NEW STRATEGIES TOWARDS THE FUNCTIONALIZATION OF C-H & C-Cl BOND OF ARYLS(HETEROARYLS) AND SYNTHESIS OF AZA-HETEROCYCLES

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by

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CERTIFICATE

This is to certify that the thesis entitled **"NEW STRATEGIES TOWARDS THE FUNCTIONALIZATION OF C-H & C-Cl BOND OF ARYLS(HETEROARYLS) AND SYNTHESIS OF AZA-HETEROCYCLES"** being submitted by **Mr. ABADH KISHOR JHA** 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 him. Mr. Abadh Kishor Jha has worked under my guidance and supervision. He has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

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

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ABSTRACT

Chapter 1: An overview of the aza-heterocycles and their importance in different fields such as drugs, natural products, and in living systems has been provided. Different approaches that are used for their functionalization and derivatization have been discussed. The importance of C-Cl bond activation, and synthetic strategies available in literature to accomplish the same have been presented.

Chapter 2: A copper catalyzed regioselective cross-coupling of *N*-tosylhydrazones with azine *N*-oxides to yield *ortho*-alkylated products in moderate to good yields is reported. The reaction is facilitated by microwave, takes place without any ligand, and uses inexpensive copper(I) iodide as the catalyst.

Chapter 3: An unprecedented $Cu(OAc)_2$ and Li*t*OBu mediated homocoupling of azine *N*-oxides to yield 2,2'-azine *N*,*N'*-dioxides is reported. This is the first instance where copper has been used to catalyze the homodimerization reaction, especially with *N*-oxides of 2-phenyl pyridine. In the absence of catalytic copper, the reaction follows an alternative pathway, and instead of dioxide yields the 2,2'-azine *N*-monoxides. The observed chemoselectivity between copper-assisted and copper-free protocols is routed through an oxidative cross-dehydrogenative coupling (CDC), and nucleophilic aromatic substitution of hydrogen (S_NAr) respectively.

Chapter 4: An unprecedented phosphine-free coupling of cheap and less reactive substrates like aryl chlorides with 1-(bromoethyl)benzene as a nucleophilic coupling partner at low Pd concentrations, under *MW* conditions to access highly regio- and stereospecific trans-stilbene derivatives. The reaction is believed to proceed via a Pd–carbene intermediate generated in situ under *MW* conditions from 1-(bromoethyl) benzene. Another key requirement in the reaction is the presence of styrene; as in its absence, Pd catalysed coupling of halogenated ethyl benzene with chloroarenes does not take place at all. DFT studies have also been carried out to obtain a thermodynamic insight into the proposed mechanism.

Chapter 5: Glucose-linked 1,2,3-triazolium ionic liquids have been synthesized as a new class of chiral solvents by copper(I) catalyzed regioselective cycloaddition of a glucose azide with a glucose alkyne followed by quaternization with methyl iodide. The tagging of glucose to triazolium core makes these molecules act as reusable ligand and solvent in copper(I) catalyzed amination of aryl halides with aqueous ammonia. While the free hydroxyl groups of sugar help in stabilizing copper(I) species during the reaction thus acting as a ligand, the triazolium salt which makes it a liquid at room temperature serves as a reusable solvent.

सार

अध्याय 1: एजा-हेटरोक्साइकल्स का एक अवलोकन और विभिन्न क्षेत्रों जैसे, दवाओं के रूप में, प्राकृतिक उत्पाद के रूप में, जीवित प्रणालियों में उनके महत्व बताये गये हैं। इसके अलावा, उनके functionalization तथा derivatization के लिए उपयोग किए जाने वाले विभिन्न तरीको पर भी चर्चा की गई है। सी-सीएल बॉन्ड activation का महत्व, और इसे पूरा करने के लिए literature में उपलब्ध सिंथेटिक रणनीतियों को प्रस्तुत किया गया है।

अध्याय 2: एन-टॉसिलहाइड्राज़ोन तथा ऐजिन एन-आक्साइड का, copper catalysed रेजीओसेलेक्टीव क्रॉस-युग्मन, ऑर्थो-एल्केलाटेड product, good to moderate yield के रूप मे देता है, के बारे में बताया गया है। प्रतिक्रिया माइक्रोवेव की मदद से कि जाती है, बिना किसी लिगैंड के होती है, और सस्ती Cu(I)। उत्प्रेरक के रूप में उपयोग करती है।

अध्याय 3: $Cu(OAc)_2$ तथा Li*t*OBu mediated ऐजिन एन-ऑक्साइड के एक अभूतपूर्व होमोकप्लिंग से 2,2'-एज़िन एन, एन-डाइऑक्साइड बनने के बारे मे बताया गया है। यह पहला उदाहरण है जहां copper का उपयोग विशेष रूप से 2-फेनिल पाइरीडिन के एन-ऑक्साइड के homodimerization को उत्प्रेरित करने के लिए किया गया है। उत्प्रेरक copper की अनुपस्थिति में, प्रतिक्रिया वैकल्पिक मार्ग का पालन करती है, और डाइऑक्साइड की बजाय 2,2'-एज़िन एन-मोनोऑक्साइड बनता है। Copper की सहायता से तथा Copper मुक्त के बीच कीमोसेलेक्टीविटी क्रमशः ऑक्सीडेटिव क्रॉस-डीहाइड्रोजनेटिव युग्मन (सीडीसी), और हाइड्रोजन का न्यूक्लियोफिलिक aromatic प्रतिस्थापन (S_NAr) के माध्यम से होता है।

अध्याय 4: कम palladium सांद्रता पर 1- (ब्रोमोएथिल) बेंजीन तथा सस्ते और कम प्रतिक्रियाशील सब्सट्रेट्स ऐरायेल क्लोराइड का फॉस्फ़िन-मुक्त अभूतपूर्व न्यूक्लियोफिलिक युग्मन, अत्यधिक रेजीओ और स्टीरियोस्पेसिफिक ट्रांस-स्टिल्बिन डेरिवेटिव देता है, जब अभिक्रिया माइक्रोवेव मे होती है। माना जाता है कि प्रतिक्रिया, 1- (ब्रोमेएथिल) बेंजीन से माइक्रोवेव के अंदर इनसीटू palladium-कार्बिन इंटरमीडिएट के माध्यम से आगे बढ़ती है। प्रतिक्रिया में एक और महत्वपूर्ण आवश्यकता स्टायरिन की उपस्थिति है, क्योंकि इसकी अनुपस्थिति में, palladium catalysed, हलोजनयुक्त एथिल बेंजीन तथा क्लोरोऐरिन्स का युग्मन बिल्कुल नहीं होता है। Proposed mechanism में थर्मोडायनामिक अंतर्दृष्टि प्राप्त करने के लिए डीएफटी अध्ययन भी किए गए हैं।

अध्याय 5: ग्लूकोज से जुड़े 1,2,3-ट्रायज़ोलियम आयनिक liquids, एक नई श्रेणी के कायरल सॉल्वैंट्स के रूप में संश्लेषित किया गया है, जिसमें Copper(I) catalysed,ग्लूकोज अल्काइन के साथ ग्लूकोज एजाइड का रेजीओसेलेक्टीव साइक्लोएडिशन के बाद मिथाइल आयोडाइड से क्वाटरनाइजेशन किया जाता है। ग्लूकोज का ट्रायज़ोलियम कोर के साथ टैगिंग इन अणुओं को copper catalysed, aryl halides का जलीय अमोनिया के साथ amination के लिऐ लिगैंड और विलायक के रूप में पुन: प्रयोज्य बनाता है। जबकि sugar का मुक्त हाइड्रोक्साइल समूह प्रतिक्रिया के दौरान copper(I) को stablize करता है, इस प्रकार प्रतिक्रिया के दौरान लिगैंड का काम करता है। ट्रायज़ोलियम salt इसे कमरे के तापमान पर तरल बनाता है, जो एक पुन: प्रयोज्य विलायक के रूप में कार्य करता है।

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GLOSSARY OF SYMBOLS AND ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
Bz	Benzyl
Bpy	2,2'-Bipyridine
bmim	1-Butyl-3-methylimidazolium
calcd	Calculated
COSY	COrrelated SpectroscopY
CDC	Cross-Dehydrogenative Coupling
CCDC	Cambridge Crystallographic Data Centre
cod	Cyclooctadiene
cat	Catalyst
coe	cis-cyclooctene
Cy	Cyclohexyl
Cp*	Pentamethylcyclopentadienyl
DNA	Deoxyribonucleic acid
dba	*trans,trans*-dibenzylidene acetone
dppf	diphenylphosphino)ferrocene
DMA	Dimethylacetamide
Dave-Phos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
DMAE	Dimethylethanolamine
DCE	Dichloroethane
DMF	Dimethylformamide
DCE	Dichloroethane
DMSO	Dimethylsulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
DEPT	Distortionless Enhancement by Polarization Transfer
DFT	Density functional theory

DLS	Dynamic light scattering
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
EtOH	Ethanol
EI-MS	Electron ionization mass *spectrometry*
Et	Ethyl
ESI	Electron spray ionization
Equiv.	Equivalent
EGFR	Epidermal growth factor receptor
GC-MS	Gas chromatography–mass spectrometry
h	Hour
HP(Cy)	Tricyclohexylphosphine
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
HSQC	Heteronuclear Single Quantum Coherence
IR	Infrared
LC-MS	Liquid chromatography–mass spectrometry
LRMS	Low resolution mass *spectrometry*
mL	Mililitre
mg	Milligram
mm	Milimetre
Max.	Maximum
Min.	Minimum
min.	Minutes
mCPBA	meta-Chloroperoxybenzoic acid
MHz	Megahertz
MW	Microwave
MeOH	Methanol
NMP	*N*-Methylpyrrolidine

NMR	Nuclear magnetic resonance
OTf	Trifluoromethanesulphonate
PivOH	Pivalic acid
Pr^i	Isopropyl
Phen	Phenenthrene
ppm	Parts per million
RNA	Ribonucleic acid
rt	Room Temperature
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
S_NAr	Nucleophilic aromatic substitution
TBAE/TBAA	Tetrabutylammonium acetate
TBAB	Tetrabutylammonium bromide
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMP	1-chloro-2,2,6,6-tetramethylpiperidine
TBHP	*tert*-Butyl hydroperoxide
Temp.	Temperature
TLC	Thin Layer Chromatography
Tos	*para*-Tolunesulfonyl
TOF	Time of Flight
^tBu	tert-butyl
TADDOL	α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5 dimethanol
Xant-Phos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthane

MATERIALS AND METHODS

Physical measurement:

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*K*α 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 N2/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).