COPPER AND PALLADIUM ASSISTED CARBON-CARBON AND CARBON-SULFUR BOND FORMATION

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by

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CERTIFICATE

This is to certify that the thesis entitled, **"COPPER AND PALLADIUM ASSISTED CARBON-CARBON AND CARBON-SULFUR BOND FORMATION"** being submitted by **Ms. Poonam Sharma** to the Indian Institute of Technology, Delhi for the award of the degree of **Doctor of Philosophy** in Chemistry, is a record of bonafide research work carried out by her. **Ms. Poonam Sharma** has worked under my guidance and supervision, and has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results contained in this dissertation have not been submitted in part or full, to any other university or institute for award of any degree or diploma.

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ABSTRACT

In past years, transition metal catalyzed reactions have attracted considerable attention of synthetic chemists due to its broad application in organic synthesis. These reactions are advantageous as the starting substrates required are small and simple molecules unlike to the traditional methods which require prefunctionalized substrates prepared by tedious functional-group interconversions.

Chapter 1 begins with a brief description of the history and modern strategies followed in the development of metal catalyzed coupling reactions for the formation of carbon-carbon and carbon-heteroatom bond. Further detailed literature regarding various synthetic approaches followed in development of carbon-carbon (C-C) and carbon-heteroatom (C-X) bond formation using copper and palladium metal as catalyst has been discussed.

In **Chapter 2** a synthetic methodology for monothiomethylation of arenes and heteroarenes facilitated by copper acetate-DMSO system in the presence of air has been developed. Pyridine and pyrimidine auxillary groups are used to control the regioselectivity of these reactions which leads to mono-methylthiolated organic moiteis in high yield.

Further in continuation to our efforts to develop new strategies for the formation of carbon-sulfur bond, in **Chapter 3** we first time report a copper acetate mediated regioselective *ortho*-arylthiolation of 2-aryl pyridines using S-aryl arenesulfonothioate as the arylthiolating agent. The reaction shows good functional group tolerance and gives the thioarylated products in 67-89% yields. The reagent is a good alternative of the unpleasant smelling arylthiols. An unprecedented insertion of arylthio unit from both the parts of the reagent (SPh and *p*-TolSO_2) in the presence of copper acetate has been shown. Indoles and imidazopyridines also undergo facile reaction at the C-3 position, and furnish the thioarylated derivates in good yields.

Chapter 4 shows styrene as a unique aryl or arylcarboxymethylene source towards aryl isocyanides in presence of Cu(II)/TBHP, and yield *N*-arylbenzamides or benzoyloxyacetanilides respectively. The chemoselectivity of the reaction is controlled by the nature of the substituents present on styrene ring. While styrenes substituted with electron-releasing alkyl and alkoxy groups yield *N*-arylbenzamides; unsubstituted styrene and those with electron withdrawing

substituents furnish benzoyloxyacetanilides as the major product. With benzylamines as substrate, *N*-arylbenzamides are formed exclusively as they act only as an aryl donor. TBHP serves as a promoter and oxygen source. Both the pathways are believed to proceed through an initial oxidative C-C bond cleavage of styrene.

Chapter 5 is based upon palladium catalyzed synthesis of aryl(hetero)aryl benzophenones and aryl benzoates from aryl(hetero)aryl halides using $CHCl_3$ as the carbonyl source in the presence of KOH. The reaction occurs in tandem through an initial carbonylation to generate an aroyl halide, which undergoes coupling with arylboronic acids, bornonates, and phenols. Direct carbonylative coupling of indoles at the third position has also been accomplished under slightly modified reaction conditions by in situ activation of the C-H bond. Notably, $CHCl_3$ is a convenient and safe alternation of CO gas, provides milder reaction conditions with high functional group tolerance, and gives the products in moderate to good yields.

सार

पिछले वर्षों में, संक्रमण धातु उत्प्रेरित प्रतिक्रियाओं ने कार्बनिक संश्लेषण में व्यापक अनुप्रयोग के कारण सिंथेटिक केमिस्टों का काफी ध्यान आकर्षित किया है। ये प्रतिक्रियाएँ लाभप्रद होती हैं क्योंकि शुरू करने के लिए आवश्यक सब्सट्रेट छोटे और सरल अणु होते हैं, जो पारंपरिक तरीकों के विपरीत होते हैं, जिनके लिए थकाऊ कार्यात्मक-समूह इंटरकन्वर्ज़न् द्वारा तैयार किए गए पूर्व-निर्धारित सब्सट्रेट की आवश्यकता होती है।

अध्याय 1 इतिहास और आधुनिक रणनीतियों के संक्षिप्त विवरण के साथ शुरू होता है, जो कार्बन-कार्बन और कार्बन-हेटेरोएटम बांड के गठन के लिए धातु उत्प्रेरित युग्मन प्रतिक्रियाओं के विकास में होता है। कार्बन-कार्बन (C-C) और कार्बन-हेटेरोएटम (C-X) बॉन्ड के निर्माण में तांबे और पैलेडियम धातु का उपयोग करके उत्प्रेरक के रूप में उपयोग किए गए विभिन्न सिंथेटिक दृष्टिकोणों के बारे में आगे विस्तृत साहित्य पर चर्चा की गई है।

अध्याय 2 में हवा की मौजूदगी में कॉपर एसीटेट-DMSO प्रणाली द्वारा सुविधा प्राप्त एरीन्स और हेटेरोएरीन्स के मोनोथायोमिथाइलेशन के लिए एक सिंथेटिक पद्धति विकसित की गई है। पिरिडिन और पिरीमिडीन ऑक्जिलरी समूहों का उपयोग इन प्रतिक्रियाओं के रिजिओसेलेक्टिविटी को नियंत्रित करने के लिए किया जाता है जो उच्च उपज में मोनो-मिथाइलथायोलेटेड कार्बनिक मोइटिस की ओर जाता है।

कार्बन-सल्फर बॉन्ड के निर्माण के लिए नई रणनीतियों को विकसित करने के हमारे प्रयासों को जारी रखते हुए, अध्याय 3 में हम पहली बार S-एराइल एरीनसल्फोनोथायोएट का उपयोग करते हुए एराइलथायोलेटिंग एजेंट के रूप में 2- पिरिडिन्स की एक तांबे असिस्टेट की मध्यस्थता वाले ऑर्थो-एराइलथायोलेशन की रिपोर्ट करते हैं। प्रतिक्रिया अच्छी कार्यात्मक समूह सहिष्णुता दिखाती है और 67-89% पैदावार में थायोलेटेड उत्पाद देती है। अभिकर्मक अप्रिय महक एराइलथायोल का एक अच्छा विकल्प है। कॉपर एसीटेट की उपस्थिति में अभिकर्मक (SPh और $PhSO_2$) के दोनों हिस्सों से एराइलथायो यूनिट का एक अभूतपूर्व सम्मिलन दिखाया गया है। इंडोल्स और इमिडाज़ोपिरीडीन भी C-3 स्थिति में सुगम प्रतिक्रिया से गुजरते हैं, और अच्छी पैदावार में थायोलेटेड व्युत्पन्न प्रस्तुत करते हैं।

अध्याय 4 स्टाइरीन को एक अनोखे एराइल या एराइलकार्बोमेथिलीन स्रोत के रूप में दर्शाता है जो कि Cu (II) / TBHP की उपस्थिति में एराइल आइसोसाइनाइड्स की ओर है, और क्रमशः *N*- एराइलबेंज़ामाइड या बेन्ज़ोयलोक्सीएसीटेनिलाइड का उत्पादन करता है। रिएक्शन की कीमोसेलेक्टिविटी को स्टाइरीन रिंग पर मौजूद सब्स्टीट्यूट्स की प्रकृति द्वारा नियंत्रित किया जाता है। जबकि इलेक्ट्रॉनों को इलेक्ट्रॉन-रिलीजिंग एल्काइल और एल्कोक्सी समूहों के साथ प्रतिस्थापित किया जाता है, *N*-एराइलबेंज़ामाइड्स उपजते हैं; असंबद्ध स्टाइरीन और इलेक्ट्रॉन को हटाने वाले पदार्थ प्रमुख उत्पाद के रूप में बेन्ज़ोयलोक्सीएसीटेनिलाइड को प्रस्तुत करते हैं। सब्सट्रेट के रूप में बेंजाइलएमीन्स के साथ, *N*-एराइलबेंज़ामाइड्स विशेष रूप से बनते हैं क्योंकि वे केवल एराइल दानकर्ता के रूप में कार्य करते हैं। TBHP एक प्रमोटर और ऑक्सीजन स्रोत के रूप में कार्य करता है। माना जाता है कि दोनों रास्ते स्टाइरीन के प्रारंभिक ऑक्सीडेटिव C-C बॉन्ड क्लीवेज के माध्यम से आगे बढ़ते हैं।

अध्याय 5 पैलेडियम उत्प्रेरित, एराइल (हेटेरो) एराइल लेकर $CHOH_3$ का KOH की उपस्थिति में कार्बोनिल स्रोत के रूप उपयोग कर एराइल (हेटेरो) एराइल बेंजोफेनोन्स और एराइल बेंजोएट्स के संश्लेषण पर आधारित है। एरोयल हैलाइड उत्पन्न करने के लिए एक प्रारंभिक

कार्बोनिलीकरण के माध्यम से अग्रानुक्रम प्रतिक्रिया होती है, जो एराइलबोरोनिक एसिड, बोरोनेट्स और फिनोल के साथ युग्मन से गुजरती है। तीसरे स्थान पर इंडोल के प्रत्यक्ष कार्बोनलाइलेटिंग युग्मन को C-H बांड के C2 सक्रियण द्वारा थोड़ा संशोधित प्रतिक्रिया स्थितियों के तहत भी पूरा किया गया है। विशेष रूप से $CHCl_3$, CO गैस का एक सुविधाजनक और सुरक्षित विकल्प है, उच्च कार्यात्मक समूह सहिष्णुता के साथ सौम्य प्रतिक्रिया की स्थिति प्रदान करता है, और उत्पादों को मध्यम से अच्छी पैदावार देता है।

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GLOSSARY OF SYMBOLS AND ABBREVIATIONS

Ac	Acetyl
ACN	Acetonitrile
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
Ar	Aryl
2-ArPy	2-arylpyridine
AQ	8-aminoquinoline
ArSSAr	Diaryl disulfide
$BF_3.Et_2O$	Borontrifluoride etherate
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bpin	Boronic acid pinacol ester
Bipy	2,2'-Bipyridine
Bq	Benzoquinone
Bz	Benzyl
Calcd.	Calculated
CCDC	Cambridge Crystallographic Data Centre
Cat.	Catalyst
CDC	Cross-Dehydrogenative Coupling
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
CuF_2	Copper difluoride
$Cu(OAc)_2$	Copper(II) acetate
$Cu(OTf)_2$	Copper triflate
CuI	Copper iodide

CuO	Copper oxide
CuTC	Copper(I) thiophene-2-carboxylate
COX	Cyclooxygenase
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	*trans,trans*-dibenzylidene acetone
dppf	diphenylphosphino)ferrocene
DMA	Dimethylacetamide
Dave-Phos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
DMAE	Dimethylethanolamine
DCE	Dichloroethane
DCPP	2,3-Dichlorophenylpiperazine
DG	Directing group
DMF	Dimethylformamide
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
DPEphos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppp	1,3-Bis(diphenylphosphino)propane
DCM	Dichloromethane
DIPEA	*N, N*-Diisopropylethylamine
DTBP	Di-*tert*-butyl peroxide
EtOH	Ethanol
EI-MS	Electron ionization mass *spectrometry*
Et	Ethyl
EtOAc	Ethyl acetate

ESI	Electron spray ionization
Equiv.	Equivalent
GC-MS	Gas chromatography–mass spectrometry
h	Hour
Hz	Hertz
Het-ar	Hetero-arenes
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
I_2	Iodine
IBX	2-Iodoxybenzoic acid
K_2CO_3	Potassium carbonate
$K_2S_2O_8$	Potassium persulfate
KHIE	Kinetic Hydrogen Isotope Effect
LRMS	Low resolution mass *spectrometry*
MAPK	Mitogen-activated protein kinase
MeOH	Methanol
mL	Mililitre
Mg	Milligram
$MgSO_4$	Magnesium sulphate
mm	Milimetre
Max.	Maximum
Min.	Minimum
min.	Minutes
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl

MCR	Multi-component reaction
MHz	Megahertz
MW	Microwave
m/z	Mass by charge ratio
Na_2SO_4	Sodium sulphate
$Na_2S_2O_3$	Sodium thiosulphate
Boc	*tert*-butyloxycarbonyl
NHC	*N*-heterocyclic carbine
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methylpyrrolidine
NMR	Nuclear magnetic resonance
Nu	Nucleophile
OAc	Acetoxy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	Trifluoromethanesulphonate
Oxa	Oxazoline
PA	Picolinamide
PEG	Polyethylene glycol
$Pd(OAc)_2$	Palladium acetate
Pd(dba)	Bis(dibenzylideneacetone)palladium
PIP	Phosphatidylinositol phosphate
Piv	Pivaloyl
PivOH	Pivalic acid
PIP	(Pyridin-2-yl)isopropyl

^{i}Pr	Isopropyl
Ph	Phenyl
Phen	Phenenthrene
PhSH	thiophenol
Ph-Me	Toluene
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium
$PhSO_2Cl$	Benzene sulfonyl chloride
$PhSO_2Na$	Sodium benzenesulfinate
$PhSO_2SPh$	S-Phenyl benzenesulfonothioate
PhSSPh	Diphenyl disulfide
ppm	Parts per million
p-tolyl	Para-toluene
PXRD	Powder X-Ray Crystallography
Rf	Retention Factor
rt	Room Temperature
TCP	1,2,3-Trichloropropane
TBAI	Tetrabutylammonium iodide
TEA	Triethylamine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl) oxidanyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TM	Transition metal
TMEDA	Tetramethylethylenediamine
TMP	1-chloro-2,2,6,6-tetramethylpiperidine
TBAF	Tetra-*n*-butylammonium fluoride

TBHP	*tert*-Butyl hydroperoxide
Temp.	Temperature
TLC	Thin Layer Chromatography
Ts	*para*-Tolunesulfonyl
TOF	Time of Flight
^{t}Bu	*tert*-butyl
TMS	Tetramethylsilane
$TMSCF_3$	Trimethyl(trifluoromethyl)silane
TMSCN	Trimethylsilyl cyanide
UV	Ultra-violet
X-Phosp	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

MATERIALS AND METHODS

Physical measurements

NMR spectra (^{1}H and ^{13}C) were measured on a Bruker DPX-300/400 MHz spectrometer. HRMS were recorded on MICROTOF-Q ll 228888.10262 using electrospray ionization (ESI) as the ionization method. Molecular mass (GC-MS) of compounds were measured on Perkin Elmer Clarus 600 C. IR spectra were recorded on Nicolet 460 (Protege) spectrophotometer in range 4000-400 cm-1. UV-vis spectroscopy was recorded on Lambda Bio 20, Perkin Elmer.

The size of nanoparticles was determined by Malvern DLS nano ZS90. EDX spectra were recorded on ZEISS EVO 50 model QuanTax 200 which is based on the SDD technology and provides an energy resolution of 127 eV at Mn K alpha. Single-crystal X-ray data of compounds was collected on Bruker SMART CCD-Diffractometer using graphite monochromated Mo*Kα* radiation (λ = 0.71073 Å). The data integration and reduction were processed with Crys Alis Pro software. The structures were solved by the direct method and then refined on *F*2 by the full matrix least-squares technique with the SHELX-97 set of software using the WinGX (version 1.80.05) program package. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were treated as riding atoms using SHELX default parameters. Molecular structures have been drawn using ORTEP software. Copies of the data can be found free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033. e-mail: deposit@ccdc.cam.ac.uk.

Analytical Information

All the isolated compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS using $CDCl_3$, D_2O and DMSO as the solvents with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given in δ (ppm) relative to TMS, the coupling constants (*J)* are given in hertz (Hz).

Chemicals and reagents

All reactions were carried out under N_2/air atmosphere in oven dried *MW* tube using CEM Discover *MW* system, oven dried seald tube under air or in septum covered oven dried round bottom flask /10 mL vial under air. All the solvents were bought from Aldrich, Alfa-aesar, Merck, Thermo Fisher and Spectrochem were used as received. For column chromatography, silica gel (230–400 mesh) from SRL Co. was used. A gradient elution using ethyl acetate-hexane was performed on Merck aluminium TLC sheets (silica gel 60F254).