SYNTHESIS OF BIOACTIVE MOLECULES BY METAL AND NON-METAL CATALYSIS

A Dissertation Submitted to the National Taiwan Normal University for the Degree of Doctor of Philosophy in Chemistry

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Abbreviations

Å	Angstrom
Ac_2O	Acetic anhydride
AcOH	Acetic acid
$AgNO_3$	Silver nitrate
AgOTf	Oxo(trifluoromethylsulfonyl)silver
$AlCl_3$	Aluminium chloride
Ar	Aryl
aq.	Aqueous
B-H	Baylis-Hillman
$BF_3.Et_2O$	Boron trifluoride diethyl etherate
(R)-BINAP	2,2'-*bis*(Dipenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	Butyloxycarbonyl
Bu	Butyl
n-BuLi	n-Butyllithium
t-Bu	*tert*-Butyl
t-BuOH	*tert*-Butanol
br	Broad (IR)
brs	Broad singlet (NMR)
Bz	Benzoyl
^oC	Degree celsius
Cat.	Catalyst
$CDCl_3$	Chloroform (deuterated)
Cm	Centimeter
CH_2ClCH_2Cl	1,2-Dichloroethane
CH_3NO_2	Nitromethane
Cs_2CO_3	Cesium carbonate
d	Doublet (NMR)
d	Day(s)
dd	Doublet of doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane

DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Methylene chloride
DEAD	Diethyl azodicarboxylate
DIEPA	*N*,*N*-Diisopropylethyl amine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EI	Electron impact
Et	Ethyl
Et_3N	Triethyl amine
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
equiv.	Equivalent(s)
FAB	Fast atom bombardment
Fe	Iron powder
FT	Fourier transform
H	Hour (s)
hν	Irradiation with light
HBr	Hydrogen bromide
HCl	Hydrochloric acid
H_2O	Water
HRMS	High resolution mass spectrometry
Hz	Hertz
IBX	*o*-Iodoxybenzoic acid
$InBr_3$	Indium tribromide
iProAc	Isopropyl acetate
IR	Infrared spectrometry
KBr	Potassium bromide (IR)
K_2CO_3	Potassium carbonate
KF	Potassium fluoride
KOH	Potassium hydroxide
LRMS	Low resolution mass spectrometry
M	Moles per liter

Me	Methyl
Me_2NH	Dimethylamine
Me_2SO_4	Dimethyl sulfate
Mg	Milligram
$MgSO_4$	Magnesium sulfate
MHz	Megahertz
Min	Minutes
mL	Milliliter(s)
mmol	Millimole(s)
MnO_2	Manganese dioxide
mol	Mole(s)
mp	Melting point
MS	Mass spectrometry
MVK	Methyl vinyl ketone
MW	Microwave
µL	Microliter (s)
N	Equivalents per liter (Normality)
NaCl	Sodium chloride
Na_2CO_3	Sodium carbonate
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NH_4Cl	Ammonium chloride
$NaIO_4$	Sodium periodate
NIS	*N*-Iodosuccinimide
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
NH_2NH_2	Hydrazine
NH_4OAc	Ammonium acetate
Na_2SO_4	Sodium sulfate
Ni_2B	Nickel boride
Nu	Nucleophile
OAc	Acetate

OsO_4	Osmium tetroxide
Pd/C	Palladium over charcoal
$Pd(PPh_3)_2Cl_2$	Bis(triphenylphosphine)palladium(II)dichloride
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
$Pd(OAc)_2$	Palladium(II)acetate
$PdCl_2$	Palladium(II)chloride
Ph_2CO	Benzophenone
Ph	Phenyl
ppm	Parts per million
q	Quartet (NMR)
R*f*	Retention factor
rt	Room temperature
s	Singlet (NMR)
$Sc(OTf)_3$	Scandium triflate
SiO_2	Silicon dioxide
S_N2	Substitution nucleophilic bimolecular
t	Triplet (NMR)
TBAF	Tetrabutylammonium fluoride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
$TMSN_3$	Trimethylsilyl azide
UV	Ultraviolet
Zn	Zinc powder

ABSTRACT OF THE THESIS

SYNTHESIS OF BIOACTIVE MOLECULES BY METAL AND NON-METAL CATALYSIS

Keywords: Metal and non-metal, naphthalenes, indole nucleus, 1,2,3-triazoles.

The content of this dissertation is divided into three parts. The part **I** is subdivided into three sections. Section A, illustrate the overview, classification and synthetic approaches on 'indole nucleus' reactions and related literature review. Section B demonstrate the 'An Easy Access to Carbazolones and 2,3-Disubstituted Indoles' *by* a Fe/AcOH-mediated intramolecular reductive *N*-heteroannulation of 3-hydroxy-2-(2-nitrophenyl)enones. Section C, describes the synthesis of '2,3-disubstituted indoles' *via* cascade reaction of 2-*N*-unprotected-2-alkynylanilines and various electron-deficient alkenes in the presence of $PdCl_2$.

Part **II** deals with the synthesis of 2-aryl benzoxazole derivatives and 1,2,3-triazoles by using transition metal catalyzed reactions. Part **II** is subdivided into three sections. Section A, deals with overview, classification and synthetic approaches of 2-aryl benzoxazole derivatives. This section also describe the overview on 1,2,3- triazole derivatives, classification and synthetic approaches from azide and alkenes. Section B, represents an efficient synthesis of 2-aryl benzoxazole derivatives having an amine or amide functionality in the aryl group at the ortho position *via* Copper-catalyzed tandem *C–N* and *C–O* bond formation. Section C, deals with the novel synthesis of substituted 1,2,3-triazoles *via* Copper(I)-catalyzed aerobic oxidative azide–alkene cycloaddition.

Part **III** deals with the synthesis of naphthalene by using non-metal, transition metal catalyzed reactions and their application towards diversity oriented synthesis. Part **III** is subdivided into three sections. Section A, deals with overview and synthetic approaches towards naphthalene derivatives. Section B, describes an efficient synthesis of naphthalenes and iodo-substituted isochromene derivatives *via* reaction of 2-(2-phenylethynyl)-Morita-Baylis-Hillman adducts using molecular iodine. The resulting iodo-substituted-derivatives utilized to couple with a array of boronic acid (Suzuki coupling), activated alkene (Heck coupling) and alkyne (Sonogashira reaction). Section C, demonstrates an efficient synthesis of naphthalenes *via* $PdCl_2$-catalyzed aerobic oxidative intermolecular cycloaddition between 2-alkenyl benzaldehydes and electron-deficient terminal alkenes.

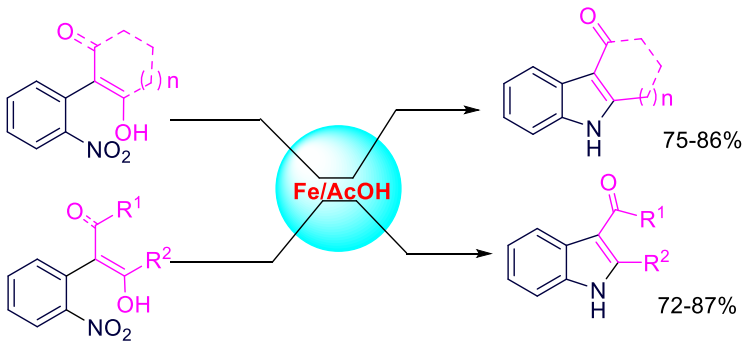
PART-I

Part-I, Section-A: Overview on "Indole Nucleus" reactions

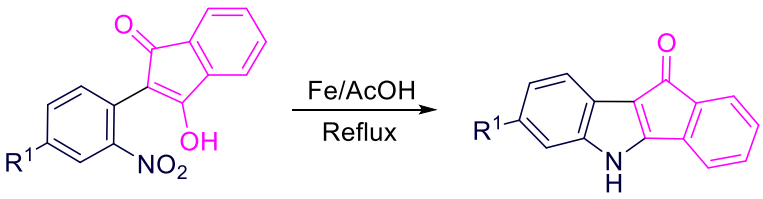
This section describes the overview, classification and synthetic approaches of "indole nucleus". This section also involves the literature survey of the "2,3-disubstituted indole derivative" reactions through cascade/tandem process.

Part-I, Section-B: An Easy Access to Carbazolones and 2,3-Disubstituted Indoles

This section disclose a simple and efficient synthetic protocol for the synthesis of library of carbazol-4-ones, 3,4-dihydrocyclopental-indol-1-one, indeno-indole and 2,3-disubstituted indole derivatives *via* Fe/AcOH-mediated *N*-heteroannulation. In addition, this approach enables easy access to indolocarbazolone and indoloquinolinone derivatives. Furthermore, the conventional Fe/AcOH system is much more cost effective than existing methods involving transition metals. Hence, short reaction time, high yield, economical viability, and the ready availability and accessibility of starting materials are salient features of this method. Furthermore, this method is also applicable to the synthesis of indolocarbazolone derivatives and the natural product precursor of cryptosanguinolentine.



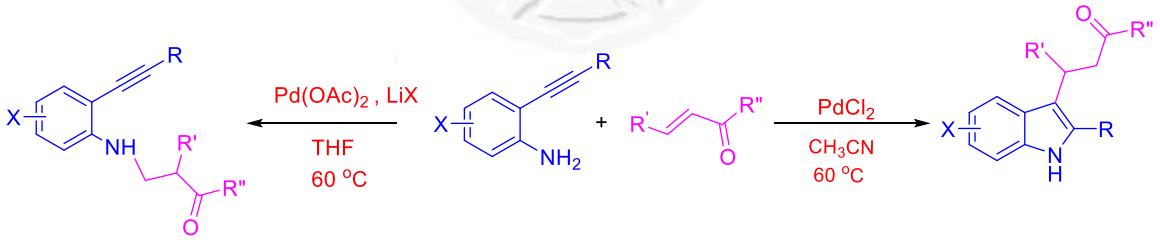
Scheme 1. Synthesis of carbazol-4-ones, 3,4-dihydrocyclopental-indol-1-one and 2,3-disubstituted indole derivatives *via* Fe/AcOH-mediated *N*-heteroannulation.



Scheme 2. Synthesis of indeno-indole derivatives from 3-hydroxy-2-(2-nitrophenyl)-1*H*-inden-1-one derivatives.

Part-I, Section-C: The $PdCl_2$-Catalyzed Sequential Heterocyclization/Michael Addition Cascade in the Synthesis of 2,3-Disubstituted Indoles

This section describes a simple and facile protocol on cascade reaction of 2-*N*-unprotected-2-alkynylanilines and various electron-deficient alkenes using $PdCl_2$ and $Pd(OAc)_2$/LiCl catalytic systems. The presence of catalytic $PdCl_2$ produces 2,3-disubstituted indole derivatives whereas in the presence of $Pd(OAc)_2$/LiCl catalytic system produces *N*-alkylated-2-alkynylaniline derivatives. The mechanism for the formation of 2,3-disubstituted indole derivatives is explained based on experimental outcome. This method offers a mild and easy method to access a variety of 2,3-disubstituted indole derivatives in moderate to good yields. Furthermore, a variety of functional groups readily tolerated under the reaction conditions employed.



Scheme 3. Synthesis of 2,3-disubstituted indole derivatives and *N*-alkylated-2-alkynylaniline derivatives *via* cascade reaction.

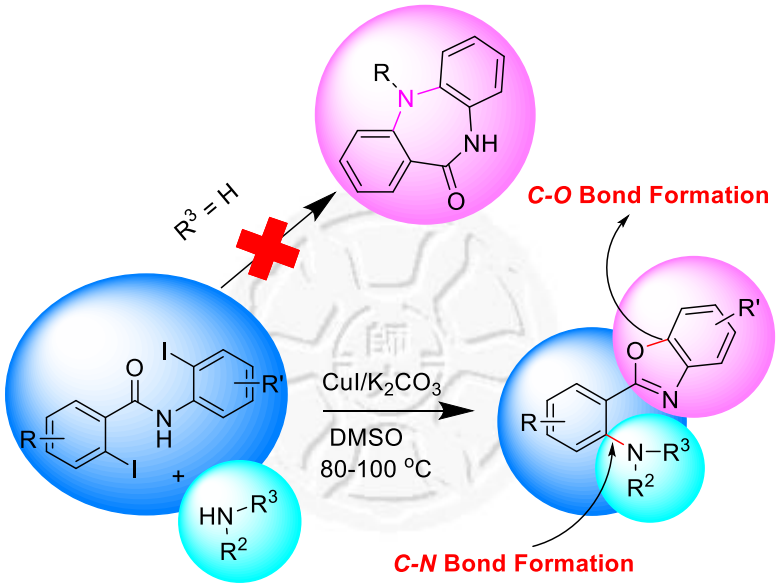
PART-II

Part-II, Section-A: Overview on 2-Aryl benzoxazoles and 1,2,3-Triazoles

The section deals with overview, classification and importance of 2-aryl benzoxazoles and 1,2,3-triazoles. This section also involves the literature survey for the synthesis 2-arylbenzoxazoles and 1,2,3-triazoles.

Part-II, Section-B: One-Pot Tandem Synthesis of 2-Aryl benzoxazole Derivatives *via* Copper-Catalyzed *C–N* and *C–O* Bond Formation

This section describes a practical and efficient synthesis of 2-aryl benzoxazole derivatives having an amine or amide functionality in the aryl group at the *ortho* position through a copper-catalyzed tandem *C–N*/*C–O* coupling strategy using readily available substrates. A wide range of nitrogen nucleophiles was investigated in this protocol, which can be used to produce a variety of 2-aryl benzoxazole derivatives in moderate to good yields. This method is simple, handy and most of the reactions were performed under ligand-free conditions.

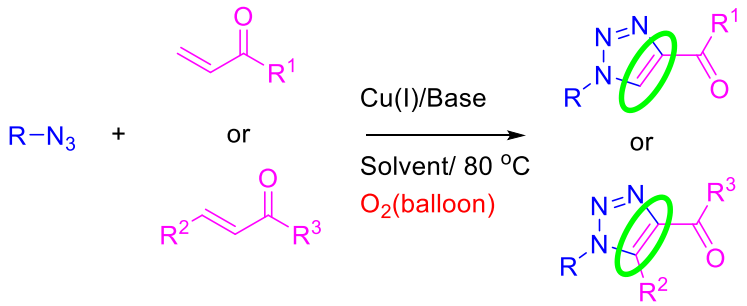


Scheme 4. Synthesis of 2-arylbenzoxazole derivatives *via* copper-catalyzed tandem *C–N*/*C–O* coupling.

Part-II, Section-C: Copper (I)-Catalyzed Aerobic Oxidative Azide–Alkene Cycloaddition: An Efficient Synthesis of Substituted 1,2,3-Triazoles

This section disclose a novel, copper (I)-promoted azide–alkene aerobic oxidative cycloaddition protocol for the regioselective synthesis of 1,4-disubstituted/1,4,5-trisubstituted 1,2,3-triazoles by using azides and various electron-deficient olefins under an oxygen atmosphere. The mechanism for the formation of 1,2,3-triazole derivatives is explained based on experimental results. A wide range of terminal and internal electron-deficient alkenes and azides were used in this reaction, which can be produces substituted 1,2,3-triazole derivatives

in moderate-to-excellent yields. This method is an easy and convenient alternative to the existing methodologies for the synthesis of substituted 1,2,3-triazole derivatives.



Scheme 5. Synthesis of 1,4-disubstituted/1,4,5-trisubstituted 1,2,3-triazoles *via* copper(I)-promoted azide–alkene aerobic oxidative cycloaddition.

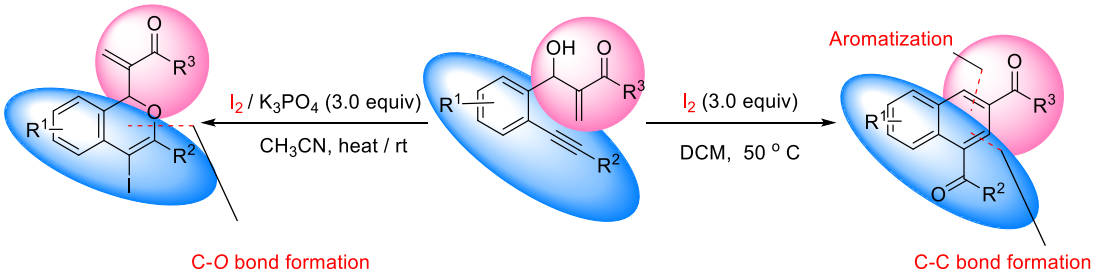
PART-III

Part-III, Section-A: Overview on Naphthalenes

The section describes the overview, importance and synthetic approaches of naphthalene derivatives. This section also include the literature survey for the synthesis of naphthalene derivatives from 2-alkynylbenzaldehyde.

Part-III, Section-B: Molecular Iodine Mediated Regioselective Switching Reaction for the Construction of Naphthalenes and Iodo-Substituted Isochromenes from 2-(2-phenylethynyl)-Morita-Baylis-Hillman Adducts

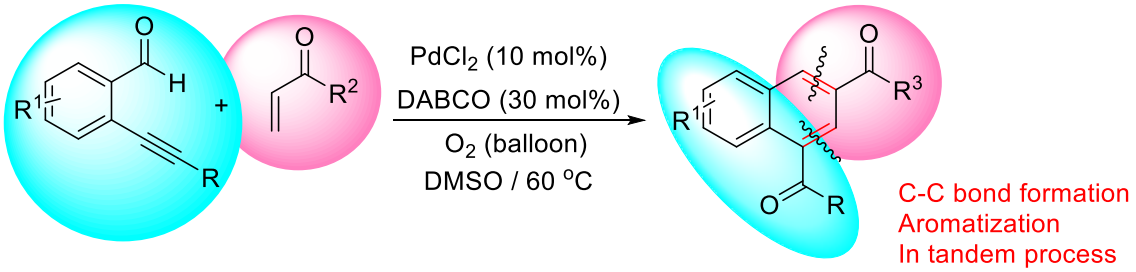
This section demonstrates a synthetic methodology for the construction of naphthyl ketones and iodo-substituted isochromene derivatives *via* iodine mediated regioselective switching reaction of 2-(2-phenylethynyl)-Morita-Baylis-Hillman adducts. In the presence of molecular iodine afford the formation of naphthalene derivatives whereas in the presence of I_2/K_3PO_4 system, produces the iodo-substituted 1*H*-isochromene and 1,3-dihydroisobenzofuran derivatives. The possible mechanisms for this reaction were proposed based on the experimental outcome. This protocol offers a mild and easy access to variety of substituted naphthalene derivatives and 1*H*-isochromene derivatives in moderate-to-good yields.



Scheme 6. Outline of the synthetic route to naphthalene and iodo-substituted isochromene derivatives.

Part-III, Section-C: $PdCl_2$-Catalyzed Aerobic Oxidative Intermolecular [4+2] Cycloaddition Reaction of 2-Alkynyl Benzaldehydes with Electron-deficient Terminal Alkenes: An Efficient Synthesis of Naphthalenes

This section describes a simple and efficient synthetic protocol for the synthesis of library of naphthyl ketone derivatives through $PdCl_2$-catalyzed aerobic oxidative intermolecular [4+2] cycloaddition reaction of 2-alkenyl benzaldehydes to electron-deficient alkenes. This method involves the intermolecular [4+2] cycloaddition of 2-alkynyl benzaldehydes to alkenes followed by aerobic oxidative aromatization in tandem process and the mechanism was proposed based on experimental results. The mild reaction conditions, good functional group tolerance, and broad range of naphthalene derivatives are salient features of this protocol.



Scheme 7. Synthesis of naphthyl ketone derivatives through tandem $PdCl_2$-catalyzed aerobic oxidative intermolecular [4+2] cycloaddition reaction of 2-alkenyl benzaldehydes to electron-deficient terminal alkenes.

中文摘要

利用金屬和非金屬催化劑合成具有生物活性之分子

關鍵字: 金屬及 非金屬, 萘, 吲哚**環**, 1,2,3-三唑.

本論文的內容被分為三個章節，第一章節可被細分為三個部分，A部分主要是對於吲哚(indole)環的反應進行概述、分類及合成方法和相關文獻的說明。B部分的標題為「Carbazolones和2,3-disubstituted Indoles的簡易方法」，內容是介紹一個利用Fe/AcOH催化分子內還原3-hydroxy-2-(2-nitrophenyl)enones的含氮雜環化反應。C部分介紹2,3-disubstituted Indole在$PdCl_2$催化下進行2-*N*-unprotected-2-alkynylanilines和多樣缺電子烯類的級聯反應(cascade reaction)。

第二章節介紹利用過渡金屬催化2-arylbenzoxazole衍生物和1,2,3-triazoles的合成。第二章節可被細分為三個部分，A部分主要是對於2-arylbenzoxazole衍生物進行概述、分類及合成方法的說明。此部分也對1,2,3-triazoles衍生物進行概述、分類及以azide和alkenes合成的方法說明。B部分介紹透過銅催化*C-N*和*C-O*鍵形成級聯反應，使2-arylbenzoxazole衍生物在芳香基團的鄰位上有胺或醯胺官能基的有效合成方法。C部分介紹一個新穎方法為透過銅催化在有氧環境下進行azide-alkene的氧化環加成反應。

第三章節介紹利用非金屬、過渡金屬催化合成naphthalene及其多元性導向的應用。第三章節可被細分為三個部分。A部分是naphthalene衍生物的概論及其合成方法。B部分描述一個有效率利用碘分子和2-(2-phenylethynyl)-Morita-Baylis-Hillman催化naphthalenes和iodo-substituted isochromene衍生物的合成。而iodo-substituted-derivatives則可以用來進行一連串的耦合反應如用硼酸、活化烯類、炔類分別可進行Suzuki coupling、Heck coupling、Sonogashira reaction。C部分介紹一個以$PdCl_2$催化2-alkenylbenzaldehydes和缺電子烯類在有氧環境下分子間氧化環加成來合成naphthalenes的的有效路徑。

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