DEHYDROGENATIVE C-C AND C-P BOND FORMATION: DIRECT ACCESS TOWARDS POLYARYLQUINONES, AXIALLY CHIRAL BI-ARYLS, PHOSPHORYLATED (HETERO)-ARENES

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by

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Submitted

in fulfilment of the requirements of the degree of Doctor of Philosophy

to the

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Dedicated to my beloved Parents, Family Members, Teachers and Friends

CERTIFICATE

This is to certify that the thesis entitled "***Dehydrogenative C-C and C-P bond formation: Direct Access Towards Polyarylquinones, Axially Chiral Bi-aryls Phosphorylated (Hetero)-Arenes***" being submitted by **Mr. Soumyadip Hore** to *Indian Institute of Technology Delhi*, for the award of the degree of **Doctor of Philosophy**, is a record of bonafide research work carried out by him. **Mr. Soumyadip Hore** has worked under my supervision and guidance and has fulfilled all the requirements for the submission of a Ph.D. thesis, which to my knowledge has reached the requisite standard and is worthy of consideration for the award of Ph.D. degree.

The work embodied in this thesis has not been submitted, in part or full, to other university or institute for the award of any degree or diploma.

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Soumyadip Hore.

Soumyadip Hore

ABSTRACT

This dissertation entitled "***Dehydrogenative C-C and C-P bond formation: Direct Access Towards Polyarylquinones, Axially Chiral Bi-aryls Phosphorylated (Hetero)-Arenes***" comprises five chapters that imply the concept of cross dehydrogenative coupling to synthesize C-C and C-P bonds. In the first two chapters using the CDC concept, direct phosphorylation has been described. The third chapter utilizes the concept of Pd-relay catalysis to synthesize diversely complex polyarylquinones. In the final part, an enantioselective version of CDC has been described using the concept of transient directing group and atropisomerism.

Chapter 1: Consist of a brief description of various C-H activation mechanism, different types of oxidative coupling reactions employed in C−C bond formation with the main emphasis on the dehydrogenative coupling of aromatic compounds is presented. In the second part of introduction the importance of chirality as well as different types of chirality is described with the main emphasis on axial chirality.

Chapter 2: Despite significant advancements in azoles phosphorylation, earlier protocols mainly focus on (benzo)thiazoles or (benz) oxazole moieties. So still, there is a lacuna in imidazole and benzimidazole phosphorylation along with the usage of the economical metal catalyst. In this context, Cu is an excellent choice due to its low expenses, ease of handling, and low toxicity. Its low reactivity makes C-H bond activation limited; as a result, Cu in C-P bond formation is rare. Herein, Cu-catalysed C-P bond formation by hetero cross dehydrogenative coupling reaction is reported. To the best of our knowledge, our protocol is the first strategy for achieving dehydrogenative C−P bond construction on

various azoles like benzothiazoles, oxazoles, benzoxazoles, imidazoles, benzimidazoles, and indoles using Cu-catalyst.

Chapter 3: The ubiquitous nature of benzofulvene (BF) and their unique impact along with widespread application on organic molecules have elicited extensive attention in the areas of medicinal, material, polymer, organometallic, and porphyrin chemistry. Due to their fascinating aromaticity, the construction of benzofulvene core demands enormous attention in the scientific community. However, to the best of our knowledge, direct functionalization through CDC has not been realized so far on benzofulvene derivatives. To overcome this burden, a direct silver mediated dehydrogenative cross-coupling of C-H and P(O)-H to synthesize phosphorylated benzofulvenes is described here. A vast library of benzofulvenes can be efficiently phosphorylated under this protocol in good to moderate yields. Further mechanistic investigation implies the radical pathway for this reaction. The synthetic power of this methodology was further demonstrated by transferring the phosphorylated product into different value-added compounds.

Chapter 4: Polyarylquinones have tremendous applications in optoelectronics, photocatalysis, bioimaging, and pharmaceutically relevant materials. However, their synthesis is often challenging and plagued with various bottleneck steps. Here, we demonstrate a relayed addition of fulvene moieties onto quinones. The developed ligand-assisted Pd-catalysed dehydrogenative [2+2+2] cycloaddition reaction enables facile access to a new class of polyarylquinones. The key to the high regioselectivity achieved is the precisely controlled addition of the two fulvene units to the quinone conferred by the Pd catalyst. The work also establishes the broad substrate scope of the reaction and delves into the mechanism of the dehydrogenative coupling reaction. Moreover, single-

crystal X-ray diffraction reveals interesting packing motifs, suggesting these materials' suitability in optoelectronics. As a practical utilization of the reaction, various synthesized polyarylquinones with structural diversity were screened for redox properties and exhibited better antioxidant or chemotherapeutic properties.

Chapter 5: In this part, utilizing imines as the transient directing groups for bi-aryl aldehydes to gain axially chiral bi-aryls containing benzofulvenes using palladium catalysis has been developed. Thus, intermolecular oxidative C-H activation involving two C(sp2)-H bonds provides feasible access to axially chiral benzofulvene with excellent enantioselectivities and good to moderate yields.

सार

"डीहाइड्रोजनेटिव कार्बन-कार्बन और कार्बन-फास्फोरस बंध गठन: डायरेक्ट एक्सेस टूवर्ड्स पॉलीएरिलक्विनोन, एक्सियली चिरल बाय-एरिल फॉस्फोराइलेटेड (हेटेरो) -एरेन्स" शीर्षक वाले इस शोध प्रबंध में पांच अध्याय शामिल हैं जो सीसी और सीपी बॉन्ड को संश्लेषित करने के लिए क्रॉस डिहाइड्रोजनेटिव कपलिंग की अवधारणा को दर्शाते हैं। सीडीसी अवधारणा का उपयोग करते हुए पहले दो अध्यायों में प्रत्यक्ष फास्फारिलीकरण का वर्णन किया गया है। तीसरा अध्याय पीडी-रिले कटैलिसीस की अवधारणा का उपयोग विविध रूप से जटिल पॉलीरिलक्विनोन को संश्लेषित करने के लिए करता है। अंतिम भाग में, क्षणिक निर्देशन समूह और एट्रोपिसोमेरिज्म की अवधारणा का उपयोग करते हुए सीडीसी के एक एनेंटियोसेलेक्टिव संस्करण का वर्णन किया गया है।

अध्याय १: विभिन्न सीएच सक्रियण तंत्र के एक संक्षिप्त विवरण से मिलकर, सुगंधित यौगिकों के डिहाइड्रोजनेटिव युग्मन पर मुख्य जोर के साथ सी-सी बांड गठन में नियोजित विभिन्न प्रकार के ऑक्सीडेटिव युग्मन प्रतिक्रियाएं प्रस्तुत की जाती हैं। परिचय के दूसरे भाग में चिरायता के महत्व के साथ-साथ विभिन्न प्रकार की चिरायता का वर्णन किया गया है जिसमें अक्षीय चिरायता पर मुख्य जोर दिया गया है।

अध्याय २: एज़ोल्स फॉस्फोराइलेशन में महत्वपूर्ण प्रगति के बावजूद, पहले के प्रोटोकॉल मुख्य रूप से (बेंजो) थियाज़ोल्स या (बेंज़) ऑक्साज़ोल मौएट्स पर ध्यान केंद्रित करते हैं। तो फिर भी, किफायती धातु उत्प्रेरक के उपयोग के साथ-साथ इमिडाज़ोल और बेंज़िमिडाज़ोल फॉस्फोराइलेशन में एक कमी है। इस संदर्भ में, कॉपर अपने कम खर्च, हैंडलिंग में आसानी और कम विषाक्तता के कारण एक उत्कृष्ट विकल्प है। इसकी कम प्रतिक्रियाशीलता सी-एच बांड सक्रियण को सीमित कर देती है; नतीजतन, सी-पी बांड गठन में सीयू दुर्लभ है। इस के साथ साथ, हेटेरो क्रॉस डिहाइड्रोजनेटिव युग्मन प्रतिक्रिया द्वारा कॉपर-उत्प्रेरित सीपी बांड गठन की सूचना दी गई है। हमारे सर्वोत्तम ज्ञान के लिए, हमारा प्रोटोकॉल विभिन्न एज़ोल्स जैसे बेंज़ोथियाज़ोल, ऑक्साज़ोल, बेंज़ोक्साज़ोल, इमिडाज़ोल, बेंज़िमिडाज़ोल और क्यू-उत्प्रेरक का उपयोग करके डिहाइड्रोजनेटिव सी-पी बॉन्ड निर्माण प्राप्त करने के लिए पहली रणनीति है।

अध्याय ३: बेंज़ोफुलवेन (बीएफ) की सर्वव्यापी प्रकृति और कार्बनिक अणुओं पर व्यापक अनुप्रयोग के साथ उनके अद्वितीय प्रभाव ने औषधीय, सामग्री, बहुलक, ऑर्गोमेटेलिक और पोर्फिरिन रसायन विज्ञान के क्षेत्रों में व्यापक ध्यान आकर्षित किया है। उनकी आकर्षक सुगंध के कारण, बेंज़ोफुलवेन

कोर का निर्माण वैज्ञानिक समुदाय में अत्यधिक ध्यान देने की मांग करता है। हालांकि, हमारे सर्वोत्तम ज्ञान के लिए, सीडीसी के माध्यम से प्रत्यक्ष कार्यात्मककरण अब तक बेंज़ोफुलवेन डेरिवेटिव पर महसूस नहीं किया गया है। इस बोझ को दूर करने के लिए, फॉस्फोराइलेटेड बेंजोफुलवेन्स को संश्लेषित करने के लिए सी-एच और पी (ओ) -एच के प्रत्यक्ष चांदी की मध्यस्थता वाले डिहाइड्रोजनेटिव क्रॉस-कपलिंग का वर्णन यहां किया गया है। बेंज़ोफुलवेन्स की एक विशाल लाइब्रेरी को इस प्रोटोकॉल के तहत अच्छे से मध्यम पैदावार में कुशलतापूर्वक फॉस्फोराइलेट किया जा सकता है। आगे की यंत्रवत जांच का तात्पर्य इस प्रतिक्रिया के लिए कट्टरपंथी मार्ग से है। इस पद्धति की सिंथेटिक शक्ति को फॉस्फोराइलेटेड उत्पाद को विभिन्न मूल्य वर्धित यौगिकों में स्थानांतरित करके प्रदर्शित किया गया था।

अध्याय ४: पॉलीएरिअलकाइन में ऑप्टोइलेक्ट्रॉनिक्स, फोटोकैटलिसिस, बायोइमेजिंग और फार्मास्युटिकल रूप से प्रासंगिक सामग्री में जबरदस्त अनुप्रयोग हैं। हालांकि, उनका संश्लेषण अक्सर चुनौतीपूर्ण होता है और विभिन्न बाधाओं से ग्रस्त होता है। यहां, हम क्विनोन पर फुलवेन मौएट्स के रिलेटेड जोड़ को प्रदर्शित करते हैं। विकसित लिगैंड-असिस्टेड पीडी-उत्प्रेरित डिहाइड्रोजनेटिव [२+२+२] साइक्लोडडिशन रिएक्शन पॉलीएरिलक्विनोन के एक नए वर्ग के लिए आसान पहुंच को सक्षम बनाता है। प्राप्त की गई उच्च रेजियोसेलेक्टिविटी की कुंजी पीडी उत्प्रेरक द्वारा प्रदान किए गए क्विनोन में दो फुलवेन इकाइयों का सटीक नियंत्रित जोड़ है। कार्य प्रतिक्रिया के व्यापक सब्सट्रेट दायरे को भी स्थापित करता है और डिहाइड्रोजनेटिव युग्मन प्रतिक्रिया के तंत्र में तल्लीन करता है। इसके अलावा, एकल-क्रिस्टल एक्स-रे विवर्तन दिलचस्प पैकिंग रूपांकनों को प्रकट करता है, जो ऑप्टोइलेक्ट्रॉनिक्स में इन सामग्रियों की उपयुक्तता का सुझाव देता है। प्रतिक्रिया के व्यावहारिक उपयोग के रूप में, संरचनात्मक विविधता वाले विभिन्न संश्लेषित पॉलीरीलक्विनोन को रेडॉक्स गुणों के लिए जांचा गया और बेहतर एंटीऑक्सीडेंट या कीमोथेराप्यूटिक गुणों का प्रदर्शन किया गया।

अध्याय ५: इस भाग में, हमने मुख्य रूप से द्वि-आरिल एल्डिहाइड के लिए क्षणिक निर्देशन समूहों के रूप में विकसित किया है, जो पैलेडियम कटैलिसीस का उपयोग करके बेंज़ोफुलवेन्स युक्त अक्षीय रूप से चिरल द्वि-आरिल प्राप्त करते हैं। इस प्रकार, दो सी (एसपी 2) -एच बांडों को शामिल करते हुए इंटरमॉलिक्युलर ऑक्सीडेटिव सीएच सक्रियण उत्कृष्ट एनेंटियोसेक्लेक्टिविटी और अच्छे से मध्यम पैदावार के साथ अक्षीय रूप से चिरल बेंजोफुलवेन के लिए संभव पहुंच प्रदान करता है।

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List of Abbreviations Used

Abbreviation	Full form
Ar	Aryl
Ac	Acetate
MeCN/CH_3CN/ACN	Acetonitrile
Ag	Silver
OAc	Acetate
$BF_3.OEt_2$	Boron trifluoride etherate
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
^{t}Bu	*tert*-Butyl
BuLi	n-Butyllithium
$CDCl_3$	Deuterated chloroform
$CHCl_2CHCl_2$	Tetrachloroethane
cm^{-1}	Wavenumbers
°C	Degrees Celsius
$Cu(OAc)_2$	Copper acetate
Cs_2CO_3	Cesium carbonate
CH_3ONa	Sodium methoxide
CsF	Cesium fluoride
DCM	Dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DMA	Dimethylacetamide
DMAP	*N*, *N*-Dimethylpyridin-4-amine
DMF	Dimethylformamide
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
d	Doublet
dd	Doublet of doublets
d6-DMSO	Deuterated dimethyl sulfoxide
DMEM	Dulbecco's Modified Eagle Medium
DPBS	Dulbecco's Phosphate-buffered Saline
δ	Chemical shift
ee	Enantiomeric excess
er	Enantimeric ratio
ESI-TOF	Electrospray ionization - Time-of-flight
EtOAc	Ethyl acetate
EtOH	Ethanol
FBS	Fetal bovine serum
FTIR	Fourier transform infrared
H_2O	Water
H_2O_2	Hydrogen peroxide
H_2DCF-DA	2′,7′-Dichlorofluorescin diacetate
HEPES	N-2-hydroxyethylpiperazine-N-2-ethane sulfonic acid
HFIP	Hexafluoro-2-propanol

h	Hour
In	Indium
$In(OTf)_3$	Indium trifluoromethanesulfonate
J	Coupling constant
λ	Wavelength
K_2CO_3	Potassium carbonate
KF	Potassium fluoride
KOH	Potassium hydroxide
KO^tBu	Potassium tert-butoxide
KOAc	Potassium acetate
LDA	Lithium diisopropylamide
LED	Light-emitting diode
LiCl	Lithium chloride
LiHMDS	Lithium bis(trimethylsilyl)amide
min	Minute
MTBE	Methyl tert-butyl ether
m	Multiplet
MHz	Megahertz
mL	Millilitre
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
µL	Microlitre
NaOH	Sodium hydroxde
NaOMe	Sodium methoxide
NaOAc	Sodium acetate
PhONa	Sodium phenoxide
p-TsOH	para-Toluenesulfonic acid
s	Singlet
Sc(OTf)3	Scandium trifluoromethanesulfonate
Na_2CO_3	Sodium carbonate
$NaHCO_3$	Sodium bicarbonate
rt	Room temprature
NaO^tBu	Sodium tert-butoxide
TBHP	tert-butyl hydroperoxide
TBAF	Tetra-N-butylammonium floride
TFA	Trifluoroacetoc acid
TFFA	Trifluoroacetic anhydride
TBPB	tert-butylperoxybenzoate
TIPS	Triisopropylsilyl
^tBuOH	tert-Butyl alcohol
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TMSAN	Trimethylsilyl acetonirile
UV	Ultraviolet
Zn	Zinc