POLYCYCLIC AROMATIC RING SYNTHESIS USING PALLADIUM CATALYZED C-H ACTIVATION AND ENAMINE-CATALYZED [3+2] CYCLOADDITION REACTIONS IN HETEROCYCLES SYNTHESIS

WANG LEI

NATIONAL UNIVERSITY OF SINGAPORE

2013
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WANG LEI
(M Sc. Peking Union Medical College)

A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY
NATIONAL UNIVERSITY OF SINGAPORE

2013
Dissertation Declaration

The work in this dissertation is the original work of Wang Lei, performed independently under the supervision of A/P Wang Jian, Chemistry Department, National University of Singapore, between 01/2009 and 01/2013.

The contents of the dissertation have been partly published in:


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Acknowledgements

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Summary

The field of Palladium-catalyzed C-H activation/functionazation has advanced rapidly in the past decade. Owing to unique properties of palladium catalysis, a number of novel transformations have been discovered, providing access to various useful synthetic building blocks. Meanwhile, the utilities of palladium catalysis have also been demonstrated in the synthesis of many biologically and pharmaceutically important molecules, particularly polyarylated aromatic and heteroaromatic compounds from readily available materials. Moreover, recent years have witnessed an explosive growth in the field of iminium and enamine catalysis. A number of novel transformations have been discovered to provide the access to various heterocycles. This dissertation describes several novel reactions including the palladium-catalyzed reactions via the C-H activation and the enamine catalysis in [3+2] cycloaddition reactions.

Chapter 1 gave a brief introduction to transition metal catalysis in a wide range of organic transformations. An evaluation of the current research progress of the palladium-catalyzed C-H activations and their applications in different synthesis transformations was subsequently elucidated with selected examples illustrating the state of the art in this research field.

Chapter 2 described the coupling of coumarins with alkynes, which proceeded through a palladium-catalyzed cascade sequence. This process provided a new route to the synthesis of highly substituted cyclopentadiene fused chromones. Postulated reaction pathway was explored to elucidate the roles of palladium catalysis in the observed transformation.

Chapter 3 disclosed an efficient method of synthesizing benzazepine heterocycles. It utilized simple and readily available isatins and alkynes, and employed a direct Pd (II)-
catalyzed oxidative cycloaddition. These heterocycles were well tolerated in the reaction, which allowing access to a number of unique molecular structures.

Chapter 4 presented a brief overview of organocatalysis, especially on the development of aminocatalysis via iminium and enamine activation. Moreover, the 1,3-dipolar cycloaddition reaction transformed via the iminium and enamine catalysis was specially emphasized. Some selected examples were illustrated this development in detailed.

Chapter 5 showed a general, organocatalytic inverse-electron-demand [3+2] cycloaddition reaction between various carbonyls and diazoacetates. The reaction was catalyzed by second amines via the enamine activation model to generate substituted pyrazoles with high levels of regioselectivity.

Chapter 6 documented an enamine catalyzed strategy to fully promote the Huisgen [3+2] cycloaddition with a broad spectrum of carbonyls and azides to access the efficient assembly of a vast pool of highly substituted 1,2,3-triazoles.
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<tr>
<td>Ac</td>
<td>Acetyl</td>
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<tr>
<td>Å</td>
<td>ångström</td>
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<td>AgI</td>
<td>Silver iodine</td>
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<td>Ag$_2$CO$_3$</td>
<td>Silver carbonate</td>
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<td>AgOAc</td>
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<td>AgOTf</td>
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<td>AlCl$_3$</td>
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<td>Ar</td>
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<tr>
<td>GPR G</td>
<td>Protein-coupled receptors</td>
</tr>
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<td>Ammonium Persulfate</td>
</tr>
<tr>
<td>NMP</td>
<td>N-Methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>NR</td>
<td>No reaction</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>Oxone</td>
<td>Potassium peroxymonosulfate</td>
</tr>
<tr>
<td>Pd(OAc)₂</td>
<td>Palladium (II) acetate</td>
</tr>
<tr>
<td>Pd(OPiv)₂</td>
<td>Palladium pivalate</td>
</tr>
<tr>
<td>Pd(TFA)₂</td>
<td>Palladium(II) trifluoroacetate</td>
</tr>
<tr>
<td>Pd₂(dba)₃</td>
<td>Tris(dibenzylideneacetone)dipalladium(0)</td>
</tr>
<tr>
<td>Pd(t-Bu₃P)₂</td>
<td>Bis(tri-tert-butylphosphine)palladium(0)</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PhMe</td>
<td>Toluene</td>
</tr>
<tr>
<td>PhCF₃</td>
<td>Trifluoromethylbenzene</td>
</tr>
<tr>
<td>PhI(OAc)₂</td>
<td>Iodosobenzene Diacetate</td>
</tr>
<tr>
<td>[Ph₂I]PF₆</td>
<td>Diphenyliodonium hexafluorophosphate</td>
</tr>
<tr>
<td>[Ph₂I]PF₄</td>
<td>Diphenyliodonium tetrafluorophosphate</td>
</tr>
<tr>
<td>PivOH</td>
<td>2,2-Dimethylpropanoic acid</td>
</tr>
<tr>
<td>Pr</td>
<td>Propyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>tAmylOH</td>
<td>2-Methyl-2-butanol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>TBAB</td>
<td>Tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoromethylacetic acid</td>
</tr>
<tr>
<td>Tf$_2$NH</td>
<td>N-Phenyl-bis(trifluoromethanesulfonimide)</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TIPBA</td>
<td>2,4,6-triisopropylbenzenesulfonic acid</td>
</tr>
<tr>
<td>TsOH</td>
<td>$p$-Toluenesulfonic acid</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
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</table>
List of Publications


Chapter 1  Introduction of Transition Metal Catalysis and Recent Research Progress of Palladium-catalyzed C-H Activations

1.1 Transition Metal Catalysis and Related Cross-coupling Reactions

Transition metal refers to the group of metals in the middle section of the periodic table. The transition metal ions outermost $d$ orbitals are incompletely filled with electrons so they can easily give and take electrons. This makes transition metals prime candidates for catalysis, either as the metal itself or as a compound based on bonding ability, variability of oxidation state and variability of co-ordination number. So the transition metal catalysts take an important role in modern organic synthesis (Table 1.1). They allow apparently impossible reactions to occur easily. This chemistry complements traditional functional-group-based chemistry and significantly broadens the scope of organic chemistry.

Among the myriad of transition metal catalyzed synthetic transformations, transition-metal catalysts catalyzed cross-coupling reactions are particularly valuable tools in synthetic chemistry, they are the most convenient ways to install important motif in many pharmaceutical relevant and biological active compounds. The term cross-coupling reaction refers to the metal-catalyzed coupling of aryl or vinyl halides/triflates with organometallic partners (Scheme 1.1). This cross-coupling reaction has been widely used both in research laboratories and industrial procedures for the formation of biaryl building blocks of complex molecules. So, the 2010 Nobel Prize in chemistry was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their great contribution
to the transition-metal (palladium) catalyzed carbon-carbon bond formation by cross-coupling reaction.\textsuperscript{2} In the next section, palladium catalyzed cross-coupling reactions are specially emphasized and discussed in detail.

**Table 1.1** Transition metals catalyzed cross-coupling reactions.\textsuperscript{3-16}

<table>
<thead>
<tr>
<th>reaction</th>
<th>reagent A</th>
<th>reagent B</th>
<th>coupling</th>
<th>transition metal</th>
<th>remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadiot-Chodkiewicz coupling</td>
<td>RC≡CH</td>
<td>sp</td>
<td>RC≡CX sp</td>
<td>cross coupling</td>
<td>Cu</td>
</tr>
<tr>
<td>Castro-Stephens coupling</td>
<td>RC≡CH</td>
<td>sp</td>
<td>Ar–X sp\textsuperscript{2}</td>
<td>cross coupling</td>
<td>Cu --</td>
</tr>
<tr>
<td>Gilman reagent coupling</td>
<td>R\textsubscript{2}CuLi</td>
<td>--</td>
<td>R–X --</td>
<td>cross coupling</td>
<td>-- --</td>
</tr>
<tr>
<td>Cassar reaction</td>
<td>Alkene</td>
<td>sp\textsuperscript{2}</td>
<td>R–X sp\textsuperscript{3}</td>
<td>cross coupling</td>
<td>Pd base required</td>
</tr>
<tr>
<td>Kumada coupling</td>
<td>Ar–MgBr</td>
<td>sp\textsuperscript{2}</td>
<td>Ar–X sp\textsuperscript{2}</td>
<td>cross coupling</td>
<td>Pd or Ni --</td>
</tr>
<tr>
<td>Heck reaction</td>
<td>alkene</td>
<td>sp\textsuperscript{2}</td>
<td>R–X sp\textsuperscript{2}</td>
<td>cross coupling</td>
<td>Pd base required</td>
</tr>
<tr>
<td>Sonogashira coupling</td>
<td>RC≡CH</td>
<td>sp</td>
<td>R–X sp\textsuperscript{3}</td>
<td>cross coupling</td>
<td>Pd and Cu base required</td>
</tr>
<tr>
<td>Negishi coupling</td>
<td>R–Zn–X</td>
<td>sp\textsuperscript{3}</td>
<td>R–X sp\textsuperscript{3}</td>
<td>cross coupling</td>
<td>Pd or Ni --</td>
</tr>
<tr>
<td>Stille cross coupling</td>
<td>R–SnR\textsubscript{3}</td>
<td>sp\textsuperscript{3}</td>
<td>R–X sp\textsuperscript{3}</td>
<td>cross coupling</td>
<td>Pd --</td>
</tr>
<tr>
<td>Suzuki reaction</td>
<td>R–B(OR)\textsubscript{2}</td>
<td>sp\textsuperscript{2}</td>
<td>R–X sp\textsuperscript{3}</td>
<td>cross coupling</td>
<td>Pd base required</td>
</tr>
<tr>
<td>Hiyama coupling</td>
<td>R–SiR\textsubscript{3}</td>
<td>sp\textsuperscript{2}</td>
<td>R–X sp\textsuperscript{3}</td>
<td>cross coupling</td>
<td>Pd base required</td>
</tr>
<tr>
<td>Buchwald-Hartwig reaction</td>
<td>R\textsubscript{2}N–R SnR\textsubscript{3}</td>
<td>sp</td>
<td>R–X sp\textsuperscript{2}</td>
<td>cross coupling</td>
<td>Pd N-C coupling, second generation free amine</td>
</tr>
<tr>
<td>Fukuyama coupling</td>
<td>RCO(SEt)</td>
<td>sp\textsuperscript{2}</td>
<td>R–Zn–I sp\textsuperscript{3}</td>
<td>cross coupling</td>
<td>Pd --</td>
</tr>
<tr>
<td>Liebeskind–Srogl coupling</td>
<td>R–B(OR)\textsubscript{2}</td>
<td>sp\textsuperscript{3}</td>
<td>RCO(SEt) sp\textsuperscript{2}</td>
<td>cross coupling</td>
<td>Pd CuTC required</td>
</tr>
</tbody>
</table>
1.2 Palladium Catalyzed Cross-coupling Reactions

\[
\begin{align*}
\text{RX} + \text{R'M} & \xrightarrow{\text{transition metal catalysts}} \text{R-R'} \\
R, R' &= \text{aryl, vinyl, alkyl} \\
X &= \text{halides, triflate, etc} \\
M &= \text{B(OH)}_2, \text{Zn, Al, Zr, etc}
\end{align*}
\]

Scheme 1.1 General cross-coupling reaction

Palladium-catalyzed cross-coupling of aryl halides and boronic acids (Suzuki coupling), organostannanes (Stille), organosiloxanes (Hiyama), organozinc compounds (Negishi), Grignard reagents (Kumada-Corriu), alkynes (Sonogashira) or olefins (Heck) have found widespread popularity in synthetic chemistry.\(^6\)\(^-\)\(^15\) These reactions involve developing methods for connecting aromatic carbon atoms together and developing synthetic transformations for making bi(hetero)aryl compounds under mild reaction conditions and with high degrees of selectivity. However, despite the structural simplicity of biaryl scaffolds and their wide abundance in medicinal agents, natural products and electronic materials, the preparation of pre-functional partners still appears to be the a challenge in academic and industrial levels.\(^17\)\(^-\)\(^19\) The installation of these pre-functional groups such as in Kumada, Negishi, Suzuki-Miyaura and similar cross-coupling reactions still involves extra synthetic steps. The factors, such as the generation of waste after the C–C bond formation, the cost associated with undesired reaction byproducts, waste disposal from the reagents limit the application scopes of these palladium catalyzed cross-couping processes. In order to improve the efficiency and atom economy of the process, palladium catalyzed C–H bond fuctionalization/activation is developed for the direct conversion of C–H bonds into carbon-oxygen, carbon-halogen, carbon-nitrogen, carbon-
sulfur, and carbon-carbon bonds, which has been broadly explored for the past 30 years.

### 1.3 Palladium-catalyzed C-H Fuctionalization/Activation

In order to demonstrate how the transition-metal can react with C–H bonds to produce C–M bonds in the process called C–H fuctionalization/activation and how to overcome the high bond dissociation energies (i.e. 110 kcal/mol for the H–C₆H₅), four types of mechanisms promoted by transition-metal catalysts will be initially introduced. These formed C–M bonds are more active than their C–H counterparts, and they can be easily converted to different functional groups. Although metal-free C–H functionalization is more widely known than the transition-metal counterparts, the transition-metal mediated transformations of saturated and unsaturated C–H bonds have emerged as a very powerful tool in synthetic chemistry. Model studied reactions of unactivated C–H bonds with stoichiometric amounts of transition-metal were identified as four main mechanisms for the transformation of C–H bonds into C–M bonds: oxidative addition, σ-bond metathesis, electrophilic substitution and 1, 2-addition (Scheme 1.2).

**Oxidative Addition:**

\[
\begin{align*}
L_nM & \xrightarrow{L} L_{n-1}M \\
& \xrightarrow{R-H} L_{n-1}M_{R-H} \\
& \xrightarrow{H} L_{n-1}M_H
\end{align*}
\]
Different transition metals have been used in the reactions for about one hundred years, however, its catalytic version of C–H functionalization/activation has only been explored for the past several decades, especially the use of palladium catalysis for this type of transformation based on its compatibility with different oxidants and ability to selectively functionalize cyclopalladated intermediates. These abilities make them exceptionally practical for applications in the C–H functionalization/activation reactions. So, in next section, a brief summary of the palladium-catalyzed C–H functionalization/activation in recent years are summarized. Direct functionalization/activation of alkenyl reactions have been specially emphasized in our investigation and are further discussed in detail.
1.3.1 Recent Development of Palladium Catalyzed C-H Functionalization/Activation reactions

Various approaches have been used in palladium-catalyzed C-H activation/C-C bond formation. In this part, a summary of recent development on palladium-catalyzed coupling of C-H bonds with organometallic reagents to form C(sp\(^3\)) – C(sp\(^3\)), C(sp\(^3\)) – C(sp\(^3\)), and C(sp\(^3\)) – C(sp\(^3\)) bonds was summarized. A lot of mechanism has been used to explain the process of these reactions which could be summarized into four types (Scheme 1.3, 1.7, 1.15, 1.21).\(^{30-32}\)

1.3.1.1 Palladium-catalyzed C(sp\(^3\)) – H Activation Reactions: Pd\(^{II}\)/Pd\(^0\) and Olefination Cycle

![Scheme 1.3 Proposed mechanism of C–H bond activation Pd\(^{II}\)/Pd\(^0\) - catalytic cycle](image-url)
The noticeable progress had been made in the development of palladium-catalyzed C–H activation/C–C bond forming process in the past several years. Researches in this field have largely focused on the discovery of new modes of catalysis and the expansion of substrate scope. Currently, C–H bonds activation via PdII/Pd0 catalytic cycle was successfully established. Yu and co-workers reported that treated oxazoline 1-1 as a directing group can promote C–H activation during an unprecedented coupling process proceeding to form 1-2 through PdII/Pd0 catalysis (Scheme 1.4).33

![Scheme 1.4 Palladium (II)-catalyzed C–H activation with organotin reagents](image)

This potential generality of palladium (II)-catalyzed C–H activation by directing group via the PdII/Pd0 catalytic cycle has been further demonstrated by Shi’s research group in the coupling of anilides 1-3 with arylsilanes 1-4 (Scheme 1.5). Arylboronic acids 1-5 were also explored under similar strategy with these highly reactive anilide substrates (Scheme 1.5).34, 35 The versatility and practicality of this model was then further explored and improved by using carboxylic acid 1-7 as the directing group and potassium aryltrifluoroborates 1-8 as the coupling partners. The use of O2 or air as the oxidant instead of Ag2CO3 and a wide range of functional groups was tolerated (Scheme 1.6).36
Scheme 1.5 Palladium (II)-catalyzed C–H activation with organosilane and organoborone reagents

Scheme 1.6 Palladium (II)-catalyzed C–H activation using carboxylic acid as directing group

Then more coupling partner was explored, especially focusing on the olefination transformations (Scheme 1.7). One of the earliest examples concerns C–H activation of benzene 1-10 by Pd(OAc)₂ and subsequent carbopalladation and β-hydride elimination to afford olefinated arenes 1-12 by Moritani (Scheme 1.8).[37] Because of the regioselectivity problem of the substrate, the concept of directing group was firstly introduced by de Vries and coworker to overcome the problem of regioselectivity (Scheme 1.9).[38] The usage of the anilide 1-3 substrate afforded high ortho selectivity, benzoquinone is
believed to be crucial for the C–C bond forming step in the reaction, and the usage of TsOH was also found to be beneficial in the transformation.

Scheme 1.7 Proposed mechanism of C–H bonds activation - olefin insertion

Scheme 1.8 Palladium (II)-catalyzed olefination of arenes
Moreover, different types of substrates were also applied to this type of C–H activation such as the indoles. Although the first case of catalytic olefination of indoles 1-16 using $\text{Pd(OAc)}_2$ and $\text{Ag}^+/\text{Cu}^{II}$ salts as the reoxidant was reported by Itahara et al (Scheme 1.10), several recent studies have advanced this chemistry.\(^{39}\) Notably, the work of Ma and Yu, in which allylic acetate 1-19 is cleverly used as the olefin partner and avoided the need for an oxidant (Scheme 1.11),\(^ {40}\) significantly developed this methodology.
Scheme 1.11 Palladium (II)-catalyzed oxidant-free olefination of indoles

To expand the synthetic utility of directed C–H activation/olefination. A concise and general route for the preparation of pyridine ortho-olefination compounds 1-23 from pyridine N-oxides 1-21 (Scheme 1.12) was reported by Chang and co-worker.\(^ {41}\)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1-18</td>
<td>1-19</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>56% yield</td>
</tr>
<tr>
<td>tAmylOH, 80 °C, 72 h</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 1.12 Palladium (II)-catalyzed olefination of pyridine N-oxides

Moreover, a recent report by Wu and co-worker described a useful olefination of quinoline N–oxides 1-24 (scheme 1.13).\(^ {42}\) The use of the quinoline N–oxides itself was crucial for C–H activation in which the N–oxides group was a key element for introducing a functional group at the position ortho to the nitrogen atom. Recently, based
on the challenges of selectivity when multiple inequivalent C–H bonds presented in the target molecule, Yu and co-worker made great contribution in this area by designing a class of easily removable nitrile-containing templates that direct the activation of distal meta-C–H bonds (more than ten bonds away) of a tethered arene 1-27. This new mode of C–H activation to a weak ‘end-on’ interaction between the linear nitrile group and the metal centre made only the meta-C–H activation possible. This new strategy for directing remote C–H activation provided a novel route for the preparation of toluene derivatives, hydrocinnamic acids, 2-biphenylcarboxylic acids, unnatural amino acids, and drug molecules with sophisticated substitution patterns that are difficult to access using conventional C–H activation methods. 43

![Scheme 1.14 Template-directed meta-selective C–H olefination of toluene derivatives](image)

**Scheme 1.14** Template-directed meta-selective C–H olefination of toluene derivatives

### 1.3.1.2 Palladium-catalyzed C(sp²)–H and C(sp³)–H Activation and Coupling Reactions: Pd^{II}/Pd^{IV} cycle

Most commonly, Palladium-catalyzed bond activation processes involved Pd⁰/ Pd^{II} and Pd^{II}/Pd⁰ as the intermediates. In contrast, the involvement of Pd^{IV} complexes as the intermediate is studied far less despite the proposal of the existence of this oxidation state
The first case that involved the Pd$^{IV}$ complexes 1-32 as the intermediate was reported by the Tremont and Rhaman. They described the first intriguing methylation of ortho C–H bonds in anilide 1-3 (Scheme 1.16). In this work, the reactivity of the cyclopalladated intermediate with MeI was established, and a plausible Pd$^{II}$/Pd$^{IV}$ mechanism was presented. 48

Scheme 1.15 Plausible mechanism of C–H bonds activation - Pd$^{IV}$/Pd$^{II}$ catalytic cycle

The proposed oxidation of palladium (II) to palladium (IV) by MeI was indicated by X-ray crystallography. The first case 1-35 was obtained by Canty and co-worker (Scheme 1.17). 49 Recently, Sanford and co-worker got the palladium (IV) complex crystal 1-36 in the acetoxylation reaction (scheme 1.17). 50

13
Scheme 1.16 Palladium (II) - catalyzed methylation of anilides and proposed mechanism

Scheme 1.17 X-ray crystallographic structure of palladium (IV) complex

Based on the Pd^{II}/Pd^{IV} cycle mechanism, Sanford and co-worker and Dauglis et al., independently designed a more general approach using directed C–H activation and [Ph₂I]PF₆ 1-38 and [Ph₂I]PF₄ 1-41 for arylation of C–H bonds (Scheme 1.18). ⁵¹,⁵² It is
proposed that this reaction proceeded through a Pd$^\text{II}$/Pd$^\text{IV}$ cycles, where the 1-38 and 1-41 took the similar role as the MeI mentioned as above.

Scheme 1.18 Arylation of C–H bonds by Pd$^\text{II}$/Pd$^\text{IV}$ cycle

Extensively, Daugulis and co-worker discovered that the arylation of C–H bonds can be performed via cheap and practical ArI 1-43 under neat conditions or using TFA as the solvent (Scheme 1.19).$^{53}$ This protocol represented the most efficient arylation reaction proceeding via Pd$^\text{II}$/Pd$^\text{IV}$ cycle. This conditions also had been applied to the arylation of C–H bonds by linkage of pyridyl group to carboxylic acid 1-49/1-51 as the directing group (Scheme 1.20) and mechanistic studies to date had been conducted with benzoic acid substrates (scheme 1.20).$^{54}$
Scheme 1.19 Arylation of C–H bonds using ArI via Pd\textsuperscript{II}/Pd\textsuperscript{IV} cycle

Scheme 1.20 Palladium (II)-catalyzed directed arylation via Pd\textsuperscript{II}/Pd\textsuperscript{IV} cycle
1.3.1.3 Palladium (II)-catalyzed C(sp$^3$) –H activation: Allylic C–H activation

As mentioned above, significant advances in directed C–H arylations and alkylations have been made, but non-directed C–H to C–C bond forming processes are more scare. Herein, the recent progress about this research area had been summarized here. The first case that mentioned this type of reaction catalyzed by palladium (II) salt 1-54a to activate the allylic C(sp$^3$) –H bond was reported by White and co-worker (Scheme 1.21-22). In the palladium (II)-mediated reaction, the DMSO was always considered promoting the re-oxidation of Pd (0) with O$_2$.

![Scheme 1.21 Mechanism of C–H bonds activation - nucleophilic attack](image)

However, in this reaction the authors deduced a crucial role of DMSO that it not only altered the reaction pathway selectivity but controlled the reaction regioselectivity.
In seeking to explain the observed reactivity, the π-allylpalladium species were described as the intermediates in direct allylic alkylation based on the research results.

Scheme 1.22 Pd (II)-catalyze oxidation of terminal olefination to allylic acetate

\[
\begin{align*}
\text{R} & \quad \text{H} \quad \text{10 mol% L Pd(OAc)}_2 \quad \text{2 eq BQ, 4Å MS} \quad \text{DMSO : AcOH (1:1 v/v)} \quad \text{air, 40 °C} \quad \text{R} \quad \text{OAc} \\
\text{1-54} & \quad \text{10 mol% L Pd(OAc)}_2 \quad \text{2 eq BQ, 4Å MS} \quad \text{DMSO : AcOH (1:1 v/v)} \quad \text{air, 40 °C} \quad \text{R} \quad \text{OAc} \\
\end{align*}
\]

69% yield 1-55

Scheme 1.23 Pd (II)-catalyze intermolecular allylic allylation

Based on this interesting reaction process, Shi and co-worker (Scheme 1.23) surveyed other different types of nucleophiles 1-56 and considered that the π-allylpalladium species was the crucial intermediate in the reaction as well as the BQ which was indicated as the vital factor in promoting the reaction via taking role as the proton acceptor and an oxidant. To expand the synthetic utility of undirected allylic C–H activation, a range of carbon nucleophiles 1-59 were investigated and the excellent yields were got if the substrates had the low pK\textsubscript{a} value and DMSO still took the crucial role in the reaction. This transformation cannot be promoted without the DMSO existence in the reaction system (Scheme 1.24). A recent report by White and co-workers described a novel nucleophile 1-60 activation strategy for promoting
intermolecular allylic C–H aminaiton that operated via electrophilic Pd (II) catalysis with acidic N-tosylcarbamate nucleophiles (pKₐ<4) (Scheme 1.25). This strategy employed exogenous catalytic amine base to elevate the concentration of anionic carbamate nucleophile that is not associated with the Pd counterion, resulting in one of the most mild and selective C-H activation.

\[ R\equiv\text{CO}_2\text{Me} \quad \text{R} = \text{CO}_2\text{Ph} \quad \text{S}_2\text{Ph} \]

**Scheme 1.24** Pd (II)-catalyze intermolecular allylic C–H alkylation reaction

Finally, efforts in establishing different type of ligands to promote the allylic C–H activation had yielded unprecedented reactivity (Scheme 1.26). The usage of a serial of designed ligand 1-64 was crucial for the allylic C–H activation especially in absence of DMSO, which were previously found to be unreacted without DMSO. Mechanistic studies indicated that the new ligand supported aerobic BQ-free catalytic turnover. It is deduced that ancillary ligands facilitate reductive elimination from Pd (II) and thereby eliminated the requirement for undesirable stoichiometric oxidants in this reaction as well.
**Scheme 1.26** Pd (II)-catalyze intermolecular aerobic allylic C–H acetoxylation

1.3.2 Recent Development of Palladium Catalyzed C–H Alkynylation

C–H functionalization/activation reactions presents an attractive and powerful strategy for the generation of different types of heteroaromatic compounds, such as indoles, carbazoles, benzothiazoles, pyridines and so on.\(^{60,61}\) However, directly C–H alkynylation and cycloaromatization of alkynes with arenes through C–H bond activation forming aromatic rings still consider as challenges. Although Rh-catalyzed annulations of phenylazoles with internal alkynes via dual C–H cleavage directed by an ortho-azole group using Cu(OAc)\(_2\) as an oxidant was successfully established by Miura et al.,\(^{62}\) the first example of palladium-catalyzed C–H alkynylation to date involved the reaction of anilides 1-65 with the bromoalkynes 1-66. A number of substituted anilides could be ortho-alkynylated 1-67 in high yield when combined together with silyl-protected bromoalkyne under catalytic palladium (II) salt (Scheme 1.27).\(^{63}\)
Scheme 1.27 Pd (II)-catalyzed directed C–H alkynylation

Subsequently, several highly substituted naphthalenes have been synthesized in moderated yields by Wu and co-worker via treatment of electron-rich arenes 1-68 with alkynes 1-69 using Pd(OAc)$_2$ as catalyst and AgOAc as oxidant.\(^6^4\) This transformation promoted via invoking a tetraphenylcyclopentadiened Pd IV complex 1-71 and following by two alkyne insertions, cylization, and Pd$^0$ recycling to generate substituted naphthalenes (Scheme 1.28).

Later, in 2010, Wu’s research group developed an efficient method for the direct aromatic ring construction of amides with alkynes catalyzed by Pd(OAc)$_2$ under mild conditions. This observation enlarged the methods to construct useful luminescent materials (Scheme 1.29).\(^6^5\) Recently, Jiao and co-workers described a Pd-catalyzed cycloaromatization of biaryls 1-74 with alkynes through dual C–H activation applying O$_2$ as oxidant \(^[34]\). This method not only provides a new way to construct aromatic ring from biaryls and internal alkynes, but also supply an efficient approach for synthesizing important polycyclic carbazoles (Scheme 1.30).\(^6^6\)
Scheme 1.28 Palladium-catalyzed synthesis of highly substituted naphthalenes

Scheme 1.29 Synthesis of highly substituted naphthalenes via directing group
Scheme 1.30 Palladim-catalyzed cycloaromatization of biaryls with alkynes

Within the same year, Jiao et al reported an unprecedented palladium-catalyzed ring expansion of indoles with alkynes using O₂ as oxidant leading to tetrahydroquinoline derivatives 1-78 with highly substituted cyclopentadienyl cores. This transformation involves dual C–H activation, one C–C bond cleavage, five new C–C bond formation and uniquely, ring-expansion of indole through a rearrangement pathway, under mild conditions (Scheme 1.31).67

Scheme 1.31 Palladium-catalyzed ring expansion reactions of indoles with alkynes

Although, great progresses in construction of aromatic rings have been reported, cycloaromatization of alkynes with different substrates through C–H activation to build synthetic and medicinal important polycyclic aromatic compounds still has limited the
scopes and has attracted considerable attention based on their increasing applications in related fields.

1.4 Project Objective

Huge advances have been made in the field of palladium catalyzed C–H activation/functionalization over the two past decades, Owing to the unique properties of palladium catalysis, both the development of novel reactions and the mechanistic study of the transformation of C–H to C–C, C–O, C–X, C–N, C–S have been greatly explored. A number of novel transformations, as described above, have been discovered, providing access to various useful synthetic building blocks. The utilities of palladium catalysis have also been demonstrated in the synthesis of many biologically and pharmaceutically important molecules, particularly polyarylated aromatic and heteroaromatic compounds from readily available materials.

Despite great advances in the development of palladium catalyzed C–H activation, there are still many challenges that remain to be addressed: a) regioselective arene C–H activation. The scope of C–C bond formation via C–H activation reactions would be greatly expanded by designing novel ligands to promote C–H activation of monosubstituted benzene regioselectively at the meta- or para-positions. b) The application of palladium catalyzed C–H activation to form complex, multifunctional substrates, especially directly C–H alkynylation, also remains a key future objective.
Challenges still exist in these fields, if solved successfully, these strategies would pave the way for the widespread application of this C–H activation chemistry for late stage derivatization of biological, pharmaceutical compounds and advanced materials. Therefore, in light of this, how to form complex, multifunctional substrates from available materials via the C–H alkynylation will be the aim for further investigation.

The main purpose of this project is to explore significant palladium-catalyzed methodologies to overcome the mentioned challenges. The specific aspect of this project is to use different types of available starting materials via directly alkynylation activation to form many potential biologically and pharmaceutically important molecules, particularly polyarylated aromatic and heteroaromatic compounds.

These results of this project should provide a concise way to synthesize different types of important molecules which contain potential biological and pharmaceutical activity. Some of these molecules can be treated as functional materials. It may also pave the way to explore more detail information of how the palladium catalyst behaves in the catalytic cycle during promoting the reactions.

Two different types of reactions to form different types of polyarylated aromatic and heteroaromatic compounds are explored. There are cyclopentadiene fused chromones, and azepine fused isatin. More specifically information will be listed in later two chapters. In chapter 2, palladium-catalyzed cascade reactions of coumarins with alkynes will be described. In chapter 3, a series of azepine fused isatin substrates will be shown in details.
Chapter 2 Palladium-catalyzed Cascade Reactions of Coumarins with Alkynes: Synthesis of Highly Substituted Cyclopentadiene Fused Chromones

The coupling of coumarins with alkynes is described, which proceeds through a palladium-catalyzed cascade sequence. This process provides a new route to the synthesis of highly substituted cyclopentadiene fused chromones.
2.1 Introduction

Polyarylated aromatic compounds are commonly found in functional materials, such as semiconductors, fluorescent and luminescent tools and materials. Owing to the importance of such framework, their synthesis has attracted considerable attention in the field of material chemistry. Alkynes, an important building block for organic transformations, have been utilized to construct polycyclic aromatic compounds via conventional synthetic methodologies involving transition metal-catalyzed ring formation reaction. These conventional synthetic methodologies involve transitional metal-catalyzed ring construction of an aromatic substrate with two alkynes. However, mono- or di-functionalized aromatic substrates, such as aryl halides and aryl boronates were required for such reaction. Most recently, C–H activation initiated cyclization reactions of alkynes has become an impressive and powerful tool for the construction of synthetically useful building blocks, such as indoles, isoquinolines, benzothiazoles, pyridines, naphthalenes and other heteroaromatic rings. Herein, we document a palladium-catalyzed cascade reaction of coumarins with alkynes involving C–H bond activation process, which could lead to highly substituted cyclopentadiene fused chromone framework. To the best of my knowledge, this is the first report to synthesize polysubstituted cyclopenta[b]chromen-9(3H)-one via this novel method.

In particular, chromones have been widely employed as important intermediates in the synthesis of many natural products and medicinal agents. They have been found to potentially possess cytotoxic (anticancer), neuroprotective, HIV-inhibitory, antimicrobial, antifungal and antioxidant activities. Interestingly, they also can serve
as a family of diet medicine because of their health-promoting effects found in the diet of humans.\textsuperscript{80} Despite the several existing methods for the synthesis of chromone derivatives,\textsuperscript{80c} there still is demand for diverse strategies which can efficiently provide variously substituted chromone systems. In this context, the significance of this synthetic methodology is highlighted by its correlation to the protocols for the preparation of chromone systems.

2.2 Results and Discussion

2.2.1 Reaction Optimization

During our investigation of Pd(OAc)$_2$ (20 mol%) catalyzed cascade reaction of 4-hydroxy-2H-chromen-2-one (2-1a) with diphenylacetylene (2-2a) in the presence of CuI as oxidant in dimethylacetamide (DMA) at 130 °C for 24 h, Cs$_2$CO$_3$ was discovered as the most efficient base and it could promote the yield of 2-3a from 24% to 52% (Table 2.1, entries 1–5). Subsequently, we examined other reaction parameters by varying oxidants, temperatures and the influence of the solvents in order to improve the reaction yield. The results were summarized in Table 2.1 and 2-2. In general, the higher reaction yields were obtained with Cu$^{II}$ oxidants (Table 2.1, entries 10 and 12, 61% and 63%, respectively). The presence of other common oxidants, such as oxone, benzoquinone (BQ), and K$_2$S$_2$O$_8$, did not favour this process (Table 2.1, entries 16–18, 17–29%). Gratifyingly, the best result with regard to reaction yield and time was obtained through the condition of 10 mol% Pd(OAc)$_2$ and 5.0 equivalent diphenylacetylene 2-2a (Table 2.1,
entry 13, 79% yield). Changing of the organic solvents from non-polar to polar did not show any improvement in the reaction yield and reaction rate (Table 2.2, entries 1–6, 12–67%). When the reaction was conducted in lower temperature, it proceeded smoothly with a lower reaction yield (Table 2.1, entry 14, 110 °C, 69%). Surprisingly, a higher reaction temperature did not increase the yield (Table 2.1, entry 14, 150 °C, 77%).

Table 2.1 Conditions optimization of palladium-catalyzed cascade reactions of coumarins with alkynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Oxidant</th>
<th>Yield/%[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>_[b]</td>
<td>CuI</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>KOH</td>
<td>CuI</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>NaOAc</td>
<td>CuI</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃</td>
<td>CuI</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>Cs₂CO₃</td>
<td>CuI</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>Cs₂CO₃</td>
<td>AgI</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>Cs₂CO₃</td>
<td>AgOAc</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>Cs₂CO₃</td>
<td>CuCl</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>Cs₂CO₃</td>
<td>CuBr</td>
<td>31</td>
</tr>
<tr>
<td>10</td>
<td>Cs₂CO₃</td>
<td>CuCl₂</td>
<td>61</td>
</tr>
<tr>
<td>11</td>
<td>Cs₂CO₃</td>
<td>Cu(OAc)₂</td>
<td>25</td>
</tr>
</tbody>
</table>
Reaction conditions: 2-1a (0.2 mmol, 1.0 equiv.), 2-2a (0.3 mmol, 1.5 equiv.), 20 mol% Pd(OAc)$_2$, base (0.4 mmol, 2.0 equiv.), oxidant (0.4 mmol, 2.0 equiv.), DMA (2 mL), 130 °C, 24 h. $^b$ None of base. $^c$ Isolated yield. $^d$ 2-2a (1.0 mmol, 5.0 equiv.), 10 mol% Pd(OAc)$_2$. $^e$ 110 °C. $^f$ 150 °C.

Table 2.2 Solvent Screening for the cascade reactions $^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield/%$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^b$</td>
<td>Toluene</td>
<td>15</td>
</tr>
<tr>
<td>2$^b$</td>
<td>DCE</td>
<td>17</td>
</tr>
<tr>
<td>3$^b$</td>
<td>CH$_3$CN</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>30</td>
</tr>
</tbody>
</table>
3 Reaction conditions: 2-1a (1.0 equiv.), 2-2a (5.0 equiv.), 10 mol% Pd(OAc)$_2$, Cs$_2$CO$_3$ (2.0 equiv.), CuBr$_2$ (2.0 equiv.), solvent (2 mL), 130 °C, 24 h. $^b$ Reflux. $^c$ Isolated yield.

2.2.2 Substrate Scope

With the optimized conditions in hand, we decided to explore the scope of this unprecedented cascade reaction. The substrate scope of Pd(OAc)$_2$ catalyzed cascade process of coumarins 2-1b to 2-1o with diphenylacetylene 2-2a was shown in Table 2.3 and it was found that a wide range of coumarines bearing electron-donating group or electron-withdrawing group, as well as naphthalene ring, afforded the desired highly substituted cyclopentadiene fused chromones 2-3b to 2-3o in moderate to good yields (Table 2.3, 49–86%). Extension of substrate scope was examined using a wide range of symmetric and asymmetric diarylacetylenes, as well as heterocyclic ring involved asymmetric alkynes (Table 2.4). Moderate to high yields was observed within 24 h (Table 2.4, 47–88%). Notably, electron-donating group involved diarylacetylenes gave higher yields (Table 2.4, 2-3p to 2-3u and 2-3y, 63–88%). On the other hand, electron-withdrawing group involved diarylacetylenes led to lower yields (Table 2.4, 2-3v to 2-3x, 47–62%).

<table>
<thead>
<tr>
<th></th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>DMSO</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>NMP</td>
<td>67</td>
</tr>
</tbody>
</table>
Table 2.3 Cascade reactions of coumarins with diphenylacetylene \^[a]\n
![Chemical structures and yields](image)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3b</td>
<td>81%</td>
<td>24 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3c</td>
<td>79%</td>
<td>24 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3d</td>
<td>84%</td>
<td>30 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3e</td>
<td>50%</td>
<td>30 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3f</td>
<td>59%</td>
<td>28 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3g</td>
<td>68%</td>
<td>30 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3h</td>
<td>62%</td>
<td>8 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3i</td>
<td>66%</td>
<td>30 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3j</td>
<td>74%</td>
<td>22 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3k</td>
<td>49%</td>
<td>18 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3l</td>
<td>67%</td>
<td>24 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3m</td>
<td>62%</td>
<td>30 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3n</td>
<td>86%</td>
<td>30 h</td>
</tr>
<tr>
<td>2-1b to 2-1o</td>
<td>2-3o</td>
<td>63%</td>
<td>30 h</td>
</tr>
</tbody>
</table>

\^[a\ Reaction conditions: 2-1b to 2-1o (1.0 equiv.), 2-2a (5.0 equiv.), 10 mol% Pd(OAc)$_2$, Cs$_2$CO$_3$ (2.0 equiv.), CuBr$_2$ (2.0 equiv.), DMA (2 mL), 130 °C.
Table 2.4 Cascade reactions of coumarins 2-1a with alkynes 2-2b to 2-2k \[a\]

![Chemical structures and reaction conditions](image)
\[^a\] Reaction conditions: \textbf{2-1a} (1.0 equiv.), \textbf{2-2b to 2-2k} (5.0 equiv.), 10 mol\% Pd(OAc)$_2$, Cs$_2$CO$_3$ (2.0 equiv.), CuBr$_2$ (2.0 equiv.), DMA (2 mL), 130 °C.

Moreover, heterocyclic ring tolerated alkyne \textbf{2-2z} was also proved to be a good substrate to afford desired product \textbf{2-3z} (Table 2.4, 60%, 20 h). Regarding to the substrates of asymmetric diarylacetylene (Table 2.4), two regioisomers were obtained with \textit{ca.} 1 : 1 ratio (Table 2.4, \textbf{2-3r}, \textbf{2-3s} to \textbf{2-3v}, and \textbf{2-3x} to \textbf{2-3z}). Interestingly, if phenyl ring bearing two CF$_3$ groups on \textit{meta} position or TMS group on \textit{para} position, an excellent ratio of regioisomers could be achieved (Table 2.4, \textbf{2-3s} and \textbf{2-3w}, ratio of regioisomers: 92:8 and 93:7, respectively). Further investigations on this type of \(\pi\)-conjugated system for the usage in functional liminescent materials, however, are still in progress.

\textbf{2.2.3 Mechanistic Investigations}

Postulated reaction pathway is summarized in Scheme 2.1. In the initial step, a regioselective direct electrophilic aromatic palladation at the 3-position of the coumarin forms a palladium complex \textbf{I}. The subsequent insertion of two diphenylacetylene molecules forms a dienylpalladium intermediate \textbf{III}, which will then undergo intramolecular 6-\textit{exo}-dig insertion into coumarin leads to a polycyclic palladium intermediate \textbf{IV}. Subsequent trapping by OH group from coumarin generated intermediate \textbf{V}. Intermediate \textbf{V} undergoes a set of rearrangements to offer a
cyclopentadiene fused intermediate \textbf{VII}. The intermediate \textbf{VII} is transferred to intermediate \textbf{VIII} via reductive elimination and Pd$^0$ is reoxidized by CuBr$_2$ to regenerate the Pd$^{II}$ catalyst for next catalytic cycle. Finally, the desired product 2-3a is obtained via a phenyl ring migration. The configuration of the compound was determined by X-ray crystal structure analysis of a suitable single crystal (Scheme 2.1, product 2-3a).

\textbf{Scheme 2.1} Postulated catalytic pathway for Pd-catalyzed cascade process.
2.3 Conclusions

In summary, we have disclosed an unprecedented palladium-catalyzed cascade reaction between coumarins and alkynes. The coupling of coumarins with alkynes in the presence of Pd(OAc)$_2$ enabled us to trigger a cascade process to furnish highly substituted cyclopentadiene fused chromone framework in moderate to high chemical yields (47–88%). Studies directed to clarify the functionalities of these compounds as well as the extension of this cascade strategy to other substrates is currently underway.

2.4 Experimental Section

2.4.1 Material and General Methods

Chemicals and solvents were purchased from commercial suppliers and used as received. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker ACF300 (300 MHz) or a AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode and API 3000™ in APCI (Heated Nebulizer) mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at
254 nm. Further visualization was achieved by staining with iodine. Flash chromatography separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel.

Compounds 2-1a and 2-2a, 2-2c, 2-2d were commercially available. Compounds 2-1b\textsuperscript{81}, 2-1e\textsuperscript{81}, 2-1f\textsuperscript{81}, 2-1h\textsuperscript{81}, 2-1l to 2-1n\textsuperscript{81}, 2-1a\textsuperscript{82}, 2-1g\textsuperscript{82}, 2-1j\textsuperscript{82}, 2-1k\textsuperscript{82}; 2-2a\textsuperscript{83}, 2-2b\textsuperscript{83}, 2-2e\textsuperscript{83}, 2-2f to 2-2l\textsuperscript{83} were prepared according to literature, respectively.

2.4.2 Representative Procedure for Palladium-catalyzed Reaction

![Chemical reaction diagram]

To a solution of diphenylacetylene 2-2a (178 mg, 1 mmol) and 4-hydroxycoumarin 2-1a (32.4 mg, 0.2 mmol) in 2 ml of dimethylacetamide, then Copper (II) bromide (89.2 mg, 0.4 mmol) as an oxidant and cesium carbonate (130.3 mg, 0.4 mmol) as an additive were added. The reaction mixture was stirred at 130°C for 24h. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 25:1 then 10:1 to afford 70.0 mg (79% yield) of the desired product 2-3a as pale white powder.
2.4.3 Analytical Data of Palladium-catalyzed Reaction

1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3\textit{H})-one (2-3\textit{a})

\[
\text{\includegraphics[width=0.2\textwidth]{2-3a.png}}
\]

\textsuperscript{1}\text{H} NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 8.31 – 8.19 (m, 1H), 7.55 (dd, \(J = 11.3, 4.2, 1\text{H}\)), 7.43 – 7.33 (m, 8H), 7.25 (ddd, \(J = 14.1, 7.1, 2.2, 9\text{H}\)), 7.01 (t, \(J = 7.3, 1\text{H}\)), 6.94 (t, \(J = 7.5, 2\text{H}\)), 6.83 – 6.75 (m, 2H); \textsuperscript{13}\text{C} NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 177.10, 173.36, 155.77, 142.68, 138.78, 137.52, 134.57, 134.25, 132.78, 130.61, 130.30, 128.91, 128.48, 127.81, 127.43, 127.35, 126.97, 126.23, 125.29, 125.21, 120.91, 118.22, 69.49.; HRMS (ESI) calcd for C\textsubscript{36}H\textsubscript{25}O\textsubscript{2} [M+H]\textsuperscript{+} 489.1849, found 489.1859.

7-methyl-1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3\textit{H})-one (2-3\textit{b})

\[
\text{\includegraphics[width=0.2\textwidth]{2-3b.png}}
\]

\textsuperscript{1}\text{H}NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.96 (s, 1H), 7.32 (ddd, \(J = 9.6, 7.7, 3.3 \text{ Hz}, 7\text{H}\)), 7.25 – 7.16 (m, 10H), 6.95 (t, \(J =7.4 \text{ Hz}, 1\text{H}\)), 6.88 (t, \(J =7.6 \text{ Hz}, 2\text{H}\)), 6.75–6.67 (m, 2H), 2.35 (s, 3H); \textsuperscript{13}\text{C} NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) = 177.61, 174.00, 154.57, 142.98, 139.34, 138.11,
135.68, 135.13, 134.77, 134.46, 131.12, 130.85, 129.42, 128.96, 128.43, 128.28, 127.93, 127.87, 127.82, 127.44, 126.11, 125.43, 121.18, 118.49, 69.92, 21.43.; HRMS (ESI) calcd for C_{37}H_{27}O_{2} [M+H]^+ 503.2006, found 503.2011.

7-isopropyl-1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3H)-one (2-3c)

![Molecular structure of 2-3c]

$^1$HNMR (500 MHz, CDCl$_3$) $\delta$ 8.34 – 7.99 (m, 1H), 7.50 (dd, $J$ =8.6, 2.2 Hz, 1H), 7.47 – 7.40 (m, 6H), 7.40 – 7.35 (m, 1H), 7.35 (s, 9H), 7.06 (t, $J$ =7.3 Hz, 1H), 6.99 (t, $J$=7.6, 2H), 6.86 (dd, $J$=19.2, 8.0 Hz, 2H), 3.04 (hept, $J$ = 6.8 Hz, 1H), 1.30 (d, $J$ = 6.9 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 177.20, 173.70, 154.32, 146.25, 142.54, 138.97, 137.70, 134.71, 134.42, 131.84, 130.70, 130.41, 128.99, 128.53, 127.84, 127.49, 127.42, 127.39, 127.00, 125.10, 123.06, 120.78, 118.14, 69.53, 33.79, 23.98.; HRMS (ESI) calcd for C$_{39}$H$_{31}$O$_2$ [M+H]$^+$ 531.2319, found 531.2337.

7-ethyl-1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3H)-one (2-3d)
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.10 (s, 1H), 7.47–7.38 (m, 6H), 7.36–7.28 (m, 11H), 7.05 (t, $J$ = 7.4 Hz, 1H), 6.98 (t, $J$ = 7.6 Hz, 2H), 6.81 (d, $J$ = 7.3, 2H), 2.75 (q, $J$ = 7.6 Hz, 2H), 1.27 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.63, 174.08, 154.73, 143.00, 142.03, 139.40, 138.14, 135.17, 134.83, 133.49, 131.15, 130.86, 129.44, 128.97, 128.44, 128.28, 127.94, 127.87, 127.83, 127.45, 125.57, 124.93, 121.23, 118.58, 69.97, 28.82, 15.98; HRMS (ESI) calcd for C$_{38}$H$_{29}$O$_2$ [M+H]$^+$ 517.2162, found 517.2173.

6,7-dimethyl-1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3H)-one (2-3e)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.01 (s, 1H), 7.45 – 7.38 (m, 6H), 7.34 – 7.27 (m, 9H), 7.22 (s, 1H), 7.09 – 7.02 (m, 1H), 6.98 (dd, $J$ = 10.4, 4.7, 2H), 6.85 – 6.78 (m, 2H), 2.35 (s, 6H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 177.33, 174.02, 154.83, 143.63, 142.81, 139.50, 138.23, 135.24, 134.91, 134.85, 131.16, 130.89, 129.43, 128.94, 128.23, 127.93, 127.84, 127.80, 127.40, 126.39, 123.56, 121.09, 118.94, 69.90, 20.71, 19.85; HRMS (ESI) calcd for C$_{38}$H$_{29}$O$_2$ [M+H]$^+$ 517.2162, found 517.2171.
8-methyl-1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3H)-one (2-3f)

![Chemical Structure](2-3f)

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.13 (dd, $J = 7.9$ Hz, 1.1, 1H), 7.46 – 7.39 (m, 7H), 7.34–7.27 (m, 10H), 7.06 (dd, $J = 6.6$, 3.8, 1.2 Hz, 1H), 6.99 (dd, $J = 10.4$, 4.8 Hz, 2H), 6.85 (dd, $J = 5.1$, 3.4 Hz, 2H), 2.36 (s, 3H);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 177.13, 174.17, 154.76, 142.89, 139.50, 138.49, 135.14, 134.77, 134.31, 131.16, 130.82, 129.37, 128.91, 128.26, 128.08, 127.90, 127.86, 127.81, 127.42, 125.63, 125.17, 124.38, 120.97, 77.69, 77.44, 77.19, 70.13, 15.92.; HRMS (ESI) calcd for C$_{37}$H$_{27}$O$_2$ [M+H]$^+$ 503.2006, found 503.2022.

7-methoxy-1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3H)-one (2-3g)

![Chemical Structure](2-3g)

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.59 (d, $J = 3.0$ Hz, 1H), 7.33 (ddd, $J = 9.6$, 7.6, 2.5 Hz, 6H), 7.28 – 7.18 (m, 10H), 7.10 (dd, $J = 9.1$, 3.0 Hz, 1H), 6.96 (t, $J = 7.3$ Hz, 1H), 6.89 (t, $J = 7.6$ Hz, 2H), 6.73 (d, $J = 7.4$ Hz, 2H), 3.78 (s, 3H);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 177.60, 173.70, 157.54, 151.05, 143.07, 139.31, 138.13, 135.11, 134.82, 131.13, 130.84,
129.43, 128.99, 128.31, 127.95, 127.88, 127.83, 127.47, 126.45, 123.12, 120.72, 120.07, 106.04, 69.89, 56.31.; HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{27}\text{O}_2 [\text{M+H}]^+ 519.1955$, found 519.1979.

6-methoxy-1,2,3,3-tetraphenylcyclopenta[\text{b}]chromen-9(3\text{H})-one (2-3h)

![Chemical structure of 2-3h]

$^1\text{H NMR}$ (500 MHz, CDCl$_3$) $\delta$ 8.15 (d, $J = 8.9$ Hz, 1H), 7.39 (td, $J = 7.6, 2.7$ Hz, 6H), 7.33 – 7.24 (m, 9H), 7.02 (t, $J = 7.3$ Hz, 1H), 6.94 (dd, $J = 13.5, 5.9$ Hz, 3H), 6.82 – 6.77 (m, 3H), 3.82 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl$_3$) $\delta$ 177.15, 173.60, 163.97, 157.99, 142.98, 139.39, 138.11, 135.15, 134.85, 131.14, 130.84, 129.43, 128.99, 128.29, 127.94, 127.87, 127.84, 127.43, 121.27, 119.51, 114.93, 101.17, 69.86, 56.24.; HRMS (EI) calcd for [M+H]$^+$ $\text{C}_{37}\text{H}_{27}\text{O}_2$ 519.1955, found 519.1967.

7-fluoro-1,2,3,3-tetraphenylcyclopenta[\text{b}]chromen-9(3\text{H})-one (2-3i)

![Chemical structure of 2-3i]
$^1$H NMR (500 MHz, CDCl$_3$) δ 7.88 (dd, $J = 8.4$, 3.1 Hz, 1H), 7.40–7.36 (m, 7H), 7.31–7.25 (m, 10H), 7.03 (t, $J = 7.4$ Hz, 1H), 6.95 (t, $J = 7.6$ Hz, 2H), 6.79 – 6.76 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 177.97, 172.99, 161.17, 159.21, 152.42, 143.51, 138.97, 137.85, 134.90, 134.57, 131.10, 130.78, 129.39, 129.06, 128.43, 128.03, 127.99, 127.92, 127.59, 127.18, 127.12, 121.48, 121.27, 120.91, 120.77, 120.70, 111.76, 111.57, 70.00; HRMS (ESI) calcd for C$_{36}$H$_{24}$O$_2$F [M+H]$^+$ 507.1755, found 408.1772.

6-chloro-1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3H)-one (2-3j)

$^1$H NMR (500 MHz, CDCl$_3$): δ 8.21 (d, $J = 8.6$, 1H), 7.48–7.35 (m, 8H), 7.35–7.26 (m, 9H), 7.06 (t, $J = 7.3$ Hz, 1H), 6.98 (t, $J = 7.6$ Hz, 2H), 6.81 (d, $J = 7.7$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 177.17, 172.68, 155.88, 143.17, 138.88, 138.53, 137.30, 134.44, 134.13, 130.65, 130.34, 128.92, 128.63, 128.02, 127.62, 127.58, 127.55, 127.47, 127.16, 126.11, 123.91, 121.29, 118.42, 69.58.; HRMS (ESI) calcd for C$_{36}$H$_{24}$O$_2$Cl [M+H]$^+$ 523.1459, found 523.1474.

7-chloro-1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3H)-one (2-3k)
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.19 (t, $J = 4.7$ Hz, 1H), 7.51 (dd, $J = 8.9$, 2.6 Hz, 1H), 7.39 – 7.33 (m, 7H), 7.31 – 7.24 (m, 9H), 7.05 – 7.00 (m, 1H), 6.95 (dd, $J = 10.5$, 4.8 Hz, 2H), 6.77 (t, $J = 1.5$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.87, 172.66, 154.62, 143.66, 138.99, 137.81, 134.93, 134.54, 133.49, 131.80, 131.14, 130.83, 129.42, 129.11, 128.49, 128.09, 128.03, 127.95, 127.65, 126.91, 126.24, 121.53, 120.45, 70.09. HRESIMS calcd for C$_{36}$H$_{24}$O$_2$Cl [M+H]$^+$ 523.1459, found 523.1464.

7-bromo-1,2,3,3-tetraphenylcyclopenta[b]chromen-9(3H)-one (2-3l)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.39 (d, $J = 2.4$ Hz, 1H), 7.69 (dd, $J = 8.9$, 2.5 Hz, 1H), 7.39 (qd, $J = 5.5$, 3.4 Hz, 7H), 7.34 – 7.28 (m, 10H), 7.09 – 7.04 (m, 1H), 6.98 (dd, $J = 10.5$, 4.7 Hz, 2H), 6.79 (dd, $J = 5.2$, 3.4 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.82, 172.50, 155.10, 143.69, 139.02, 137.82, 136.25, 134.96, 134.53, 131.16, 130.83, 129.50, 129.43, 129.10, 128.48, 128.08, 128.02, 127.93, 127.65, 127.31, 121.63, 120.67, 119.28, 70.12. HRESIMS calcd for C$_{36}$H$_{24}$O$_2$Br [M+H]$^+$ 567.0954, found 567.0957.
1,2,3,3,7-pentaphenylcyclopenta[b]chromen-9(3H)-one (2-3m)

\[
\text{H NMR (500 MHz, CDCl}_3\text{)} \, \delta \, 8.52 \, (s, \, 1H), \, 7.87 - 7.84 \, (m, \, 1H), \, 7.64 \, (d, \, J = 7.1 \, Hz, \, 2H), \\
7.54 - 7.39 \, (m, \, 9H), \, 7.36 - 7.27 \, (m, \, 10H), \, 7.07 \, (t, \, J = 7.3 \, Hz, \, 1H), \, 6.99 \, (t, \, J = 7.5 \, Hz, \, 2H), \, 6.83 \, (d, \, J = 7.2 \, Hz, \, 2H).
\]

\[\text{13C NMR (125 MHz, CDCl}_3\text{)} \, \delta \, 177.72, \, 173.95, \, 155.72, \, 143.28, \, 139.90, \, 139.26, \, 138.91, \, 138.02, \, 135.08, \, 134.73, \, 132.16, \, 131.15, \, 130.87, \, 129.45, \, 129.04, \, 128.37, \, 128.26, \, 127.98, \, 127.88, \, 127.61, \, 127.53, \, 125.95, \, 124.66, \, 121.46, \, 119.27, \, 70.04; \, \text{HRESIMS calcd for C}_{42}\text{H}_{29}\text{O}_{2} [M+H]^+ 565.2161, \, \text{found} 565.2159.\]

8,9,10,10-tetraphenylbenzo[h]cyclopenta[b]chromen-7(10H)-one (2-3n)

\[
\text{H NMR (500 MHz, CDCl}_3\text{)} \, \delta \, 8.33 \, (d, \, J = 8.3 \, Hz, \, 1H), \, 8.26 \, (d, \, J = 8.7 \, Hz, \, 1H), \, 7.91 \, (d, \, J = 8.0 \, Hz, \, 1H), \, 7.78 \, (d, \, J = 8.7 \, Hz, \, 1H), \, 7.69 - 7.64 \, (m, \, 1H), \, 7.63 - 7.58 \, (m, \, 1H), \, 7.53 - 7.47 \, (m, \, 6H), \, 7.39 - 7.30 \, (m, \, 9H), \, 7.12 - 7.07 \, (m, \, 1H), \, 7.02 \, (dd, \, J = 10.3, \, 4.7 \, Hz, \, 2H), \, 6.89 \, (dd, \, J = 5.2, \, 3.4 \, Hz, \, 2H).
\]

\[\text{13C NMR (125 MHz, CDCl}_3\text{)} \, \delta \, 176.54, \, 173.92, \, 153.47, \, 143.55, \, 139.47, \, 138.37, \, 136.07, \, 135.13, \, 134.71, \, 131.24, \, 131.15, \, 130.93, \, 129.43, \, 129.11, \, 128.42, \, 128.26, \, 127.98, \, 127.79, \, 127.71, \, 127.41, \, 125.01, \, 124.66, \, 121.46, \, 119.27, \, 70.04; \, \text{HRESIMS calcd for C}_{42}\text{H}_{29}\text{O}_{2} [M+H]^+ 565.2161, \, \text{found} 565.2159.\]
128.01, 127.90, 127.60, 127.53, 125.73, 124.65, 122.58, 122.09, 121.90, 70.23;
HRESIMS calcd for C_{20}H_{27}O_{2} [M+H]^+ 539.2006, found 539.2017.

1,2,3,3-tetraphenylbenzo[g]cyclopenta[h]chromen-11(3H)-one (2-3o)

![Image of 1,2,3,3-tetraphenylbenzo[g]cyclopenta[h]chromen-11(3H)-one (2-3o)]

$^{1}$H NMR (500 MHz, CDCl$_3$) δ 10.17 (d, $J = 8.7$ Hz, 1H), 8.02 (d, $J = 9.1$Hz, 1H), 7.89 (d, $J = 7.9$ Hz, 1H), 7.70 (t, $J = 7.4$ Hz, 1H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.46 (ddd, $J = 10.8$, 6.8, 6.1 Hz, 7H), 7.35 – 7.30 (m, 9H), 7.09 – 7.02 (m, 1H), 6.99 (t, $J = 7.6$ Hz, 2H), 6.82 (d, $J = 7.4$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 176.20, 174.81, 157.38, 143.92, 139.78, 138.14, 135.25, 135.21, 134.98, 131.67, 131.32, 131.22, 130.84, 129.47, 129.33, 129.03, 128.48, 128.34, 127.97, 127.93, 127.48, 126.95, 123.80, 119.02, 118.30, 69.63; HRESIMS calcd for C$_{40}$H$_{27}$O$_{2}$ [M+H]^+ 539.2006, found 539.2017.

1,2,3,3-tetrap-tolytcyclopenta[h]chromen-9(3H)-one (2-3p)

![Image of 1,2,3,3-tetrap-tolytcyclopenta[h]chromen-9(3H)-one (2-3p)]
1H NMR (500 MHz, CDCl$_3$) δ 8.27 (dd, $J=7.9$, 1.4 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.40 (dd, $J = 10.4$, 6.1 Hz, 2H), 7.33 – 7.29 (m, 6H), 7.13 (m, 6H), 6.81 (d, $J = 8.1$ Hz, 2H), 6.75 (d, $J = 8.1$ Hz, 2H), 2.37 (s, 3H), 2.36 (s, 6H), 2.21 (s, 3H); 13C NMR (125 MHz, CDCl$_3$) δ 177.89, 173.91, 156.33, 142.91, 138.56, 137.87, 137.32, 136.88, 135.29, 133.06, 132.30, 132.24, 130.97, 130.70, 129.64, 129.43, 128.90, 128.68, 128.66, 127.89, 126.79, 125.97, 125.55, 121.47, 118.72, 69.21, 21.86, 21.58, 21.5.; HRESIMS calcd for C$_{40}$H$_{33}$O$_2$ [M+H]$^+$ 545.2475, found 545.2493.

1,2,3,3-tetrakis(4-methoxyphenyl)cyclopenta[b]chromen-9(3H)-one (2-3q)

1H NMR (500 MHz, CDCl$_3$) δ 8.26 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.41 – 7.26 (m, 8H), 6.85 – 6.79 (m, 6H), 6.78 – 6.74 (t, $J = 9.3$ Hz, 2H), 6.54 (t, $J = 9.3$ Hz, 2H), 3.81 (s, 3H), 3.78 (s, 6H), 3.68 (s, 3H); 13C NMR (125 MHz, CDCl$_3$) δ 177.96, 173.94, 159.44, 159.17, 158.68, 156.13, 142.44, 137.35, 133.07, 132.12, 130.47, 130.32, 130.11, 127.62, 127.34, 126.61, 125.76, 125.52, 121.01, 118.60, 114.26, 113.77, 113.42, 113.33, 68.32, 55.57, 55.48, 55.31.; HRESIMS (complex as standard) calcd for C$_{40}$H$_{33}$O$_6$ [M+H]$^+$ 609.2272, found 609.2285.
1,3-bis(4-ethylphenyl)-2,3-bis(4-hexylphenyl)cyclopenta[b]chromen-9(3H)-one or 2,3-bis(4-methoxyphenyl)-1,3-diphenylcyclopenta[b]chromen-9(3H)-one (2-3r)

Ratio of regioisomers 55:45; Spectrum data of a or b: $^1$H NMR (500 MHz, CDCl$_3$) δ 8.28 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.61 – 7.58 (m, 1H), 7.45 – 7.38 (m, 7H), 7.35 – 7.29 (m, 7H), 6.88 – 6.85 (m, 2H), 6.78 – 6.74 (m, 2H), 6.55 – 6.52 (m, 2H), 3.82 (s, 3H), 3.69 (s, 3H); $^1$C NMR (125 MHz, CDCl$_3$) δ 177.72, 173.92, 159.65, 158.90, 156.31, 143.13, 138.52, 138.18, 135.17, 133.19, 132.24, 130.88, 130.68, 129.84, 129.40, 128.98, 128.22, 127.93, 127.78, 127.43, 126.78, 125.88, 125.65, 121.36, 118.74, 114.42, 113.48, 69.22, 55.72, 55.44.; HRESIMS (complex as standard) calcd for C$_{38}$H$_{29}$O$_4$ [M+H]$^+$ 549.2060, found 549.2074.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.31 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.64 – 7.57 (m, 1H), 7.47 – 7.30 (m, 12H), 7.10 – 6.99 (m, 3H), 6.90 – 6.83 (m, 5H), 3.83 (s, 3H), 3.82 (s, 3H); $^1$C NMR (125 MHz, CDCl$_3$) δ 177.97, 174.02, 159.60, 159.36, 156.24, 142.57, 138.61, 138.43, 135.43, 133.22, 132.19, 131.13, 130.62, 129.75, 129.34, 128.92, 128.19, 127.98, 127.33, 127.07, 126.73, 125.84, 125.67, 121.19, 118.70, 114.36, 113.36, 69.22, 55.66,
55.56; HRESIMS (complex as standard) calcd for C_{38}H_{29}O_{4} [M+H]^+ 549.2060, found 549.2074.

1,3-diphenyl-2,3-bis(4-(trimethylsilyl)phenyl)cyclopenta[b]chromen-9(3H)-one or 2,3-diphenyl-1,3-bis(4-(trimethylsilyl)phenyl)cyclopenta[b]chromen-9(3H)-one (2-3s)

Ratio of regioisomers 53:47; Spectrum data of a or b: \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 8.30 (dd, \textit{J} = 8.0, 1.5 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.49 – 7.36 (m, 12H), 7.31 – 7.29 (m, 3H), 7.06 (t, \textit{J} = 7.4 Hz, 1H), 6.99 (t, \textit{J} = 7.6 Hz, 2H), 6.81 (d, \textit{J} = 1.1Hz, 2H), 0.28 (s, 6H), 0.28 (s, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 177.68, 173.88, 156.28, 143.20, 140.62, 139.73, 139.32, 138.45, 138.07, 135.19, 135.03, 133.97, 133.25, 132.80, 131.22, 130.03, 129.44, 129.05, 128.95, 128.78, 128.26, 127.93, 127.44, 126.78, 125.84, 125.70, 121.45, 118.76, 70.00, -0.59, -0.67.; HRESIMS (complex as standard) calcd for C_{42}H_{31}O_{2}Si_{2}[M+H]^+ 633.2640, found 633.2670.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.26 (td, $J = 7.7$, 1.4 Hz, 1H), 7.58 (ddd, $J = 8.6$, 7.2, 1.6 Hz, 1H), 7.47 – 7.36 (m, 11H), 7.34 – 7.28 (m, 5H), 7.12 (d, $J = 8.1$ Hz, 2H), 6.79 (d, $J = 8.0$ Hz, 2H), 0.27 (s, 9H), 0.16 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.65, 173.88, 156.32, 143.07, 140.62, 139.43, 139.38, 138.47, 138.46, 138.09, 135.33, 135.08, 133.98, 133.24, 133.05, 132.86, 130.79, 130.20, 129.52, 128.96, 128.86, 128.46, 128.26, 127.95, 127.90, 126.77, 125.85, 125.69, 121.49, 118.79, 69.74, -0.67, 0.74; HRESIMS (complex as standard) calcd for C$_{42}$H$_{41}$O$_2$Si$_2$[M+H]$^+$ 633.2640, found 633.2670.

1,3-bis(3,4-dimethylphenyl)-2,3-diphenylcyclopenta[b]chromen-9(3H)-one or 2,3-bis(3,4-dimethyl phenyl)-1,3-diphenylcyclopenta[b]chromen-9(3H)-one (2-3t)

Ratio of regioisomers 59:41; Spectrum data of a or b: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.18 (dd, $J = 8.0$, 1.4 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.30 (ddd, $J = 8.3$, 6.9, 5.4 Hz, 4H), 7.22 – 7.17 (m, 4H), 6.95 – 6.84 (m, 7H), 6.80 (s, 1H), 6.73 – 6.68 (m, 2H), 2.16 (s, 6H), 2.15 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.67, 173.88, 156.33, 143.00, 139.34, 138.40, 138.37, 137.83, 137.01, 135.38, 134.76, 133.13, 131.18, 129.97, 129.62, 129.52, 128.87, 128.49, 128.13, 127.72, 127.23, 126.81, 125.95, 125.58, 121.71, 118.79, 69.89, 21.94,
HRESIMS (complex as standard) calcd for C_{40}H_{33}O_{2} [M+H]^+ 545.2475, found 545.2486.

1H NMR (500 MHz, CDCl₃) δ 8.27 – 8.25 (m, 1H), 7.58 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H), 7.43 – 7.37 (m, 6H), 7.29 – 7.26 (m, 7H), 6.98 – 6.95 (m, 3H), 6.66 (s, 1H), 6.32 (s, 1H), 2.25 (s, 6H), 1.98 (s, 6H); 13C NMR (125 MHz, CDCl₃) δ 177.65, 173.98, 156.38, 143.70, 138.77, 138.45, 138.30, 137.93, 136.86, 135.15, 134.82, 133.17, 131.27, 130.88, 130.76, 129.96, 129.67, 129.50, 129.26, 128.99, 128.91, 128.82, 128.15, 127.88, 127.76, 127.72, 127.40, 127.21, 126.78, 125.94, 125.63, 121.53, 118.81, 69.82, 21.93, 21.64.; HRESIMS (complex as standard) calcd for C_{40}H_{33}O_{2} [M+H]^+ 545.2475, found 545.2486.

1,3-bis(4-ethylphenyl)-2,3-bis(4-hexylphenyl)cyclopenta[b]chroomen-9(3H)-one or 2,3-bis(4-ethyl-phenyl)-1,3-bis(4-hexylphenyl)cyclopenta[b]chroomen-9(3H)-one (2-3u)
Ratio of regioisomers 61:39; Spectrum data of a or b: $^1$H NMR (500 MHz, CDCl$_3$) δ 8.31 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.61 – 7.59 (m, 1H), 7.45 – 7.32 (m, 8H), 7.19 – 7.13 (m, 6H), 6.84 (d, $J = 8.2$ Hz, 2H), 6.76 (d, $J = 8.2$Hz, 2H), 2.72 – 2.62 (m, 8H), 2.56 – 2.50 (m, 2H), 1.42 – 1.25 (m, 18H), 1.19 – 1.14 (m, 2H), 1.01 – 0.89 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 178.00, 173.98, 156.31, 144.09, 143.12, 143.07, 142.88, 142.28, 138.52, 135.46, 135.41, 133.05, 132.61, 132.37, 131.03, 130.72, 129.51, 129.41, 128.88, 128.36, 127.91, 127.28, 126.76, 125.93, 125.54, 121.44, 118.76, 69.19, 36.32, 36.04, 32.24, 32.17, 31.66, 31.61, 29.50, 28.88, 28.83, 23.12, 23.07, 15.70, 15.49, 14.58, 14.55; HRESIMS (complex as standard) calcd for C$_{52}$H$_{57}$O$_2$ [M+H]$^+$ 713.4353, found 713.4369.

Spectrum data of a and b as complex; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.34 – 8.28 (m, 1H), 7.58 (m, 2H), 7.45 – 7.32 (m, 7H), 7.24 – 7.06 (m, 6H), 6.94 – 6.89 (m, 1H), 6.83 (d, $J = 8.1$ Hz, 2H), 6.76 (d, $J = 8.1$ Hz, 2H), 2.75 – 2.46 (m, 12H), 1.41 – 1.21 (m, 18H), 0.97 – 0.87 (m, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 177.98, 173.96, 171.55, 166.89, 161.64, 161.54, 156.36, 156.30, 144.60, 144.52, 144.08, 143.49, 143.39, 143.29, 143.21, 142.87, 142.09, 141.80, 138.45, 135.74, 135.61, 135.49, 135.44, 134.55, 133.05, 132.82, 132.67, 132.55, 132.48, 132.32, 130.99, 130.84, 130.77, 130.66, 130.31, 130.22, 129.69, 129.49, 129.39, 129.35, 129.26, 128.86, 128.38, 128.34, 128.27, 128.19, 127.92, 127.85, 127.55, 127.29, 126.85, 126.76, 126.44, 125.94, 125.54, 125.45, 121.46, 118.75, 118.54, 69.28, 67.41, 36.04, 35.94, 32.21, 32.17, 32.13, 31.66, 31.64, 31.36, 29.54, 29.49, 29.19, 29.16, 28.88, 23.09, 23.07, 15.70, 14.56, 14.54, 14.52; HRESIMS (complex as standard) calcd for C$_{52}$H$_{57}$O$_2$ [M+H]$^+$ 713.4353, found 713.4369.
1,3-bis(4-fluorophenyl)-2,3-diphenylcyclopenta[b] chromen-9(3H)-one or 2,3-bis(4-fluoro-phenyl)-1,3-diphenylcyclopenta[b] chromen-9(3H)-one (2-3v)

[Chemical structure images]

Ratio of regioisomers 51:49; Spectrum data of a or b: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.27 (dd, \(J = 8.0, 1.4\) Hz, 1H), 7.66 – 7.59 (m, 1H), 7.43 – 7.29 (m, 11H), 7.08 (t, \(J = 7.4\) Hz, 1H), 7.02 – 6.94 (m, 6H), 6.78 – 6.75 (m, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 176.96, 173.51, 163.24, 161.37, 161.28, 155.83, 142.86, 137.89, 137.36, 134.34, 133.15, 133.06, 132.22, 132.16, 130.67, 130.63, 130.61, 130.00, 128.96, 128.80, 128.70, 128.57, 128.10, 127.74, 127.34, 126.32, 125.47, 125.28, 120.63, 118.29, 115.62, 115.44, 114.57, 114.40, 68.97; HRESIMS (complex as standard) calcd for C\(_{36}\)H\(_{23}\)O\(_2\)F\(_2\)[M+H]\(^+\) 525.1661, found 525.1665.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.27 (dd, \(J = 7.9, 1.3\) Hz, 1H), 7.63 – 7.58 (m, 1H), 7.44 – 7.28 (m, 13H), 7.00 (dd, \(J = 14.5, 5.9\) Hz, 2H), 6.79 – 6.74 (m, 2H), 6.69 (t, \(J = 8.7\) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 176.85, 173.38, 163.37, 162.78, 161.39, 160.81, 155.84, 153.19, 141.50, 139.25, 137.33, 133.95, 133.11, 133.02, 132.30, 132.24, 130.63,
130.57, 130.49, 130.30, 128.91, 128.78, 128.76, 128.66, 128.16, 127.71, 127.57, 126.38, 125.45, 125.34, 120.81, 118.26, 115.71, 115.54, 114.82, 114.65, 68.94; HRESIMS (complex as standard) calcd for C\textsubscript{36}H\textsubscript{23}O\textsubscript{2}F\textsubscript{2}[M+H]\textsuperscript{+} 525.1661, found 525.1665.

1,3-bis (4-fluorophenyl)-2,3-diphenylcyclopenta[b]chromen-9(3H)-one or 2,3-bis (3,5-bis (trifluoromethyl)phenyl)-1,3-diphenylcyclopenta[b]chromen-9(3H)-one (2-3w)

Ratio of regioisomers 73:27; Spectrum data of a or b: \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 8.34 (dd, \(J = 8.2, 1.4\) Hz, 1H), 7.87 (s, 1H), 7.85 (s, 2H), 7.79 (s, 3H), 7.72 – 7.69 (m, 1H), 7.50 – 7.43 (m, 5H), 7.34 – 7.31 (m, 2H), 7.21 (t, \(J = 7.5\) Hz, 1H), 7.11 (t, \(J = 7.7\) Hz, 2H), 6.70 – 6.67 (m, 2H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 175.67, 173.77, 156.34, 144.86, 140.34, 137.78, 136.30, 135.76, 134.23, 133.09, 132.59, 132.32, 131.33, 131.22, 130.96, 129.91, 129.53, 129.06, 128.99, 128.93, 127.07, 126.49, 125.50, 124.83, 124.54, 122.66, 122.37, 121.95, 120.72, 118.74, 70.04.; HRESIMS (complex as standard) calcd for C\textsubscript{40}H\textsubscript{21}O\textsubscript{12}F\textsubscript{12}[M+H]\textsuperscript{+} 761.1344, found 761.1364.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.30 (dd, $J = 8.2$, 1.5 Hz, 1H), 7.90 (s, 3H), 7.71 – 7.67 (m, 1H), 7.59 (s, 1H), 7.48 (dd, $J = 9.6$, 5.3 Hz, 5H), 7.40 (s, 5H), 7.34 – 7.30 (m, 2H), 7.16 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.94, 173.54, 156.37, 143.98, 140.39, 138.31, 136.38, 135.97, 134.21, 133.05, 132.95, 132.78, 131.92, 131.66, 130.78, 130.23, 130.16, 129.81, 129.41, 129.30, 128.74, 128.70, 127.02, 126.52, 125.67, 124.44, 124.31, 122.97, 122.27, 122.15, 121.48, 121.33, 118.71, 69.16.; HRESIMS (complex as standard) calcd for C$_{40}$H$_{21}$O$_2$F$_{12}$[M+H]$^+$ 761.1344, found 761.1364.

1,3-bis(3-nitrophenyl)-2,3-diphenylcyclopenta[b]chromen-9(3H)-one and 2,3-bis(3-nitrophenyl)-1,3-diphenylcyclopenta[b]chromen-9(3H)-one (2-3x)

Ratio of regioisomers 52:48; Spectrum data of a and b as complex: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.33 – 8.22 (m, 4H), 8.22 – 8.10 (m, 3H), 7.93 – 7.89 (m, 1H), 7.80 – 7.72 (m, 2H), 7.72 (s, 2H), 7.66 – 7.60 (m, 3H), 7.53 (dt, $J = 20.9$, 8.0 Hz, 3H), 7.47 – 7.30 (m, 20H), 7.20 – 7.15 (m, 2H), 7.12 (t, $J = 7.4$ Hz, 1H), 7.04 (q, $J = 7.8$ Hz, 2H), 6.77 – 6.71 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ = 176.43, 176.22, 173.79, 173.60, 156.32, 156.28, 148.99, 148.82, 148.11, 148.01, 144.40, 142.81, 139.91, 139.87, 139.28, 137.84,
136.98, 136.90, 136.41, 136.16, 135.85, 135.21, 135.09, 134.01, 133.95, 133.38, 130.98, 130.48, 130.40, 130.09, 129.88, 129.65, 129.43, 129.31, 129.25, 129.02, 128.94, 128.87, 128.80, 128.68, 128.44, 126.88, 126.81, 126.32, 126.29, 125.92, 125.63, 125.47, 125.43, 124.42, 124.32, 123.86, 123.66, 123.12, 122.69, 121.27, 120.91, 118.80, 118.73, 69.97, 69.36; HRESIMS (complex as standard) calcd for C_{36}H_{23}O_{6}N_{2} [M+H]^+ 579.1551, found 579.1545.

1,3-di(naphthalen-2-yl)-2,3-diphenylcyclopenta[b]chromen-9(3H)-one or 2,3-di(naphthalene -2-yl)-1,3-diphenylcyclopenta[b]chromen-9(3H)-one (2-3y)

![2-3y](image)

Ratio of regioisomers 59:41; Spectrum data of a or b: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.31 (d, $J = 7.7$ Hz, 1H), 7.95 (d, $J = 15.5$ Hz, 2H), 7.80 (m, 6H), 7.49 (m, 14H), 7.02 (dd, $J = 16.0, 9.1$ Hz, 1H), 6.96 – 6.85 (m, 4H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 177.17, 173.54, 155.92, 143.22, 138.94, 137.55, 135.09, 134.66, 133.39, 133.00, 132.92, 132.88, 132.86, 131.95, 130.75, 129.65, 129.12, 128.65, 128.48, 128.32, 128.24, 128.20, 128.01, 127.66, 127.58, 127.17, 126.77, 126.74, 126.44, 126.39, 126.29, 125.90, 125.69, 125.44, 125.35,
121.30, 118.34, 69.79; HRESIMS (complex as standard) calcd for C_{44}H_{29}O_{2} [M+H]^+ 589.2162, found 589.2176.

^1^H NMR (500 MHz, CDCl₃) δ 8.30 (d, J = 7.7 Hz, 1H), 7.97 (s, 1H), 7.84 – 7.72 (m, 3H), 7.63 – 7.54 (m, 4H), 7.48 (m, 4H), 7.42 – 7.25 (m, 14H), 6.93 (d, J = 8.5 Hz, 1H). ^1^C NMR (125 MHz, CDCl₃) δ 177.20, 173.51, 155.90, 142.52, 139.52, 137.56, 135.10, 134.35, 133.36, 132.91, 132.70, 132.28, 132.22, 130.48, 129.68, 129.15, 128.87, 128.67, 128.25, 128.16, 128.08, 128.01, 127.63, 127.55, 127.35, 126.90, 126.76, 126.44, 126.36, 126.29, 125.94, 125.65, 125.43, 125.35, 121.16, 118.32, 69.69.; HRESIMS (complex as standard) calcd for C_{44}H_{29}O_{2} [M+H]^+ 589.2162, found 589.2176.

1,3-diphenyl-2,3-di(thiophen-2-yl)cyclopenta[b]chromen-9(3H)-one or 2,3-diphenyl-1,3-di(thio-phen-2-yl)cyclopenta[b]chromen-9(3H)-one (2-3z)

Ratio of regioisomers 66:34; Spectrum data of a or b: ^1^H NMR (500 MHz, CDCl₃) δ 8.34 (dd, J = 8.0, 1.6 Hz, 1H), 7.65 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H), 7.50 – 7.43 (m, 3H), 7.38 – 7.34 (m, 5H), 7.28 – 7.25 (m, 2H), 7.22 (t, J = 5.8 Hz, 1H), 7.11 (dd, J = 3.9, 2.8 Hz, 3H),
7.02 – 6.99 (m, 2H), 6.89 – 6.87 (m, 2H).; $^{13}$C NMR (125 MHz, CDCl$_3$) δ 176.51, 174.00, 156.07, 143.90, 139.35, 137.80, 135.32, 134.91, 133.53, 132.20, 131.56, 131.04, 129.24, 128.78, 128.66, 128.33, 128.26, 127.04, 127.01, 126.93, 126.78, 126.00, 125.94, 125.87, 120.44, 118.71, 66.47; HRESIMS (complex as standard) calcd for C$_{32}$H$_{21}$O$_2$S$_2$ [M+H]$^+$ 501.0977, found 501.0996.

Spectrum data of a and b as complex: $^1$H NMR (500 MHz, CDCl$_3$ ) δ = 8.35 (d, $J = 7.9$ Hz, 2H), 8.25 (d, $J = 7.9$ Hz, 1H), 7.64 (dt, $J = 11.0$, 8.6 Hz, 2H), 7.57 – 7.53 (m, 2H), 7.50 – 7.44 (m, 6H), 7.40 (m, 9H), 7.32 – 7.24 (m, 3H), 7.22 (t, $J = 7.3$ Hz, 1H), 7.13 (t, $J = 7.5$ Hz, 4H), 7.06 (dd, $J = 8.6$, 4.5 Hz, 1H), 7.04 – 7.00 (m, 2H), 6.90 (d, $J = 7.8$ Hz, 2H), 6.74 (t, $J = 4.2$ Hz, 1H), 6.60 (d, $J = 3.4$ Hz, 1H).; $^{13}$C NMR (125 MHz, CDCl$_3$ ) δ = 176.49, 176.36, 173.97, 173.91, 156.28, 156.05, 143.89, 139.34, 138.29, 137.78, 137.56, 137.17, 136.33, 135.30, 134.90, 133.52, 133.45, 132.19, 131.54, 131.04, 130.41, 129.33, 129.22, 129.10, 129.07, 128.89, 128.77, 128.70, 128.64, 128.59, 128.32, 128.25, 127.03, 127.00, 126.91, 126.76, 126.67, 126.52, 126.36, 125.99, 125.93, 125.86, 125.74, 120.90, 120.42, 118.78, 118.69, 66.46, 65.74.; HRESIMS (complex as standard) calcd for C$_{32}$H$_{21}$O$_2$S$_2$ [M+H]$^+$ 501.0977, found 501.0996.
2.4.4 X-Ray Crystallographic Analysis

The configuration of the product 2-3a was assigned by X-ray crystallographic analysis of a single crystal of 2-3a (Figure 2.1). The configurations of other products were assigned by analogy.

![Figure 2.1 X-ray structure of 2-3a](image)

**Table 2.5** Crystal data and structure refinement for 2-3a.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>a427</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C36 H24 O2</td>
</tr>
<tr>
<td>Formula weight</td>
<td>488.55</td>
</tr>
<tr>
<td>Temperature</td>
<td>223(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
</tbody>
</table>
Crystal system: Monoclinic

Space group: P2(1)/n

Unit cell dimensions:
\[ a = 12.4946(8) \, \text{Å}, \quad \text{a}= 90^\circ. \]
\[ b = 9.7428(7) \, \text{Å}, \quad \text{b}= 92.355(2)^\circ. \]
\[ c = 21.0397(15) \, \text{Å}, \quad \text{g}= 90^\circ. \]

Volume: \( 2559.0(3) \, \text{Å}^3 \)

\( Z \): 4

Density (calculated): 1.268 Mg/m\(^3\)

Absorption coefficient: 0.077 mm\(^{-1}\)

\( F(000) \): 1024

Crystal size: 0.50 x 0.16 x 0.12 mm\(^3\)

The \( \theta \) range for data collection: 1.86 to 27.50\(^\circ\).

Index ranges:
\[-14\leq h\leq 16, \quad -12\leq k\leq 12, \quad -27\leq l\leq 25\]

Reflections collected: 17688

Independent reflections: 5876 [\( R(\text{int}) = 0.0419 \)]

Completeness to theta = 27.50\(^\circ\): 99.9\%

Absorption correction: Semi-empirical from equivalents

Max. and min. transmission: 0.9908 and 0.9624

Refinement method: Full-matrix least-squares on \( F^2 \)

Data / restraints / parameters: 5876 / 0 / 343

Goodness-of-fit on \( F^2 \): 1.092

Final R indices [\( I>2\sigma(I) \)]:
\[ R1 = 0.0600, \quad wR2 = 0.1256 \]
R indices (all data)  \[ R_1 = 0.0817, \quad wR_2 = 0.1357 \]

Largest diff. peak and hole  \[ 0.290 \text{ and } -0.293 \text{ e.Å}^{-3} \]
An efficient synthesis of benzazepine heterocycles method was developed. It utilizes simple and readily available isatins and alkynes, and employs a direct Pd (II)-catalyzed oxidative cycloaddition. These heterocycles are well tolerated in the reaction, which allowing access to a number of unique molecular structures. The significance of benzazepine scaffold as design element should render this method attractive for synthetic and medicinal chemistry.
3.1 Introduction

The wealth of nitrogen-containing heterocycles in biologically active molecules has attracted chemists to develop increasingly efficient methods toward their synthesis.\textsuperscript{84} Recently, chemists have turned to their attention to solve the finite nature of chemical feedstocks coupled with the negative impacts of manufacturing waste.\textsuperscript{85} In this regard, directed C–H activation towards the formation of C–C and C–heteroatom bonds has received the most attractive and substantial attention because of its sustainable and environmentally benign features.\textsuperscript{86} In particular, Pd-catalyzed oxidative cycloaddition of alkynes by C–H/N–H bond cleavages have proven reliable to form the corresponding nitrogen-containing heterocycles through an atom- and step-economical synthetic manner.\textsuperscript{87} In recent elegant reports, Jiao \textit{et al.} described a direct approach for constructing indoles from anilines and alkynes by Pd-catalyzed oxidative C–H/N–H activation, involving a five-membered ring cyclization (Scheme 3.1a).\textsuperscript{88} In addition, other transition metals (\textit{e.g.} Ru and Rh) have also been applied to assemble indole and other five-membered ring structure based nitrogen-containing heterocycles via a similar strategy.\textsuperscript{89}

More recently, a one-pot Pd-catalyzed C–H/N–H activation of alkynes has been reported to facilitate an isoquinolinone synthesis, which including a nitrogen-containing six-membered ring formation.\textsuperscript{90} Although these protocols have proved to be effective, as demonstrated by their utilization in constructing five- or six-membered ring involved N-heterocycles, Pd-catalyzed oxidative cyclization for the direct synthesis of a nitrogen-containing seven-membered ring still remains a challenge task (Scheme 3.1c).
Scheme 3.1 Pd-catalyzed oxidative cycloaddition for five- to seven-membered ring formation, involving a C–H/N–H activation. a) Indole synthesis. b) Isoquinolone synthesis. c) Benzazepine synthesis.

Figure 3.1 Examples of benzazepine pharmaceuticals.
Benzazepines, known as a seven-membered ring based nitrogen-containing heterocycles, are ubiquitous bioactive scaffolds which are closely linked to pharmaceutical activity, and play a significant role as a structural design element in medicinal chemistry. As exemplified in Figure 3.1, Mozavaptan is used as an orally effective, nonpeptide arginine vasopressin V-2 receptor antagonist. Lotensin is a prescription medication that has been licensed for treating high blood pressure (hypertension), congestive heart failure, and chronic renal failure by inhibiting angiotensin-converting enzyme (ACE) in human subjects. Anafranil is identified as an antiobsessional drug that belongs to the class of pharmacologic agents known as tricyclic antidepressants. Besides anafranil, its analogues, tienopramine and amezepine are also classified as antidepressants.

Reported methods for benzazepine synthesis are mainly requiring multiple synthetic steps. A direct intermolecular and efficient methods starting from simple and readily available starting materials would not only enable a new set of accessible scaffolds, but also allow additional and late-stage modification of existing compounds having biological properties. To address this limitation, we dedicated to utilize a direct C–H/N–H activation method to construct benzazepine scaffold. We envisioned that such proposed strategy could be applied to the efficient production of valuable benzazepine heterocycles from simple and readily available alkynes and isatins via a direct oxidative cycloaddition.
3.2 Results and Discussion

3.2.1 Reaction Optimization

Our investigation began with the Pd-catalyzed oxidative cycloaddition of isatin 3-1a and diphenylacetylene 3-2a to give the corresponding benzazepine 3-3aa (Table 3.1). In experiments to optimize reaction parameters, the best results were obtained with a catalytic amount of Pd(OAc)$_2$ as catalyst and a stoichiometric amount of AgOAc as oxidant in a mixed solvent of MeCN/1,4-Dioxane (v/v = 1:1) (Table 3.2, entry 18). Under these conditions, conversion was complete within 24 h at 120 °C (entry 18, 83% isolated yield). Variation of oxidants (Table 3.1, entries 2–15), or solvents (Table 3.2, entries 1–18) led to a decrease in chemical yield. The effect of temperature is also summarized in Table 3.2 (entries 16–20), a similar yield was achieved at a slightly low temperature (100 °C, 81%, entry 18). However, further lowering the temperature led to a slow reaction conversion (entries 19–20, 56% and 18%, respectively). Moreover, the ratio of 3-1a/3-2a is sensitive to a high degree of conversion. For example, changing the ratio of 3-1a/3-2a from 1:5 to 1:3 generated a significant loss of reaction yield Table 3.1 (entries 3 and 4). Notably, N$_2$ is likely essential to the reaction. As highlighted in Table 3.1, while the reaction carried out in air, only a moderate reaction yield was obtained under standard conditions Table 3.2 (entry 17, 55%).
Table 3.1 Conditions optimization of palladium-catalyzed oxidative cycloaddition \([a]\)

![Chemical structure and reaction equation]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant([b])</th>
<th>Additive([c])</th>
<th>Yield (%)([d])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>CuI</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>CuBr</td>
<td>–</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>AgCO(_2)CF(_3)</td>
<td>–</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>AgSbF(_6)</td>
<td>–</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>AgI</td>
<td>–</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>CuOAc</td>
<td>–</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>CuCl(_2)</td>
<td>–</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>CuBr(_2)</td>
<td>–</td>
<td>&lt;5</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)(_2)</td>
<td>–</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>BQ([e])</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>(NH(_4))(_2)S(_2)O(_8)</td>
<td>–</td>
<td>&lt;5</td>
</tr>
<tr>
<td>13</td>
<td>Phl(OAc)(_2)</td>
<td>–</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>Oxone</td>
<td>–</td>
<td>&lt;5</td>
</tr>
<tr>
<td><strong>15</strong></td>
<td>AgOAc</td>
<td>–</td>
<td><strong>77</strong></td>
</tr>
<tr>
<td>16</td>
<td>AgOAc</td>
<td>–</td>
<td>38([f])</td>
</tr>
<tr>
<td>17</td>
<td>AgOAc</td>
<td>HOAc</td>
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<tr>
<td>18</td>
<td>AgOAc</td>
<td>TFA</td>
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Table 3.2 Optimization of solvent and temperature $^{[a]}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Yield [%]$^{[b]}$</th>
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<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>100</td>
<td>53$^{[c]}$</td>
</tr>
<tr>
<td>2</td>
<td>1,4-Dioxane</td>
<td>100</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>Diglyme$^{[d]}$</td>
<td>120</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>Acetone</td>
<td>40</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>120</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>1,4-Dioxane</td>
<td>100</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>DCE$^{[e]}$</td>
<td>100</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>80</td>
<td>&lt;5</td>
</tr>
<tr>
<td>9</td>
<td>i-PrOH</td>
<td>100</td>
<td>&lt;5</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>---</td>
<td>---</td>
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</tr>
<tr>
<td>10</td>
<td>DMF</td>
<td>120</td>
<td>77</td>
</tr>
<tr>
<td>11</td>
<td>DMA[^f]</td>
<td>120</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>DMSO</td>
<td>120</td>
<td>15</td>
</tr>
<tr>
<td>13</td>
<td>NMP[^g]</td>
<td>120</td>
<td>58</td>
</tr>
<tr>
<td>14</td>
<td>MeCN/DMF (v/v = 1:1)</td>
<td>120</td>
<td>35</td>
</tr>
<tr>
<td>15</td>
<td>MeCN/NMP (v/v = 1:1)</td>
<td>120</td>
<td>28</td>
</tr>
<tr>
<td>16</td>
<td>MeCN/1,4-Dioxane (v/v = 1:1)</td>
<td>120</td>
<td>83</td>
</tr>
<tr>
<td>17</td>
<td>MeCN/1,4-Dioxane (v/v = 1:1)</td>
<td>120</td>
<td>55[^h]</td>
</tr>
<tr>
<td>18</td>
<td>MeCN/1,4-Dioxane (v/v = 1:1)</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>19</td>
<td>MeCN/1,4-Dioxane (v/v = 1:1)</td>
<td>80</td>
<td>56</td>
</tr>
<tr>
<td>20</td>
<td>MeCN/1,4-Dioxane (v/v = 1:1)</td>
<td>60</td>
<td>18</td>
</tr>
</tbody>
</table>

[^a]: Reaction conditions: solvent (2.0 mL), 1a (0.2 mmol, 1.0 equiv.), 2a (1.0 mmol, 5.0 equiv.), 10 mol% Pd(OAc)$_2$, AgOAc (2.0 equiv.), 24 h and N$_2$.
[^b]: Isolated yield after column purification.
[^c]: Two rounds.
[^d]: Diethylene glycol dimethyl ether.
[^e]: Dichloroethane.
[^f]: Dimethylacetamide.
[^g]: N-Methyl-2-pyrrolidone.
[^h]: Air used to replace N$_2$.

### 3.2.2 Substrate Scope

After identifying the optimized conditions, the scope of istains **3-1** were examined. As presented in Table 3.3, the substitution pattern of istains could be varied successfully: C5-substituted electron-withdrawing, neutral and electron-donating substituents were tolerated and demonstrated remarkably high yields in all cases (**3-3ba** to **3-3fa**, **3-3ja** to
Table 3.3 Scope of isatins $^[a]$  

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-1b to 3-1o</td>
<td>95%</td>
<td>30 h</td>
</tr>
<tr>
<td>3-2a</td>
<td>74%</td>
<td>30 h</td>
</tr>
<tr>
<td>3-3a</td>
<td>74%</td>
<td>30 h</td>
</tr>
<tr>
<td>3-3aa</td>
<td>55%</td>
<td>30 h</td>
</tr>
<tr>
<td>3-3ba to 3-3oa</td>
<td>95%</td>
<td>12 h</td>
</tr>
<tr>
<td>3-3ca</td>
<td>93%</td>
<td>30 h</td>
</tr>
<tr>
<td>3-3da</td>
<td>92%</td>
<td>28 h</td>
</tr>
<tr>
<td>3-3ea</td>
<td>75%</td>
<td>36 h</td>
</tr>
<tr>
<td>3-3fa</td>
<td>95%</td>
<td>12 h</td>
</tr>
<tr>
<td>3-3ga</td>
<td>75%</td>
<td>30 h</td>
</tr>
<tr>
<td>3-3ha</td>
<td>81%</td>
<td>30 h</td>
</tr>
<tr>
<td>3-3ia</td>
<td>88%</td>
<td>12 h</td>
</tr>
<tr>
<td>3-3ja</td>
<td>83%</td>
<td>22 h</td>
</tr>
<tr>
<td>3-3ka</td>
<td>71%</td>
<td>33 h</td>
</tr>
<tr>
<td>3-3la</td>
<td>82%</td>
<td>30 h</td>
</tr>
<tr>
<td>3-3ma</td>
<td>60%</td>
<td>30 h</td>
</tr>
</tbody>
</table>

* Reaction conditions: MeCN/1,4-Dioxane (v/v = 1:1) (2 mL), 3-1b to 3-1o (0.2 mmol, 1.0 equiv.), 3-2a (1.0 mmol, 5.0 equiv.), 10 mol% Pd(OAc)$_2$, 100 °C, 24 h and N$_2$.  

---

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3-3ka). Especially substrates with electron-withdrawing and/or electron-donating substituents at the 4- or 7-position also showed moderate to high reactivity and afforded the corresponding benzazepine products (Table 3.3, 3-3ga to 3-3ha, 3-3la to 3-3oa). To further indicate the generality and potential of our approach, a series of alkynes 3-2 were explored to react with 3-1a in the reaction. With respect to alkyne substituents, the reaction shows broad substrate tolerance among internal alkynes. Electron-rich tolanes participate in high yields (Table 3.4, 3-3ab and 3-3ac, 3-3ae and 3-3af) while electron-deficient systems are somewhat recalcitrant (Table 3.4, 3-3ad and 3-3ah). Heteroaryl, ester and aliphatic alkynes are also tolerated (3-3ak, 3-3am, 3-3al). When unsymmetric alkynes are employed, two regioisomers are usually observed (3-3ae to 3-3ak). In addition, a symmetric diethyl alkyne, 2-butyne was also examined in this system, but surprisingly generated an unknown structure (not shown). Gratifyingly, a series of unique and unexpected pyrrole fused 3-indolinone structures were obtained with the use of a naphthalene-ring based isatin 3-1t under somewhat currently unknown reaction mechanism (Table 3.5). Notably, although two molecules of diphenylacetylene 3-2a participated in reaction, a combination of one phenyl ring, one carbon atom, and one oxygen atom diminished from the desired structure. Surprisingly, when a carbazole 3-1p reacted with diphenylacetylene 3-2a, the corresponding carbazole-fused azepine 3-3pa was obtained in 87% yield (Scheme 3.1). This finding will greatly enrich the diversity of our synthetic application.
Table 3.4 Scope of alkynes \(^{[a]}\)

\[
\begin{align*}
\text{3-1a} & + R^1 & \text{Pd(OAc)}_2 \quad (10 \text{ mol\%}) & \xrightarrow{\text{AgOAc, 100 °C, N}_2} \text{3-3ab to 3-3am} \\
\text{MeCN/1,4-Dioxane (v/v = 1:1) (2 mL)}, & 3-1a (0.2 \text{ mmol, 1.0 equiv.}), & 3-2b \text{ to 3-2m} (1.0 \text{ mmol, 5.0 equiv.}), & 10 \text{ mol\% Pd(OAc)}_2, 100 \text{ °C, 24 h and N}_2.
\end{align*}
\]

\[^{[a]}\] Reaction conditions: MeCN/1,4-Dioxane (v/v = 1:1) (2 mL), 3-1a (0.2 mmol, 1.0 equiv.), 3-2b to 3-2m (1.0 mmol, 5.0 equiv.), 10 mol\% Pd(OAc)$_2$, 100 °C, 24 h and N$_2$.  

\[^{[b]}\] r.r. was determined by NMR (r.r. = ratio of regioisomers).
Table 3.5 Synthesis of pyrrole fused 3-indolinones $^a$

<table>
<thead>
<tr>
<th>Reaction conditions:</th>
<th>Pd(OAc)$_2$ (10 mol%)</th>
<th>AgOAc, 100 °C, N$_2$</th>
<th>MeCN/1,4-Dioxane (v/v = 1:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-1t</td>
<td>3-2a, 3-2c, 3-2d, 3-2j, 3-2o</td>
<td>3-3ta, 3-3tc, 3-3td, 3-3to</td>
<td></td>
</tr>
<tr>
<td>[a]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>R'</td>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>

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3-3ta, 63%, 30 h  
3-3tc, 62%, 50 h  
3-3td, 52%, 60 h  
3-3tj, 71%, 19:1 (r.r.$^a$)  
3-3to, 48% (87%$^b$)  

$^a$ Reaction conditions: MeCN/1,4-Dioxane (v/v = 1:1) (2 mL), 3-1t (0.2 mmol, 1.0 equiv.), 3-2a, 3-2c, 3-2d, 3-2j, and 3-2o (1.0 mmol, 5.0 equiv.), 10 mol% Pd(OAc)$_2$, 100 °C, and N$_2$.  
$^b$ r.r. was determined by NMR (r.r. = ratio of regioisomers).  
$^c$ Isolated yield after the recovery of starting materials.
3.2.3 Synthetic transformations of benzazepine 3aa.

The multifunctional characteristics of the palladium-catalyzed oxidative cycloaddition products can be used in chemoselective transformations to access various frameworks with high degrees of adduct 3-3aa was readily converted to polysubstituted quinoline 3-4 only by using 2.0 equivalents of meta-chloroperoxybenzoic acid (m-CPBA). The structure of polysubstituted quinoline 3-4 was approved by X-ray structure analysis. Pleasingly, a common hydrogenation process rapidly triggered a complete conversion and afforded an unexpected dimer 3-5 in only 0.5 h. Moreover, the C1–C2 bond cleavage proceeded smoothly by a FeCl₃ catalyst, affording a mixture of ring opened analogous 3-7 and 3-8 (ratio = 55:45) bearing an acyl chloride and acyl azide functional group on nitrogen, respectively. Notably, a dehydrogenation process, in the presence of Cu(OTf)₂ and AlCl₃ as promoters, eventually allowed benzazepine 3-3aa converte to a complex 3-6, which potentially used for pigments and dyes due to its typical π-conjugated system.
3.2.4 Control experiment and competition experiment

To gain some mechanistic insights into the process of this reaction, control experiments were conducted (scheme 3). To address the importance and irreplaceability of C7–H and N–H bonds, substrates 3-1q (C7–Cl vs C7–H), 3-1r (N–Me vs N–H) and 3-1s (oxindole vs isatin 3-1a) were tested and no any desired cycloaddition adducts were detected (Scheme 3). This result reveals that C7–H and N–H both are critical reaction sites and blocking any of these two sites will cause a failure of the reaction. To further understand the effect of the substitution pattern, two competition experiments were conducted (Table 3.6). The more electron-rich isatin 3-1f apparently reacted faster than more electron-deficient isatin 3-1j (Table 3.6, 3-3fa:3-3ja = 19:11). On the other hand, the more electron-rich alkyne 3-2c was more favoured in this oxidative cycloaddition. However, the more electron-deficient alkyne 3-2d was failed to generate the targeting product 3-3ad. Instead, a new oxidative adduct 3-3ax was obtained.
Scheme 3.3 Synthetic transformations of benzazepine 3-3aa

Reaction conditions: a) 3-3aa (0.1 mmol), m-CPBA (0.2 mmol), DCM (2 mL), r.t., 0.5 h, 85%; b) 3-3aa (0.1 mmol), 10% Pd/C, H₂ balloon, THF (2 mL), r.t., 0.5 h, 95%; c) 3-3aa (0.1 mmol), FeCl₃ (0.5 mmol), TMSN₃ (2 mmol), DCE (3 mL), 60 °C, 6 h, 57%; d) 3-3aa (0.1 mmol), Cu(OTf)₂ (4.5 mmol), AlCl₃ (5 mmol), CS₂ (10 mL), r.t., 24 h, 61%.
Scheme 3.4 Control experiments.

Reactions conditions: MeCN/1,4-Dioxane (v/v = 1:1) (2 mL), 3-1q to 3-1s (0.2 mmol, 1.0 equiv.), 3-2a (1.0 mmol, 5.0 equiv.), 10 mol% Pd(OAc)$_2$, 100 °C, 24 h and N$_2$.

Table 3.6 Competition experiments.
3.2.5 Mechanistic Investigations

On the basis of known transition-metal-catalyzed C–H activation/oxidative cycloaddition reactions, a possible mechanism is proposed to the present catalytic reaction (Scheme 3.4).

Scheme 3.5 Plausible catalytic cycles

The formation of benzazepine 3-3aa can probably start with a palladation of isatin 3-1a to yield the arylpalladium acetate 3-9 (Scheme 3.4, route A). The followed syn-addition of arylpalladium acetate 3-9 to diphenylacetylene 3-2a would generate the vinylpalladium intermediate 3-10. Then the insertion of another molecule of 3-2a will be proceeded to afford the butadienylpalladium intermediate 3-11. Finally, intramolecular palladation of 3-11 would lead to palladabenzocycloheptatriene 3-13, which subsequently would undergo reductive elimination to yield benzazepine 3-3aa. An alternative pathway
could start from the reaction of Pd(OAc)$_2$ with two molecules of diphenylacetylene 3-2a to give a proposed palladacyclopentadiene intermediate 3-12 (Scheme 3.4, route B),$^{97}$ which transferring to intermediate palladabenzocycloheptatriene 3-13 by the incorporation of isatin 3-1a. Hereafter, a reductive elimination of the palladabenzocycloheptatriene 3-13 would lead to the desired benzazepine 3-3aa. Simultaneously, the Pd (0) species produced in the reduction/elimination step are eventually re-oxidized by the addition of Ag(OAc)$_2$ as oxidant to regenerate Pd(II).

### 3.3 Conclusions

In summary, we have developed an efficient synthesis of benzazepine heterocycles. The method utilizes simple and readily available isatins and alkynes, and employs a direct Pd (II)-catalyzed oxidative cycloaddition. We found that heterocycles are well tolerated in the reaction, which allowing access to a number of unique molecular structures. The significance of benzazepine scaffold as design element should render this method attractive for synthetic and medicinal chemistry. We believe that this work will arouse more research interest in efficient synthesis of other biologically active heterocycles. Such studies are actively under way in this laboratory, and more results will be reported in due course.

### 3.4 Experimental Section
3.4.1 Material and General Methods

Chemicals and solvents were purchased from commercial suppliers and used as received. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker ACF300 (300 MHz) or a AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform $\delta$ 7.26), carbon (chloroform $\delta$ 77.0) or tetramethylsilane (TMS $\delta$ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine. Flash chromatography separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel.

Compounds 3-1a, 3-1f, 3-1g, 3-1h, 3-1i, 3-2a, 3-2j, 3-2k, 3-2l and 3-2m were commercially available. Compounds 3-1b to 3-1e$^9$, 3-1j to 3-1o$^9$; 3-2b to 3-2k$^9$ were prepared according to literature, respectively.

3.4.2 Representative Procedure for Palladium-catalyzed Reaction
To a solution of diphenylacetylene 3-2a (178.0 mg, 1.0 mmol) and isatin 3-1a (29.4 mg, 0.2 mmol) in 2.0 ml MeCN/1,4-dioxane (v/v = 1:1), palladium diacetate (4.5 mg, 0.02 mmol) and silver acetate (66.4 mg, 0.4 mmol) were added. The reaction was refluxed at 100 °C for 24 h and cooled to room temperature. The reaction mixture was extracted with DCM for 3 times, and combined organic layers were then dried over anhydrous MgSO₄, filtered, and the solvent removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc=25:1 then 10:1 to afford 81.3 mg (81% yield) of the desired product 3-3aa as red powder.

To a solution of diphenylacetylene 3-2a (178 mg, 1 mmol) and 1H-benzo[g]indole-2,3-dione 3-1t (39.4 mg, 0.2 mmol) in 2.0 ml MeCN/1,4-dioxane (v/v = 1:1) was added palladium (II) acetate (4.5 mg, 0.02 mmol) as and silver acetate (66.4 mg, 0.4 mmol). The reaction was refluxed at 100 °C for 30 h and then cooled to room temperature. The
reaction mixture was extracted with DCM three times. The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and eluted by hexane/EtOAc=25:1 then 10:1 to afford 56.3 mg (63 % yield) of the desired product 3-3ta as dark red powder.

3.4.3 Competition Experiments.

To a solution of diphenylacetylene 3-2a (178.0 mg, 1.0 mmol), 5-methoxyisatin 3-1f (35.4 mg, 0.2 mmol) and 5-chloroisatin 3-1j (36.2 mg, 0.2 mmol) in 2.0 ml MeCN/1, 4-dioxane (v/v = 1:1) was added palladium diacetate (4.5 mg, 0.02 mmol) as catalyst and silver acetate (66.4 mg, 0.4 mmol) as an oxidant. The reaction was refluxed at at 100 °C for 12 h. The reaction mixture was cooled to room temperature and extracted with DCM three times. The combined organic phases were dried over anhydrous MgSO₄, filtered,
and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and eluted by hexane/EtOAc = 50:1 then 5:1 to afford \textbf{3-3fa} (20.2 mg) and \textbf{3-3ja} (11.4 mg) respectively.

To a solution of bis (4-methoxyphenyl) acetylene \textbf{3-2c} (238 mg, 1 mmol), bis (4-chlorophenyl) acetylene \textbf{3-2d} (246.0 mg, 1.0 mmol) and isatin (29.4 mg, 0.2 mmol) in 2.0 ml MeCN/1, 4-dioxane (v/v = 1:1) was added palladium (II) acetate (4.5 mg, 0.02 mmol) as catalyst and silver acetate (66.4 mg, 0.4 mmol) as an oxidant. The reaction was refluxed at 100 °C for 24 h. The reaction mixture was cooled to room temperature and extracted with DCM three times. The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and eluted by hexane/EtOAc = 25:1 then 3:1 to afford \textbf{3-3ac} (43.0 mg) and \textbf{3-3ax} (32.0 mg) respectively.

\section*{3.4.4 Synthetic Transformations of Benzazepine 3-3aa.}

\textbf{Product 3-4} \textsuperscript{100}

To a stirred solution of \textbf{3-3aa} (50.1 mg, 0.1 mmol) in DCM (2.0 mL) was added \textit{m}-CPBA (0.2 mmol). The resulting mixture was stirred at r.t. for 0.5 h. After the conversion was complete indicated by TLC, the solvent was removed by evaporation and the residue was purified by silica gel flash chromatography and eluted by hexane/EtOAc=20:1 to afford 34.1 mg of product \textbf{3-4} (85 \% yield) as white solid.

\textbf{Product 3-5} \textsuperscript{101}
To a stirred solution of 3-3aa (50.1 mg, 0.1 mmol) in THF (2.0 mL) was added Pd/C (10 % w/w). The resulting mixture was stirred at r.t. for 0.5 h under H₂ balloon. After complete conversion as indicated by TLC, the solvent was removed by evaporation and the residue was directly purified by silica gel flash chromatography and eluted by hexane/EtOAc=20:1 to afford 50.2 mg of product 3-5 (95 % yield) as white solid.

Product 3-6

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To a mixture of copper (II)-trifluoromethanesulfonate (1.64 g, 4.5 mmol) and aluminum chloride (667 mg, 5 mmol) in carbon disulfide (10 mL), 3-3aa (50.0 mg, 0.1 mmol) was added. After stirring at room temperature for 24 h under N₂, the mixture was poured into H₂O and extracted with DCM three times. The combined organic phases were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and eluted by hexane/EtOAc = 20:1 then 4:1 to afford 30.2 mg of product 3-6 (61 % yield) as dark green powder.

Product 3-7 and 3-8

To a stirred solution of 3-3aa (50.1 mg, 0.1 mmol) in 1, 2-dichloroethane (3.0 mL) were added TMSN₃ (2.0 mmol) and FeCl₃ (0.5 mmol). The resulting mixture was stirred at 60 °C for 6 h. After complete conversion as indicated by TLC, the solvent was removed by evaporation and the residue was diluted with water and extracted with ethyl acetate (3 x 10.0 mL). The combined organic layers were dried over anhydrous MgSO₄ and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel using hexane/ethyl acetate (20:1) as eluent to afford the 3-7 and 3-8 as a complex (30.4 mg, 57 %).

3.4.5 Analytical Data of Palladium-catalyzed Reaction
4,5,6,7-Tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3aa)

\[
\text{\textbf{3-3aa}}
\]

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 7.56 (dd, J = 7.3, 1.2 \text{ Hz}, 1\text{H}), 7.23 - 6.92 (m, 18\text{H}), 6.79 - 6.75 (m, 4\text{H});\) \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta 181.83, 161.85, 160.11, 145.38, 141.57, 140.51, 140.24, 139.62, 138.22, 137.25, 135.87, 131.39, 130.79, 130.76, 130.67, 130.42, 128.39, 128.27, 128.19, 127.58, 127.48, 127.07, 126.86, 126.27, 124.68, 121.71;\) HRMS (ESI) calcd for C\(_{36}\)H\(_{24}\)NO\(_2\) [M+H]\(^+\) 502.1802, found 502.1801.

9-Methyl-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3ba)

\[
\text{\textbf{3-3ba}}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.37 (s, 1\text{H}), 7.13 - 6.87 (m, 17\text{H}), 6.72 (m, 4\text{H}), 2.24 (s, 3\text{H});\) \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 182.03, 162.12, 158.11, 145.26, 142.09, 140.59,
140.49, 140.37, 139.55, 138.33, 136.91, 136.23, 135.88, 131.42, 130.77, 130.70, 130.53, 130.41, 128.34, 128.24, 128.14, 127.55, 127.44, 127.41, 127.01, 126.79, 124.93, 121.79, 21.30; HRMS (ESI) calcd for C_{37}H_{26}NO_{2} [M+H]^+ 516.1958, found 516.1965.

9-Isopropyl-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3ca)

![Chemical Structure](image)

\[ \text{3-3ca} \]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.42\) (t, \(J = 9.9\) Hz, 1H), 7.13 – 6.90 (m, 17H), 6.79 – 6.72 (m, 4H), 2.76 (hept, \(J = 6.9\) Hz, 1H), 1.14 (d, \(J = 6.9\) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 182.14, 162.05, 158.30, 147.15, 145.00, 140.57, 140.42, 140.39, 139.71, 138.36, 136.90, 135.90, 131.47, 130.79, 130.75, 130.63, 130.43, 128.25, 128.21, 128.11, 127.53, 127.43, 127.40, 127.00, 126.79, 122.29, 121.69, 33.84, 23.91; HRMS (ESI) calcd for C_{39}H_{30}NO_{2} [M+H]^+ 544.2271, found 544.2286.

9-\textit{tert}-Butyl-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3da)
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.54 (d, $J = 2.0$ Hz, 1H), 7.15 (d, $J = 2.0$ Hz, 1H), 7.13 – 6.97 (m, 10H), 6.93 – 6.88 (m, 6H), 6.76 – 6.73 (m, 4H), 1.15 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 182.24, 161.96, 158.02, 149.53, 144.83, 140.65, 140.44, 140.33, 139.89, 139.57, 138.44, 136.87, 135.92, 131.50, 130.77, 130.47, 130.39, 128.24, 128.19, 128.10, 127.53, 127.45, 127.39, 126.99, 126.80, 121.46, 121.32, 35.05, 31.28; HRMS (ESI) calcd for C$_{40}$H$_{32}$NO$_2$ [M+H]$^+$ 558.2428, found 558.2438.

9-Heptyl-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3ea)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.34 (d, $J = 1.6$ Hz, 1H), 7.13 – 6.95 (m, 11H), 6.93 – 6.88 (m, 7H), 6.76 – 6.72 (m, 4H), 2.44 (t, $J = 7.6$ Hz, 2H), 1.54 – 1.44 (m, 2H), 1.31 – 1.16 (m, 8H), 0.92 – 0.85 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 182.09, 162.07, 158.26, 145.11, 141.75, 141.22, 140.61, 140.54, 140.41, 139.70, 138.38, 136.95,
9-Methoxy-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3fa)

![Chemical structure of 3-3fa]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.14 – 7.00 (m, 11H), 6.96 – 6.88 (m, 6H), 6.76 – 6.72 (m, 5H), 3.73 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 182.06, 162.21, 158.22, 154.23, 145.80, 140.76, 140.34, 140.27, 139.12, 138.28, 136.66, 135.78, 132.17, 131.43, 130.69, 130.60, 130.42, 128.89, 128.42, 128.25, 128.18, 127.56, 127.47, 127.02, 126.85, 122.10, 107.20, 56.34; HRMS (ESI) calcd for C$_{37}$H$_{26}$NO$_3$ [M+H]$^+$ 532.1907, found 532.1914.

8,10-Dimethyl-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3ga)
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.06 – 6.96 (m, 14H), 6.82 – 6.80 (m, 5H), 6.73 – 6.70 (m, 2H), 2.61 (s, 3H), 1.79 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 181.86, 164.20, 163.56, 151.74, 145.31, 141.89, 141.57, 140.05, 139.67, 139.32, 137.77, 137.56, 135.57, 131.47, 131.30, 131.26, 130.95, 130.38, 128.24, 128.18, 127.85, 127.63, 127.44, 127.35, 127.03, 127.00, 118.97, 23.22, 18.17; HRMS (ESI) calcd for C$_{38}$H$_{28}$NO$_2$ [M+H]$^+$ 530.2115, found 530.2122.

8,9,10-Trimethoxy-4,5,6,7-tetraphenylazepino[3,2,1-$h_i$]indole-1,2-dione (3-3ha)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.05 – 6.88 (m, 16H), 6.76 – 6.74 (m, 2H), 6.70 – 6.68 (m, 2H), 4.35 (s, 3H), 3.77 (s, 3H), 3.21 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 176.84, 163.06, 162.44, 159.32, 155.81, 143.82, 142.14, 141.56, 141.18, 139.42, 138.14, 137.78,
137.66, 135.62, 131.38, 131.29, 130.29, 130.23, 130.09, 128.26, 128.20, 127.67, 127.55, 127.37, 127.27, 126.90, 126.81, 118.13, 109.23, 63.38, 61.74, 60.97; HRMS (ESI) calcd for C$_{39}$H$_{30}$NO$_{5}$ [M+H]$^+$ 592.2118, found 592.2128.

9-Fluoro-4,5,6,7-tetraphenylazepino[3,2,1-$hi$]indole-1,2-dione (3-3ia)

1H NMR (500 MHz, CDCl$_3$): δ 7.24 (dd, $J$ = 5.8, 2.6 Hz, 1H), 7.21 – 6.89 (m, 17H), 6.76 – 6.74 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 181.27, 161.84, 161.64, 159.87, 156.06, 146.78, 140.72, 139.98, 139.88, 138.68, 137.90, 137.22, 135.56, 132.93, 132.88, 131.33, 130.59, 130.45, 130.40, 128.63, 128.34, 127.86, 127.77, 127.65, 127.56, 127.19, 127.04, 122.13, 122.07, 111.12, 110.92; HRMS (ESI) calcd for C$_{36}$H$_{23}$F NO$_2$ [M+H]$^+$ 520.1707, found 520.1709.

9-chloro-4,5,6,7-tetraphenylazepino[3,2,1-$hi$]indole-1,2-dione (3-3ja)
9-Bromo-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3ka)

\[ \text{3-3ka} \]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.55 (dd, $J = 7.4$, 1.2 Hz, 1H), 7.18 – 6.99 (m, 11H), 6.96 – 6.91 (m, 6H), 6.77 – 6.74 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 181.89, 161.81, 160.22, 145.31, 141.49, 140.55, 140.41, 140.23, 139.57, 138.21, 139.28, 135.97, 131.41, 130.80, 130.78, 130.68, 130.49, 128.40, 128.28, 128.22, 127.59, 127.49, 127.47, 127.10,
126.90, 126.32, 124.72, 121.70; HRMS (ESI) calcd for C_{36}H_{25}BrNO_2 [M+H]^+ 580.0907, found 580.0920.

10-Chloro-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3la)

\[ \text{H NMR (500 MHz, CDCl}_3\text{): } \delta \text{ 7.12 (t, } J = 7.3 \text{ Hz, 2H), 7.10 – 6.89 (m, 16H), 6.74 – 6.71 (m, 4H); } \]

\[ \text{C NMR (125 MHz, CDCl}_3\text{): } \delta 178.79, 160.97, 160.66, 145.42, 141.57, 140.30, 140.15, 139.96, 139.08, 137.95, 137.70, 135.66, 133.43, 131.30, 130.71, 130.61, 130.41, 129.07, 128.53, 128.35, 128.32, 127.64, 127.59, 127.52, 127.19, 126.98, 118.77; HRMS (ESI) calcd for C_{36}H_{23}ClNO_2 [M+H]^+ 536.1412, found 536.1419. \]

10-Bromo-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3ma)
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.21 (d, $J = 8.5$ Hz, 1H), 7.15 – 7.01 (m, 8H), 7.00 – 6.88 (m, 9H), 6.77 – 6.68 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 179.30, 161.21, 160.95, 145.54, 141.44, 140.30, 140.20, 139.99, 139.20, 137.94, 137.81, 135.67, 131.31, 130.81, 130.74, 130.60, 130.43, 129.62, 128.53, 128.36, 127.66, 127.53, 127.21, 127.00, 121.31, 120.43; HRMS (ESI) calcd for C$_{36}$H$_{23}$BrNO$_2$ [M+H]$^+$ 580.0907, found 580.0899.

8-Chloro-4,5,6,7-tetraphenylazepino[3,2,1-$h$]indole-1,2-dione (3-3na)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.56 (d, $J = 8.0$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.06 – 6.98 (m, 14H), 6.85 – 6.81 (m, 4H), 6.74 – 6.72 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 180.76, 164.96, 162.52, 147.62, 146.34, 142.16, 140.19, 139.15, 138.29, 138.05, 137.16, 135.06, 131.39, 131.12, 130.98, 130.26, 129.16, 128.62, 128.36, 127.79, 127.72, 127.62,
127.58, 127.33, 127.28, 124.79, 120.36; HRMS (ESI) calcd for C_{36}H_{23}ClNO_{2} [M+H]^+ 536.1412, found 536.1418.

8-Bromo-4,5,6,7-tetraphenylazepino[3,2,1-hi]indole-1,2-dione (3-3oa)

![3-3oa](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.46 (m, 2H), 7.08 – 6.97 (m, 14H), 6.84 – 6.79 (m, 4H), 6.72 (d, $J$ = 7.0 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 181.04, 164.92, 162.47, 147.72, 140.06, 139.41, 139.23, 138.25, 137.12, 137.02, 135.00, 132.51, 132.11, 131.71, 131.41, 131.00, 128.68, 128.38, 127.85, 127.68, 127.62, 127.38, 127.33, 124.49, 120.86; HRMS (ESI) calcd for C$_{36}$H$_{23}$BrNO$_2$ [M+H]$^+$ 580.0907, found 580.0909.

4,5,6,7-Tetraphenylazepino[3,2,1-jk]carbazole (3-3pa)

![3-3pa](image)
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.91 (d, $J = 7.5$ Hz, 1H), 7.78 (d, $J = 7.0$ Hz, 2H), 7.14 – 6.79 (m, 22H), 6.73 (d, $J = 8.0$ Hz, 1H), 6.57 – 6.55 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 154.27, 143.83, 143.50, 143.06, 142.48, 141.86, 141.79, 139.99, 138.26, 132.35, 132.18, 131.23, 131.17, 130.86, 130.10, 129.00, 128.04, 127.50, 127.34, 127.29, 126.69, 126.55, 126.43, 126.35, 126.03, 125.72, 123.29, 121.47, 120.10, 119.08, 117.04; HRMS (ESI) calcd for C$_{40}$H$_{28}$N [M+H]$^+$ 522.2216, found 522.2213.

4,5,6,7-Tetraphenylazepino[3,2,1-h]indole-1,2-dione (3-3ab)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53 – 7.51 (m, 1H), 7.19 (dd, $J = 7.9$, 1.0 Hz, 1H), 7.08 – 7.05 (m, 1H), 6.96 – 6.94 (m, 4H), 6.92 – 6.85 (m, 4H), 6.76 (d, $J = 7.8$ Hz, 4H), 6.67 (m, 4H), 2.23 (s, 3H), 2.17 (s, 6H), 2.16 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 182.03, 162.14, 160.23, 145.62, 141.49, 140.25, 139.03, 137.80, 137.66, 137.44, 137.41, 136.86, 136.38, 136.15, 135.38, 133.07, 131.38, 131.30, 131.17, 130.89, 130.67, 130.63, 130.51, 130.27, 129.04, 128.99, 128.33, 128.26, 128.12, 127.50, 126.05, 125.99, 124.23, 121.61, 21.61, 21.54, 21.51; HRMS (ESI) calcd for C$_{40}$H$_{32}$NO$_2$ [M+H]$^+$ 558.2428, found 558.2436.
4,5,6,7-Tetrakis(4-methoxyphenyl)azepino[3,2,1-hi]indole-1,2-dione (3-3ac)

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.51 (d, $J = 7.0$ Hz, 1H), 7.19 (dd, $J = 7.9$, 1.1 Hz, 1H), 7.07 (t, $J = 7.6$ Hz, 1H), 6.98 (d, $J = 8.8$ Hz, 2H), 6.90 (d, $J = 7.0$ Hz, 2H), 6.70 – 6.65 (m, 7H), 6.59 (d, $J = 7.9$ Hz, 2H), 6.50 (dd, $J = 8.8$, 2.5 Hz, 4H), 3.70 (s, 3H), 3.66 (s, 3H), 3.64 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 181.97, 162.06, 160.01, 158.95, 158.63, 158.39, 158.19, 145.41, 141.49, 140.11, 138.94, 137.06, 133.15, 133.00, 132.39, 131.93, 131.76, 131.64, 131.39, 130.83, 128.32, 125.98, 124.23, 121.56, 113.74, 113.67, 113.33, 113.03, 112.86, 55.41, 55.31; HRMS (ESI) calcd for C$_{40}$H$_{32}$NO$_6$ [M+H]$^+$ 622.2224, found 622.2244.

4,5,6,7-Tetrakis(4-chlorophenyl)azepino[3,2,1-hi]indole-1,2-dione (3-3ad)
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.55 (d, $J = 7.0$ Hz, 1H), 7.13 – 7.04 (m, 6H), 6.97 – 6.93 (m, 6H), 6.90 – 6.87 (m, 2H), 6.65 – 6.62 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 181.10, 161.35, 159.69, 143.87, 141.51, 140.34, 139.75, 138.40, 138.06, 136.07, 135.74, 134.57, 133.97, 133.71, 133.69, 133.46, 132.50, 131.86, 131.81, 131.59, 129.95, 129.03, 128.92, 128.40, 128.28, 126.70, 125.38, 121.88; HRMS (ESI) calcd for C$_{36}$H$_{19}$NCl$_4$NaO$_2$ [M+Na]$^+$ 660.0062, found 660.0088.

4,6-Bis(4-ethylphenyl)-5,7-bis(4-heptylphenyl)azepino[3,2,1-hi]indole-1,2-dione and 5,7-bis(4-ethylphenyl)-4,6-bis(4-hexylphenyl)azepino[3,2,1-hi]indole-1,2-dione (3-3ae)
Ratio of regioisomers = 11:9; Spectrum data of \( \text{a} \) and \( \text{b} \); \(^1\)H NMR (500 MHz, CDCl\(_3\)):
\[\delta 7.53 \ (d, \ J = 7.3 \text{ Hz}, 1\text{H}), 7.21 - 7.19 \ (\text{m}, 1\text{H}), 7.07 \ (t, \ J = 8.0 \text{ Hz}, 1\text{H}), 6.99 - 6.85 \ (\text{m}, 8\text{H}), 6.77 - 6.72 \ (\text{m}, 4\text{H}), 6.67 - 6.62 \ (\text{m}, 4\text{H}), 2.55 - 2.41 \ (\text{m}, 8\text{H}), 1.51 - 1.45 \ (\text{m}, 2\text{H}), 1.36 - 1.09 \ (\text{m}, 20\text{H}), 0.92 - 0.87 \ (\text{m}, 6\text{H}); \]
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)):
\[\delta 182.15, 162.05, 160.25, 145.77, 143.74, 143.10, 142.75, 142.73, 142.54, 142.51, 141.81, 141.54, 141.29, 141.27, 141.07, 141.04, 140.21, 140.08, 140.04, 139.12, 139.09, 139.04, 138.05, 138.03, 137.80, 137.77, 137.49, 137.44, 137.40, 135.74, 133.36, 133.33, 133.29, 131.35, 131.31, 131.26, 130.85, 130.77, 130.70, 130.64, 130.57, 130.33, 128.54, 128.27, 128.16, 127.67, 127.61, 127.54, 127.52, 127.40, 127.38, 126.84, 126.73, 126.02, 124.26, 124.24, 121.61, 35.97, 35.90, 35.78, 32.10, 32.08, 32.06, 31.47, 31.24, 30.15, 29.19, 29.11, 28.89, 28.87, 28.84, 28.82, 28.79, 23.05, 23.00, 22.98, 15.79, 15.62, 15.31, 14.57, 14.55, 14.49; \]
HRMS (ESI) calcd for C\(_{52}\)H\(_{56}\)NO\(_2\) [M+H]\(^+\) 726.4306, found 726.4326.

5,7-Bis(4-(methylthio)phenyl)-4,6-diphenylazepino[3,2,1-\(hi\)]indole-1,2-dione and 4,6-bis(4-(methylthio)phenyl)-5,7-diphenylazepino[3,2,1-\(hi\)]indole-1,2-dione (3-3af)
Ratio of regioisomers = 11:9; Spectrum data of a and b; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.54 (dd, $J$ = 7.5, 2.5 Hz, 1H), 7.17 – 7.06 (m, 5H), 7.01 – 6.90 (m, 11H), 6.83 – 6.71 (m, 4H), 6.66 – 7.06 (m, 1H), 2.38 – 2.34 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 181.69, 161.83, 161.79, 160.05, 159.99, 145.50, 144.71, 141.54, 141.51, 140.39, 140.12, 139.95, 139.91, 139.03, 138.72, 138.68, 138.08, 138.06, 137.81, 137.32, 137.30, 137.13, 136.99, 136.93, 136.57, 132.32, 132.27, 131.70, 131.28, 131.16, 131.03, 130.99, 130.80, 130.71, 130.65, 130.58, 130.31, 128.48, 128.35, 128.23, 127.77, 127.68, 127.56, 127.20, 127.15, 127.01, 126.93, 126.24, 126.03, 125.86, 125.42, 125.33, 124.67, 124.63, 121.66, 15.73, 15.60; HRMS (ESI) calcd for C$_{38}$H$_{28}$NO$_2$S$_2$ [M+H]$^+$ 594.1556, found 594.1579.

4,6-Diphenyl-5,7-bis(4-((trimethylsilyl)phenyl)azepino[3,2,1-hi]indole-1,2-dione or 5,7-diphenyl-4,6-bis(4-((trimethylsilyl)phenyl)azepino[3,2,1-hi]indole-1,2-dione (3-3ag)

Ratio of regioisomers = 3:2; Spectrum data of a or b; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.55 (dd, $J$ = 7.5, 1.5 Hz, 1H), 7.27 – 7.25 (m, 3H), 7.21 – 7.18 (m, 3H), 7.11 (t, $J$ = 7.5 Hz, 1H), 7.03 (d, $J$ = 8.5 Hz, 2H), 6.97 – 6.91 (m, 8H), 6.78 – 6.74 (m, 4H), 0.19 (s, 9H), 0.15 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 181.97, 162.01, 160.31, 145.37, 141.63, 140.80,
140.47, 140.44, 140.26, 139.56, 138.24, 137.39, 136.10, 133.26, 133.19, 131.40, 130.87, 130.68, 130.00, 129.55, 127.58, 127.46, 127.00, 126.79, 126.25, 124.59, 121.71, -0.74, -0.79; HRMS (ESI) calcd for C_{42}H_{40}NO_{2}Si_{2} [M+H]^+ 646.2592, found 646.2605.

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.55 (dd, \(J = 7.5, 1.0\) Hz, 1H), 7.18 – 7.00 (m, 16H), 6.70 – 6.67 (m, 4H), 0.15 (s, 9H), 0.13 (s, 9H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 181.92, 161.90, 160.17, 145.53, 141.55, 140.63, 140.56, 140.12, 139.29, 138.91, 138.69, 138.60, 137.41, 135.91, 132.38, 132.29, 130.96, 130.82, 130.58, 130.44, 129.86, 128.40, 128.30, 128.13, 127.42, 126.23, 124.60, 121.72, -0.76, -0.79; HRMS (ESI) calcd for C\(_{42}\)H\(_{40}\)NO\(_2\)Si\(_2\) [M+H]^+ 646.2592, found 646.2605.

5,7-Bis(3,5-bis(trifluoromethyl)phenyl)-4,6-diphenylazepino[3,2,1-hi]indole-1,2-dione or 4,6-bis(3,5-bis(trifluoromethyl)phenyl)-5,7-diphenylazepino[3,2,1-hi]indole-1,2-dione (3-3ah)

Ratio of regioisomers = 7:3; Spectrum data of a or b; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) = 7.66 – 7.63 (m, 2H), 7.50 – 7.47 (m, 3H), 7.18 (t, \(J = 7.5\) Hz, 1H), 7.09 – 7.03 (m, 9H),
7.00 – 6.97 (m, 2H), 6.70 – 6.65 (dd, J = 7.5, 1.5 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 180.74, 160.87, 159.89, 145.81, 143.77, 142.17, 140.93, 140.21, 138.47, 138.34, 134.62, 132.63, 132.08, 131.90, 131.82, 131.10, 130.86, 130.84, 130.21, 130.04, 129.07, 129.00, 128.84, 128.61, 128.30, 127.19, 126.01, 124.40, 124.33, 122.28, 122.23, 122.16, 121.75, 121.72, 121.00; HRMS (ESI) calcd for C$_{40}$H$_{19}$F$_{12}$NNaO$_2$ [M+Na]$^+$ 796.1116, found 796.1140.

$^1$H NMR (500 MHz, CDCl$_3$): δ = 7.60 (dd, J = 7.5, 2.0 Hz, 1H), 7.46 (s, 2H), 7.23 – 7.06 (m, 14H), 7.00 (d, J = 7.0 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 180.70, 160.96, 159.32, 144.17, 143.73, 142.02, 140.33, 138.94, 134.42, 132.04, 131.79, 131.74, 131.52, 131.47, 130.79, 130.17, 130.13, 129.40, 129.28, 129.12, 128.85, 128.56, 127.03, 126.17, 124.25, 122.13, 122.08, 122.01, 121.22, 121.05; HRMS (ESI) calcd for C$_{40}$H$_{19}$F$_{12}$NNaO$_2$ [M+Na]$^+$ 796.1116, found 796.1140.
5,7-Bis(4-tert-butylphenyl)-4,6-bis(4-chlorophenyl)azepino[3,2,1-hi]indole-1,2-dione and 4,6-bis(4-tert-butylphenyl)-5,7-bis(4-chlorophenyl)azepino[3,2,1-hi] indole-1,2-dione (3-3ai)

Ratio of regioisomers = 2:1; Spectrum data of a and b; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53 – 7.51 (m, 2H), 7.18 – 7.13 (m, 1H), 7.10 – 7.03 (m, 12H), 6.98 – 6.86 (m, 15H), 6.72 – 6.69 (m, 4H), 6.66 – 6.63 (m, 4H), 1.26 – 1.18 (m, 36H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 181.76, 161.89, 161.78, 160.25, 160.03, 151.36, 151.27, 150.74, 150.34, 145.70, 143.56, 141.70, 141.58, 141.27, 141.24, 140.63, 139.07, 138.80, 138.47, 136.98, 136.95, 136.88, 136.75, 135.67, 135.42, 133.39, 133.07, 132.91, 132.83, 132.76, 132.67, 132.41, 132.32, 132.22, 132.15, 132.00, 130.65, 130.55, 130.22, 130.04, 130.00, 128.66, 127.99, 127.84, 127.69, 126.31, 125.41, 125.31, 125.30, 124.82, 124.74, 124.65, 121.79, 121.77, 34.92, 34.82, 31.65, 31.55; HRMS (ESI) calcd for C44H38Cl$_2$NO$_2$ [M+H]$^+$ 682.2274, found 682.2305.
5,7-Di(naphthalen-2-yl)-4,6-diphenylazepino[3,2,1-hi]indole-1,2-dione and 4,6-di(naphthalen-2-yl)-5,7-diphenylazepino[3,2,1-hi]indole-1,2-dione (3-3aj)

![Chemical structures](image)

Ratio of regioisomers = 3:2; Spectrum data of a or b: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.77 – 7.57 (m, 7H), 7.51 – 7.36 (m, 6H), 7.34 – 7.06 (m, 8H), 6.04 – 6.87 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 181.76, 161.90, 161.86, 161.83, 160.19, 145.80, 145.71, 145.29, 145.20, 141.72, 141.60, 141.04, 140.40, 140.16, 140.09, 139.55, 138.14, 138.03, 137.87, 137.80, 137.76, 137.07, 135.80, 133.23, 133.06, 132.96, 132.94, 132.87, 132.50, 132.29, 132.21, 131.32, 130.88, 130.70, 130.65, 130.61, 130.43, 130.34, 129.95, 129.47, 129.04, 129.00, 128.62, 128.44, 128.32, 128.26, 128.18, 128.13, 128.10, 128.03, 127.99, 127.87, 127.84, 127.80, 127.69, 127.65, 127.57, 127.53, 127.46, 127.16, 126.97, 126.94, 126.83, 126.70, 126.60, 126.55, 126.44, 126.31, 126.24, 126.18, 126.14, 124.78, 124.74, 124.72, 121.78; HRMS (ESI) calcd for C$_{44}$H$_{27}$NNaO$_2$ [M+Na]$^+$ 624.1934, found 624.1958.
4,6-Diphenyl-5,7-di(thiophen-3-yl)azepino[3,2,1-hi]indole-1,2-dione and 5,7-diphenyl-4,6-di(thiophen-3-yl)azepino[3,2,1-hi]indole-1,2-dione (3-3ak)

Ratio of regioisomers = 3:2; Spectrum data of a or b: $^1$H NMR (500 MHz, CDCl$_3$): δ 7.62 (d, $J = 7.5$ Hz, 1H), 7.57 (d, $J = 7.5$ Hz, 1H), 7.43 (d, $J = 7.0$ Hz, 1H), 7.32 – 7.29 (m, 5H), 7.22 – 7.18 (m, 14H), 7.16 – 7.10 (m, 8H), 6.95 – 6.93 (m, 1H), 6.86 – 6.78 (m, 6H), 6.70 (dd, $J = 5.2$, 3.7 Hz, 2H), 6.60 (dd, $J = 5.2$, 3.7 Hz, 1H), 6.44 (d, $J = 3.0$ Hz, 1H);

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 181.56, 181.46, 162.29, 162.07, 159.40, 159.27, 147.39, 142.06, 141.64, 141.59, 141.50, 141.40, 141.26, 140.62, 140.50, 139.90, 139.43, 138.32, 137.88, 137.36, 135.83, 134.96, 133.63, 133.13, 133.04, 132.90, 132.87, 131.71, 131.02, 130.94, 130.71, 130.63, 130.44, 130.26, 130.03, 129.90, 128.96, 128.83, 128.46, 128.00, 127.78, 127.62, 127.58, 127.33, 127.13, 126.94, 126.89, 126.80, 126.74, 126.72, 126.65, 126.42, 126.22, 126.18, 125.12, 124.76, 124.73, 122.15, 122.09; HRMS (ESI) calcd for C$_{32}$H$_{19}$NNaO$_2$S$_2$ [M+Na]$^+$ 536.0749, found 536.0756.
4,6-Dimethyl-5,7-diphenylazepino[3,2,1-hi]indole-1,2-dione and 5,7-dimethyl-4,6-diphenylazepino[3,2,1-hi]indole-1,2-dione (3-3al)

Ratio of regioisomers = 13:7; Spectrum data of a or b; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.46 – 7.28 (m, 9H), 7.08 (d, $J = 7.0$ Hz, 2H), 7.01 (t, $J = 7.5$ Hz, 1H), 6.92 (d, $J = 8.0$ Hz, 1H), 1.97 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 182.58, 162.28, 162.03, 158.33, 141.55, 141.13, 140.40, 139.28, 138.25, 136.37, 135.26, 131.14, 130.44, 130.12, 129.20, 129.02, 128.06, 128.02, 125.95, 123.89, 121.65, 23.67, 19.31; HRMS (ESI) calcd for C$_{26}$H$_{20}$NO$_2$ [M+H]$^+$ 378.1489, found 378.1485.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.46 – 7.41 (m, 3H), 7.38 (t, $J = 7.0$ Hz, 3H), 7.34 – 7.25 (m, 1H), 7.21 (d, $J = 7.0$ Hz, 2H), 7.11 (d, $J = 7.0$ Hz, 2H), 7.02 – 6.99 (m, 1H), 6.90 (dd, $J = 7.9$, 2.0 Hz, 1H), 1.85 (s, 3H), 1.79 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 182.24, 161.41, 159.58, 141.51, 140.94, 140.54, 137.29, 136.51, 131.38, 131.04, 130.38, 129.88, 129.58, 129.26, 129.09, 128.78, 128.65, 128.47, 128.23, 128.09, 125.82, 123.81, 121.25, 21.90, 19.75; HRMS (ESI) calcd for C$_{26}$H$_{20}$NO$_2$ [M+H]$^+$ 378.1489, found 378.1485.
Dimethyl 1,2-dioxo-4,6-diphenyl-1,2-dihydroazepino[3,2,1-hi]indole-5,7-dicarboxylate

(3-3am)

\[
\begin{align*}
\text{3-3am}
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.58 (dd, \(J = 8.0, 1.5\) Hz, 1H), 7.41 (dd, \(J = 7.0, 3.5\) Hz, 4H), 7.37 – 7.34 (m, 2H), 7.31 – 7.29 (m, 2H), 7.22 – 7.19 (m, 2H), 7.12 – 7.09 (m, 1H), 7.02 (dd, \(J = 7.5, 1.5\) Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 180.35, 166.69, 166.20, 160.26, 158.82, 147.32, 145.88, 142.52, 139.16, 133.99, 132.51, 129.95, 129.75, 129.58, 129.48, 129.26, 128.88, 128.72, 126.90, 126.60, 124.48, 121.97, 52.77, 52.58; HRMS (ESI) calcd for C\(_{28}\)H\(_{20}\)NO\(_6\) [M+H]\(^+\) 466.1285, found 466.1277.

8, 9, 10-Triphenyl-7H-benzo[g]pyrrolo[1,2-a]indol-7-one (3-3ta)

\[
\begin{align*}
\text{3-3ta}
\end{align*}
\]
\[ \text{\[^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 7.76 (t, J = 8.0 \text{ Hz, 2H}), 7.63 (d, J = 8.0 \text{ Hz, 1H}), 7.56 - 7.54 \text{ (m, 2H), 7.46 (t, J = 8.5 \text{ Hz, 1H}), 7.38 - 7.30 \text{ (m, 8H), 7.20 - 7.17 \text{ (m, 3H), 7.02 (dd, J = 7.0, 2.0 \text{ Hz, 2H}), 6.81 - 6.77 (t, J = 8.0 \text{ Hz, 1H}), 6.67 (d, J = 8.5 \text{ Hz, 1H); } ^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta 179.85, 144.00, 138.77, 136.91, 134.11, 132.69, 132.23, 131.73, 131.56, 131.28, 130.24, 129.92, 129.72, 129.49, 129.29, 128.76, 128.49, 128.31, 128.10, 127.22, 127.08, 126.20, 125.58, 121.40, 120.06; HRMS (ESI) calcd for C}_{33}\text{H}_{22}\text{NO } [\text{M+H}]^+ 448.1696, \text{ found 448.1698.}} \]

8,9,10-Tris(4-methoxyphenyl)-7\text{H}-benzo[g]pyrrolo[1,2-\text{a}]indol-7-one (3-3tc)

\[ \text{\[^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 7.76 - 7.72 \text{ (m, 2H), 7.62 (d, J = 8.5 \text{ Hz, 1H}), 7.54 (dd, J = 7.0, 2.0 \text{ Hz, 2H), 7.26 (d, J = 1.5 \text{ Hz, 1H}), 7.25 (d, J = 1.5 \text{ Hz, 2H), 6.93 (dd, J = 7.0, 2.0 \text{ Hz, 2H), 6.89 (t, J = 2.0 \text{ Hz, 2H}), 6.84 (dd, J = 7.0, 2.5 \text{ Hz, 2H), 6.77 (d, J = 8.5 \text{ Hz, 1H), 6.76 - 6.74 \text{ (m, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H); } ^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta 179.59, 160.77, 160.07, 158.79, 143.87, 138.71, 137.21, 133.01, 132.63, 132.42, 131.70, 129.38, 129.28, 129.02, 127.96, 126.76, 126.72, 126.13, 125.75, 125.07,}} \]

108
124.34, 121.47, 120.11, 114.97, 114.06, 113.77, 55.88, 55.67, 55.59; HRMS (ESI) calcd for C_{36}H_{27}NNaO_4 [M+Na]^+ 560.1832, found 560.1837.

8, 9, 10-Tris(4-chlorophenyl)-7H-benzo[g]pyrrolo[1,2-a]indol-7-one (3-3td)

\[
\begin{align*}
\text{O} & \\
\text{Cl} & \text{Cl} \\
\text{Cl} & \text{Cl} \\
\end{align*}
\]

\(3-3\text{td}\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.78 (d, J = 8.5 \text{ Hz}, 1\text{H}), 7.73 (d, J = 8.0 \text{ Hz}, 1\text{H}), 7.67 (d, J = 8.0 \text{ Hz}, 1\text{H}), 7.45 - 7.42 (m, 2\text{H}), 7.39 - 7.36 (m, 3\text{H}), 7.30 - 7.26 (m, 4\text{H}), 7.22 - 7.20 (m, 2\text{H}), 6.93 - 6.89 (m, 3\text{H}), 6.72 (d, J = 8.5 \text{ Hz}, 1\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 179.78, 143.82, 138.92, 136.33, 135.39, 134.87, 133.70, 132.98, 132.44, 132.11, 131.47, 130.73, 130.59, 130.01, 129.64, 129.57, 129.19, 128.82, 128.66, 128.61, 128.47, 127.57, 126.47, 125.20, 121.25, 120.15; \) HRMS (ESI) calcd for C_{33}H_{19}Cl_3NNaO [M+Na]^+ 572.0346, found 572.0353.
8. 10-Di(naphthalen-2-yl)-9-phenyl-7H-benzo[g]pyrrolo[1,2-α]indol-7-one (3-3tj)

\[
\begin{align*}
\text{Ratio of regioisomers} & = 19:1; \\
\text{Spectrum data of a and b:}^{1} & \text{H NMR (500 MHz, CDCl}_3): \delta \ 8.15 (s, 1H), 7.83 – 7.72 (m, 4H), 7.67 – 7.55 (m, 3H), 7.49 – 7.12 (m, 14H), 7.05 (dd, } J = 8.0, 2.0 \text{ Hz, 1H}), 6.83 – 6.77 (m, 1H), 6.69 (dd, } J = 8.5, 4.0 \text{ Hz, 1H}); \quad ^{13} \text{C NMR (125 MHz, CDCl}_3): \delta 179.87, 144.04, 144.02, 138.81, 137.02, 134.17, 133.68, 133.63, 133.54, 132.73, 132.69, 132.63, 132.37, 132.26, 131.77, 131.53, 131.35, 130.29, 130.23, 130.13, 130.04, 129.97, 129.77, 129.65, 129.59, 129.54, 129.37, 129.33, 129.15, 129.07, 128.85, 128.82, 128.58, 128.39, 128.13, 128.06, 128.01, 127.98, 127.88, 127.64, 127.31, 127.14, 126.79, 126.33, 126.29, 126.24, 125.62, 121.46, 120.10; \quad \text{HRMS (ESI) calcd for } C_{41}H_{25}NNaO [M+Na]^+ 570.1828, \text{ found 560.1837.}
\end{align*}
\]

8.9.10-Tris(4-(trifluoromethyl)phenyl)-7H-benzo[g]pyrrolo[1,2-α]indol-7-one (3-3to)
H NMR (500 MHz, CDCl₃): δ 7.78 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.68 – 7.60 (m, 3H), 7.59 – 7.56 (m, 4H), 7.52 – 7.49 (m, 4H), 7.39 – 7.36 (m, 1H), 7.09 (t, J = 8.0 Hz, 2H), 6.82 – 6.79 (m, 1H), 6.50 (d, J = 8.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 179.86, 143.82, 139.06, 137.10, 135.76, 134.87, 134.49, 132.52, 132.21, 131.39, 130.68, 130.62, 130.41, 129.88, 129.70, 128.72, 128.48, 128.04, 126.78, 126.75, 126.59, 125.99, 125.96, 125.64, 125.61, 124.83, 123.44, 121.15, 120.22; HRMS (ESI) calcd for C₃₆H₁₉F₉NO [M+H]⁺ 652.1322, found 652.1316.

4,5-bis(4-chlorophenyl)-6,7-bis(4-methoxyphenyl)azepino[3,2,1-hi]indole-1,2-dione or 6,7-bis(4-chlorophenyl)-4,5-bis(4-methoxyphenyl)azepino[3,2,1-hi]indole-1,2-dione (3-3ax)
1H NMR (500 MHz, CDCl₃): δ 7.56 – 7.54 (m, 1H), 7.15 – 7.09 (m, 3H), 6.97 – 6.87 (m, 5H), 6.69 – 6.60 (m, 6H), 6.52 (d, J = 8.5 Hz, 2H), 3.69 (s, 3H), 3.68 (s, 3H); 13C NMR (125 MHz, CDCl₃): δ 181.66, 161.88, 160.15, 159.16, 158.66, 144.99, 141.22, 141.14, 138.82, 138.72, 138.61, 135.92, 133.70, 133.03, 132.57, 132.42, 132.06, 131.92, 131.75, 131.58, 130.32, 130.13, 128.90, 128.79, 128.10, 127.98, 126.32, 124.92, 121.80, 113.84, 113.33, 113.79, 113.28, 113.15, 55.46; HRMS (ESI) calcd for C₃₈H₂₅Cl₂NNaO [M+Na]^+ 652.1053, found 652.1071.

2,3,4-Triphenylquinoline-8-carboxylic acid (3-4)

1H NMR (500 MHz, CDCl₃) δ 8.73 (d, J = 7.5 Hz, 1H), 7.76 (dd, J = 7.5, 1.5 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.42 – 7.40 (m, 2H), 7.35 – 7.27 (m, 6H), 7.17 – 7.16 (m, 5H), 6.94 (dd, J = 7.5, 1.5 Hz, 2H); 13C NMR (125 MHz, CDCl₃) δ 168.06, 158.33, 151.17, 144.97, 139.13, 137.24, 136.24, 135.60, 134.40, 132.53, 131.66, 130.46, 130.36, 129.46, 128.65, 128.59, 128.52, 128.26, 127.62, 127.51, 127.48, 124.96; HRMS (ESI) calcd for C₂₈H₂₀NO₂ [M+H]^+ 402.1489, found 402.1481.
1,1'-Dihydroxy-4,5,5',6,6',7,7',8'-octaphenyl-1,1'-biazepino[3,2,1-\textit{hi}]indole-2,2'(1\textit{H},1'\textit{H})-dione (3-5)

\begin{center}
\includegraphics[width=0.5\textwidth]{3-5.png}
\end{center}

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.12 – 6.73 (m, 46H), 4.50 (s, 1H), 3.71 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.57, 143.67, 143.64, 140.66, 140.59, 140.13, 138.51, 136.27, 134.23, 134.13, 131.61, 130.97, 130.73, 130.59, 130.52, 128.31, 128.22, 128.11, 127.82, 127.77, 127.39, 127.30, 127.02, 126.83, 126.54, 12; HRMS (ESI) calcd for C$_{72}$H$_{48}$N$_2$NaO$_4$ [M+Na]$^+$ 1027.3506, found 1027.3460.

Aromatic compound (3-6)
\[ ^1\text{H NMR (500 MHz, CDCl}_3 \] \( \delta \) 8.70 (d, \( J = 8.0, 1\text{H} \)), 8.66 (d, \( J = 8.0, 1\text{H} \)), 8.27 (d, \( J = 8.0, 1\text{H} \)), 8.07 (d, \( J = 8.0 \text{ Hz, 1H} \)), 7.87 (d, \( J = 8.0, 1\text{H} \)), 7.75 (t, \( J = 8.5, 1\text{H} \)), 7.67 (t, \( J = 7.5, 1\text{H} \)), 7.62 – 7.54 (m, 2H), 7.35 – 7.29 (m, 2H), 7.24 – 7.14 (m, 4H), 7.01 (t, \( J = 7.5 \text{ Hz, 1H} \)); \( ^{13}\text{C NMR is not available due to poor solubility of this compound; MS (ESI) found 496.1; HRMS (ESI) calcd for C}_{36}\text{H}_{18}\text{NO}_2 [\text{M+H}]^+ 496.1332, found 496.1350.} \]

9-Cyano-2,3,4,5-tetraphenyl-1\text{-}H\text{-}benzo[\text{b}]azepine-1-carbonyl chloride and 9-cyano-2,3,4,5-tetraphenyl-1\text{-}H\text{-}benzo[\text{b}]azepine-1-carbonyl azide (3-7 and 3-8)

\[ \text{Ratio of regioisomers = 55:45, } ^1\text{H NMR (500 MHz, CDCl}_3 \] \( \delta \) 7.71 – 7.56 (m, 2H), 7.45 – 7.29 (m, 3H), 7.22 – 6.98 (m, 13H), 6.92 – 6.79 (m, 5H); \( ^{13}\text{C NMR (125 MHz, CDCl}_3 \] \( \delta \) 157.13, 156.69, 150.98, 150.06, 144.99, 141.97, 141.83, 141.27, 140.25, 140.22, 139.89, 139.18, 138.99, 138.93, 138.59, 138.21, 137.55, 137.43, 137.02, 135.96, 135.83, 135.53,
135.41, 134.23, 134.00, 133.79, 133.43, 131.77, 131.38, 131.33, 131.28, 131.21, 131.15,
131.01, 130.89, 130.86, 130.83, 130.80, 129.29, 128.99, 128.88, 128.74, 128.66, 128.50,
128.45, 128.33, 128.30, 128.20, 128.16, 128.14, 128.10, 127.94, 127.84, 127.51, 127.43,
127.40, 127.38, 126.94, 116.25, 116.04, 115.89, 112.46, 112.23, 111.64; HRMS (ESI) calcd for C_{36}H_{25}ClN_{2}NaO [M+Na]^+ 557.1392, found 557.1402 and C_{36}H_{23}N_{2}NaO [M+Na]^+ 564.1795, found 564.1809.
3.5 X-Ray Crystallographic Analysis

3.5.1 X-Ray Crystallographic Analysis of Benzazepine Product and Pyrrole Fused 3-indolinones

The configuration of the product 3-3da was assigned by X-ray crystallographic analysis of a single crystal of 3-3da (Figure 3.2). The configurations of other products were assigned by analogy.

![X-ray structure of 3-3da](image)

**Figure 3.2** X-ray structure of 3-3da

**Table 3.7** Crystal data and structure refinement for 3-3da

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<th>Property</th>
<th>Value</th>
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</thead>
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<td>Temperature</td>
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</tr>
<tr>
<td>Property</td>
<td>Value</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------------------</td>
</tr>
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</tr>
<tr>
<td>Crystal system</td>
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</tr>
<tr>
<td>Space group</td>
<td>P2(1)/n</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
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<td>a</td>
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</tr>
<tr>
<td>b</td>
<td>13.5180(18) Å, b= 107.639(3)°</td>
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<tr>
<td>c</td>
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<td>Z</td>
<td>8</td>
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<td>Density (calculated)</td>
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<tr>
<td>Crystal size</td>
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<td>Reflections collected</td>
<td>41963</td>
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<tr>
<td>Independent reflections</td>
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<td>Completeness to theta = 27.50°</td>
<td>99.9 %</td>
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<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9955 and 0.9693</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<tr>
<td>Data / restraints / parameters</td>
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<tr>
<td>Goodness-of-fit on F²</td>
<td>0.987</td>
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</tbody>
</table>
Final R indices [I > 2σ(I)]

R1 = 0.0759, wR2 = 0.1489

R indices (all data)

R1 = 0.1683, wR2 = 0.1855

Largest diff. peak and hole

0.548 and -0.523 e.Å⁻³

The configuration of the product 3-3ta was assigned by X-ray crystallographic analysis of a single crystal of 3-3ta (Figure 3.3). The configurations of other products were assigned by analogy.

![Figure 3.3 X-ray structure of 3-3ta](image)

**Table 3.8** Crystal data and structure refinement for 3-3ta

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C₃₃H₂₁N O</td>
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<tr>
<td>Formula weight</td>
<td>447.51</td>
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</tbody>
</table>
Temperature 223(2) K
Wavelength 0.71073 Å
Crystal system Triclinic
Space group P-1
Unit cell dimensions
\[ a = 10.2494(5) \text{ Å} \quad a = 114.7120(10)°. \]
\[ b = 12.0514(6) \text{ Å} \quad b = 96.4520(10)°. \]
\[ c = 13.5778(7) \text{ Å} \quad g = 106.3700(10)°. \]
Volume 1409.87(12) Å³
\( Z \) 2
Density (calculated) 1.335 Mg/m³
Absorption coefficient 0.353 mm⁻¹
\( F(000) \) 584
Crystal size 0.60 x 0.46 x 0.28 mm³
Theta range for data collection 1.71 to 27.49°
Index ranges \(-13 \leq h \leq 13, -15 \leq k \leq 15, -17 \leq l \leq 17\)
Reflections collected 18377
Independent reflections 6458 \([R\text{(int)} = 0.0298]\)
Completeness to theta = 27.50° 99.8 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.9075 and 0.8160
Refinement method Full-matrix least-squares on \( F^2 \)
Data / restraints / parameters 6458 / 0 / 352
3.5.2 X-Ray Crystallographic Analysis of Synthetic transformation of Benzazepine

3-3aa

Figure 3.4 X-ray structure of 3-4

Table 3.9 Crystal data and structure refinement for 3-4

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<tr>
<td>----------------------------------------------</td>
<td>----------------------------</td>
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<td>Wavelength</td>
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<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
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<td>Space group</td>
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<td>c</td>
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<td>Z</td>
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<tr>
<td>Density (calculated)</td>
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<td>Absorption coefficient</td>
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<td>F(000)</td>
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<td>Crystal size</td>
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<td>Reflections collected</td>
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<td>Independent reflections</td>
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<tr>
<td>Max. and min. transmission</td>
<td>0.9917 and 0.9673</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3533 / 0 / 284</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.009</td>
</tr>
</tbody>
</table>
Final R indices [I>2sigma(I)] \[ R1 = 0.0807, \text{wR2} = 0.2075 \]

R indices (all data) \[ R1 = 0.1305, \text{wR2} = 0.2388 \]

Largest diff. peak and hole \[ 0.389 \text{ and } -0.413 \text{ e.Å}^{-3} \]

Figure 3.5 X-ray structure of 3-5

Table 3.10 Crystal data and structure refinement for 3-5

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{78.25}H_{60.50}N_2O_{7.25}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>1144.79</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)/c</td>
</tr>
</tbody>
</table>
Unit cell dimensions

\[ a = 13.6777(11) \text{ Å} \quad a = 90^\circ. \]
\[ b = 29.760(2) \text{ Å} \quad b = 111.566(2)^\circ. \]
\[ c = 16.5143(13) \text{ Å} \quad g = 90^\circ. \]

Volume \[6251.6(9) \text{ Å}^3\]

\[ Z \]

4

Density (calculated) \[1.216 \text{ Mg/m}^3\]

Absorption coefficient \[0.078 \text{ mm}^{-1}\]

\[ F(000) \]

2408

Crystal size \[0.28 \times 0.18 \times 0.10 \text{ mm}^3\]

Theta range for data collection \[1.49 \text{ to } 25.00^\circ\]

Index ranges \[-14 \leq h \leq 16, \ -35 \leq k \leq 32, \ -19 \leq l \leq 19\]

Reflections collected \[36618\]

Independent reflections \[11018 \quad [R(\text{int}) = 0.1100]\]

Completeness to theta = 25.00° \[100.0\ %\]

Absorption correction Semi-empirical from equivalents

Max. and min. transmission \[0.9923 \text{ and } 0.9786\]

Refinement method Full-matrix least-squares on \[ F^2\]

Data / restraints / parameters \[11018 / 402 / 889\]

Goodness-of-fit on \[ F^2\] \[1.035\]

Final R indices \([I>2\sigma(I)]\) \[R1 = 0.0901, wR2 = 0.1947\]

R indices (all data) \[R1 = 0.1465, wR2 = 0.2214\]

Largest diff. peak and hole \[0.539 \text{ and } -0.372 \text{ e.Å}^{-3}\]
Figure 3.6 X-ray structures of 3-7 and 3-8

Table 3.11 Crystal data and structure refinement for 3-7 and 3-8

<table>
<thead>
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<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{38}H_{28.50}Cl_{0.50}N_{3.38}O_{1.50}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>574.12</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>I2/a</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 18.527(3) Å</td>
</tr>
<tr>
<td></td>
<td>a= 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 10.1040(14) Å</td>
</tr>
<tr>
<td></td>
<td>b= 98.228(3)°.</td>
</tr>
<tr>
<td></td>
<td>c = 32.704(4) Å</td>
</tr>
<tr>
<td></td>
<td>g = 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>6059.1(14) Å³</td>
</tr>
</tbody>
</table>
The crystal is monoclinic, space group $\text{I2}/a$. The asymmetric unit contains mixtures of the compounds $\text{C}_{36}\text{H}_{23}\text{N}_4\text{O}$ and $\text{C}_{36}\text{H}_{23}\text{NOCl}$ with the occupancy ratio=45:55, and a quarter hexane and two quarterly occupied methanol. H atoms of the solvents were not located but were included in the formula. Final R values are $R_1=0.0639$ and $wR_2=0.1763$ for 2-
theta up to 55°.

3.5.3 X-Ray Crystallographic Analysis of two regioisomers of unasymmetric alkynes product

The two regioisomers configuration of the product 3-3ah was assigned by X-ray crystallographic analysis of a single crystal of 3-3ah-a and 3-3ah-b (Figure 3.7, 3.8). The configurations of other products were assigned by analogy.

Figure 3.7 X-ray structures of 3-3ah-a

Table 3.12 Crystal data and structure refinement for 3-3ah-a

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{40}H_{19}F_{12}NO_{2}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>773.56</td>
</tr>
</tbody>
</table>
Temperature 100(2) K
Wavelength 0.71073 Å
Crystal system Triclinic
Space group P-1
Unit cell dimensions a = 8.4075(5) Å  α = 91.8990(10)°.
b = 11.0590(6) Å  β = 90.9700(10)°.
c = 17.9296(10) Å  γ = 92.3290(10)°.
Volume 1664.50(16) Å³
Z 2
Density (calculated) 1.543 Mg/m³
Absorption coefficient 0.141 mm⁻¹
F(000) 780
Crystal size 0.31 x 0.19 x 0.05 mm³
Theta range for data collection 1.84 to 25.00°
Index ranges -9<=h<=9, -13<=k<=13, -21<=l<=21
Reflections collected 17908
Independent reflections 5847 [R(int) = 0.0422]
Completeness to theta = 25.00° 99.9 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.7456 and 0.6844
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 5847 / 92 / 493
Figure 3.8 X-ray structures of 3-3ah-b

Table 3.13 Crystal data and structure refinement for 3-3ah-b

<table>
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<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{40}H_{19}F_{12}NO_{2}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>773.56</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.6455(19) Å</td>
</tr>
<tr>
<td></td>
<td>a= 99.181(3)°.</td>
</tr>
<tr>
<td></td>
<td>b = 18.488(4) Å</td>
</tr>
<tr>
<td></td>
<td>b= 99.391(3)°.</td>
</tr>
</tbody>
</table>
$c = 22.049(5) \text{ Å} \quad g = 101.856(3)^\circ$.

Volume $3334.2(13) \text{ Å}^3$

$Z$ 4

Density (calculated) 1.541 Mg/m$^3$

Absorption coefficient 0.141 mm$^{-1}$

$F(000)$ 1560

Crystal size 0.60 x 0.40 x 0.20 mm$^3$

Theta range for data collection 0.96 to 27.50$^\circ$

Index ranges $-11 \leq h \leq 11$, $-24 \leq k \leq 23$, $0 \leq l \leq 28$

Reflections collected 14797

Independent reflections 14797 [R(int) = 0.0000]

Completeness to theta = 27.50$^\circ$ 96.5 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.745685 and 0.579236

Refinement method Full-matrix least-squares on $F^2$

Data / restraints / parameters 14797 / 425 / 1029

Goodness-of-fit on $F^2$ 1.057

Final R indices [I>2sigma(I)] $R1 = 0.0997$, $wR2 = 0.2334$

R indices (all data) $R1 = 0.1703$, $wR2 = 0.2850$

Largest diff. peak and hole 0.929 and -0.668 e.Å$^{-3}$
Reference


- **103.** Yadav, J. S.; Reddy, B. V.; Praneeth, K. *Tetrahedron Lett.* **2008**, *49*, 4742.
Chapter 4 Enamine and Iminium Organocatalysis

4.1 Organocatalysis

Organocatalysis refers to the use of small organic molecules to catalyze different organic reactions, is a relatively new and popular field within the domain of important biological and pharmaceutical molecules synthesis, especially about the related chiral molecule (or enantioselective) synthesis. Organocatalysis can be divided into five major areas based on the generic modes of activation (Scheme 4.1), one is enamine catalysis, which promotes reaction via enamine intermediates generated from secondary amine catalysis or primary amine catalysis with related ketones or aldehydes, the other one is the iminium catalysis which is desired based on the capacity of the reversible formation of iminium ions from α,β-unsaturated aldehydes with chiral or non-chiral amines, another one is hydrogen-bond catalysis that the activation of a substrate and organization of the transition state could occur through well-defined hydrogen-bonding interaction. Recently, the electrophilicity of the singly occupied molecular orbital (SOMO) catalysis based on the concept that one-electron oxidant of an electron-rich enamine selectively can generate a reactive radical cation with three π-electrons is introduced by MacMillan and counterion catalysis which are known generated a transient ion pair during the transformation cycle is fruitful establishing by Jacobsen.

Organocatalysis became a focus of research in the late 1990s and 2000s. Began with the ground-breaking work of Denmark, Jacobsen, List, MacMillan, Maruoka and many others researchers, organocatalytic methods, especially the asymmetric organocatalytic methods, were developed fast in the last decade. Although huge advantages have been achieved in using these different types of catalysis in related transformations, here only recent
Scheme 4.1 Generic modes of activation used in organocatalysis

Enamine catalysis

$$R\text{-}Z\text{=}X\equiv Y$$
$$R = \text{any organic chain or ring system}$$
$$X = C, N, O, S$$
$$Y = \text{generic organic atom}$$
$$Z = \text{alkyl, H}$$

Iminium catalysis

$$R = \text{alkyl, aryl}$$

Hydrogen-bonding catalysis

$$X = O, NR$$
$$R, R', R'' = \text{alkyl, aryl}$$

SOMO catalysis

$$R = \text{alkyl, aryl}$$

Counterion catalysis

$$X = O, NR$$
$$R, R', R'', R''' = \text{alkyl, aryl}$$

Scheme 4.1 Generic modes of activation used in organocatalysis
progress of iminium and enamine catalysis will be emphasized in the following section.

**4.2 Iminium and Enamine Catalysis**

The iminium and enamine catalytic reactions can be regarded as amine-based reactions.\(^{11}\) The fundamental concept of iminium catalysis, proposed by MacMillan in 2000, \(^{9a}\) involves the reversible condensation of a secondary amine 4-1 with α, β-unsaturated aldehyde 4-2 to give the corresponding iminium ion 4-3. The formation of this iminium ion simulates the \(p\)-electronics and equilibrium dynamics traditionally associated with Lewis acid activation lowering the energy of the LUMO of the \(p\)-system and promoting subsequent hydrolysis reaction. Later, similar iminium catalysis was successfully applied in the other D-A reactions,\(^{12, 13}\) 1, 3 – dipolar cycloadditions,\(^{14}\) and conjugate additions.\(^{15}\) Moreover, epoxidation, cyclopropanations, and conjugate reductions which catalyzed by iminium catalysis were also well developed recently.\(^{16-19}\)

The enamine catalysis, on the other hand, refers to primary and secondary amines 4-7 of electrophilic substitution reaction in the \(\alpha\)-position of carbonyl compounds 4-8 and related reactions via enamine intermediates. In such transformations an enamine intermediate 4-10 is formed by reacting a carbonyl compound with an amine under dehydration conditions.\(^{20}\)

Reactions of the enamine can proceed via an addition or substitution route depending on the nature of the reaction partner. Iminium ions 4-11/4-12 are usually generated, which are then hydrolyzed to generate the products. In addition to carbonyl compounds (C=O) in aldol reactions, \(^{8d}\)
enamine catalysis were widely applied in other organic reactions involving many different electrophiles, such as azodicarboxylates (N=N) in α-aminations, imines (C=N) in Mannich reactions, nitrosobenzene (O=N) in α-aminoxylation, Michael acceptors (C=C).

Scheme 4.2 Parallels between iminium and enamine catalysis

in conjugated additions, others C-C bonds or C-halide bonds formation. Enamines react readily with a wide variety of electrophiles, and the range of reactions that can be catalyzed by enamine catalysis is summarized in Scheme 4.3.

Recent years have witnessed an explosive growth in the field of enamine catalysis. In these two types of catalysis, the basis of iminium catalysis is from lowering the energy of the LUMO energy of the system, which makes them more electrophilic, acidic, and more prone to certain pericyclic reactions. And the reversible generation of enamines from a catalytic amount of an amine and a carbonyl compound is the basis of enamine catalysis. The key process to form the enamine intermediate is the HOMO increasing effect. Meanwhile, the
iminium catalysis and enamine catalysis are closely related. Iminium catalysis promotes reaction via enamine, while enamine catalysis activates reaction via iminium ion formation.

Secondary amine and primary amine mediated enamine or iminium catalysis has achieved great success in many symmetric and asymmetric transformations, several reviews on this topic have appeared and highlighted these progresses. Here, only the cycloadditions reactions catalyzed by iminium or enamine will be outlined and 1, 3-dipolar cycloadditions reactions will be specially emphasized, as well as its application to the synthesis of important compounds including natural products, pharmaceuticals.

Scheme 4.3 A range of transformations can be promoted by enamine catalysis
4.2.1 Secondary and Primary Amine-Mediated Enamine and Iminium Catalysis in [4+2] and [4+3] Cycloaddition Reactions

4.2.1.1 [4+2] Cycloaddition Reactions

The Diels-Alder [4+2] cycloaddition has evolved to become an integral transformation that is routinely exploited in total synthesis since its original discovery in 1928. Great attentions have been focused on developing the symmetric and asymmetric variants of this type of reaction. Based on the importance and wide application of this cycloaddition, iminium and enamine catalysis are also apply into this transformation.

The pioneering work was explored by MacMillan and co-workers, the use of the imidazolidininium salt to generate iminium ion intermediates was identified as a new catalytic strategy for the activation of \( \alpha, \beta \)-unsaturated carbonyl compounds towards cycloaddition (Scheme 4.4).  

![Scheme 4.4](image)

Scheme 4.4 [4+2] cycloaddition using imidazolidinone catalyst

The major deficiency in the use of 4-15 was the low levels of diastereoselectivity observed in these transformations. Improvements have been achieved using biaryl catalyst 4-20 and diarylsilyl ether 4-21. Applying 4-20 as the catalyst in the cycloaddition between cyclopentadiene and cinnamaldehyde impressively improved the diastereoselectivity from 1:5.5 (\textit{endo}: \textit{exo}) to 1:20 (\textit{endo}: \textit{exo}) (Scheme 4.5). However, long reaction time and -20 °C temperature are needed in this transformation which detracted from the practicality of the
Then, the 4-21 was explored to promote the same transformation (Scheme 4.5). The improvement of diastereoselectivity and reaction conditions made the practicality of this transformation.

\[
\begin{align*}
\text{Scheme 4.5 Improved exo-selectivity using new iminium activator}
\end{align*}
\]

Base on these observations, modifications to the architecture of imidazolidinone catalyst provided the furyl derivative 4-22 which proved to be a powerful catalyst for the asymmetric D-A cycloaddition of simple \( \alpha, \beta \) – unsaturated ketones.\(^{12}\) Although the high enantioselectivity and good diastereoselectivity for cyclohexenyl ketones, the imidazolidinone catalyst could not be widely used as others ketones activator. This chemical challenge was successfully solved by Jorgensen and co-worker via the new imidazolidinone catalyst 4-26 desired (Scheme 4.6). Currently, this catalyst has broad applicability in different transformations.\(^{43-48}\)
Scheme 4.6 Iminium activator of simple enones and acyclic enones

Moreover, more cycloadditions have been explored based on similar strategies via the intramolecular pathway. Recently, several succeeded cases applied the imidazolidinone derivatives 4-30 in the intramolecular cycloadditions to produce complex carbocyclic ring structures which had been exploited in synthesis to prepare a number of natural products via biomimetic routes (Scheme 4.7).13,49

Scheme 4.7 Iminium activator of intramolecular cycloaddition
The transformation that used secondary armines as the catalyst in the concept of LUMO energy lowering iminium ion activation has been reported widely within the literature. The similar mode of this activation was also possible to use primary amines as efficient catalysts. Although few reports have been published in this area, initial results suggested it would become an equally fruitful field with broad application. In particular, the reduced steric bulk around the catalytic nitrogen has allowed for expansion of the scope of these reactions to more hindered substrates (Scheme 4.8).

\[
\begin{align*}
R^1 & \quad \text{O} \\
R^2 & \quad \text{N} \\
\text{HX} & \quad \text{RNH}_2
\end{align*}
\]

**Scheme 4.8** Activation mode of substitute acroleins via primary and secondary amines

The enatioselective Diels-Alder reaction of \(\alpha\)-acyloxyacroleins was firstly reported by Ishihara and co-worker via a complex triamine catalyst,\(^{50}\) subsequently, they explored a binaphtyl catalyst 4-45 which gave high yield and enantioselectivities within the same transformation.\(^{51, 52}\)

\[
\begin{align*}
\text{Scheme 4.9} & \quad \text{Iminium activator of intermolecular cycloaddition via primary amine} \\
\end{align*}
\]

Later, Deng and co-worker reported an interesting expansion to the scope of dienes that could be adopted as partners within the [4+2] cycloaddition. Diels-Alder [4+2] adducts were
provided by the presence of the catalytic amount primary cinchona alkaloid 4-49 (Scheme 4.10).\(^{53}\)

Scheme 4.10 Primary amine as iminium catalysis in [4+2] cycloaddition

**4.2.1.2 [4+3] Cycloaddition Reactions**

In comparison to the preceding classes of cycloaddition mentioned above, the [4+3] strategies, a powerful process with which to access seven membered rings, have received far less attention. Harmata showed that imidazolidinone could be applied to catalyze the reaction of substituted furans and silyloxypentadienals with high levels of selectivity (Scheme 4.11).\(^{54}\) These high levels of selectivity were not maintained for unsubstituted furans and explored the way to further develop this as robust synthetic strategy.

Scheme 4.11 Secondary amine as iminium catalysis in [4+3] cycloaddition
4.2.2 Secondary and Primary Amine-Mediated Enamine and Iminium 
Catalysis in [3+2] Cycloaddition Reactions

The [3+2] cycloaddition strategy provides an effective way to assemble valuable 
intermediates for the construction of biologically and pharmaceutically important alkaloids, 
amino acids, amino carbohydrates and β-lactams. These reactions almost involve the 
concerted pericyclic addition of a dipole and a dipolarophile called 1, 3-dipolar cycloaddition 
reaction also known as the Huisgen cycloaddition reaction, and more detail information 
about this type of cycloaddition will be emphasized in next sections.

4.2.2.1 The Background of 1, 3-Dipolar Cycloaddition Reactions

The 1, 3-dipolar cycloaddition reaction involves the formation of a 5-membered 
heterocyclic compound through a reaction between a 1, 3-dipolar compound and a 
dipolarophile. Dipolarophiles are usually alkenes or alkynes while 1, 3-dipolar compounds 
are compounds which contain one or more heteroatoms and contain at least one resonance 
structure that represents a charged dipole separated by a single atom. Examples of 1, 3-
dipolar compounds include azides and diazo compounds. Scheme 4.12 shows the various 
resonance structures of these 1, 3-dipoar compounds. Structure A represents the structure 
commonly presented while structures B and C represent the resonance structures that exist as 
1, 3-dipolar compounds.

The first dipole and 1, 3-dipolar cycloaddition was discovered by Curtius and Buchner 
in the 1880’s. Basically, 1, 3-dipoles can be divided into two different types: the allyl 
anion type and the propargyl/allenyl anion type (Scheme 4.13).
Scheme 4.12 Examples of 1, 3-dipoar compounds and their resonance structures

The allyl anion type is bent and has four electrons in three parallel $p$ orbitals perpendicular to the plane of the dipole (Scheme 4.13). The propargyl/allenyl anion type dipole is normally linear. The central atom is occasionally presented as hypervalent and is limited to nitrogen (Scheme 4.13). The other dipole atoms can be carbon, oxygen and...
nitrogen. Other main group IV, V, VI elements such as phosphorus and sulfur can also be grouped in dipoles.

Dipolarophiles showed less diversity than dipoles. Substituted alkenes and alkynes are the most commonly treated as dipolarophiles. Carbonyl, enamine, iminium and cyano groups which contain double or triple bonds with heteroatoms can also be considered as dipolarophiles.

Two original proposals for the mechanism of the 1, 3-dipolar cycloaddition have been explored: the concerted cycloaddition mechanism, proposed by Rolf Huisgen, and the stepwise mechanism involving a diradical intermediate, proposed by Firestone. The former proposal is now generally accepted. The 1, 3-dipole reacts with the dipolarophile in a concerted, asynchronous, and symmetry-allowed \( \pi^4 + \pi^2 \) fashion through a six-electron transition state. The stereochemistry of the reactants could be transferred to the product. For example, the 1, 3-DC of benzonitrile oxide with trans-dideuterated ethylene gave exclusively the trans-isoxazoline (Scheme 4.14).

![Scheme 4.14 Concerted and stepwise pathway of 1, 3-dipolar cycloaddition](image)

For those step-wise 1, 3-dipolar cycloaddition, the process involves in generating a charge-separated intermediate and is followed by charge recombination to form the heterocycle.
The concerted 1,3-dipolar cycloaddition can be interpreted by frontier molecular orbital theory (FMO). Based on FMO, frontier molecular orbitals of the 1,3-dipole must overlap with the molecular orbitals of the same symmetry of the dipolarophile (Scheme 4.15). This overlap can be achieved in three ways, dominated by smallest energy gap of the orbital pairs.

Scheme 4.15 FMO interpretation of 1,3-dipole cycloaddition

One is the FMO interaction between the highest occupied molecular orbital (HOMO) of the dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile. A second type is dominated by the reaction between the HOMO of the dipolarophile and the LUMO of the dipole (Scheme 4.15). The last type is HOMO of the dipole can pair with LUMO of the dipolarophile; alternatively, HOMO of the dipolarophile can pair with LUMO of the dipole.

Based on this FMO, two strategies are used to accelerate the cycloaddition reaction. In the first strategy, Lewis acids are introduced to lower the LUMO of the dipolarophile (Scheme 4.16). Under such conditions the dipole reacts through its HOMO to generate the cycloaddition product. Alternatively, additives that increase the electron density of the dipolarophile can accelerate cycloaddition via an HOMO (dipolarophile)-LUMO (dipole)
interaction (Scheme 4.16). This approach is less common than the Lewis acid-based methods, but is most notably operative in the copper-catalyzed synthesis of triazoles from alkynes and azides. These two strategies increase the transformation efficiency which provides an efficient and convergent approach to generate multi-functionalized five-membered heterocycles or carbocycles containing several contiguous stereocenters in a single operation. So, recent development of applications about these strategies and transformations will be discussed in details in next sections.

**Scheme 4.16** General strategies to accelerate 1, 3-dipolar cycloaddition

### 4.2.2.2 Iminium Catalyzed [3+2] Cycloaddition Reactions

The usage of iminium and enamine catalysts in forming biological and pharmaceutical important compounds via 1, 3-dipolar cycloaddition is fruitful. The pioneering work was explored by MacMillan and co-workers. The iminium ion activation was effective in the reaction of [3+2] cycloaddition between nitrones 4-58 and α, β-unsaturated aldehydes 4-59 (Scheme 4.17). Although the transformations needed long reaction times varying between 96 h to 160 h, the product of the yields and enantioselectivities was excellent. These excellent ee can be explained by the transition state model 4-62 in which the benzyl arm of the catalyst successfully blocked the Re-face of α, β-unsaturated carbonyl group.
Similarly, Karlson and co-workers showed an interesting series of structurally diverse chiral secondary amines 4-63 in the cycloaddition of nitrones 4-64 with 1-cycloalkene-1-carboxaldehyde 4-65, in which the best catalyst was explored from the proline derivatives (Scheme 4.18). 79, 80

Then, more proline derivatives were explored in different [3+2] cycloaddition reactions. The initial transformation reported by MacMillan was explored again. 14 Interestingly, L-prolinol derived catalyst 4-68 indicated excellent levels of catalyst activity via high diastereoselectivity, high enantioselectivity and short reaction times (Scheme 4.19). 81 Moreover, others 1, 3-dipolars were also employed in this [3+2] cycloaddition reactions which catalyzed by prolinol derivatives.
Scheme 4.19 [3+2] cycloaddition using prolinol derivatives

Chen’s research group discovered that L-prolinol derivatives 4-62 can promote the reaction between azomethine imines 4-63 and α, β-unsaturated aldehydes (Scheme 4.20).\textsuperscript{82}

Scheme 4.20 Prolinol derivatives promoted [3+2] cycloaddition

Subsequently, Vicario and co-workers proved that azomethine ylides 4-67 produced \textit{in situ} can also be effective in prolinol derivatives 4-66 catalyzed [3+2] cycloaddition reactions (Scheme 4.21).\textsuperscript{83} Addition of water was found to significantly accelerate the reaction and the free hydroxyl group within the catalyst structure was essential for the high selectivities observed in these two transformations.

Scheme 4.21 [3+2] cycloaddition of azomethine ylides with unsaturated aldehydes
Also, the scope of iminium ion catalyzed [3+2] cycloaddition with azomethine imines 4-70 was extended again by Chen and co-workers. Cyclic α, β-unsaturated ketones 4-71 were encompassed using primary amine 4-69 as the catalyst. Although long reaction time was required, impressive level of asymmetric induction and excellent yields were achieved in these transformations.

**Scheme 4.22** Primary amine as iminium activator in [3+2] cycloaddition

### 4.2.2.3 Enamine Catalyzed [3+2] Cycloaddition Reactions

As mentioned above, the primary and secondary amine catalysis in [3+2] cycloaddition reactions via the iminium activation model have been successfully established from the work of different research groups. However, these transformations are only suited for α, β-unsaturated aldehydes or α, β-unsaturated ketones. Therefore, this limitation largely restricts the diverse application of these strategies in the preparation of biological and pharmaceutical heterocycles. In brief, the advent of novel methods that are devoid of these deficiencies would be of great value and particularly necessary to the synthetic community. Carbonyl, enamine, iminium and cyano groups, as mentioned, which contain double or triple bonds with heteroatoms can also be treated as dipolarophiles. Encouraging by this fundamental strategy, the primary and secondary amine catalysis in [3+2] cycloaddition reactions via the enamine activation model are positively exploring.
The pioneering work was explored by Wang and co-workers in 2011 (Scheme 4.23). The first organocatalytic method for the [3+2] cycloaddition reaction of azides 4-74 with enamine was developed to produce 1,4,5-trisubstituted-1,2,3-triazoles 4-76 with high efficiency, regiospecificity, and functional-group tolerance. Active enamine 4-77 tautomerized from an iminium ion was treated as the intermediate during this transformation. This case was the first one to build the intermediate enamine species as the dipolarophiles during the 1, 3-dipolar cycloaddition.
4.3 Project Objective

Recent years have witnessed an explosive growth in the field of iminium and enamine catalysis. Primary and secondary amines as catalysis in the cycloaddition transformation of biological and pharmaceutical compounds via the iminium activation model have been greatly explored. A number of novel transformations, as described above, have been discovered to provide the access to various biological and pharmaceutical important heterocycles.

Despite these advances in the development of iminium and enamine catalysis in different cycloaddition transformations, there are still many challenges that remain to be addressed: a) the scope of substrates via iminium activation model would be greatly expanded by applying others types of 1, 3-dipoles in building important transformations. b) The application of enamine activation model in symmetric and asymmetric 1, 3-dipolar cycloaddition reactions to form biological and pharmaceutical important substrates also remains a key future objective. This strategy would pave the way for the widespread application of this cycloaddition chemistry if enamine catalysis concept can be applied in the related transformations. Therefore, in light of this, how to apply the enamine activation model in symmetric and asymmetric 1, 3-dipolar cycloaddition reactions will be the aim for further investigations.

The main purpose of this project is to explore significant enamine activation methodologies to overcome the mentioned challenges. The specific aspect of this project is using different types of available starting materials via enamine catalyzed transformations to form many potential biological and pharmaceutical important molecules.
These significant results of this project should provide a concise way to synthesize different types of heterocycles. It may also pave the way to explore more detail information of how the enamine catalysis takes the role in the catalytic cycle during promoting the reactions.

Two different types of reactions to related heterocycles are explored. There are 1,2,3-triazoles and pyrazoles. More specifically information will be listed in later two chapters.
A general, organocatalytic inverse-electron-demand [3+2] cycloaddition reaction between various carbonyls and diazoacetates has been developed. The reaction is catalyzed by second amines, “green promoter”, to generate substituted pyrazoles with high levels of regioselectivity.
5.1 Introduction

Pyrazole is widely found as the core structure in a large variety of compounds that possess important agrochemical and pharmaceutical activities, and the recent successful discovery of pyrazole-based anti-inflammatory COX-II inhibitor and insecticide Fipronil have amplified the importance of pyrazoles to even a greater extent. Among the varied synthetic protocols to pyrazoles, the 1,3-dipolar cycloaddition of a diazo compound and an alkyne (Scheme 5.1a), and the cyclocondensation of a hydrazine with a 1,3-dicarbonyl compound (Scheme 5.1b) are two of most frequently used methods. However, carcinogenic hydrazines, toxic transitional metals, somewhat limited substrate scope and uncontrolled regioselectivity greatly reduce the attractiveness of these known approaches.

![Scheme 5.1 Two general approaches to polysubstituted pyrazoles](image)

Although the 1,3-dipolar cycloaddition of electron-rich diazo compounds to alkynes is known, the development of efficient process using electron-deficient diazo compounds is much less reported, attributing to the increased HOMO(dipolarophile)-LUMO(dipole) energy gap between diazo compounds and alkynes. One common method has been applied to generate pyrazole ring by incorporating either Lewis acids or transition metals to lower the LUMO of the alkyne dipolarphiles. Another attractive, but less common complementary strategy is the HOMO-raising activation of the alkynes by forming metal acetylides. For example, in 2007, Ready research group reported a mild copper-promoted cycloaddition of diazocarbonyl compounds and acetylides. Later, Liang disclosed a Zn(II) catalyzed
intermolecular cycloaddition of various α-diazo carbonyl molecules to terminal alkynes.\[95b\\]
To the best of our knowledge, no such organocatalytic cycloaddition method has been reported by raising the HOMO of the dipolarphiles to achieve the target pyrazole ring.

![Scheme 5.2](image)

**Scheme 5.2** This work: enamines as active synthetic intermediates, allowing the inverse electron-demand [3+2] cycloaddition to generate pyrazoles at room temperature. HOMO = highest occupied molecular orbital, LUMO = lowest unoccupied molecular orbital.

In the course of our study on the intermolecular cycloaddition of carbonyls and diazoacetates, we made an interesting finding (Scheme 5.2): the in situ formed enamine (versus metal acetylide) can promote the cycloaddition to achieve the targeting pyrazole ring. We envision that this reaction may contain an unusual organocatalytic HOMO-raising type inverse-electron-demand (IED) 1, 3-dipolar [3+2] cycloaddition process. In addition, this efficient pyrazole synthetic protocol can start from readily available and simple starting materials, carbonyls and diazoacetates. Moreover, a high conversion of the reaction can be achieved at room temperature.
5.2 Results and Discussion

5.2.1 Reaction Optimization

Initial experiments were conducted by using cyclohexanone 5-2a and ethyl diazoacetate 5-1a in the presence of 10 mol% loading of amine catalysts, such as primary amines (5-VIII and 5-IX), secondary amines (5-I, 5-II, 5-III, 5-IV and 5-V) and tertiary amines (5-VI and 5-VII). Among the catalysts tested (Table 5.1), pyrrolidine 5-I is identified as the most effective catalyst for this transformation. Further optimization of the standard reaction parameters revealed that the solvent is the crucial factor for improving the catalysis. When the reaction was carried out in DMSO, reactivity was positively influenced, leading to the desired product 5-3aa in 87% yield. Other solvents, such as toluene, MeCN, DCE, CHCl₃, THF, MeOH, IPA, DMA, DMF, and 1, 4-dioxane, significantly diminished the chemical yields (Table 5.1, <5-64%). Lowering the catalyst loading to 5 mol% resulted in a longer reaction time (90% yield after 72 h). Changing the 5-1a/5-2a ratio from 1:1 to 1:3 indicated a slightly beneficial effect on the efficacy of the reaction (Table 5.1, 71% and 87%, respectively). Finally, the best compromise was achieved when performing the cycloaddition reaction at room temperature, using 10 mol% of second amine 5-I and 1:2 ratio of 1a/2a in DMSO.

5.2.2 Substrate Scope

With the optimized reaction conditions in hand, we then investigated a variety of ketones with ethyl diazoacetate 5-1a in the reaction catalyzed by second amine 5-I (10 mol%) at room temperature. The results are summarized in Table 5.2. Interestingly, among the various examined ketones, cyclic ketones appeared as the substrates of choice, from six to eight member ring, gave good to excellent yields under standard conditions (Table 5.2, 5-3aa to 5-
The best yield, however, was obtained with cycloheptanone, which afforded the corresponding pyrazole in 96% isolated yield (Table 5.2, 5-3ai). It is worth noting that dissymmetrical cyclic ketone afforded a high level of regioselectivity. For example, 3, 3-dimethylcyclohexanone led to a single regioisomer 5-3af (Table 5.2), in which the heterocycle is furthest from the gem-dimethyl group for steric reasons. On the other hand, 4, 4-dimethylcyclohexanone furnished pyrazole 5-3ae (Table 5.2), which is an isomer of 5-3af. The regioselectivity can be explained by the cycloaddition occurring with most stabilized enamine.

Table 5.1 Conditions optimization of enamine-promoted IED [3+2] Cycloaddition [a]

| Cat. (10 mol%) | DMF, 46% | DMA, 38% | IPA, 64% | MeOH, 57% | THF, 56% | 1,4-Dioxane, <5% | Toluene, 30% | MeCN, 31% | DCE, 31% | CHCl₃, 13% | DMSO, 86%[b] | DMSO, 87%c | DMSO, 90%d | DMSO, 71%e | DMSO, 87%f |
|---------------|-----------|-----------|-----------|-----------|-----------|----------------|-------------|-----------|-----------|-----------|-------------|-------------|-------------|-------------|-------------|-------------|
| 5-I           | DMF        | DMA       | IPA       | MeOH      | THF       | 1,4-Dioxane    | Toluene     | MeCN      | DCE       | CHCl₃      | DMSO        | DMSO        | DMSO        | DMSO        | DMSO        |
| 5-II          | DMF        | DMA       | IPA       | MeOH      | THF       | 1,4-Dioxane    | Toluene     | MeCN      | DCE       | CHCl₃      | DMSO        | DMSO        | DMSO        | DMSO        | DMSO        |
| 5-III         | DMF        | DMA       | IPA       | MeOH      | THF       | 1,4-Dioxane    | Toluene     | MeCN      | DCE       | CHCl₃      | DMSO        | DMSO        | DMSO        | DMSO        | DMSO        |
| 5-IV          | DMF        | DMA       | IPA       | MeOH      | THF       | 1,4-Dioxane    | Toluene     | MeCN      | DCE       | CHCl₃      | DMSO        | DMSO        | DMSO        | DMSO        | DMSO        |
| 5-V           | DMF        | DMA       | IPA       | MeOH      | THF       | 1,4-Dioxane    | Toluene     | MeCN      | DCE       | CHCl₃      | DMSO        | DMSO        | DMSO        | DMSO        | DMSO        |
| 5-VI          | DMF        | DMA       | IPA       | MeOH      | THF       | 1,4-Dioxane    | Toluene     | MeCN      | DCE       | CHCl₃      | DMSO        | DMSO        | DMSO        | DMSO        | DMSO        |
| 5-VII         | DMF        | DMA       | IPA       | MeOH      | THF       | 1,4-Dioxane    | Toluene     | MeCN      | DCE       | CHCl₃      | DMSO        | DMSO        | DMSO        | DMSO        | DMSO        |
| 5-VIII        | DMF        | DMA       | IPA       | MeOH      | THF       | 1,4-Dioxane    | Toluene     | MeCN      | DCE       | CHCl₃      | DMSO        | DMSO        | DMSO        | DMSO        | DMSO        |
| 5-IX          | DMF        | DMA       | IPA       | MeOH      | THF       | 1,4-Dioxane    | Toluene     | MeCN      | DCE       | CHCl₃      | DMSO        | DMSO        | DMSO        | DMSO        | DMSO        |

[a] Reaction conditions: 5-1a (0.2 mmol), 5-2a (0.4 mmol), DMSO (0.4 mL), room temperature.; b 20 mol% cat. 5-I, 5 h.; c 10 mol% cat. 5-I, 12 h.; d 5 mol% cat. 5-I, 72 h.; e 5-2a (0.2 mmol). f 5-2a (0.6 mmol).
Symmetric and dissymmetrical acyclic ketones both gave good yields under the same conditions (Table 5.2, 5-3ak, 5-3al). Pleasingly, phenones, such as acetophenone and propiophenone were both reactive and afforded good yields, although a higher reaction temperature required (Table 5.2, 5-3am and 5-3an, 77% and 71%, 80 °C, 24 h).

**Table 5.2** Substrate scope of ketones

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
<th>Reaction Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-3aa</td>
<td>87%</td>
<td>12 h</td>
</tr>
<tr>
<td>5-3ab</td>
<td>85%</td>
<td>8 h</td>
</tr>
<tr>
<td>5-3ac</td>
<td>78%</td>
<td>12 h</td>
</tr>
<tr>
<td>5-3ad</td>
<td>81%</td>
<td>12 h</td>
</tr>
<tr>
<td>5-3ae</td>
<td>89%</td>
<td>12 h</td>
</tr>
<tr>
<td>5-3af</td>
<td>83%</td>
<td>16 h</td>
</tr>
<tr>
<td>5-3ag</td>
<td>80%</td>
<td>18 h</td>
</tr>
<tr>
<td>5-3ah</td>
<td>75%</td>
<td>8 h</td>
</tr>
<tr>
<td>5-3ai</td>
<td>96%</td>
<td>8 h</td>
</tr>
<tr>
<td>5-3aj</td>
<td>83%</td>
<td>8 h</td>
</tr>
<tr>
<td>5-3ak</td>
<td>77%</td>
<td>24 h</td>
</tr>
<tr>
<td>5-3ai</td>
<td>81%</td>
<td>24 h</td>
</tr>
<tr>
<td>5-3am</td>
<td>77%</td>
<td>24 h</td>
</tr>
<tr>
<td>5-3an</td>
<td>71%</td>
<td>24 h</td>
</tr>
<tr>
<td>5-3ba</td>
<td>88%</td>
<td>12 h</td>
</tr>
<tr>
<td>5-3ca</td>
<td>79%</td>
<td>18 h</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 5-1a to 5-1c (0.2 mmol), 5-2a to 5-2n (0.4 mmol), DMSO (0.4 mL), 5-I (10 mol%), room temperature. <sup>b</sup> 80 °C.
Two other diazoacetates (Table 5.2, 5-1b and 5-1c) were also explored and both afforded good yields in the presence of the standard conditions (Table 5.2, 5-3ba and 5-3ca). Moreover, a regioselective cycloaddition of diazoacetate with enaminoesters and enamiones, formed in situ from activated ketones (β-ketoesters, β-diketones) and a catalytic amount of secondary amine 5-I, was investigated. Noteworthily, ketones carrying simply functional groups (e.g. β-ester and -ketone) could also be successfully employed (Table 5.3, 5-3ao to 5-3ar), achieving results similar to those obtained for the general ketone counterparts (Table 5.3, 81-91%, 8-12 h). To further indicate the generality and potential of our approach, other types of carbonyls (e.g. aldehydes) were explored in the reaction with diazoacetates 5-1a to 5-c. However, catalyst 5-I indicated a slow conversion based on previous standard conditions.

Table 5.3 Substrate scope of 1,3-dicarbonyls

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction %</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-3ao</td>
<td>81%</td>
<td>12 h</td>
</tr>
<tr>
<td>5-3ap</td>
<td>91%</td>
<td>8 h</td>
</tr>
<tr>
<td>5-3aq</td>
<td>89%</td>
<td>12 h</td>
</tr>
<tr>
<td>5-3ar</td>
<td>87%</td>
<td>12 h</td>
</tr>
</tbody>
</table>

* Reaction conditions: 5-1a (0.2 mmol), 5-2o to 5-2r (0.4 mmol), DMSO (0.4 mL), 5-I (10 mol%), room temperature.

Finally, acyclic secondary diethyl amine 5-IV was identified to be the best promoter in the reaction of diazoacetates with aldehydes after further optimizing the reaction parameters.
As outlined in Table 5.4, the corresponding adducts 5-3 were obtained in moderate to excellent yields (51-96%). A certain level of variation is possible at the side chain of the carbonyl group. For example, straight-chain aldehydes having different lengths were tolerated, which gave the cycloadducts in good to high yields (Table 5.4, 76-94%, 18-40 h). Pleasingly, aldehydes suffered with more bulky alkyl chains were also afforded good yields (Table 5.4, 5-3ai’ and 5-3am’, 80% and 74%, respectively). Moreover, the catalytic reaction was also applicable to functionalized aldehydes. Aldehydes bearing aromatic ring, heteroatom, and alkenyl motifs were fully compatible with the method (Table 5.4, 5-3aj’ to 5-3ap’, 51-81%).

Table 5.4 Substrate scope of aldehydes

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-1a to 5-1c</td>
<td>+ 5-2a’ to 5-2q’</td>
<td>R = CH₃, 5-3aa’, 94%, 24 h</td>
<td>5-IV (20 mol%)</td>
</tr>
<tr>
<td>5-3ai’</td>
<td>80%</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>5-3aj’</td>
<td>72%</td>
<td>30 h</td>
<td></td>
</tr>
<tr>
<td>5-3ak’</td>
<td>72%</td>
<td>30 h</td>
<td></td>
</tr>
<tr>
<td>5-3al’</td>
<td>81%</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>5-3am’</td>
<td>74%, 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-3an’</td>
<td>80%, 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-3ao’</td>
<td>74%, 24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-3ap’</td>
<td>55%, 30h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-3aq’</td>
<td>51%, 24h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
To further illustrate the unique catalytic specificity of catalysts in the reaction, we conducted competition experiments. As highlighted in Scheme 5.3, propionaldehyde (5-2a') reacts with ethyl diazoacetate (5-1a) much faster than 3-pentanone (5-2l) in the presence of acyclic secondary diethyl amine 5-IV as catalyst (Scheme 5.3, only 5-3aa' formed, 49% yield). On the contrary, the propionaldehyde (5-2a') reacts with ethyl diazoacetate (5-1a) much slower than 3-pentanone (5-2l) in the presence of cyclic secondary amine 5-I as catalyst (Scheme 5.4, only 5-3al formed, 55% yield). Moreover, the reaction was not only limited to ethyl diazoacetate as the methyl and benzyl diazoacetates performed similarly in the cycloaddition (Table 5.4, 5-3bc' and 5-3cc', 96% and 86%, respectively).

Scheme 5.3 Competition experiments $^a$

$^a$ Reaction conditions: 1a (0.2 mmol), 2a' (0.2 mmol), 2l (0.2 mmol), DMSO (0.4 mL), cat. (20 mol%), room temperature, 12 h.
5.2.3 Application of the method

With the ability to engage a wide range of carbonyls in this reaction, we sought to apply this method to the synthesis of GPR 109a agonist 5-8 in only two steps (Scheme 5.4). To begin, ethyl diazoacetate 5-1a was treated with 2-pentanone 5-2v followed by addition of cat. 5-I (10 mol%) to furnish the intermediate pyrazole 5-3av in 75% yield (Scheme 5.4). Subsequent hydrolysis allows intermediate pyrazole 5-3av convert to the target, GPR 109a agonist 5-8 in a moderate yield (Scheme 5.4, 53%).

Scheme 5.4 A concise synthesis of GPR 109a agonist 5-8

5.2.4 Mechanistic Investigations

Our postulated reaction pathways are summarized in Scheme 5.5. While the reaction mechanism is unclear at this stage, it is still believed that the sequence is triggered by the generation of enamine 5-4 via the condensation of pentanal 5-2c' and diethylamine 5-IV. Enamine 5-4 acts as the electron-rich olefinic partner, and reacts with a deuterium benzyl diazoacetate 5-1d via an inverse-electron-demand 1,3-dipolar [3+2] cycloaddition process to access the intermediate 5-5. Notably, this cycloaddition process demonstrates a high regioselectivity, which leading to directly introduce a diverse set of substituents to pyrazole scaffold. Intermediate 5-5 can convert to intermediate 5-6 after tautomerization triggered by a 1,3-hydride shift. A subsequent and selective C-H bond-breaking induces the formation of
the active intermediate 5-7. To prove our hypothesis on selective C-H bond-breaking, we conducted a deuterium-labeling experiment (Scheme 5.6). The enamine promoted cycloaddition reaction carried out with β-deuterated benzyl diazoacetate 5-1d yielded 5-3dc without any deuterium incorporation on the pyrazole ring, which supporting our proposed selective C-H\textsubscript{1} bond-breaking (Scheme 5.6). We envision that the C-H\textsubscript{1} bond is activated by the adjacent electron-withdrawing ester group, which resulting a priority bond cleavage than C-H\textsubscript{2}. Lastly, an elimination step followed by a tautomerization leads to the generation of the final product 5-3dc'.

**Scheme 5.5** Postulated mechanism
5.3 Conclusions

In summary, a general, organocatalytic inverse-electron-demand [3+2] cycloaddition reaction between various carbonyls and diazoacetates has been developed. The reaction is catalyzed by second amines, “green promoter”, to generate substituted pyrazoles with high levels of regioselectivity. It is noteworthy that this [3+2] cycloaddition proceeds efficiently under room temperature with a simple and inexpensive catalyst. Considering the large variety and ready availability of the starting materials (e.g. ketones, β-ketoesters, β-diketones, and aldehydes) and the operational simplicity, a convenient, practical and highly modular pyrazole synthesis has been developed. We believe that this work will arouse more research interest in organocatalytic synthesis of other biologically active heterocycles. Such studies are actively under way in this laboratory, and more results will be reported in due course.

5.4 Experimental Section

5.4.1 Material and General Methods

Chemicals and solvents were purchased from commercial suppliers and used as received. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker ACF300 (300 MHz) or a AMX500 (500 MHz)
MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethylsilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine. Flash chromatography separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel.

Compounds 5-1a to 5-1c, 5-2q to 5-2u, 5-2o to 5-2q were prepared according to literature, respectively. Compounds 5-2a to 5-2p, 5-2v, 5-2a' to 5-2n' were commercially available.

5.4.2 Representative Procedures for the Synthesis of Pyrazoles

a) IED-[3+2] Cycloaddition of Ketones:

\[
\text{N}_2 \quad \text{O} \quad \text{H} \quad \text{5-1a} \quad + \quad \text{5-2a} \quad \xrightarrow{10 \text{ mol% pyrrolidine}} \quad \text{DMSO, r. t.} \quad \text{5-3aa}
\]

To a solution of cyclohexanone 5-2a (0.4 mmol, 2.0 equiv) in DMSO was added 10 mol % pyrrolidine and then ethyl 2-diazoacetate 5-1a (0.2 mmol, 1.0 equiv.). The reaction was stirred at r.t. for 12 h. The solution was then evaporated to dryness under reduced pressure to
give a crude residue which was purified by silica gel column chromatography eluted by hexane/EtOAc = 10:1 then 4:1 to afford 32 mg (87% yield) of 5-3aa as pale yellow oil.

b) IED-[3+2] Cyloaddition of Aldehydes:

To a solution of pentanal 5-2c' (1.0 mmol, 5.0 equiv.) in DMSO was added 20 mol % diethylamine as catalyst and then ethyl 2-diazoacetate 5-1a (0.2 mmol, 1.0 equiv.). The reaction was stirred at r.t. for 24 h. The solution was then evaporated to dryness under reduced pressure to give a crude residue which was purified by silica gel column chromatography eluted by hexane/EtOAc = 10:1 then 4:1 to afford 5-3ac' (32 mg, 86% yield) as pale yellow oil.

c) GPR 109a Synthesis:

To a solution of pentan-2-one 5-2v (0.4 mmol, 2.0 equiv.) in DMSO was added 10 mol% pyrrolidine as catalyst and ethyl 2-diazoacetate 5-1a (0.2 mmol, 1.0 equiv.). The reaction was stirred at r.t. for 12 h. The solution was then evaporated to dryness under reduced pressure to give a crude residue which was purified by silica gel column chromatography eluted by hexane/EtOAc = 10:1 then 4:1 to afford 27 mg (75% yield) of 5-3av as pale yellow oil. Then
followed with the procedure as reported in literature, the GPR 109a agonist was finally obtained in 53% yield.

d) Procedure for Competition Reaction:

To a solution of propionaldehyde 5-1b' (0.2 mmol, 1.0 equiv.) and pentan-3-one 5-1l (0.2 mmol, 1.0 equiv) in DMSO was added 20 mol% pyrrolidine as catalyst and then ethyl 2-diazoacetate 5-2a (0.2 mmol, 1.0 equiv.). The reaction was stirred at r.t. for 12 h. The solution was then evaporated to dryness under reduced pressure to give a crude residue which was purified by silica gel column chromatography eluted by hexane/EtOAc = 15:1 then 4:1 to afford 20 mg (55% yield) of 5-3al as pale yellow oil.

To a solution of propionaldehyde 5-1b' (0.2 mmol, 1.0 equiv.), and pentan-3-one 5-1l (0.2 mmol, 1.0 equiv.) in DMSO was added 20 mol % diethylamine as catalyst and then ethyl 2-diazoacetate 5-2a (0.2 mmol, 1.0 equiv). The reaction was stirred at r.t. for 12 h. The solution was then evaporated to dryness under reduced pressure to give a crude residue which was purified by silica gel column chromatography eluted by hexane/EtOAc = 10:1 then 4:1 to afford 16 mg (49% yield) of 5-3aa' as pale yellow oil.
e) Synthesis of Benzyl α-Deuteriodiazoacetate\textsuperscript{95a, 96b, 101}

Benzyl alcohol (0.54 g, 5 mmol) was dissolved in ethyl acetoacetate (6.5 g, 50 mmol) and then refluxed under N\textsubscript{2} for 5 h. Unreacted ethyl acetoacetate was removed under reduced pressure, and benzyl acetoacetate was purified by flash chromatography (5% ethyl acetate in hexanes) for next step.

To a solution of benzyl acetoacetate (960 mg, 5 mmol) in acetonitrile (10 ml) was added Et\textsubscript{3}N (653 mg, 6.5 mmol). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.08 g, 5.5 mmol) in acetonitrile (10 ml) was added slowly. The reaction mixture was allowed to warm up to r.t. After stirring for 10 h, solvent was removed under reduced pressure. The residue was dissolved in ether and washed with 5% aqueous KOH solution. To a solution of the crude benzyl 2-diazo-acetoacetate (1.03 g, 5.0 mmol) in acetonitrile (15 mL) was added 5% KOH (20 mL), and then the reaction was stirred at r.t. for 1 h. The reaction mixture was extracted with ether, and the organic layer was separated, dried over Mg\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure which was purified by flash chromatography (hexane: ethyl acetate from 100:1 to 10:1) to provide benzyl diazoacetate as a yellow liquid.

Benzyl diazoacetate (5.0 mmol) was combined with anhydrous ether (30 mL) in a 100 mL Morton flask. About 30 mL of 10% NaOD in D\textsubscript{2}O was added, and the complex solution was vigorously stirred for 1 day at room temperature. The two layers were separated and the organic layer was collected by syringe, and then dried by MgSO\textsubscript{4}. The solution was filtered and carefully concentrated by rotary evaporation at room temperature. This procedure was repeated two to three times, each time using fresh 10% NaOD in D\textsubscript{2}O until \textsuperscript{1}H NMR analysis indicated that deuterium incorporation at C(α) was >98% by comparing the residual NMR C(α)-H signal at δ 4.82 to the single peak at δ 5.24.
f) Deuterium Labeling Experiments.

Initially, fresh prepared benzyl α-D-diazoacetate 5-1d (0.2 mmol, 1.0 equiv., >98% D) was added into the solution of pentanal 5-2c' (1.0 mmol, 3.0 equiv.) and 20 mol % diethylamine in anhydrous DMSO, then vigorously stirred at r.t. for 12 h. The reaction was then stopped and evaporated to dryness under reduced pressure to give a crude residue which was purified by silica gel column chromatography eluted by hexane/EtOAc = 10:1 then 4:1 to afford 5-3dc'. $^1$H NMR analysis indicated that 3dc' (assumed deuterium product) was exactly same as 5-3cc' (non-deuterated product) which indicated by the NMR of residual hydrogen signal at δ 6.62. In addition, several others reaction factors (D$_6$-DMSO and/or D$_2$O) which may affect the labeling experiments were also examined, but $^1$H NMR data of 3dc'-2 to 3dc'-3 indicate that no deuterium incorporated pyrazole was formed.
5.4.3 Analytical Data of the Pyrazoles

Ethyl 4, 5, 6, 7-tetrahydro-1H-indazole-3-carboxylate (5-3aa)

![Chemical Structure of 5-3aa]

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.35 (q, $J$ = 7.5 Hz, 2H), 2.74 (t, $J$ = 6.2 Hz, 2H), 2.68 (t, $J$ = 6.2 Hz, 2H), 1.80-1.74 (m, 4H), 1.35 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.58, 145.27, 136.25, 119.78, 60.93, 23.31, 22.98, 22.47, 21.89, 14.73; HRMS (ESI): calcd. for C$_{10}$H$_{14}$N$_2$O$_2$ [M-H] $^{−}$ 193.0977, found 193.0983.

Ethyl 6-ethyl-4, 5, 6, 7-tetrahydro-1H-indazole-3-carboxylate (5-3ab)

![Chemical Structure of 5-3ab]

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.35 (q, $J$ = 7.5 Hz, 2H), 2.94 - 2.85 (m, 2H), 2.66 - 2.60 (m, 1H), 2.26 - 2.18 (m, 1H), 1.96 - 1.93 (m, 1H), 1.68 - 1.66 (m, 1H), 1.50 - 1.27 (m, 6H), 0.96 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.21, 146.55, 135.20, 120.15, 61.08, 36.39, 29.45, 29.01, 28.66, 21.30, 14.79, 12.00; HRMS (ESI): calcd. for C$_{12}$H$_{18}$N$_2$O$_2$ [M-H]$^{−}$ 221.1290, found 221.1287.

Diethyl 4, 5, 6, 7-tetrahydro-1H-indazole-3, 6-dicarboxylate (5-3ac)

![Chemical Structure of 5-3ac]

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.35 (q, $J$ = 7.5 Hz, 2H), 4.17 (q, $J$ = 7.0 Hz, 2H), 3.03 - 2.87 (m, 3H), 2.82 - 2.68 (m, 2H), 2.21 - 2.15 (m, 1H), 1.87 - 1.80 (m, 1H), 1.36 (t, $J$ = 7.5 Hz,
3H), 1.26 (t, J = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 175.18, 161.78, 130.45, 128.77, 119.28, 61.26, 61.18, 40.21, 26.38, 25.28, 20.89, 14.76, 14.65; HRMS (ESI): calcd. for C$_{13}$H$_{18}$N$_2$O$_4$ [M-H] - 265.1188, found 265.1182.

**Ethyl 1', 4', 5', 7'-tetrahydropyrido [1, 3] dioxolane-2, 6'-indazole]-3'-carboxylate (5-3ad)**

\[
\text{Ethyl 1', 4', 5', 7'-tetrahydropyrido [1, 3] dioxolane-2, 6'-indazole]-3'-carboxylate (5-3ad)}
\]

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.35 (q, J = 7.0 Hz, 2H), 4.02 – 4.00 (m, 4H), 2.94 (t, J = 7.0 Hz, 4H), 1.93 (t, J = 7.0 Hz, 2H), 1.35 (t, J = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 161.38, 148.51, 140.56, 118.90, 109.10, 65.15, 61.27, 34.03, 32.18, 19.52, 14.77; HRMS (ESI): calcd. For C$_{12}$H$_{16}$N$_2$O$_4$ [M-H] - 251.1032, found 251.1029.

**Ethyl 6, 6-dimethyl-4, 5, 6, 7-tetrahydro-1H-indazole-3-carboxylate (5-3ae)**

\[
\text{Ethyl 6, 6-dimethyl-4, 5, 6, 7-tetrahydro-1H-indazole-3-carboxylate (5-3ae)}
\]

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.36 (q, J = 7.5 Hz, 2H), 2.74 (t, J = 6.5 Hz, 2H), 2.45 (s, 2H), 1.53 (t, J = 6.5 Hz, 2H), 1.37 (t, J = 7.5 Hz, 3H), 0.99 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.11, 146.90, 134.98, 118.90, 61.12, 36.38, 36.34, 30.79, 28.31, 19.16, 14.81; HRMS (ESI): calcd. for C$_{12}$H$_{18}$N$_2$O$_2$ [M-H] - 221.1290, found 221.1293.

**Ethyl 6, 6-dimethyl-4, 5, 6, 7-tetrahydro-1H-indazole-3-carboxylate (5-3af)**

\[
\text{Ethyl 6, 6-dimethyl-4, 5, 6, 7-tetrahydro-1H-indazole-3-carboxylate (5-3af)}
\]
$^1$H NMR (500 MHz, CDCl$_3$): δ 4.36 (q, $J = 7.5$ Hz, 2H), 2.69 (t, $J = 7.0$ Hz, 2H), 2.53 (s, 2H), 1.58 (t, $J = 7.0$ Hz, 2H), 1.37 (t, $J = 7.5$ Hz, 3H), 0.99 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.07, 145.53, 135.41, 120.13, 61.14, 35.96, 35.61, 30.37, 28.38, 19.81, 14.81; HRMS (ESI): calcd. for C$_{12}$H$_{18}$N$_2$O$_2$ [M-H]$^-$ 221.1290, found 221.129.

**Ethyl 1, 4, 5, 7-tetrahydropyrano [3, 4-c] pyrazole-3-carboxylate (5-3ag)**

![5-3ag](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.79 (s, 2H), 4.38 (q, $J = 7.0$ Hz, 2H), 3.90 (t, $J = 5.6$ Hz, 2H), 2.88 (t, $J = 5.6$ Hz, 2H), 1.38 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 160.82, 147.59, 132.15, 117.40, 65.45, 64.78, 61.56, 23.02, 14.77; HRMS(ESI): calcd. for C$_9$H$_{12}$N$_2$O$_3$ [M-H]$^-$ 195.0770, found 195.0777.

**Ethyl 1, 4, 5, 7- tetrahydrothiopyrano [3, 4-c] pyrazole-3-carboxylate (5-3ah)**

![5-3ah](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.36 (q, $J = 7.0$ Hz, 2H), 3.78 (s, 2H), 3.07 (t, $J = 6.0$ Hz, 2H), 2.85 (t, $J = 6.0$ Hz, 2H), 1.36 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 161.33, 143.58, 134.16, 119.46, 61.46, 26.79, 24.38, 14.76; HRMS(ESI): calcd. for C$_9$H$_{12}$N$_2$O$_3$S [M-H]$^-$ 211.0541, found 211.0545.

**Ethyl 1, 4, 5, 6, 7, 8-hexahydrocyclohepta[c]pyrazole-3-carboxylate (5-3ai)**

![5-3ai](image)
$^1$H NMR (500 MHz, CDCl$_3$): δ 4.36 (q, $J = 7.0$ Hz, 2H), 2.92 (t, $J = 6.0$ Hz, 2H), 2.81 (t, $J = 6.0$ Hz, 2H), 1.92 – 1.80 (m, 2H), 1.69 – 1.60 (m, 4H), 1.37 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 161.53, 151.60, 134.06, 124.53, 60.61, 32.11, 28.38, 27.19, 24.16, 14.21; HRMS (ESI): calcd. for C$_{11}$H$_{16}$N$_2$O$_2$ [M-H]$^-$ 207.1134, found 207.1142.

**Ethyl 4, 5, 6, 7, 8, 9-hexahydro-1H-cycloocta[c]pyrazole-3-carboxylate (5-3aj)**

![Ethyl 4, 5, 6, 7, 8, 9-hexahydro-1H-cycloocta[c]pyrazole-3-carboxylate (5-3aj)](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.37 (q, $J = 7.0$ Hz, 2H), 2.87 (t, $J = 6.5$ Hz, 2H), 2.78 (t, $J = 6.5$ Hz, 2H), 1.71 – 1.66 (m, 4H), 1.48 – 1.46 (m, 2H), 1.40 – 1.25 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 161.11, 150.72, 133.61, 122.63, 60.72, 30.18, 29.18, 25.66, 25.53, 25.42, 21.36, 14.30; HRMS (ESI): calcd. for C$_{12}$H$_{18}$N$_2$O$_2$ [M-H]$^-$ 221.1290, found 221.1296.

**Ethyl 4, 5-dimethyl-1H-pyrazole-3-carboxylate (5-3ak)**

![Ethyl 4, 5-dimethyl-1H-pyrazole-3-carboxylate (5-3ak)](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.34 (q, $J = 7.0$ Hz, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 1.36 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.29, 144.28, 136.41, 118.07, 61.06, 14.71, 10.88, 9.09; HRMS(ESI): calcd. for C$_{8}$H$_{12}$N$_2$O$_2$ [M-H]$^-$ 167.0821, found 167.0825.

**Ethyl 4-ethyl-5-methyl-1H-pyrazole-3-carboxylate (5-3al)**

![Ethyl 4-ethyl-5-methyl-1H-pyrazole-3-carboxylate (5-3al)](image)
$^1$H NMR (500 MHz, CDCl$_3$): δ 4.35 (q, $J = 7.0$ Hz, 2H), 2.68 (q, $J = 7.5$ Hz, 2H), 2.25 (s, 3H), 1.35 (t, $J = 7.5$ Hz, 2H), 1.10 (t, $J = 7.0$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.03, 144.24, 135.68, 124.77, 61.09, 17.26, 15.46, 14.68, 10.95; HRMS(ESI): calcd. for C$_9$H$_{14}$N$_2$O$_2$ [M-H]$^-$ 181.0977, found 181.0982.

**Ethyl 4-phenyl-1H-pyrazole-3-carboxylate (5-3am)**

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.98 (s, 1H), 7.54 (d, $J = 7.0$ Hz, 2H), 7.40 (t, $J = 7.0$ Hz, 2H), 7.34 (t, $J = 7.5$ Hz, 1H), 4.34 (t, $J = 7.0$ Hz, 2H), 1.29 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 161.16, 131.71, 129.50, 127.97, 127.50, 125.61, 61.14, 14.08; HRMS(ESI): calcd. for C$_{12}$H$_{12}$N$_2$O$_2$ [M-H]$^-$ 215.0821, found 215.0827.

**Ethyl 5-methyl-4-phenyl-1H-pyrazole-3-carboxylate (5-3an)**

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.39 (t, $J = 7.0$ Hz, 2H), 7.33 (q, $J = 7.0$ Hz, 3H), 4.25 (q, $J = 7.5$ Hz, 2H), 2.29 (s, 3H), 1.20 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 161.77, 132.60, 130.69, 129.42, 129.11, 128.28, 127.67, 123.70, 61.31, 14.43, 11.51; HRMS(ESI): calcd. for C$_{13}$H$_{14}$N$_2$O$_2$ [M-H]$^-$ 229.0977, found 229.0985.

**Methyl 4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (5-3ba)**
**Benzyl 4,5,6,7-tetrahydro-1H-indazole-3-carboxylate (5-3ca)**

![](image1.png)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.40 (d, $J$ = 7.0 Hz, 2H), 7.38 – 7.30 (m, 3H), 5.34 (s, 2H), 2.73 (t, $J$ = 5.7 Hz, 2H), 2.64 (t, $J$ = 5.7 Hz, 2H), 1.76 – 1.72 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 162.10, 145.97, 136.31, 135.40, 129.01, 128.67, 128.64, 120.25, 66.73, 23.28, 22.99, 22.60, 21.94; HRMS(ESI): calcd. for C$_{15}$H$_{15}$N$_2$O$_2$ [M-H]$^-$ 255.1139, found 255.1132.

**Diethyl 4-phenyl-1H-pyrazole-3,5-dicarboxylate (5-3ao)**

![](image2.png)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.41 – 7.36 (m, 3H), 7.35 – 7.32 (m, 2H), 4.25 (q, $J$ = 7.5 Hz, 4H), 1.19 (t, $J$ = 7.5 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.16, 130.43, 130.10, 127.88, 127.81, 127.24, 61.27, 13.77; HRMS(ESI): calcd. for C$_{13}$H$_{16}$N$_2$O$_4$ [M-H]$^-$ 287.1032, found 287.1039.
Ethyl 5-benzoyl-4-phenyl-1H-pyrazole-3-carboxylate (5-3ap)

\[
\text{- NMR (500 MHz, CDCl}_3\text{): } \delta 7.88 (d, J = 7.0 \text{ Hz, 2H}), 7.48 (t, J = 7.5 \text{ Hz, 1H}), 7.37 - 7.23 \text{ (m, 7H)}, 4.31 (q, J = 7.5 \text{ Hz, 2H}), 1.22 (t, J = 7.5 \text{ Hz, 3H}); ^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta 188.48, 160.64, 146.38, 137.08, 135.34, 133.44, 130.86, 130.83, 130.59, 128.82, 128.48, 128.20, 127.94, 61.97, 14.28; HRMS(ESI): calcd. for C_{19}H_{16}N_{2}O_{3} [M-H]^- 319.1083, found 319.1092.
\]

Ethyl 4-phenyl-5-(thiophene-3-carbonyl)-1H-pyrazole-3-carboxylate (5-3aq)

\[
\text{- NMR (500 MHz, CDCl}_3\text{): } \delta 8.10 (s, 1H), 7.68 (d, J = 4.5 \text{ Hz, 1H}), 7.44 - 7.35 \text{ (m, 6H)}, 7.12 (t, J = 4.5 \text{ Hz, 1H}), 4.29 (q, J = 7.5 \text{ Hz, 2H}), 1.19 (t, J = 7.5 \text{ Hz, 3H}); ^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta 179.65, 160.03, 143.36, 136.16, 135.33, 130.84, 130.71, 128.62, 128.42, 128.30, 128.19, 127.95, 62.11, 14.22; HRMS(ESI): calcd. for C_{17}H_{14}N_{2}O_{3}S [M-H]^- 325.0647, found 325.0654.
\]

Ethyl 4-phenyl-5-(2-phenylacetyl)-1H-pyrazole-3-carboxylate (5-3ar)
$^1$H NMR (500 MHz, CDCl$_3$): δ 12.17 (s, 1H) 7.41-7.35 (m, 3H), 7.34 – 7.33 (m, 2H), 7.30 – 7.23 (m, 3H), 7.22 – 7.19 (m, 2H), 4.25 (q, $J = 7.0$ Hz, 2H), 4.19 (s, 2H), 1.18 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 192.44, 160.57, 134.20, 130.56, 130.16, 128.85, 128.53, 128.14, 127.55, 127.30, 61.91, 46.90, 14.21; HRMS(ESI): calcd. for C$_{20}$H$_{18}$N$_2$O$_3$ [M-H]$^-$ 333.1239, found 333.1249.

**Ethyl 5-methyl-1H-pyrazole-3-carboxylate (5-3aa')**

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.58 (s, 1H), 4.37 (q, $J = 7.0$ Hz, 2H), 2.37 (s, 3H), 1.36 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.51, 143.26, 142.25, 107.63, 61.29, 14.69, 11.80; HRMS(ESI): calcd. for C$_7$H$_9$N$_2$O$_2$ [M-H]$^-$ 153.0670, found 153.0672.

**Ethyl 5-ethyl-1H-pyrazole-3-carboxylate (5-3ab')**

$^1$H NMR (500 MHz, CDCl$_3$): δ 8.59 (s, 1H), 6.57 (s, 1H), 4.34 (q, $J = 7.0$ Hz, 2H), 2.72 (q, $J = 7.5$ Hz, 2H), 1.32 (t, $J = 7.0$ Hz, 3H), 1.24 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.61, 149.35, 142.18, 106.05, 61.22, 19.71, 14.66, 13.68; HRMS(ESI): calcd. for C$_8$H$_{11}$N$_2$O$_2$ [M-H]$^-$ 167.0826, found 167.0826.

**Ethyl 5-propyl-1H-pyrazole-3-carboxylate (5-3ac')**
1H NMR (500 MHz, CDCl₃): δ 6.57 (s, 1H), 4.35 (q, J = 7.0 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 1.67 – 1.60 (m, 2H), 1.33 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H); 13C NMR (125 MHz, CDCl₃): δ 162.50, 148.18, 142.00, 106.74, 61.27, 28.47, 22.85, 14.70, 14.08; HRMS(ESI): calcd. for C₉H₁₃N₂O₂ [M-H]⁻ 181.0983, found 181.0977.

Ethyl 5-butyl-1H-pyrazole-3-carboxylate (5-3ad')

![Diagram of 5-3ad'](5-3ad')

1H NMR (500 MHz, CDCl₃): δ 9.42 (s, 1H), 6.55 (d, J = 2.5 Hz, 1H), 4.32 (q, J = 7.0 Hz, 2H), 2.66 (q, J = 7.5 Hz, 2H), 1.61 – 1.55 (m, 2H), 1.33 – 1.28 (m, 5H), 0.85 (t, J = 7.5 Hz, 3H); 13C NMR (125 MHz, CDCl₃): δ 162.66, 147.88, 142.27, 106.48, 61.16, 31.57, 25.95, 22.56, 14.63, 14.10; HRMS(ESI): calcd. for C₁₀H₁₅N₂O₂ [M-H]⁻ 195.1139, found 195.1142.

Ethyl 5-pentyl-1H-pyrazole-3-carboxylate (5-3ae')

![Diagram of 5-3ae'](5-3ae')

1H NMR (500 MHz, CDCl₃): δ 8.93 (s, 1H), 6.56 (s, 1H), 4.33 (q, J = 7.0 Hz, 2H), 2.68 – 2.65 (m, 2H), 1.62 – 1.60 (m, 2H), 1.34 – 1.27 (m, 7H), 0.85 (t, J = 7.0 Hz, 3H); 13C NMR (125 MHz, CDCl₃): δ 162.59, 148.11, 142.17, 106.56, 61.22, 31.69, 29.21, 26.33, 22.75, 14.67, 14.34.; HRMS(ESI): calcd. for C₁₁H₁₇N₂O₂ [M-H]⁻ 209.1296, found 209.1295.

Ethyl 5-heptyl-1H-pyrazole-3-carboxylate (5-3af')
Ethyl 5-octyl-1H-pyrazole-3-carboxylate (5-3ag')

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.58 (s, 1H), 4.37 – 4.33 (m, 2H), 2.67 (t, $J = 7.5$ Hz, 2H), 1.64 – 1.61 (m, 2H), 1.37 – 1.24 (m, 13H), 0.85 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.42, 148.62, 141.84, 106.73, 61.33, 32.28, 29.73, 29.68, 29.58, 26.56, 23.09, 14.74, 14.53; HRMS(ESI): calcd. for C$_{14}$H$_{23}$N$_2$O$_2$ [M-H]’ 251.1765, found 251.1754.

Ethyl 5-nonyl-1H-pyrazole-3-carboxylate (5-3ah')

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.60 (s, 1H), 4.38 (q, $J = 7.5$ Hz, 2H), 2.70 (t, $J = 7.5$ Hz, 2H), 1.67 – 1.62 (m, 2H), 1.39 – 1.27 (m, 11H), 0.86 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.43, 148.65, 142.05, 106.73, 61.30, 32.16, 29.59, 29.55, 29.43, 26.59, 23.06, 14.73, 14.49; HRMS(ESI): calcd. for C$_{13}$H$_{21}$N$_2$O$_2$ [M-H]’ 237.1609, found 237.1604.
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.58 (s, 1H), 4.36 (q, $J = 7.0$ Hz, 2H), 2.67 (t, $J = 7.5$ Hz, 2H), 1.65 – 1.60 (m, 2H), 1.37 – 1.24 (m, 15H), 0.86 (t, $J = 6.5$ Hz , 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.22, 148.85, 141.52, 106.87, 61.39, 32.32, 29.93, 29.78, 29.74, 29.59, 26.74, 23.12, 14.76, 14.56; HRMS(ESI): calcd. for C$_{15}$H$_{25}$N$_2$O$_2$ [M-H]$^-$ 265.1922, found 265.1927.

**Ethyl 5-isopropyl-1H-pyrazole-3-carboxylate (5-3ai')**

![Structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.55 (d, $J = 1.8$ Hz, 1H), 4.33 – 4.29 (m, 2H), 3.04 – 2.98 (m, 1H), 1.29 (t, $J = 7.5$ Hz, 3H), 1.23 (d, $J = 7.0$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.51, 154.07, 141.73, 104.82, 61.18, 26.57, 22.72, 14.63; HRMS(ESI): calcd. for C$_9$H$_{13}$N$_2$O$_2$ [M-H]$^-$ 181.0983, found 181.0977.

**Ethyl 5-benzyl-1H-pyrazole-3-carboxylate (5-3aj')**

![Structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.3 (t, $J = 8.0$ Hz, 2H), 7.25 (m, 3H), 6.59 (s, 1H), 4.36 (q, $J = 7.0$ Hz, 2H), 4.08 (s, 2H), 1.36 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 161.82, 148.44, 140.74, 138.66, 129.16, 127.15, 107.87, 61.49, 33.44, 14.70; HRMS(ESI): calcd. for C$_{13}$H$_{13}$N$_2$O$_2$ [M-H]$^-$ 229.0983, found 229.0980.

**Ethyl 5-(4-methoxybenzyl)-1H-pyrazole-3-carboxylate (5-3ak')**
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.12 (d, $J$ = 8.5 Hz, 2H), 6.83 (d, $J$ = 8.5 Hz, 2H), 6.55 (s, 1H), 4.33 (q, $J$ = 7.0 Hz, 2H), 3.98 (s, 2H), 3.78 (s, 3H), 1.33 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 161.83, 158.86, 148.85, 140.78, 130.61, 130.16, 114.58, 107.72, 61.49, 55.73, 32.54, 14.71; HRMS(ESI): calcd. for C$_{14}$H$_{15}$N$_2$O$_3$ [M-H] 259.1088, found 259.1089.

**Ethyl 5-(methylthiomethyl)-1H-pyrazole-3-carboxylate (5-3al')**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.77 (s, 1H), 4.38 (q, $J$ = 7.5 Hz, 2H), 3.74 (s, 2H), 2.05 (s, 3H), 1.38 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 161.13, 147.85, 139.41, 108.31, 61.75, 29.94, 15.67, 14.74; HRMS(ESI): calcd. for C$_8$H$_{11}$N$_2$O$_2$S [M-H] 199.0547, found 199.0544.

**Ethyl 5-(1-phenylethyl)-1H-pyrazole-3-carboxylate (5-3am')**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.30 (t, $J$ = 7.5 Hz, 2H), 7.23 – 7.19 (m, 3H), 6.64 (s, 1H), 4.33 (q, $J$ = 7.0 Hz, 2H), 4.21 (q, $J$ = 7.5 Hz, 1H), 1.65 (d, $J$ = 7.5 Hz, 3H), 1.34 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 161.98, 153.02, 144.40, 140.86, 129.12, 127.76, 127.22,
106.68, 61.47, 38.14, 21.79, 14.69.; HRMS(ESI): calcd. for C\textsubscript{14}H\textsubscript{15}N\textsubscript{2}O\textsubscript{2} [M-H] 243.1139, found 243.1128.

**Ethyl 5-((6-methylhept-5-en-2-yl)-1H-pyrazole-3-carboxylate (5-3an')**

![Chemical Structure](image)

\[^1\text{H}\text{NMR}\ (500 \text{ MHz}, \text{CDCl}_3): \delta 6.58\ (s, 1\text{H}), 5.04\ (t, J = 7.0 \text{ Hz, 1H}), 4.34\ (q, J = 7.5 \text{ Hz, 2H}), 2.91\ (dd, J = 14.1, 7.0 \text{ Hz, 1H}), 1.93 – 1.91\ (m, 2\text{H}), 1.66 – 1.54\ (m, 5\text{H}), 1.51\ (s, 3\text{H}), 1.34\ (t, J = 7.5 \text{ Hz, 3H}), 1.25\ (d, J = 7.0 \text{ Hz, 3H}); \[^{13}\text{C}\text{NMR}\ (125 \text{ MHz, CDCl}_3): \delta 162.29, 153.68, 141.42, 132.40, 124.23, 105.41, 61.30, 37.46, 31.68, 26.09, 26.06, 20.95, 18.07, 14.71; HRMS(ESI): calcd. for C\textsubscript{14}H\textsubscript{21}N\textsubscript{2}O\textsubscript{2} [M-H] 249.1609, found 249.162.]

**Ethyl 5-((2-benzoyl-3-ethoxy-3-oxopropyl)-1H-pyrazole-3-carboxylate (5-3ao')**

![Chemical Structure](image)

\[^1\text{H}\text{NMR}\ (500 \text{ MHz, CDCl}_3): \delta 7.99\ (d, J = 8.0 \text{ Hz, 2H}), 7.57 – 7.55\ (m, 1\text{H}), 7.45\ (t, J = 8.0 \text{ Hz, 2H}), 6.64\ (s, 1\text{H}), 4.77\ (t, J = 7.0 \text{ Hz, 1H}), 4.32\ (t, J = 7.0 \text{ Hz, 2H}), 4.11\ (q, J = 7.0 \text{ Hz, 2H}), 3.39\ (d, J = 7.0 \text{ Hz, 2H}), 1.33\ (t, J = 7.0 \text{ Hz, 3H}), 1.11\ (t, J = 7.0 \text{ Hz, 3H}); \[^{13}\text{C}\text{NMR}\ (125 \text{ MHz, CDCl}_3): \delta 194.87, 169.57, 161.52, 146.22, 136.27, 134.25, 129.29, 129.22, 108.35, 62.33, 61.55, 54.32, 26.26, 14.69, 14.32; HRMS(ESI): calcd. for C\textsubscript{18}H\textsubscript{19}N\textsubscript{2}O\textsubscript{5} [M-H] 343.1299, found 343.1302.}
Ethyl 5-(2-(ethoxycarbonyl)-3-oxobutyl)-1H-pyrazole-3-carboxylate (5-3ap')

\[
\text{O} \quad \begin{array}{c}
\text{O} \quad \text{EtOOC} \\
\text{5-3ap'}
\end{array}
\]

\( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 6.62 (s, 1H), 4.36 (q, \( J = 7.0 \) Hz, 2H), 4.23 – 4.16 (m, 1H), 3.90 (t, \( J = 7.0 \) Hz, 1H), 3.23 – 3.20 (m, 2H), 2.28 (s, 3H), 1.36 (t, \( J = 7.5 \) Hz, 3H), 1.25 (t, \( J = 7.0 \) Hz, 3H); \(^{13}C\) NMR (125 MHz, CDCl\(_3\)): \( \delta \) 202.74, 169.33, 161.28, 146.65, 139.80, 108.28, 62.37, 61.65, 59.34, 30.14, 25.47, 14.73, 14.48; HRMS(ESI): calcd. for C\(_{13}\)H\(_{17}\)N\(_2\)O\(_5\) [M-H]\(^+\) 281.2243, found 281.2237.

Ethyl 5-((1H-indol-3-yl)methyl)-1H-pyrazole-3-carboxylate (5-3aq')

\[
\text{O} \quad \text{N} \quad \text{NH} \\
\text{5-3aq'}
\]

\( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 8.13 (s, 1H), 7.48 (d, \( J = 8.0 \) Hz, 1H), 7.36 (d, \( J = 8.0 \) Hz, 1H), 7.20 (t, \( J = 7.5 \) Hz, 1H), 7.09 (t, \( J = 7.5 \) Hz, 1H), 7.02 (s, 1H), 6.66 (s, 1H), 4.34 (q, \( J = 7.0 \) Hz, 2H), 4.17 (s, 2H), 1.35 (t, \( J = 7.0 \) Hz, 3H); \(^{13}C\) NMR (125 MHz, CDCl\(_3\)): \( \delta \) 161.95, 136.90, 132.18, 130.01, 127.42, 123.01, 122.87, 120.21, 119.24, 112.61, 111.76, 107.57, 61.51, 23.37, 14.75; HRMS(ESI): calcd. for C\(_{13}\)H\(_{17}\)N\(_2\)O\(_5\) [M-H]\(^+\) 281.2243, found 281.2237.

methyl 5-propyl-1H-pyrazole-3-carboxylate (5-3be')

\[
\text{O} \quad \text{N} \quad \text{NH} \\
\text{5-3be'}
\]
$^1$H NMR (500 MHz, CDCl$_3$): δ 6.60 (s, 1H), 3.88 (s, 3H), 2.67 (t, $J = 7.5$ Hz, 2H), 1.67 (q, $J = 7.5$ Hz, 2H), 0.94 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 163.05, 147.81, 142.12, 106.73, 52.23, 28.27, 22.80, 14.04; HRMS (ESI): calcd. for C$_8$H$_{11}$N$_2$O$_2$ [M-H]$^-$ 167.0826, found 167.0832.

benzyl 5-propyl-1H-pyrazole-3-carboxylate (5-3cc')

![Chemical Structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.40 (d, $J = 7.0$ Hz, 2H), 7.37 – 7.32 (m, 3H), 6.60 (s, 1H), 5.35 (s, 2H), 2.60 (t, $J = 7.5$ Hz, 2H), 1.64 – 1.58 (m, 2H), 0.90 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.41, 147.72, 142.00, 136.21, 128.95, 128.69, 128.65, 106.81, 66.83, 28.18, 22.72, 14.02; HRMS (ESI): calcd. for C$_{14}$H$_{15}$N$_2$O$_2$ [M-H]$^-$ 243.1139, found 243.1135.

Ethyl 5-ethyl-4-methyl-1H-pyrazole-3-carboxylate (5-3av)

![Chemical Structure](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ 4.35 (q, $J = 7.0$ Hz, 2H), 2.68 (q, $J = 7.5$ Hz, 2H), 2.25 (s, 3H), 1.39 (t, $J = 7.0$ Hz, 3H), 1.25 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 162.00, 144.24, 135.68, 124.77, 61.09, 17.26, 15.46, 14.69, 10.95; HRMS (ESI): calcd. for C$_9$H$_{14}$N$_2$O$_2$ [M-H]$^-$ 181.0977, found 181.0982.

5-ethyl-4-methyl-1H-pyrazole-3-carboxylic acid (5-8)

![Chemical Structure](image)
$^1$H NMR (500 MHz, $d^6$-DMSO): $\delta$ 12.84 (s, 1H), 2.54 (q, $J = 7.5$ Hz, 2H), 2.13 (s, 3H), 1.14 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (125 MHz, $d^6$-DMSO): $\delta$ 162.98, 147.57, 136.18, 115.37, 17.93, 13.40, 8.38; HRMS(ESI): calcd. for C$_7$H$_9$N$_2$O$_2$ [M-H]$^-$ 153.0670, found 153.0669.

5.4.4 X-Ray Crystallographic Analysis

The configuration of the product 5-3aa was assigned by X-ray crystallographic analysis of a single crystal of 5-3aa (Figure 5.1). The configurations of other products were assigned by analogy.

![Figure 5.1 X-ray structure of 5-3aa](image)

**Table 5.5** Crystal data and structure refinement for 5-3aa

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C$<em>{10}$H$</em>{14}$N$_2$O$_2$</td>
</tr>
<tr>
<td>Formula weight</td>
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</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Property</td>
<td>Value</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)/n</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 12.4631(10) Å, a= 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 15.2751(13) Å, b= 108.852(2)°.</td>
</tr>
<tr>
<td></td>
<td>c = 16.8492(14) Å, g = 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>3035.6(4) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>12</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.275 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.090 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>1248</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.60 x 0.50 x 0.36 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.79 to 27.50°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-13&lt;=h&lt;=16, -19&lt;=k&lt;=19, -21&lt;=l&lt;=14</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>20637</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>6946 [R(int) = 0.0398]</td>
</tr>
<tr>
<td>Completeness to theta = 27.50°</td>
<td>99.5 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9683 and 0.9479</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>6946 / 42 / 413</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.064</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0566, wR2 = 0.1406</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0741, wR2 = 0.1505</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.571 and -0.434 e.Å⁻³</td>
</tr>
</tbody>
</table>
Chapter 6 Amine-catalyzed [3+2] Huisgen Cycloaddition Strategy for the Efficient Assembly of Highly Substituted 1,2,3-triazoles

An enamine catalyzed strategy is utilized to fully promote the Huisgen [3+2] cycloaddition with a broad spectrum of carbonyls and azides to access the efficient assembly of a vast pool of highly substituted 1,2,3-triazoles.
6.1 Introduction

Organocatalytic activation of readily available substrates has led to the rapid development of many reactions in the last decade. Enamine catalysis, as one of the most powerful tools, has been extensively investigated and reported to undergo a diverse set of transformations based on the enamine intermediates generated by catalysis process. Although many transformations have been reported, the enamine-azide [3+2] Huisgen cycloaddition still remains a challenging topic. Recently we discovered the first example of organocatalytic regiospecific enamide-azide [3+2] cycloadditions of alpha-functionalized ketones to azides (Scheme 6.1a). However, we recognized that the substituents at the 4-position on the 1,2,3-triazole skeleton were largely identified and just defined as electron-withdrawing groups. This limitation will potentially restrict the wide applications of this synthetic methodology. Herein, we wish to report our further endeavors in the examples of amine-catalyzed [3+2] cycloadditions on a broad spectrum of carbonyls and azides to access the efficient assembly of a vast pool of highly substituted 1,2,3-triazoles (Scheme 6.1b).

Scheme 6.1 Strategies to form 1,2,3-triazoles

The 1,2,3-triazole core is a privileged scaffold that is featured in a large number of...
bioactive molecules.\textsuperscript{104} Additionally, 1,2,3-triazole moieties are attractive connections in biological systems because they are stable to metabolic degradation and capable of hydrogen bonding to biomolecular targets and which can also improve the solubility.\textsuperscript{105} Although the 1,2,3-triazole does not occur in nature, it has biological activity.\textsuperscript{106} Thereby, the significance of triazole compounds in medicinal chemistry is indubitable. In light of their occurrence in a broad spectrum of important pharmaceutically active compounds, such as those examples outlined in Scheme 6.3,\textsuperscript{104a-w} highly substituted 1,2,3-triazoles have triggered a sustainably increasing attention in the synthetic chemistry community. Although significant preparation methods of such motifs are reported in some elegant works, the example of synthetic methodologies to quickly and regiospecifically construct 1,4,5-trisubstituted 1,2,3-triazoles are extremely demanding.\textsuperscript{107}

\begin{center}
\begin{tikzpicture}
  \node[black, text=black, align=center] at (0,0) {
    \begin{minipage}{0.8\textwidth}
      \includegraphics[width=\linewidth]{diagram}
    \end{minipage}
  }
  \node[black, text=black, align=center] at (4.5,0.5) {\textbf{Organocatalytic Strategy}}
  \node[black, text=black, align=center] at (4.5,0.3) {1. Regiospecificity}
  \node[black, text=black, align=center] at (4.5,0.1) {2. Broad substrate scope}
\end{tikzpicture}
\end{center}

\textbf{Scheme 6.2. Methods for the synthesis of highly substituted 1,2,3-triazoles}

While some direct protocols to 1,2,3-triazoles, including tradition thermal\textsuperscript{60,68,108} or metal-free\textsuperscript{107c-d, f} \[3+2\] cycloadditions of linear alkynes or highly strained alkynes with azides, have been described, these reactions are often slow because of high activation energy (ca. 24-16 kcal.mol)\textsuperscript{109} and also produce a mixture of regioisomers (Scheme 6.2). The Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) has been developed as a powerful tool to
access 1,2,3-triazole molecules, but is usually restricted to terminal alkynes and only facilitates 1,4-disubstituted 1,2,3-triazole formation (Scheme 6.2). In addition, in spite of its vast successes in industry, this strategy is not ideal for biological applications. Recent studies indicate that Cu(I) can cause oxidative DNA degradation. Although the careful selection of Cu(I)-stabilizing ligands can avoid DNA degradation and even facilitate this cycloaddition process in living organism. However, Cu itself caused cytotoxicity may remain an issue when pharmaceutical therapeutics are desired. Therefore, in search of ideal strategy to replace known methods, we believe that a metal-free, enamine catalyzed, and broad substrate tolerant method would be the first preferred solution.

Scheme 6.3 Representative examples of bioactive 1,2,3-triazoles

### 6.2 Results and Discussion

#### 6.2.1 Reaction Optimization for Highly Substituted 1,2,3-triazoles
Optimization studies of organocatalytic enamine-azide [3+2] cycloaddition were initiated by an investigation of phenyl azide 6-1a and cyclohexanone 6-2a in the presence of a catalytic amount of secondary α–amino acid, L–proline (6-I; Table 6.1). The initial experimental result shows that only 40% yield was obtained in 24 h. To improve the catalytic activity, we then examined six-member ring based secondary amine catalysts 6-III and 6-IV. It is noted that the ring size is not crucial for reaction yield and rate (Table 6.1, 33% and 44% yield, respectively). Moreover, a diverse set of acyclic secondary amines were tested, but exhibited a poorer catalytic performance (24%, <5%, and <5%; respectively). Besides secondary amine, primary amine 6-IX and tertiary amine 6-VIII were also evaluated in this model reaction system. As shown in Table 6.1, tertiary amine 6-VIII had no catalytic activity in the process (<5% yield).

Table 6.1 Evaluation of organocatalysts [a]

<table>
<thead>
<tr>
<th>Cat.</th>
<th>Ph–N3 + 6-2a</th>
<th>Reaction conditions: 6-1a (0.25 mmol), 6-2a (0.5 mmol), DMSO (0.5 mL).</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-I</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>40% yield</td>
</tr>
<tr>
<td>6-II</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>84% yield</td>
</tr>
<tr>
<td>6-III</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>33% yield</td>
</tr>
<tr>
<td>6-IV</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>44% yield</td>
</tr>
<tr>
<td>6-V</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>24% yield</td>
</tr>
<tr>
<td>6-VI</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>&lt;5% yield</td>
</tr>
<tr>
<td>6-VII</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>&lt;5% yield</td>
</tr>
<tr>
<td>6-VIII</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>&lt;5% yield</td>
</tr>
<tr>
<td>6-IX</td>
<td><img src="https://via.placeholder.com/150" alt="Image" /></td>
<td>26% yield</td>
</tr>
</tbody>
</table>
Primary amine 6-IX just afforded a 26% yield in 24 h too. Finally a substituent-free, less bulky secondary amine, pyrrolidine 6-II indicated a higher activity (84%, 24 h). After identifying the suitable catalyst 6-II, we attempted to optimize the reaction by varying different other parameters systemically. Initially, various solvents including NMP, DMF, DMA, MeOH, 1, 4-Dioxane, DCE, Toluene, and CH₃CN were screened, and we eventually discovered that the high yield in polar solvent could be a result of strengthened polar interaction among substrates, and catalyst. Screening showed that no obvious improvement in reaction rate and yield could be achieved by other solvents. We have also investigated the temperature and catalyst loading. As expected, a lower temperature (50 °C) or lower catalyst loading (5 mol%) incurred a significant decrease in yield. Consequently, pyrrolidine 6-II and DMSO were found to be effective in offering appreciable results in organocatalytic enamine-azide [3+2] cycloaddition process.

Table 6.2 Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Yield (%)</th>
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</thead>
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<tr>
<td>1</td>
<td>I</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>II</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>II</td>
<td>DMSO</td>
<td>80</td>
<td>48</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>II</td>
<td>DMSO</td>
<td>60</td>
<td>48</td>
<td>54</td>
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<tr>
<td>5</td>
<td>II</td>
<td>DMSO</td>
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<td>72</td>
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<td>Toluene</td>
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<td>72</td>
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<td>16</td>
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<td>1,4-Dioxane</td>
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<td>80</td>
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<tr>
<td>14</td>
<td>II</td>
<td>DCE</td>
<td>80</td>
<td>72</td>
<td>54</td>
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<tr>
<td>15</td>
<td>II</td>
<td>CHCl₃</td>
<td>80</td>
<td>72</td>
<td>60</td>
</tr>
<tr>
<td>16</td>
<td>III</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>17</td>
<td>IV</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>44</td>
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<tr>
<td>18</td>
<td>V</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>24</td>
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<tr>
<td>19</td>
<td>VI</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>&lt;5</td>
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<tr>
<td>20</td>
<td>VII</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>&lt;5</td>
</tr>
<tr>
<td>21</td>
<td>VIII</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>&lt;5</td>
</tr>
<tr>
<td>22</td>
<td>IX</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>26</td>
</tr>
</tbody>
</table>

Unless otherwise noted, the reaction conditions were as follows: 0.5 M in solvent, and the ratio of 6-1a/6-2a is 1:2, 20 mol% catalyst. 10 mol% catalyst, 48 h, 60 ºC. 10 mol% catalyst, 120 h, 60 ºC. Isolated yield of product 6-3a. N-Methyl-2-pyrrolidone (NMP) as solvent. Dimethylacetamide (DMA) as solvent. 1,2-Dichloroethane (DCE) as solvent.

6.2.2 Substrate Scope

Once the optimized conditions were identified (Table 6.1), substrates were examined. The scope of amine-catalyzed [3+2] Huisgen cycloaddition of azides is indicated by the examples listed in Table 6.3. It was found that the pyrrolidine 6-II–catalyzed cycloaddition was applicable to a variety of azides 6-1a to 6-11 to afford 1,2,3-triazoles in moderate to high yields (Table 6.3, 45–88%). The reactions were performed smoothly and rarely affected by the electronic nature of the substituents on the aromatic rings. Electron-withdrawing (Table 6.3, entries 5, 6, and 8), electron-donating (Table 6.3, entries 2–4, and 10), or electron-neutral (Table 6.3, entry 1) groups on the phenyl ring of azides did not affect the reaction. In some cases, the steric effect appeared to have negative effects on the reaction yield. For example, an ester group at o–position on the phenyl ring gave a lower yield (Table 6.3, entry 9, 45%). Notably, naphthalene ring was also suitable for this system (Table 6.3, entry 12, 60%). If a lower catalyst loading (10 mol%) was employed, the reaction still afforded a good yield in a
reasonable time (Table 6.3, 78%, 30 h). However, the reaction dramatically slowed down (<5% yield, 24 h) when an alkyl (ethyl group) azide was applied to replace the phenyl azide. Slow conversion of starting material was detected by $^1$H NMR analysis. We envision that the delocalization of the aromatic system (phenyl ring) may stabilize the 1, 3-dipolar azide and its intermediate to lead a high reaction rate and yield.

Table 6.3 Substrate scope of azides $^{[a]}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product$^{[b]}$</th>
<th>Entry</th>
<th>Product$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6-3aa; 84% 24 h</td>
<td>7</td>
<td>6-3ga; 75% 12 h</td>
</tr>
<tr>
<td>2</td>
<td>6-3ba; 88%; 16 h (78%; 30 h)$^{[c]}$</td>
<td>8</td>
<td>6-3ha; 62% 24 h</td>
</tr>
<tr>
<td>3</td>
<td>6-3ca; 85% 14 h</td>
<td>9</td>
<td>6-3la; 45% 18 h</td>
</tr>
<tr>
<td>4</td>
<td>6-3da; 72% 12 h</td>
<td>10</td>
<td>6-3ja; 80% 20 h</td>
</tr>
<tr>
<td>5</td>
<td>6-3ea; 72% 16 h</td>
<td>11</td>
<td>6-3ka; 67% 10 h</td>
</tr>
</tbody>
</table>
Reaction conditions: 6-1a to 6-1i (0.25 mmol, 1.0 equiv.), 6-2a (0.5 mmol, 2.0 equiv.), DMSO (0.5 mL), 20 mol% catalyst 6-II at 80 °C. \(^b\) Yield of isolated product. \([c]\) 10 mol% of catalyst.

Having investigated the reactivity of azides, we then evaluated carbonyls (Table 6.4). To our delight, this method can tolerate a broad range of unmodified, commercially available carbonyl compounds. Cyclic six-member ring based ketones gave good to high yields (Table 6.4, entries 1–6). This six-member ring can bear alkyl, ester, dialkyl, or ketal groups on the \(p\)-or \(m\)-positions of ketones (Table 6.4, entries 1–5). Furthermore, this six-member ring can also tolerate a heteroatom (Table 6.4, entry 6). Interestingly, seven or eight-member ring sized cyclic ketones efficiently provided high yields under standard conditions which demonstrated the ring size of ketones had limited effect on this cycloaddition (Table 6.4, entries 7–8, 94% and 85%, respectively). To prove the high efficiency exhibited in seven or eight member ring based ketones, we therefore reduced the catalyst loading from 20 mol% to 10 mol%. The reaction still afforded a 89% yield in 30 h (Table 6.4, entry 7). It is noteworthy that acyclic ketones also gave appreciable reaction yields (Table 6.4, entries 9–10). For example in Table 3, dissymmetric acyclic ketone 2-butane 6-2j showed a 75% yield in 24 h, and did not observe any other regioisomers in this reaction process. Symmetric acyclic ketone 3-pentanone 6-2k supported a 65% yield in 20 h. Additionally, a phenyl ring fused cyclohexanone 6-2l attended reaction also happened at room temperature (Table 6.4, entry 11).
and afforded a slightly lower yield due to the undesirable instability and decomposition of product 6-3al under this reaction condition (Table 6.4, entry 11, 57%, 10 h). Except for the above types of ketones 6-2a to 6-2l, we also examined some β-functionalized ketones (Table 6.4, entries 12–16). Gratifyingly, β-ketonitrile 6-2m, 1,3-diketone 6-2n, and β-ester ketone 6-2o exhibited high efficiency and high reaction yields (Table 6.4, entries 12–14, 90–95%). Appreciatively, an alkyl azide 6-1n can be involved in this process to react with active β-ketonitrile and afforded an appreciable synthetic yield (Table 6.4, entry 16, 80%, 24 h). In contrast to our previous reported results for catalyzed by the acyclic secondary amine catalyst (diethyl amine 6-V),\textsuperscript{85} we found that the cyclic second amine (pyrrolidine 6-II) can also efficiently catalyze these transformations in the presence of current optimized reaction conditions. The regioselectivity of product 6-3aa and 6-3ac was determined by using single crystal X-ray diffraction analysis.

To further extend the scope of azides, we then examined a tosyl azide 6-1n. As showed in Scheme 6.4, the reaction is completely different. In this case, the pyrrolidine 6-II worked as a starting material to easily access the installation of a biological interest compound, N-tosyl amidine 6-3na in 85% yield. We deduce that when the triazoline ring carries an electron-withdrawing group at the N1-position, it is very labile. Thus, the first formed triazoline intermediate decomposes immediately to produce amidine 6-3na through rearrangement and loss of the N₂. Surprisingly, L-proline showed no activity in this reaction. However, β-tetralone 6-2l reacted with tosyl azide 6-1n in the presence of L-proline and efficiently produced the desired triazole compound 6-3nl (Eq. (b), 85%, 5 h, r.t.). In this case, no amidine product was formed. It may be due to the steric hindered carboxylic group. It will inhibit the potential rearrangement and prohibit the formation of the crowded amidine. Subsequent attempts to introduce two linear and less
bulky aldehydes (propionaldehyde 6-2r and 2-phenylacetaldehyde 6-2s) to the reaction were unsuccessfully. The failure to achieve the desired triazoles might be attributed to the competitive self-aldol reaction.

Table 6.4 Substrate scope of carbonyls \[\text{[a]}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>6-2b to 6-2i</th>
<th>Product([b])</th>
<th>Entry</th>
<th>6-2j to 6-2p</th>
<th>Product([b])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6-2b</td>
<td>6-3ab: 73% 16 h</td>
<td>7</td>
<td>6-2h</td>
<td>6-3ah: 94%; 20 h (89%; 30 h)[d]\</td>
</tr>
<tr>
<td>2</td>
<td>6-2c</td>
<td>6-3ac: 63% 24 h</td>
<td>8</td>
<td>6-2i</td>
<td>6-3ai: 85% 14 h</td>
</tr>
<tr>
<td>3</td>
<td>6-2d</td>
<td>6-3ad: 77% 12 h</td>
<td>9</td>
<td>6-2j</td>
<td>6-3aj: 75% 24 h</td>
</tr>
<tr>
<td>4</td>
<td>6-2e</td>
<td>6-3ae: 71% 20 h</td>
<td>10</td>
<td>6-2k</td>
<td>6-3ak: 65% 20 h</td>
</tr>
<tr>
<td>5</td>
<td>6-2f</td>
<td>6-3af: 75% 24 h</td>
<td>11</td>
<td>6-2l</td>
<td>6-3al: 57% 10 h</td>
</tr>
<tr>
<td>6</td>
<td>6-2g</td>
<td>6-3ag: 82% 20 h</td>
<td>12</td>
<td>6-2m</td>
<td>6-3am: 95% 12 h</td>
</tr>
</tbody>
</table>
Reaction conditions: 6-1a or 6-1m (0.25 mmol, 1.0 equiv.), 6-2a (0.5 mmol, 2.0 equiv.), DMSO (0.5 mL), 20 mol% 6-II at 80 °C. \(^b\) Yield of isolated product. \(^c\) 10 mol% of 6-II. \(^d\) Room temperature. \(^e\) 70 °C.

Scheme 6.4 The scope of tosyl azide
Thus, the first formated triazoline intermediate decomposes immediately to produce amidine 6-3na through rearrangement and loss of the N₂. Surprisingly, L-proline showed no activity in this reaction. However, β-tetralone 6-2l reacted with tosyl azide 6-1n in the presence of L-proline and efficiently produced the desired triazole compound 6-3nl (Scheme 6.4, 85%, 5 h, r.t.). In this case, no amidine product was formed. It may be due to the steric hindered carboxylic group. It will inhibit the potential rearrangement and prohibit the formation of the crowded amidine. Subsequent attempts to introduce two linear and less bulkyl aldehydes (propionaldehyde 6-2r and 2-phenylacetaldehyde 6-2s) to the reaction were unsuccessfully. The failure to achieve the desired triazoles might be attributed to the competitive self-aldol reaction.

6.2.3 Application and Plausible Reaction Mechanism

To demonstrate the synthetic utility of this methodology, we applied it to the synthesis of CB1 cannabinoid receptor antagonist (Scheme 6.5). The catalyst 6-II–catalyzed Huisgen [3+2] cycloaddition between azide 6-1n and β-keto ester 6-2q under optimized reaction conditions enabled the installation of the intermediate 6-3nq in 98% yield in 0.5 h. The 6-3nq is a key intermediate and can be converted into target CB1 cannabinoid receptor antagonist followed by known method.
**Scheme 6.5** Synthesis of CB1 cannabinoid receptor antagonist \(^{113}\)

\[
\begin{align*}
\text{N}_3 & \quad \text{Cl} & \quad \text{Cl} & \quad \text{6-1n} \\
\text{Cl} & \quad \text{Cl} & \quad \text{6-2q} & \quad \text{DMSO, 80 °C} \\
& \quad \text{N}_3 & \quad \text{N}_3 & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{CB1 cannabinoid receptor antagonist} \\
\end{align*}
\]

As shown in Scheme 6.6, we proposed a plausible catalytic cycle to explain the reaction pathway. While the reaction mechanism is still unclear at this stage, it is believed that the sequence is triggered by the generation of enamine 6-4 via the condensation of carbonyl 6-2a and catalyst pyrrolidine 6-II. Enamine 6-4 acts as the electron-rich olefinic partner, and reacts with phenyl azide 6-1a via a Huisgen 1,3-dipolar cycloaddition process to access the intermediate, triazoline 6-5.

**Scheme 6.6** Plausible mechanism of [3+2] Huisgen Cycloaddition
More importantly, this process demonstrates a complete and unique regiospecificity which led us readily to introduce a diverse set of functional substituents to desired 1, 4, and 5 positions. In fact, except for enamine-triggered cycloaddition process, enolate-triggered cycloaddition process catalyzed by organic base can also potentially afford desired intermediate 6-5. Apparently, the results of the catalyst screening revealed that the process catalyzed by an organic base, such as tertiary amine 6-VIII (Table 1, <5% yield), will not be the main contribution for 1,2,3-triazole synthesis. Thereafter, a plausible 1,3-hydride shift might assist the formation of a zwitterion 6-7. Finally, an elimination step caused the generation of final product, regioselective 1,2,3,-triazole 6-3aa. Meanwhile, the catalyst 6-II was released and applied to next catalytic cycle. According to our experimental evidence, we predict that the rate-determining step is probably the 1,3-dipolar cycloaddition process. The observation of enamine formation process via LCMS suggests that the catalytic cycle accumulates at this stage. In addition, no further evidence indicates the presence of the triazoline intermediate 6-5. Finally, we are aware that the existence of active catalytic enamine specie will provide a more reliable picture for reaction mechanism.

6.3 Conclusions

Driven by the lack of efficient synthesis of highly substituted 1,2,3-triazoles, herein, we have developed an enamine catalyzed strategy by using small organic molecule as organocatalyst to fully promote the Huisgen [3+2] cycloaddition on a broad spectrum of carbonyls and azides to access the efficient assembly of a vast pool of highly substituted 1,2,3-triazoles. Especially the employment of the commonly used and commercially available carbonyls have resulted in an introduction of a diverse set of functional groups, such as alkyls, aryls, nitriles, esters, ketones, etc, to the 1, 4, or 5 position on 1,2,3-triazole scaffold. This might be manipulated for accessing more useful sophisticated heterocyclic compounds. More
significantly, the reaction process exhibits a complete regioselectivity with none of regioisomer formation. The versatility of amine catalyzed Huisgen cycloaddition seems endless, yet we are still in the early development stages of this concept-driven research. In addition, we believe that the presented methodology opens access to more interesting compounds which are available for potential biological evaluation. Further extension of this synthetic strategy to other types of reactions is under way in our laboratory and will be presented in due course.

6.4 Experimental Section

6.4.1 Material and General Methods

Chemicals and solvents were purchased from commercial suppliers and used as received. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker ACF300 (300 MHz) or a AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0) or tetramethysilane (TMS δ 0.00) was used as a reference. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode and API 3000™ in APCI (Heated Nebulizer) mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with iodine. Flash chromatography separations were performed on Merck 60 (0.040-0.063 mm) mesh silica gel.
Compounds 6-1a to 6-1l were prepared according to literature, \(^{114}\) respectively. Compounds 6-2b to 6-2m were commercially available.

### 6.4.2 Representative Procedure for Enamine-azide [3+2] Cycloaddition

![Chemical Reaction](attachment:image.png)

To a solution of phenyl azide 6-1a (0.25 mmol, 1 equiv.), cyclohexanone 6-2a (0.5 mmol, 2.0 equiv.) in 0.5 ml of DMSO, pyrrolidine (4.1 μL, 0.05 mmol, 0.2 equiv.) as catalyst was added. The reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 10:1 then 4:1 to afford 42 mg (84% yield) of the desired product 6-3aa as a pale-yellow oil.

To a solution of 3,4-dihydronaphthalen-2(1H)-one 6-2a (0.5 mmol, 2.0 equiv.) in 0.5 ml DMSO, pyrrolidine (4.1 μL, 0.05 mmol, 0.2 equiv.) or L-proline (5.7 mg, 0.05 mmol, 0.2 equiv.) as catalyst was added. The reaction was continued for another 0.5 h, and then azidobenzene 6-1a (0.25 mmol, 1.0 equiv.) (pyrrolidine as catalyst) or 4-methylbenzenesulfonyl azide 6-1n (0.25 mmol, 1.0 equiv.) (L-proline as catalyst) was added to the reaction system. The reaction mixture was stirred at room temperature for 1-10 h. The
crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 10:1 then 4:1 to afford aim product.

6.4.3 Analytical Data for Enamine-azide [3+2] Cycloaddition

1-Phenyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3aa)

The title compound was prepared according to the general procedure described above in 84% yield; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.57 – 7.50 (m, 4H), 7.47 – 7.43 (m, 1H), 2.85 (t, $J$ = 4.9 Hz, 2H), 2.75 (t, $J$ = 5.0 Hz, 2H), 1.93 – 1.84 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 144.43, 137.37, 132.47, 129.89, 129.02, 123.56, 23.20, 22.92, 22.39, 22.27; HRMS (ESI) calcd for C$_{12}$H$_{14}$N$_3$ [M+H]$^+$ 200.1182, found 200.1186.

1-(4-Methoxyphenyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ba)

The title compound was prepared according to the general procedure described above in 88% yield; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.47 – 7.37 (m, 2H), 7.04 – 6.91 (m, 2H), 3.84 (s, 3H), 2.80 (s, 2H), 2.65 (s, 2H), 1.84 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.10, 144.12, 132.52, 130.39, 125.11, 114.96, 56.01, 23.14, 22.93, 22.38, 21.98; HRMS (ESI) calcd for C$_{13}$H$_{16}$N$_3$O [M+H]$^+$ 230.1288, found 230.1294.
1-(4-Isopropylphenyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ca)

The title compound was prepared according to the general procedure described above in 85% yield; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.46 (dd, $J = 8.4$ Hz, 1.6 Hz, 2H), 7.38 – 7.35 (m, 2H), 2.99 (m, 1H), 2.84 (d, $J = 4.9$ Hz, 2H), 2.74 (d, $J = 5.2$ Hz, 2H), 1.88 (m, 4H), 1.30 (d, $J = 7.2$ Hz, 6H).; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 149.97, 144.24, 135.08, 132.44, 127.84, 123.53, 34.28, 24.32, 23.18, 22.93, 22.40, 22.19; HRMS (ESI) calcd for C$_{15}$H$_{20}$N$_3$ [M+H]$^+$ 242.1652, found 242.1659.

1-(4-Heptylphenyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3da)

The title compound was prepared according to the general procedure described above in 72% yield; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.45 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 2.84 (t, $J = 5.2$ Hz, 2H), 2.73 (t, $J = 5.2$ Hz, 2H), 2.70 – 2.65 (m, 2H), 1.91 – 1.83 (m, 4H), 1.72 – 1.61 (m, 2H), 1.40 – 1.25 (m, 8H), 0.90 (t, $J = 6.9$ Hz, 3H).; $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 144.30, 144.18, 135.11, 132.48, 129.83, 123.51, 36.03, 32.27, 31.80, 29.67, 29.62, 23.27, 23.13, 23.02, 22.47, 22.27, 14.56; HRMS (ESI) calcd for C$_{19}$H$_{28}$N$_3$ [M+H]$^+$ 298.2278, found 298.2290.

1-(4-Chlorophenyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ea)
The title compound was prepared according to the general procedure described above in 72% yield; NMR (500 MHz, CDCl₃): δ 7.56 – 7.41 (m, 4H), 2.83-2.78 (m, 2H), 2.76-2.65 (m, 1H), 1.91 – 1.82 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): δ 144.70, 135.86, 134.88, 132.44, 130.12, 124.64, 23.15, 22.8222.35, 22.28; HRMS (ESI) calcd for C₁₂H₁₃ClN₃ [M+H]^+ 234.0793, found 234.0795.

1-(4-((Trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3fa)

The title compound was prepared according to the general procedure described above in 68% yield; ¹H NMR (500 MHz, CDCl₃): δ 7.82 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H), 2.86 (d, J = 5.9 Hz, 2H), 2.82 (d, J = 6.0 Hz, 2H), 1.96 – 1.88 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): δ 145.10, 140.14, 132.54, 131.08, 127.28, 127.25, 127.22, 127.19, 125.17, 123.35, 123.01, 23.19, 22.78, 22.56, 22.36; HRMS (ESI) calcd for C₁₃H₁₃F₃N₃ [M+H]^+ 268.1056, found 268.1064.

1-(3-Isopropoxyphenyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ga)
The title compound was prepared according to the general procedure described above in 75% yield; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.40 (t, $J = 8.1$ Hz, 1H), 7.15 – 7.05 (m, 2H), 6.97 (dd, $J = 8.3$, 1.9 Hz, 1H), 4.62 (hept, $J = 6.1$ Hz, 1H), 2.85 (t, $J = 5.1$ Hz, 2H), 2.76 (t, $J = 5.0$ Hz, 2H), 1.95 – 1.84 (m, 4H), 1.37 (d, $J = 5.6$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 159.24, 144.48, 138.45, 132.52, 130.64, 116.68, 115.36, 111.19, 70.93, 23.29, 23.00, 22.46; HRMS (ESI) calcd for C$_{15}$H$_{20}$N$_3$O [M+H]$^+$ 258.1601, found 258.1609.

1-(3-Chlorophenyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ha)

![6-3ha](image)

The title compound was prepared according to the general procedure described above in 62% yield; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.62 (d, $J = 1.7$ Hz, 1H), 7.52 – 7.43 (m, 3H), 2.86 (s, 2H), 2.78 (s, 2H), 1.91 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 144.80, 138.34, 135.70, 132.52, 131.00, 129.15, 123.69, 121.49, 23.84, 22.37; HRMS calcd for C$_{12}$H$_{12}$ClN$_3$ [M+H]$^+$ 234.0793, found 234.0802.

Ethyl 2-(4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazol-1-yl)benzoate (6-3ia)

![6-3ia](image)

The title compound was prepared according to the general procedure described above in 45% yield; $^1$H NMR (500 MHz, CDCl$_3$): δ 8.08 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.69 (td, $J = 7.7$, 1.6 Hz, 1H), 7.62 (td, $J = 7.6$, 1.3 Hz, 1H), 7.40 (dd, $J = 7.8$, 1.1 Hz, 1H), 4.18 – 4.10 (m, 2H), 2.90 – 2.83 (m, 2H), 2.53 – 2.46 (m, 2H), 1.90 – 1.84 (m, 4H), 1.11 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 165.62, 143.14, 136.01, 134.62, 133.13, 131.95, 130.36, 129.32, 128.29, 62.03, 23.15, 22.95, 22.30, 20.81, 14.29; HRMS (ESI) calcd for C$_{15}$H$_{18}$N$_3$O$_2$ [M+H]$^+$ 272.1394, found 272.1403.
1-(3,5-Dimethylphenyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ja)

The title compound was prepared according to the general procedure described above in 80% yield; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.16 (s, 2H), 7.09 (s, 1H), 2.84 (t, $J = 5.1$ Hz, 2H), 2.74 (t, $J = 5.0$ Hz, 2H), 2.40 (s, 6H), 1.92 – 1.84 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 144.24, 139.76, 137.18, 132.41, 130.66, 121.35, 23.21, 22.97, 22.42, 22.28, 21.72; HRMS (ESI) calcd for C$_{14}$H$_{18}$N$_3$ [M+H]$^+$ 228.1495, found 228.1500.

1-(4-Cloro-3-methylphenyl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ka)

The title compound was prepared according to the general procedure described above in 67% yield; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.51 – 7.46 (m, 2H), 7.31 (dd, $J = 8.5$, 2.5 Hz, 1H), 2.84 (d, $J = 5.4$ Hz, 2H), 2.77 – 2.71 (m, 2H), 2.46 (s, 3H), 1.91 – 1.86 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 144.59, 138.21, 135.74, 135.04, 132.45, 130.36, 125.90, 121.90, 23.18, 22.88, 22.38, 22.28, 20.70; HRMS (ESI) calcd for C$_{13}$H$_{15}$ClN$_3$ [M+H]$^+$ 248.0949, found 248.0956.

1-(Naphthalen-1-yl)-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3la)
The title compound was prepared according to the general procedure described above in 60% yield; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 8.04 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 7.5 Hz, 2H), 7.56 – 7.50 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 2.94 (t, J = 6.1 Hz, 2H), 2.48 – 2.40 (m, 2H), 1.97 – 1.90 (m, 2H), 1.90 – 1.82 (m, 2H).; \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 143.58, 135.03, 134.64, 133.31, 130.74, 129.85, 128.69, 128.17, 127.41, 125.51, 124.90, 123.08, 23.19, 22.95, 22.43, 20.95; HRMS (ESI) calcd for C\textsubscript{16}H\textsubscript{16}N\textsubscript{3}[M+H]\textsuperscript{+} 250.1339, found 250.1350.

5-Ethyl-1-phenyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ab)

The title compound was prepared according to the general procedure described above in 73% yield; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 7.62 – 7.49 (m, 4H), 7.49 – 7.43 (m, 1H), 3.04 (dd, J = 15.8, 5.0 Hz, 1H), 2.84 – 2.70 (m, 2H), 2.40 (dd, J = 15.0, 10.0 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.77 (d, J = 5.6 Hz, 1H), 1.56 – 1.46 (m, 3H), 1.03 (t, J = 7.4 Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 144.38, 136.98, 132.07, 129.47, 128.57, 123.01, 36.03, 28.85, 28.36, 27.91, 21.23, 11.65; HRMS calcd for C\textsubscript{14}H\textsubscript{18}N\textsubscript{3}[M+H]\textsuperscript{+} 228.1495, found 228.1493.

Ethyl 1-phenyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole-5-carboxylate (6-3ac)

The title compound was prepared according to the general procedure described above in 63% yield; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ 7.57 – 7.50 (m, 4H), 7.48 – 7.43 (m, 1H), 4.23 – 4.17 (m, 2H), 3.19 (dd, J = 16.0, 5.7 Hz, 1H), 3.09 – 3.00 (m, 1H), 2.94 – 2.78 (m, 3H), 2.39 – 2.24 (m, 1H), 1.99 (ddt, J = 19.5, 15.9, 5.8 Hz, 1H), 1.34 – 1.26 (m, 3H); \textsuperscript{13}C NMR (125
5,5-Dimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ad)

The title compound was prepared according to the general procedure described above in 77% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.60 (m, 2H), 7.54 (m, 2H), 7.49 – 7.44 (m, 1H), 2.77 (t, J = 6.4 Hz, 2H), 2.65 (s, 2H), 1.66 (t, J = 6.4 Hz, 2H), 1.09 (s, 6H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 144.66, 137.49, 131.34, 129.93, 129.03, 123.44, 36.20, 36.10, 31.00, 28.22, 19.51;\) HRMS (ESI) calcd for C\(_{15}\)H\(_{18}\)N\(_3\) [M+H]\(^+\) 272.1394, found 272.1406.

6,6-Dimethyl-1-phenyl-4,5,6,7-tetrahydro-1H-benzo[d][1,2,3]triazole (6-3ae)

The title compound was prepared according to the general procedure described above in 71% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.56 – 7.48 (m, 4H), 7.44 (m, 1H), 2.84 (t, J = 6.5 Hz, 2H), 2.51 (s, 2H), 1.66 (t, J = 6.5 Hz, 2H), 1.02 (s, 6H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 142.91, 136.90, 132.03, 129.48, 128.62, 123.22, 35.62, 35.41, 31.21, 27.80, 19.16;\) HRMS (ESI) calcd for C\(_{14}\)H\(_{18}\)N\(_3\) [M+H]\(^+\) 228.1459, found 228.1492.

1-Phenyl-1,4,6,7-tetrahydrospiro[benzo[d][1,2,3]triazole-5,2'-[1,3]dioxolane] (6-3af)
The title compound was prepared according to the general procedure described above in 75% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.59 – 7.50 (m, 4H), 7.49 – 7.44 (m, 1H), 4.14 – 4.00 (m, 4H), 3.09 (s, 2H), 2.96 – 2.86 (m, 2H), 2.09 – 1.99 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 143.22, 137.17, 131.39, 129.95, 129.21, 123.53, 108.74, 65.25, 33.60, 32.17, 19.59; HRMS (ESI) calcd for C\(_{14}\)H\(_{15}\)N\(_3\)O\(_2\) [M+H]\(^+\) 258.1237, found 258.1242.

1-Phenyl-1,4,6,7-tetrahydrothiopyrano[3,4-\(d\)][1,2,3]triazole (6-3ag)

\[
\begin{array}{c}
N=S \\
6-3ag
\end{array}
\]

The title compound was prepared according to the general procedure described above in 82% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.59 – 7.53 (m, 2H), 7.51 (m, 3H), 3.96 (s, 2H), 3.06 – 2.99 (m, 2H), 2.94 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 140.39, 136.71, 132.34, 130.05, 129.65, 124.28, 26.06, 24.97, 23.90; HRMS (ESI) calcd for C\(_{11}\)H\(_{12}\)N\(_3\)S [M+H]\(^+\) 218.0746, found 218.0746.

1-Phenyl-1,4,5,6,7,8-hexahydrocyclohepta[\(d\)][1,2,3]triazole (6-3ah)

\[
\begin{array}{c}
N=N \\
6-3ah
\end{array}
\]

The title compound was prepared according to the general procedure described above in 94% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ = 7.56 – 7.45 (m, 3H), 7.43 – 7.39 (m, 2H), 2.99 – 2.94 (m, 2H), 2.74 (m, 2H), 1.87 (m, 2H), 1.80 – 1.73 (m, 2H), 1.73 – 1.64 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ = 147.71, 136.92, 136.02, 129.72, 129.55, 125.71, 31.28, 27.59, 27.45, 27.42, 25.12; HRMS (ESI) calcd for C\(_{13}\)H\(_{16}\)N\(_3\) [M+H]\(^+\) 214.1339, found 214.1342.

1-Phenyl-4,5,6,7,8,9-hexahydro-1\(H\)-cycloocta[\(d\)][1,2,3]triazole (6-3ai)
The title compound was prepared according to the general procedure described above in 85% yield; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.56 – 7.47 (m, 3H), 7.45 – 7.41 (m, 2H), 3.02 – 2.94 (m, 2H), 2.75 (m, 2H), 1.89 – 1.71 (m, 4H), 1.54 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 145.45, 137.06, 134.42, 129.80, 129.70, 125.69, 28.57, 27.87, 25.97, 25.67, 24.85, 22.43; HRMS (ESI) calcd for C$_{14}$H$_{18}$N$_3$ [M+H]$^+$ 228.1495, found 228.1494.

4,5-dimethyl-1-phenyl-1H-1,2,3-triazole (6-3ai)

The title compound was prepared according to the general procedure described above in 75% yield; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.57 – 7.49 (m, 3H), 7.49 – 7.44 (m, 2H), 2.36 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 141.49, 137.27, 130.12, 129.86, 129.59, 125.27, 10.75, 9.22; HRMS (ESI) calcd for C$_{10}$H$_{11}$N$_3$ [M+H]$^+$ 174.1026, found 174.1024.

4-ethyl-5-methyl-1-phenyl-1H-1,2,3-triazole (6-3ak)

The title compound was prepared according to the general procedure described above in 65% yield; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.58 – 7.49 (m, 3H), 7.46 – 7.42 (m, 2H), 2.69 (q, $J$ = 7.6 Hz, 2H), 2.39 (s, 3H), 1.09 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 140.94, 137.31, 135.78, 129.89, 129.82, 125.76, 16.71, 13.60, 10.89; HRMS (ESI) calcd for C$_{11}$H$_{14}$N$_3$ [M+H]$^+$ 188.1182, found 188.1185.
3-Phenyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazole (6-3al)

The title compound was prepared according to the general procedure described above in 65% yield; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.05 (d, $J = 7.4$ Hz, 1H), 7.63 – 7.57 (m, 4H), 7.53 (m, 1H), 7.38 (dd, $J = 7.4$, 1.9 Hz, 1H), 7.31 – 7.24 (m, 2H), 3.16 – 3.09 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 144.58, 137.01, 134.03, 132.81, 130.11, 129.45, 129.05, 128.59, 128.09, 127.88, 123.74, 122.81, 29.32, 20.71; HRMS (ESI) calcd for C$_{16}$H$_{14}$N$_3$ [M+H]$^+$ 248.1182, found 248.1187.

1,5-Diphenyl-1H-1,2,3-triazole-4-carbonitrile (6-3am)

The title compound was prepared according to the general procedure described above in 95% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.52 – 7.41 (m, 6H), 7.36 – 7.32 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 145.5, 135.3, 131.0, 130.2, 129.7, 129.3, 128.9, 125.1, 123.3, 120.5, 112.0. HRMS (ESI) calcd for C$_{15}$H$_{10}$N$_4$ 246.0905, found 246.0903.

(1,5-Diphenyl-1H-1,2,3-triazol-4-yl)(phenyl)methanone (6-3an)
The title compound was prepared according to the general procedure described above in 92% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.29 (d, $J = 7.2$ Hz, 2H), 7.59 (t, $J = 7.2$ Hz, 1H), 7.49 (t, $J = 7.8$ Hz, 2H), 7.41 – 7.31 (m, 10H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 187.3, 144.2, 141.8, 137.8, 136.5, 133.7, 131.3, 130.8, 130.5, 130.1, 130.0, 129.1, 128.9, 126.7, 125.9. HRMS (ESI) calcd for C$_{21}$H$_{15}$N$_3$O 325.1215, found 325.1212.

**Ethyl 1,5-diphenyl-1H-1,2,3-triazole-4-carboxylate (6-3ao)**

![Image of 6-3ao](image)

The title compound was prepared according to the general procedure described above in 90% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.45 – 7.36 (m, 6H), 7.33 – 7.28 (m, 4H), 4.39 (q, $J = 7.2$ Hz, 2H), 1.35 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 161.6, 141.5, 137.6, 136.5, 130.9, 130.5, 130.1, 130.0, 129.0, 126.4, 125.9, 61.8, 14.8. HRMS (ESI) calcd for C$_{17}$H$_{15}$N$_3$O$_2$ 293.1164, found 293.1162.

**Ethyl 5-ethyl-1-phenyl-1H-1,2,3-triazole-4-carboxylate (6-3ap)**

![Image of 6-3ap](image)

The title compound was prepared according to the general procedure described above in 92% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.56 – 7.39 (m, 5H), 4.44 (q, $J = 7.1$ Hz, 2H), 2.97 (q, $J = 7.5$ Hz, 2H), 1.42 (t, $J = 7.1$ Hz, 3H), 1.14 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$):
δ 161.5, 144.4, 136.0, 135.5, 130.2, 129.6, 125.6, 60.9, 16.9, 14.3, 13.1. HRMS (ESI) calcd for C_{13}H_{15}N_{3}O_{2} 245.1164, found 245.1162.

1-Benzyl-5-phenyl-1H-1,2,3-triazole-4-carbonitrile (6-3mm)

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{CN} \\
\text{6-3mm}
\end{array}
\]

The title compound was prepared according to the general procedure described above in 80% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): δ 7.60 – 7.48 (m, 3H), 7.36 – 7.29 (m, 5H), 5.55 (s, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), TMS): δ 144.5, 134.6, 131.9, 130.2, 129.7, 129.6, 129.4, 128.0, 123.9, 121.1, 112.6, 53.3; HRMS (ESI) calcd for C_{16}H_{12}N_{4} 260.1062, found 260.1060.

\(N\)-(cyclopentyl(pyrrolidin-1-yl)methylene)-4-methylbenzenesulfonamide (6-3na)

\[
\begin{array}{c}
\text{Me} \\
\text{S} \\
\text{N} \\
\text{O} \\
\text{6-3na}
\end{array}
\]

The title compound was prepared according to the general procedure described above in 85% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 7.83 (d, \(J = 8.2\) Hz, 2H), 7.22 (d, \(J = 8.2\) Hz, 2H), 3.72 – 3.60 (m, 3H), 3.54 (t, \(J = 6.5\) Hz, 2H), 2.38 (s, 3H), 2.00 – 1.73 (m, 10H), 1.66 – 1.57 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 168.31, 142.49, 141.26, 128.93, 126.01, 50.76, 48.68, 43.75, 29.58, 26.45, 26.25, 23.80, 21.40; HRMS (ESI) calcd for C_{17}H_{25}N_{2}O_{2}S [M+H]\(^+\) 321.1631, found 321.1624.
3-Tosyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazole (6-3nl)

![Image of 3-Tosyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazole (6-3nl)]

The title compound was prepared according to the general procedure described above in 84% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 8.00\) (d, \(J = 8.3\) Hz, 2H), 7.92 (d, \(J = 7.4\) Hz, 1H), 7.39 (d, \(J = 8.1\) Hz, 2H), 7.32 – 7.21 (m, 3H), 3.29 (t, \(J = 7.9\) Hz, 2H), 3.11 (t, \(J = 7.9\) Hz, 2H), 2.46 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 147.10, 143.68, 133.84, 133.76, 133.48, 130.45, 128.36, 128.17, 127.33, 127.11, 122.48, 28.05, 21.80, 20.15\); HRMS (ESI) calced for C\(_{17}\)H\(_{16}\)N\(_3\)O\(_2\)S [M+H]\(^+\) 326.0958, found 326.0962.

Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,3-triazole-4-carboxylate (6-3nq)

The title compound was prepared according to the general procedure described above in 98% yield; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.51\) (s, 1H), 7.40 (m, 2H), 7.35 (m, 2H), 7.29 – 7.23 (m, 2H), 4.41 (q, \(J = 7.1\) Hz, 2H), 1.37 (t, \(J = 7.1\) Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 160.59, 141.62, 137.55, 136.52, 136.36, 132.56, 131.87, 131.15, 130.51, 130.14, 128.63, 128.21, 123.25, 61.41, 14.09\).
6.4.4 X-Ray Crystallographic Analysis

The configuration of the product 6-3aa was assigned by X-ray crystallographic analysis of a single crystal of 6-3aa (Figure 6.1). The configurations of other products were assigned by analogy.

![Figure 6.1 X-ray structure of 6-3aa](image)

**Table 6.5 Crystal data and structure refinement for 6-3aa**

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Reference


Examples of pyrazole synthesis via Lewis acid or metal catalyzed [3+2] cycloaddition, see:


Selected examples of pyrazole synthesis by nucleophilic substitution and transition metal catalyzed C-N bond formation:


