of celite. The volatile materials were removed under reduced pressure and the crude material purified by column chromatography on Florisil (hexane-EtOAc = 2:1).

Chapter 2 Oxidative Cyclization of 4-Phenylbutanoylsilane to Prepare *α*-tetralone

4-phenyl-1-(trimethylsilyl)butan-1-one (4a):[56]



To a solution of 1-(phenoxymethyl)benzotriazole (3.0 g, 13.3 mmol) in THF (100 mL) at -78 °C was added *n*-BuLi (1.6 M in hexane, 8.3 mL, 13.3 mmol) and the solution was

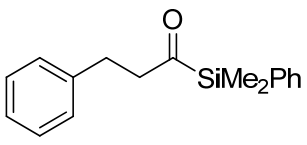
stirred for 5 min at this temperature. Chlorotrimethylsilane (1.7 mL, 13.3 mmol) was added, and the mixture was stirred at this temperature for 5 min, adding a second portion of *n*-BuLi (1.6 M in hexane, 8.3 mL, 13.3 mmol) and the solution was stirred for 5 min. After addition of 3-phenylpropyl bromide (2.0 mL, 13.3 mmol), the solution was kept at -78 °C for 5 min and allowed to increase to room temperature over 1 h. Then the solution was quenched with water and the organic layer was extracted with diethyl ether. The combined organic extracts were dried over magnesium sulphate, concentrated under reduced pressure, and the residue was dissolved in 40 mL of acetic acid and 10 mL of H_2O. The solution was heated at 80 °C for 0.5 h. After cooling, the solution was quenched with water and the organic layer extracted with diethyl ether, and the combined extracts were washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica (Hexane: EtOAc = 50: 1) to afford the compound in 56% yield (2 steps).

Colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (9H, s), 1.86 (2H, tt, J = 7.6, 7.6 Hz), 2.58 (2H, t, J = 7.6 Hz), 2.62 (2H, t, J = 7.2 Hz), 7.15-7.20 (3H, m), 7.26-7.29 (2H, m);

^{13}C NMR (100 MHz, $CDCl_3$) δ -3.2, 23.7, 35.2, 47.5, 125.8, 128.3, 128.4, 141.8, 248.1.

1-(dimethyl(phenyl)silyl)-3-phenylpropan-1-one (4d):[57]

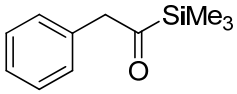


Colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.48 (6H, s), 2.78 (t, J = 8 Hz, 2H), 2.90 (t, J = 8 Hz, 2H), 7.08 (d, J = 8 Hz, 2H), 7.16 (t, J = 8 Hz, 1H), 7.24 (m, 2H), 7.41 (m, 3H), 7.53 (d, J = 7

Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, 28.2, 50.4, 125.9, 128.2, 128.3, 128.4, 129.9, 134.0, 134.2, 141.5, 245.1.

2-phenyl-1-(trimethylsilyl)ethanone (**4e**)**:**



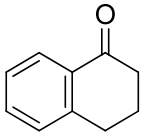
Colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (9H, s), 3.83 (2H, s), 7.10-7.12 (2H, m), 7.21-7.24 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.8, 55.5, 126.8, 128.6, 129.9, 133.1, 244.2.

General procedure for synthesis of *α*-tetralone

To a toluene solution (0.2 mL) of 4-phenyl-1-trimethylsilylbutan-1-one (44 mg, 0.2mmol) was added ethyl 2-iodoacetate (128 mg, 0.6 mmol) and the mixture was heated at 150 °C for 36 h in a sealed tube under N_2 atmospher. After evaporation of the solvent, the crude products were purified by PTLC (hexane: diethyl acetate = 5:1) to afford 1,2,3,4-tetrahydronaphthalen-1-one (**4b**) in 38% yield.

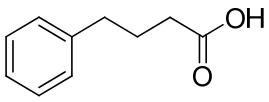
1,2,3,4-tetrahydronaphthalen-1-one (4b):[58]



Colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11-2.18 (2H, m), 2.65 (2H, t, J = 6.4 Hz), 2.97 (2H, t, J = 6 Hz), 7.24-7.32 (2H, m), 7.46-7.49 (1H, m), 8.05 (1H, d, J = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 29.8, 39.2, 126.5, 127.2, 1327, 133.4, 144.6, 198.4.

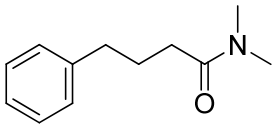
4-phenylbutanoic acid (4c):[59]



Colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96-2.01 (m, 2H), 2.39 (t, J = 7.5 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 7.17-7.21 (m, 3H), 7.28 (dd, J = 7.5, 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 33.3, 35.0, 126.0, 128.4, 128.5, 141.2, 179.5.

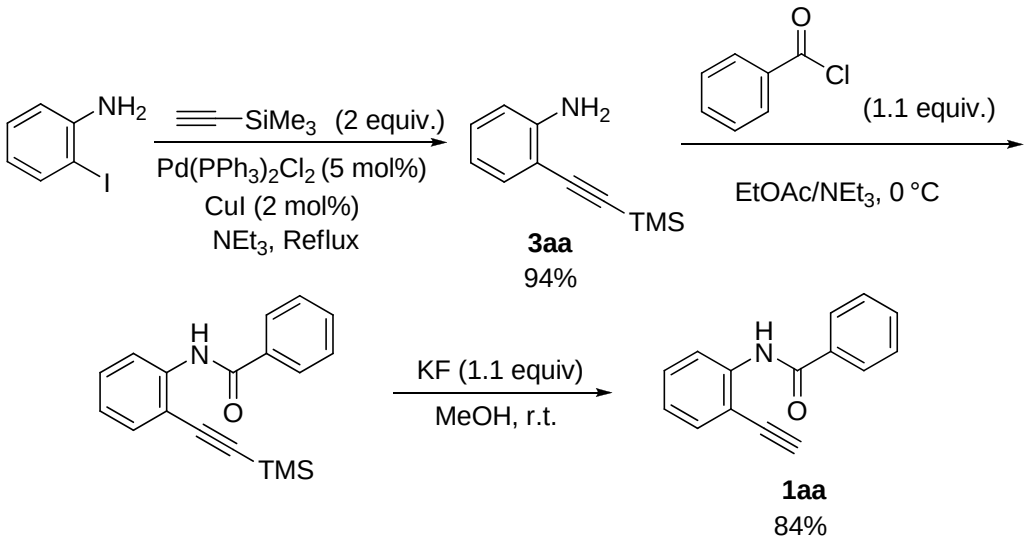
***N*,*N*-dimethyl-4-phenylbutanamide (4f):**[60]



^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87 (m, 2 H), 2.21 (t, 2 H, J = 7.4 Hz_2), 2.57 (t, 2 H, J = 7.5 Hz), 2.83 (s, 6 H), 7.06-7.20 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 32.4, 35.3, 35.4, 37.2, 125.8, 128.3, 128.5, 141.8, 172.8.

Chapter 3 $W(CO)_6$-Mediated 7-*endo* Cyclization of *N*-Acyl-*o*-alkynylanilines

General procedure to synthesis *N*-(2-ethynylphenyl)amide derivatives **1aa-1aj**



Typical procedure:[51]

Step 1.Procedure for Cassar-Sonogashira coupling reaction

To a solution of 2-iodoaniline (1.10 g, 5.0 mmol) in dry Et_3N (25 mL), ethynyltrimethyl -silane (1.41 mL, 10.0 mmol), $PdCl_2(PPh_3)_2$ (0.07 g, 0.1 mmol) and CuI (0.0048 g, 0.025 mmol) was added. The mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was filtered through Celite using toluene as solvent. The volatile material was then removed in vacuum and purified by flash column chromatography (silica gel; hexane: ethyl acetate = 1: 200) to give 2-((trimethylsilyl)ethynyl)aniline (0.89 g, 4.7 mmol) which was used for the next step.

Step 2 Procedure for the acetylation of amines

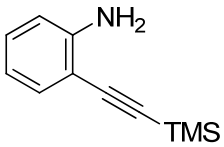
To a solution of the 2-((trimethylsilyl)ethynyl)aniline (1 mmol) in diethyl ether (5 mL), triethylamine (2 mmol) was added and the mixture was cooled to 0 ºC. Then, acetyl chloride (2 mmol) was added dropwise. The resulting mixture was stirred at the same temperature for 12 h until completion the reaction (TLC). The reaction was quenched with ice-water and extracted with ethyl acetate. The organic layer was then washed with $NaHCO_3$ (sat.) and brine, dried over magnesium sulfate and the solvent was removed

under reduced pressure, crude *N*-(2-((trimethylsilyl)ethynyl)phenyl)benzamide was afforded, which was used directly for the next step.

Step 3 Procedure for deprotonation

To a solution of crude *N*-(2-((trimethylsilyl)ethynyl)phenyl)benzamide in 30 mL of methanol was added potassium fluoride (0.290 g, 5.0 mmol) and stirred at room temperature for 2 h. After evaporation of solvent, crude *N*-(2-ethynylphenyl)benzamide was extracted with dichloromethane thrice. The organic layer was then washed with brine and dried with magnesium sulfate. After evaporation of solvent, the crude residue was purified by flash column chromatography (silica gel; hexane: ethyl acetate = 1:20), affording *N*-(2-ethynylphenyl)benzamide (0.97 g, 4.4 mmol) in 81% yield.

2-((trimethylsilyl)ethynyl)aniline (3aa):[18]

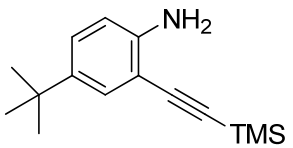


Yield: 94%; Yellow oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 8H), 4.24 (s, br, 2H), 6.68 (d, J = 7.8 Hz, 2H), 7.10-7.15 (m, 1H), 7.30-7.35 (m, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 0.2, 99.8, 101.9, 107.8, 114.2, 117.7, 128.7, 129.9, 132.3, 133.6, 148.3.

4-tert-butyl-2-((trimethylsilyl)ethynyl)aniline (3ab):[61]

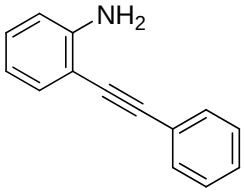


Yield: 86%; Yellow oil;

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.28 (s, 9H), 1.28 (s, 9H), 4.15 (s, br, 2H), 6.65 (d, J = 8.4 Hz, 1H), 7.19 (dd, J = 2.1, 8.4, 1H), 7.32 (d, J = 2.1 Hz, 1 H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 0.7, 31.3, 33.8, 99.0, 102.4, 107.3, 114.1, 127.2, 128.7, 140.6, 145.9.

2-(phenylethynyl)aniline (3ac):[62]

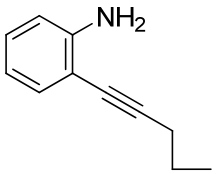


Yield 96%; Light yellow solid; mp: 93-95 °C;

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (s, br, 2H), 6.76-6.71 (m, 2H), 7.16 (ddd, J = 1.6, 7.4, 8.2 Hz, 1H), 7.40-7.35 (m, 4H), 7.56-7.53 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 85.8, 94.6, 107.9, 114.3, 117.9, 123.3, 128.2, 128.3, 129.7, 131.4, 132.1, 147.7.

2-(pent-1-ynyl)aniline (3ad):[48a]

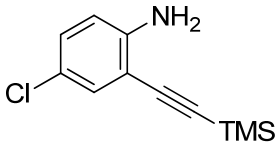


Yield: 52%; Light yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J = 6 Hz, 3H), 1.59 (m, 2H), 2.40 (t, J = 6 Hz, 2H), 4.10 (s, br, 2H), 6.39-7.29 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 21.6, 22.3, 77.1, 95.5, 108.9, 114.1, 117.8, 128.7, 132.0, 147.5.

4-chloro-2-((trimethylsilyl)ethynyl)aniline (3ae):[46a]

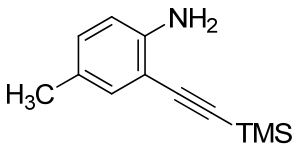


Yield: 87%; Yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 2.4 Hz, 1H), 7.07 (dd, J = 2.4, 8.7 Hz, 1H), 6.60 (d, J = 8.7 Hz, 1H), 4.24 (s, br, 2H), 0.26 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 0.0, 100.3, 101.0, 109.0, 115.2, 121.9, 129.8, 131.4, 146.8.

4-methyl-2-((trimethylsilyl)ethynyl)aniline (3af):[46a]

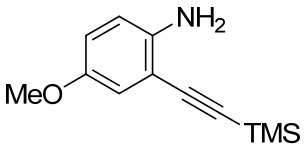


Yield: 92%, Yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ, 0.26 (s, 9H), 2.23 (s, 3H), 4.10(br, 2H), 6.61 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.14 (s, 1H);

^{13}C (100 MHz, $CDCl_3$) δ 0.1, 20.2, 99.3 101.9, 107.7, 114.3, 127.0, 130.8, 132.4, 145.9.

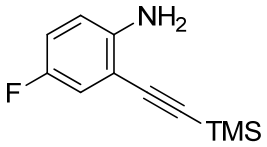
4-methoxy-2-((trimethylsilyl)ethynyl)aniline (3ag):[63]



Yield: 90%;

^{1}H NMR (400 MHz, $CDCl_3$) δ, 0.26 (s, 9H), 3.85 (s, 3H), 4.10 (br, 2H), 6.49 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 7.27 (s, 1H);

4-Fluoro-2-(trimethylsilylethynyl)aniline (**3ah**)**:**[64]

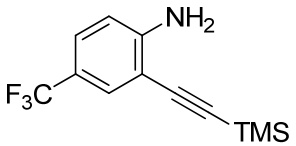


Yield: 85%; Brown oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (s, 9H), 4.08 (s, br, 2H), 6.59 (dd, 1H, J = 8.5 Hz, 3 Hz), 6.83 (td, 1H, J = 8.5 Hz, 3 Hz), 6.97 (dd, 1H, J = 8.5 Hz, 3 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 0.0, 100.7 (d, J = 1.9 Hz), 100.8, 108.5 (d, J = 9.7 Hz), 115.2 (d, J = 8.5 Hz), 117.1 (d, J = 22.9 Hz), 117.8 (d, J = 22.9 Hz), 144.7, 155.1 (d, J = 234.7 Hz);

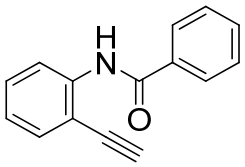
4-trifluoro-2-((trimethylsilyl)ethynyl)aniline (3ai):[65]



Yield: 86% orange oil;

1H NMR ($CDCl_3$) δ: 0.27 (s, 9H), 4.54 (s, 2H), 6.70 (d, J = 5.5 H_Z, 1H), 7.31 (dd, J = 5.5, 1.2 H_Z, 1H), 7.54 (d, J = 1.2 H_Z, 1H).

***N*-(2-ethynylphenyl)benzamide (1aa):[51]**



Yield: 81%; White solid; mp: 104-106 °C;

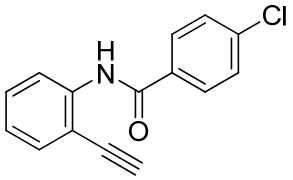
IR (NaCl, CH_2Cl_2) 3402, 3296, 3053, 2100, 1678, 1578, 1307, 1265, 894, 733, 706, 673 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 1H), 7.09 (dt, J = 0.9, 7.7 Hz, 1H), 7.44 (t, J = 8.0, 1H), 7.49-7.62 (m, 4H), 7.93 (dt, J = 1.5, 6.6 Hz, 2H), 8.62 (d, J = 8.4 Hz, 1H), 8.79 (s, br, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 84.7, 111.0, 119.3, 123.4, 127.0, 128.9, 130.3, 132.0, 132.1, 134.7, 139.8, 165.1;

ESIHRMS: Found: m/z 222.0928. Calcd for $C_{15}H_{12}NO$: $(M+H)^+$ 222.0919.

4-chloro-*N*-(2-ethynylphenyl)benzamide (1ab):



Yield: 75%; White solid; mp: 90-92 °C;

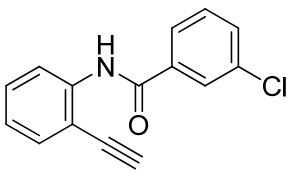
IR (NaCl, CH_2Cl_2) 3402, 3294, 3053, 1684, 1580, 1312, 1256, 1096, 895, 851, 738, 704 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (1H, s), 6.93 (t, J = 7.5 Hz, 1H), 7.17-7.33 (m, 4H), 7.75 (d, J = 8.4 Hz, 2H), 8.28 (d, J = 7.8 Hz, 1H), 8.85 (s, br, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 79.4, 84.8, 111.1, 119.4, 123.7, 128.5, 129.2, 130.4, 132.2, 133.2, 138.4, 139.5, 164.2;

ESIHRMS: Found: m/z 256.0532. Calcd for $C_{15}H_{11}NOCl$: $(M+H)^+$ 256.0529.

3-chloro-*N*-(2-ethynylphenyl)benzamide (1ac):



Yield: 77%; White solid; mp: 85-87 °C;

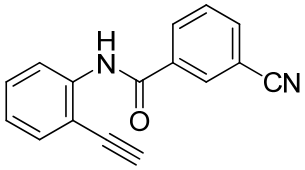
IR (NaCl, CH_2Cl_2) 3464, 3055, 1682, 1593, 1340, 1265, 1206, 887, 871, 840, 732, 704, 646 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.39-7.54 (m, 4H), 7.76 (d, J = 7.8 Hz, 1H), 7.91 (s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.71 (s, br, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 79.3, 85.0, 111.2, 119.4, 123.8, 125.0, 127.7, 130.2, 130.4, 132.1, 132.2, 135.2, 136.5, 139.4, 163.8;

ESIHRMS: Found: m/z 256.0540. Calcd for $C_{15}H_{11}NOCl$: $(M+H)^+$ 256.0529.

3-cyano-*N*-(2-ethynylphenyl)benzamide (1ad):



Yield: 73%; White solid; mp: 115-116 °C;

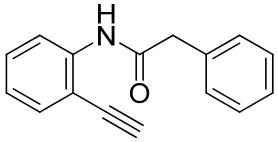
IR (NaCl, CH_2Cl_2) 3404, 3296, 3053, 1686, 1580, 1310, 1265, 894, 810, 736, 704, 680, 619, 548 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 1H), 7.40-8.14 (m, 6H), 8.19 (s, 1H), 8.52 (d, J = 7.8 Hz, 1H), 8.71 (s, br, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 79.2, 85.2, 111.4, 113.5, 117.9, 119.5, 124.2, 130.0, 130.5, 130.9, 131.1, 132.3, 135.2, 136.0, 139.0, 163.0;

ESIHRMS: Found: m/z 247.0870. Calcd for $C_{16}H_{11}N_2O$: $(M+H)^+$ 247.0871.

***N*-(2-ethynylphenyl)-2-phenylacetamide (1ae):**



Yield: 65%; White solid; mp: 85-87 °C;

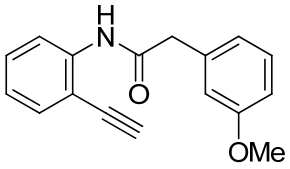
IR (NaCl, CH_2Cl_2) 3456, 2102, 1636, 1522, 1447, 1265, 895, 729, 704, 660, 617, 534 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 3.28 (s, 1H), 4.04 (s, 2H), 7.24 (t, J = 7.5 Hz,1H), 7.55-7.68 (m, 7H), 8.24 (s, br, 1H), 8.70 (d, J = 9.0 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 45.3, 76.7, 78.4, 84.2, 110.8, 118.9, 123.4, 127.7, 130.2, 131.9, 134.1, 139.6, 169.2;

ESIHRMS: Found: m/z 236.1080. Calcd for $C_{16}H_{14}NO$: $(M+H)^+$ 236.1075.

_N_-(2-ethynylphenyl)-2-(3-methoxyphenyl)acetamide (1af):



Yield: 66%; Off-white solid; mp: 62-66 °C;

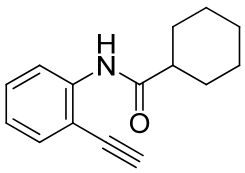
IR (NaCl, CH_2Cl_2) 3437, 3296, 3057, 2100, 1674, 1584, 1491, 1264, 1153, 1040, 733, 702, 617, 579, 540, 523 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 1H), 3.77 (s, 2H), 3.82 (s, 3H), 6.87-7.04 (m, 4H), 7.29-7.36 (m, 3H), 8.04 (s, br, 1H), 8.43 (d, J = 8.1 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 45.3, 55.3, 78.6, 84.2, 110.8, 113.6, 115.4, 119.0, 122.4, 123.4, 130.2, 130.5, 131.9, 135.6, 141.6, 160.3, 169.0;

ESIHRMS: Found: m/z 266.1178. Calcd for $C_{17}H_{16}NO_2$: $(M+H)^+$ 266.1181.

_N_-(2-ethynylphenyl)cyclohexanecarboxamide (1ag):



Yield: 75%; White solid; mp: 87-89 °C;

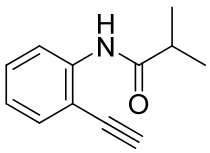
IR (NaCl, CH_2Cl_2) 3465, 3296, 2986, 2102, 1681, 1578, 1445, 1265, 1169, 949, 727, 702, 617, 530 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.15–2.10 (m, 10H), 2.30 (tt, J = 3.9, 11.8 Hz,1H), 3.53 (s, 1H), 7.02 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 8.02 (s, br, 1H), 8.44 (d, J = 8.4 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 25.7, 29.7, 46.7, 79.4, 84.3, 110.6, 119.4, 123.1, 130.3, 132.1, 139.8, 174.3;

ESIHRMS: Found: m/z 228.1381. Calcd for $C_{15}H_{18}NO$: $(M+H)^+$ 228.1388.

_N_-(2-ethynylphenyl)isobutyramide (1ah):



Yield: 77%; White solid; mp: 61-63 °C;

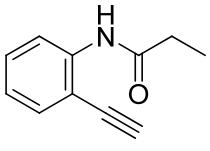
IR (NaCl, CH_2Cl_2) 3464, 3258, 2100, 1636, 1520, 1265, 729, 705, 667, 601, 553, 542, 530 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, J = 6.9 Hz, 6H), 2.58 (m, 1H), 3.53 (s, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 8.02 (s, br, 1H), 8.43 (d, J = 8.4 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 37.0, 79.4, 84.4, 110.7, 119.3, 123.2, 130.2, 132.1, 139.8, 175.2;

ESIHRMS: Found: m/z 188.1074. Calcd for $C_{12}H_{14}NO$: $(M+H)^+$ 188.1075.

_N_-(2-ethynylphenyl)propionamide (1ai):



Yield: 83%; White solid; mp: 52-54 °C;

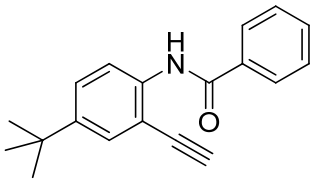
IR (NaCl, CH_2Cl_2) 3456, 3265, 2100, 1635, 1508, 1444, 1265, 730, 705, 664, 617, 546, 536 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.5 Hz, 3H), 2.44 (q, J = 7.5 Hz, 2H), 3.50 (s, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.94 (s, 1H), 8.41 (d, J = 8.1 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6, 31.0, 79.3, 84.4, 110.5, 119.3, 123.2, 130.2, 132.1, 139.7, 172.0;

ESIHRMS: Found: m/z 174.0922. Calcd for $C_{11}H_{12}NO$: $(M+H)^+$ 174.0919.

_N_-(4-tert-butyl-2-ethynylphenyl)benzamide (1aj) :



Yield: 76%; White solid; mp: 133-137 °C;

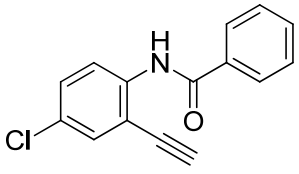
IR (NaCl, CH_2Cl_2) 3456, 3371, 2102, 1645, 1518, 1310, 736, 704, 667, 637, 527 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 3.58 (s, 1H), 7.53 (m, 5H), 7.92 (s, 1H), 8.52 (d, J = 7.2 Hz, 1H), 8.73 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 31.2, 34.4, 80.0, 84.1, 110.7, 119.2, 127.1, 127.6, 128.9, 129.0, 132.0, 134.9, 137.4, 146.6, 165.1;

ESIHRMS: Found: m/z 278.1552. Calcd for $C_{19}H_{20}NO$: $(M+H)^+$ 278.1545.

_N_-(4-chloro-2-ethynylphenyl)benzamide (1ak):



Yield: 84%; White solid; mp: 136-138 °C;

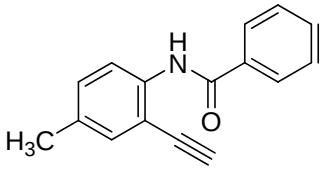
IR (NaCl, CH_2Cl_2) 3294, 3053, 1265, 738, 496, 438, 411cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 1H), 7.39 (dd, J = 2.4, 8.9, 1H), 7.47-7.61 (m, 4H), 7.90-7.92 (m, 2H), 8.58 (d, J = 8.9, 1H), 8.73 (s, br, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 78.2, 85.7, 112.4, 120.5, 127.0, 128.3, 129.0, 130.4, 131.7, 132.3, 134.4, 138.4, 165.2;

ESIHRMS: Found: m/z 256.0529. Calcd for $C_{15}H_{11}ClNO$: $(M+H)^+$ 256.0529.

_N_-(4-methyl-2-ethynylphenyl)benzamide (1al):



Yield: 87%; White solid; mp: 106-107 °C;

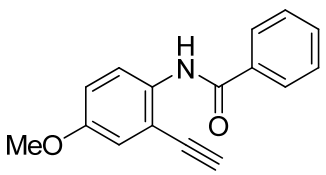
IR (NaCl, CH_2Cl_2) 3294, 3053, 1265, 738, 494, 476, 444, 415 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.55 (s, 1H), 7.24 (d, J = 8.7, 1H), 7.32 (s, 1H), 7.49-7.58 (m, 3H), 7.92 (d, J = 7.2, 2H), 8.47 (d, J = 8.4, 1H), 8.73 (s, br, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 79.6, 84.2, 110.9, 119.2, 127.0, 128.9, 131.1, 132.0, 132.4, 133.1, 134.9, 137.4, 165.1;

ESIHRMS: Found: m/z 236.1080. Calcd for $C_{16}H_{14}NO$: $(M+H)^+$ 236.1075.

_N_-(4-methoxy-2-ethynylphenyl)benzamide (1am):



Yield: 78%; White solid; mp: 119-121 °C;

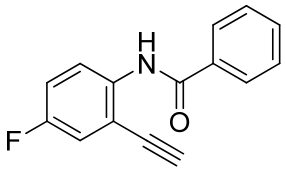
IR (NaCl, CH_2Cl_2) 3294, 3053, 1522, 1265, 738, 492, 465, 434, 415 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 1H), 3.80 (s, 3H), 6.97-7.02 (m, 2H), 7.48-7.55 (m, 3H), 7.90 (d, J = 8.0, 2H), 8.40 (d, J = 9.0, 1H), 8.60 (s, br, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 79.4, 84.4, 112.2, 116.4, 116.6, 121.0, 127.0, 128.9, 131.9, 133.4, 134.8, 155.3, 165.0;

ESIHRMS: Found: m/z 252.1030. Calcd for $C_{16}H_{14}NO_2$: $(M+H)^+$ 252.1025.

_N_-(4-fluoro-2-ethynylphenyl)benzamide (1an):



Yield: 82%; White solid; mp: 105-106 °C;

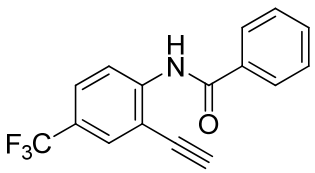
IR (NaCl, CH_2Cl_2) 3294, 3053, 1678, 1265, 738, 491, 462, 430, 405 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 1H), 7.11-7.21 (m, 2H), 7.49-7.60 (m, 3H), 7.91 (d, J = 7.8, 2H), 8.58 (dd, J = 5.2, 9.2, 1H), 8.68 (s, br, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 78.37 ($^{5}J_{C\text{-}F}$ = 3.1 Hz), 85.5, 112.44 ($^{3}J_{C\text{-}F}$ = 9.3 Hz), 117.44 ($^{2}J_{C\text{-}F}$ = 22 Hz), 118.48 ($^{2}J_{C\text{-}F}$ = 24.4 Hz), 121.09 ($^{3}J_{C\text{-}F}$ = 7.9 Hz), 127.0, 128.9, 132.1, 134.5, 136.18 ($^{4}J_{C\text{-}F}$ = 2.8 Hz), 158.0 ($^{1}J_{C\text{-}F}$ = 242.6 Hz), 165.1;

ESIHRMS: Found: m/z 240.0817. Calcd for $C_{15}H_{11}FNO$: $(M+H)^+$ 240.0825.

_N_-(4-trifluoromethyl-2-ethynylphenyl)benzamide (1ap):



Yield: 76%; White solid; mp: 99-101 °C;

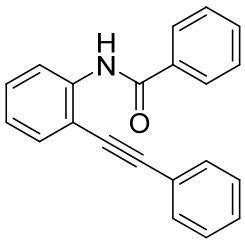
IR (NaCl, CH_2Cl_2) 3294, 3053, 1526, 1265, 740, 492, 480, 465, 448, 432 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 1H), 7.51-7.62 (m, 3H), 7.65 (d, J = 8.8, 1H), 7.76 (s, 1H), 7.92 (d, J = 7.6, 2H), 8.77 (d, J = 8.8, 1H), 8.90 (s, br, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 78.1, 86.1, 111.1, 119.1, 123.6 ($^1J_{C\text{-}F}$ = 270 Hz), 125.5 ($^2J_{C\text{-}F}$ = 33 Hz), 127.1, 127.28 ($^3J_{C\text{-}F}$ = 3.6 Hz), 129.0, 129.23 ($^3J_{C\text{-}F}$ = 3.8 Hz), 132.5, 134.1, 142.5, 165.3;

ESIHRMS: Found: m/z 290.0791. Calcd for $C_{16}H_{11}F_3NO$: $(M+H)^+$ 290.0793.

***N*-(2-(phenylethynyl)phenyl)benzamide (1aa')**:[49n, 66]



Yield: 85%; White solid; mp: 117-119 °C;

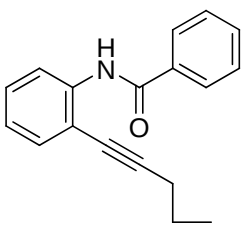
IR (NaCl, CH_2Cl_2) 3456, 3236, 3053, 2304, 1678, 1580, 1521, 1448,1421, 1310, 759, 750, 698, 621, 557 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (t, J = 7.4 Hz, 1H), 7.26-7.56 (m, 10H), 7.99-8.11 (m, 2H), 8.64 (d, J = 8.4 Hz, 1H), 8.96 (s, br, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 84.5, 97.0, 112.3, 119.2, 122.3, 123.6, 127.0, 128.7, 128.9, 129.0, 130.0, 131.4, 131.5, 132.1, 135.0, 139.1, 165.1;

ESIHRMS: Found: m/z 298.1232. Calcd for $C_{21}H_{16}NO$: $(M+H)^+$ 298.1232.

***N*-(2-(pent-1-ynyl)phenyl)benzamide (1ab'):**[49n]



Yield: 45%; Pale yellow oil;

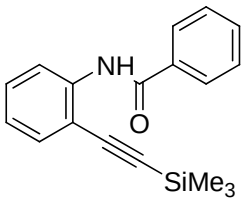
IR (NaCl, CH_2Cl_2) 3394, 2962, 1682, 1581, 1520, 1450, 1311, 756 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, J = 1.67, 3H), 1.61 (qt, J = 7.2, 7.2 Hz, 2H), 2.49 (t, J = 6.9 Hz, 2H), 7.04 (td, J = 1.2 Hz, 7.5 Hz, 1H), 7.31-7.60 (5H, m), 7.93 (d, J = 6.9 Hz, 2H), 8.60 (d, J = 8.1 Hz, 1H), 8.87 (s, br, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 21.4, 22.1, 40.1, 96.0, 112.9, 118.8, 123.2, 126.8, 128.6, 128.8, 130.3, 131.3, 131.6, 131.7, 132.9, 138.9, 164.9;

ESIHRMS: Found: m/z 264.1391. Calcd for $C_{18}H_{18}NO$: $(M+H)^+$ 264.1388.

_N_-(2-((trimethylsilyl)ethynyl)phenyl)benzamide (1ac'):[51a]



Yield: 83%; White solid; mp: 85-89 °C;

IR (NaCl, CH_2Cl_2) 3456, 3377, 2986, 2149, 1678, 1578, 1521, 1421, 1309, 1265, 894, 864, 844, 758, 717, 698 cm^{-1};

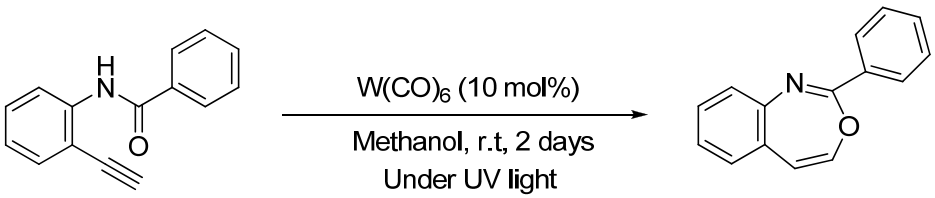
^1H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 9H), 7.05 (td, J = 0.9 Hz, 7.5 Hz, 1H), 7.38-7.64 (m, 5H), 7.97 (m, 2H), 8.65 (d, J = 8.4 Hz, 1H), 8.97 (s, br, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 100.2, 102.4, 111.9, 118.7, 123.1, 126.9, 128.6, 129.9, 131.4, 131.8, 134.6, 139.5, 164.7;

ESIHRMS: Found: m/z 294.1320. Calcd for $C_{18}H_{20}NOSi$: $(M+H)^+$ 294.1314.

General procedure for $W(CO)_6$-mediated 7-*endo* cyclization of *N*-Acyl-*o*-alkynylanilines

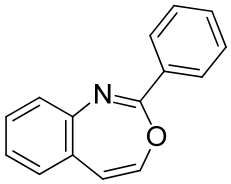
General Procedure:



1aa **2aa**
86%

To a solution of *N*-(2ethynyl phenyl) benzamide, (**1aa**) (66.4 mg, 0.3 mmol) in methanol (3 mL) was added $W(CO)_6$ (10.5 mg, 0.03 mmol) at room temperature and stirred for 2 days under UV light. Methanol was then removed in vacuum and the crude residue was purified by flash column chromatography (silica gel; hexane: ethyl acetate = 19: 1), affording 2-phenylbenzo[d][1,3]oxazepine (**2aa**) (57.0 mg, 0.26 mmol) in 86% yield.

2-phenylbenzo[*d*][1,3]oxazepine (2aa):[67]



Yield: 86%; Colorless oil;

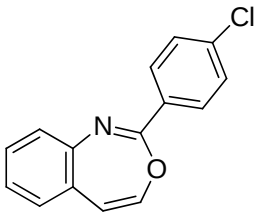
IR (NaCl, CH_2Cl_2) 2089, 1645, 1636, 1452, 1342, 1265, 1205, 744, 732, 704, 667 632, 597 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 4 Hz, 1H), 7.30-7.75 (m, 9H) 8.42 (d, J = 8.0 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 108.5, 116.4, 120.9, 123.9, 124.9, 127.6, 128.6, 129.1, 130.8, 131.9, 134.6, 136.0, 168.7;

ESIHRMS: Found: m/z 222.0922. Calcd for $C_{15}H_{12}NO$: $(M+H)^+$ 222.0919.

2-(4-chlorophenyl)benzo[*d*][1,3]oxazepine (2ab):



Yield: 98%; White Solid; mp: 113-115 °C;

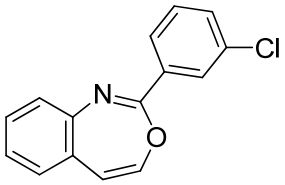
IR (NaCl, CH_2Cl_2) 3055, 1682, 1645, 1593, 1452, 1340, 1265, 887, 840, 732, 704, 640, 601, 528 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (d, *J* = 3.6 Hz, 1H), 7.23 (d, *J* = 3.6 Hz, 1H), 7.28-7.40 (m, 2H), 7.49-7.67 (m, 5H), 8.36 (d, *J* = 8.4 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) *δ* 108.9, 116.3, 120.9, 124.1, 125.0, 127.1, 128.9, 130.6, 130.7, 132.9, 135.9, 138.3 167.5;

ESIHRMS: Found: m/z 256.0534. Calcd for $C_{15}H_{11}NOCl$: $(M+H)^+$ 256.0529.

2-(3-chlorophenyl)benzo[*d*][1,3]oxazepine (2ac):



Yield: 97%; White Solid; mp: 95-99 °C;

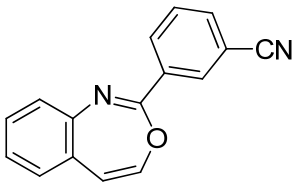
IR (NaCl, CH_2Cl_2) 3243, 2089, 1635, 1265, 894, 729, 705, 667, 557, 542 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) *δ* 6.63 (d, *J* = 3.6 Hz, 1H), 7.23 (d, *J* = 3.6 Hz, 1H), 7.29-7.47(m, 3H), 7.55 (t, *J* = 7.5 Hz, 3H), 7.71 (s, 1H), 8.39 (d, *J* =8.1 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) *δ* 109.2, 116.4, 120.9, 124.2, 125.1, 127.1, 129.1, 129.9, 130.8, 131.9, 134.8, 135.9, 136.3, 167.1;

ESIHRMS: Found: m/z 256.0527. Calcd for $C_{15}H_{11}NOCl$: $(M+H)^+$ 256.0529.

3-(benzo[*d*][1,3]oxazepin-2-yl)benzonitrile (2ad):



Yield: 50%; White Solid; mp: 73-75 °C.

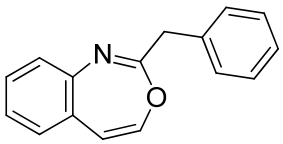
IR (NaCl, CH_2Cl_2) 3057, 2075, 1645, 1452, 1265, 894, 736, 704, 678, 634, 522 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 6.67 (d, J = 3.9, 1H), 7.16 (d, J=3.6 Hz, 1H), 7.32-7.44 (m, 2H), 7.61-7.70 (m, 2H), 7.88 (t, J = 1.2 Hz, 1H), 7.97 (dt, J = 1.5, 7.8 Hz, 1H), 8.02 (1H, s), 8.38 (1H, d, J = 8.1 Hz);

^{13}C NMR (400 MHz) δ ppm 109.9, 113.3, 116.4, 117.6, 121.2, 124.5, 125.4, 126.6, 129.7, 130.8, 132.5, 133.0, 135.0, 135.92, 135.95, 166.2;

ESIHRMS: Found: m/z 247.0873. Calcd for $C_{16}H_{11}N_2O$: $(M+H)^+$ 247.0871.

2-benzylbenzo[*d*][1,3]oxazepine (2ae):



Yield: 95%; White Solid; mp: 67-69 °C;

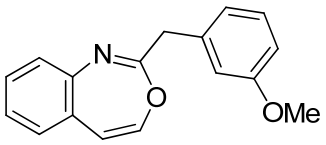
IR (NaCl, CH_2Cl_2) 3053, 2684, 2304, 1636, 1607, 1452, 1265, 894, 736, 705, 669, 609, 597, 551 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (s, 2H), 6.58 (d, J = 3.6 Hz, 1H), 7.20-7.36 (m, 7H), 7.45 (d, J = 3.9 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 8.4 Hz, 1H);

^{13}C NMR (400 MHz) δ ppm 42.9, 106.3, 106.9, 109.4, 116.7, 120.8, 123.8, 124.8, 125.2, 127.4, 130.3, 133.4, 135.8, 169.3;

ESIHRMS: Found: m/z 236.1071. Calcd for $C_{16}H_{14}NO$: $(M+H)^+$ 236.1075.

2-(3-methoxybenzyl)benzo[*d*][1,3]oxazepine (2af):



Yield: 96%; Colorless oil;

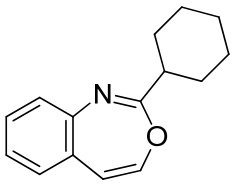
IR (NaCl) 3377, 2089, 1684, 1636, 1491, 1263, 1151, 1050, 731, 715, 692, 667, 601, 570, 536 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 4.17 (s, 2H), 6.58 (d, J = 3.3 Hz, 1H), 6.79-6.89 (m, 3H), 7.25-7.36 (m, 3H), 7.45 (d, J = 3.9 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 8.49 (d, J = 8.4 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 43.0, 55.2, 109.4, 112.8, 114.8, 116.7, 120.8, 121.3, 123.8, 124.9, 125.2, 129.9, 130.3, 134.8, 135.7, 159.9, 169.1;

ESIHRMS: Found: m/z 266.1182. Calcd for $C_{17}H_{16}NO_2$: $(M+H)^+$ 266.1181.

2-cyclohexylbenzo[d][1,3]oxazepine (2ag):



Yield: 85%; White Solid; mp: 97-98 °C;

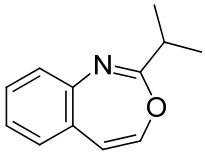
IR (NaCl, CH_2Cl_2) 3456, 3377, 2089, 1683, 1635, 1490, 1346, 1107, 1049, 731, 715, 692, 667, 617, 570, 536 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.23-1.47(m, 3H), 1.61-1.78 (m, 3H), 1.87-2.03 (m, 4H), 3.00 (m, 1H), 6.63 (d, J = 3.6 Hz, 1H), 7.23-7.37 (m, 2H), 7.49 (d, J = 3.6 Hz, 1H) 7.55 (d, J = 7.2 Hz, 1H), 8.49 (1H, d, J = 8.1 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6, 25.7, 29.6, 43.7, 108.8, 116.8, 120.6, 123.5, 124.6, 125.0, 130.4, 135.7, 174.9;

ESIHRMS: Found: m/z 228.1391. Calcd for $C_{15}H_{18}NO$: $(M+H)^+$ 228.1388.

2-isopropylbenzo[*d*][1,3]oxazepine (2ah):



Yield: 95%; White Solid; mp: 50-52 °C;

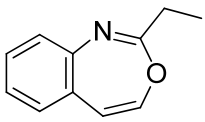
IR (NaCl, CH_2Cl_2) 3387, 2088, 1635, 1451, 1265, 729, 704, 667, 542, 535 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, J = 6.6 Hz, 6H), 3.30 (m, 1H), 6.64 (d, J = 3.6 Hz, 1H), 7.24-7.38 (m, 2H), 7.48 (d, J = 3.9 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 33.7, 109.0, 116.8, 120.7, 123.6, 124.5, 125.1, 130.3, 135.8, 175.7;

ESIHRMS: Found: m/z 188.1080. Calcd for $C_{12}H_{14}NO$: $(M+H)^+$ 188.1075.

2-ethylbenzo[*d*][1,3]oxazepine (2ai):



Yield: 83%; White Solid; mp: 58-62 °C;

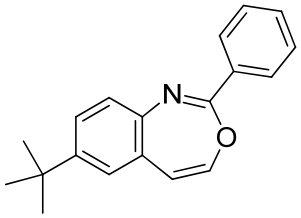
IR (NaCl, CH_2Cl_2) 3456, 2088, 1645, 1635, 1452, 1265, 736, 704, 545, 536 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.2 Hz, 3H), 2.93 (q, J = 7.2 Hz, 2H), 6.62 (d, J = 3.6 Hz, 1H), 7.23-7.39 (m, 2H), 7.44 (d, J = 3.6 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 8.46 (d, J = 8.1 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 29.1, 108.9, 116.5, 120.7, 123.5, 124.5, 125.0, 130.1, 135.6, 172.1;

ESIHRMS: Found: m/z 174.0919. Calcd for $C_{11}H_{12}NO$: $(M+H)^+$ 174.0919.

7-tert-butyl-2-phenylbenzo[*d*][1,3]oxazepine (2aj):



Yield: 88%; White Solid; mp: 72-73 °C;

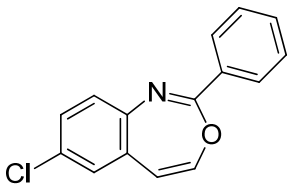
IR (NaCl, CH_2Cl_2) 3456, 3053, 2966, 2305, 1681, 1645, 1363, 1337, 1265, 883, 823, 736, 665, 636, 540, 524 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 9H), 6.57 (d, J = 3.9 Hz, 1H), 7.25 (d, *J* = 3.9 Hz, 1H), 7.43-7.60 (m, 5H), 7.70 (d, *J* = 6.6 Hz, 2H), 8.29 (d, *J* = 8.7 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 31.7, 34.7, 108.8, 115.8, 117.0, 122.8, 127.5, 128.5, 129.1, 130.7, 131.7, 134.0, 134.7, 147.1, 168.5;

ESIHRMS: Found: m/z 278.1543. Calcd for $C_{19}H_{20}NO$: $(M+H)^+$ 278.1545.

7-chloro-2-phenylbenzo[d][1,3]oxazepine (2ak):



Yield: 88%; White Solid; mp: 100-102 °C;

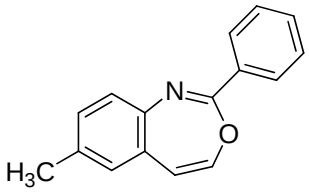
IR (NaCl, CH_2Cl_2) 3053, 1687, 1645, 1365, 1337, 1265, 737, 494, 426, 414 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (d, J = 3.8 Hz, 1H), 7.32-7.35 (m, 2H), 7.52-7.55 (m, 2H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.60-7.74 (m, 3H), 8.34 (d, *J* = 8.8 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 107.8, 117.8, 120.5, 125.1, 128.6, 128.8, 129.1, 129.4, 132.0, 132.1, 134.1, 134.4, 168.5;

ESIHRMS: Found: m/z 256.0536. Calcd for $C_{15}H_{11}ClNO$: $(M+H)^+$ 256.0529.

7-methyl-2-phenylbenzo[*d*][1,3]oxazepine (2al) :[67b]



Yield: 90%; White solid; mp: 89-91 °C;

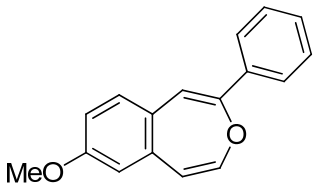
IR (NaCl, CH_2Cl_2) 3053, 1685, 1367, 1338, 1265 741, 493, 450, 434, 414 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 6.52 (d, J = 3.7 Hz, 1H), 7.19 (dd, J = 1.2, 8.4, 1H), 7.24-7.25 (m, 1H), 7.38 (s, 1H), 7.49-7.72 (m, 5H), 8.26 (d, J = 8.4 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 108.4, 116.0, 120.8, 126.2, 127.6, 128.5, 129.1, 131.0, 131.7, 133.5, 134.2, 134.7, 168.5;

ESIHRMS: Found: m/z 236.1069. Calcd for $C_{16}H_{14}NO$: $(M+H)^+$ 236.1075.

7-methoxy-2-phenylbenzo[*d*][1,3]oxazepine (2am):



Yield: 92%; White Solid; mp: 114-115°C;

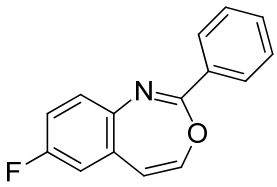
IR (NaCl, CH_2Cl_2) 3053, 2922, 2305, 1681, 1265 748, 496, 465, 453,428 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.54(m, 1H), 6.98-7.00 (dd, J = 2.5, 8.9, 1H), 7.06 (d, J = 2.5 Hz, 1H), 7.25 (m, 1H), 7.49-7.72 (m, 5H), 8.32 (d, J = 8.9 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 103.6, 108.5, 113.3, 117.2, 128.2, 128.5, 129.1, 130.7, 131.7, 131.8, 134.6, 156.7, 168.3;

ESIHRMS: Found: m/z 252.1023. Calcd for $C_{16}H_{14}NO_2$: $(M+H)^+$ 252.1025.

7-fluoro-2-phenylbenzo[*d*][1,3]oxazepine (2an):



Yield: 89%; White Solid; mp: 76 °C;

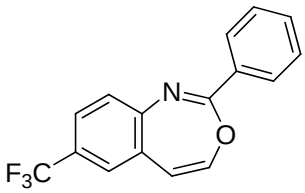
IR (NaCl, CH_2Cl_2) 3053, 2986, 1688, 1465, 1265 738, 492, 480, 460, 446, 430 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, J = 4.0 Hz, 1H), 7.08-7.13 (m, 1H), 7.23-7.26 (m, 1H), 7.32 (d, J = 3.6, 1H), 7.50-7.63 (m, 3H), 7.71-7.73 (m, 2H), 8.38 (dd, J = 4.7, 9.0, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 106.4 ($^2J_{C\text{-}F}$ = 23.8 Hz), 108.2 ($^4J_{C\text{-}F}$ = 4.1 Hz), 112.6 ($^2J_{C\text{-}F}$ = 24.8 Hz), 117.4 ($^3J_{C\text{-}F}$ = 9.0 Hz), 128.6, 129.08, 129.12, 131.7 ($^3J_{C\text{-}F}$ = 10.0 Hz), 132.0, 132.4, 134.2, 159.8 ($^1J_{C\text{-}F}$ = 238.9 Hz), 168.4.

ESIHRMS: Found: m/z 240.0828. Calcd for $C_{15}H_{11}FNO$: $(M+H)^+$ 240.0825.

7-trifluoromethyl-2-phenylbenzo[d][1,3]oxazepine (2ap):



Yield: 88%; White Solid; mp: 112 °C;

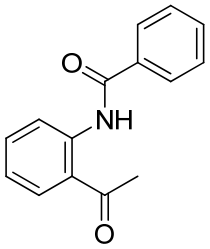
IR (NaCl, CH_2Cl_2) 3053, 1694, 1645, 1337, 1265 740, 492, 465, 450, 434 cm^{-1};

^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, J = 3.8 Hz, 1H), 7.42 (d, J = 3.8, 1H), 7.54-7.77 (m, 6H), 7.90 (s, 1H), 8.48 (d, J = 8.7, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 108.4, 116.6, 118.3 (q, $^3J_{C\text{-}F}$ = 4.2 Hz), 121.67 (q, $^3J_{C\text{-}F}$ = 3.6 Hz), 124.6 (d, $^1J_{C\text{-}F}$ = 273.7 Hz), 126.1 (d, $^2J_{C\text{-}F}$ = 35.7 Hz), 128.7, 129.2, 129.3, 130.4, 132.4, 133.9, 137.5, 168.6;

ESIHRMS: Found: m/z 290.0793. Calcd for $C_{16}H_{11}F_3NO$: $(M+H)^+$ 290.0793.

***N*-(2-acetylphenyl) benzamide (2ax):**_ENREF_3_132[68]



Yield: 89%; White solid; mp: 99-100°C;

IR (NaCl, CH_2Cl_2) 3053, 1653, 1584, 1450, 1265, 1166, 1099, 959, 895, 746, 701, 609 494, 430, 415 cm^{-1};

^{1}H-NMR (400 MHz, CDCl3) δ 2.73 (s, 3H), 7.17 (m, 1H), 7.54 (m, 3H), 7.61 (m, 1H), 7.96 (dd, J = 8.0, 1.2 Hz, 1H), 8.07 (m, 2H), 8.99 (d, J = 8.4 Hz, 1H);

^{13}C-NMR (100 MHz, CDCl3) δ 28.6, 120.9, 122.0, 122.5, 127.5, 128.8, 131.8, 132.0, 134.9, 135.4, 141.5, 166.2, 203;

ESIHRMS: Found: m/z 240.1020. Calcd for $C_{15}H_{14}NO_2$: $(M+H)^+$ 240.1025.

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List of Publications and Conferences

1. Hiroyuki Tanabe, Xinyao He, Prasath Kothandaraman, Motoki Yamane*. Oxidative Preparation of Aromatic Orthocarboxylates from Aldehydes. *Synlett.* **2010**, 1190-1192.
2. Wei Ren, Xinyao He, Huiqi Tang, and Motoki Yamane*. $W(CO)_6$-Catalyzed Highly Regioselective Synthesis of 3,1-Benzoxazepines from *N*-Acyl-*o*-alkynylanilines. **2013**, *Prepared for publication.*
3. Xinyao He, Hiroyuki Tanabe, Motoki Yamane. Oxidative Preparation of Aromatic Orthocarboxylate from Aldehyde. *6th Asian-European Symposium, Singapore, June* **2010** (poster presentation).