

**DEVELOPMENT OF TRANSITION METAL CATALYSTS  
FOR C-H BOND FUNCTIONALIZATION OF ARYL  
KETONES, SULFONES, AND CARBOXAMIDES**

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**Development of transition metal catalysts for C-H  
bond functionalization of aryl ketones, sulfones, and  
carboxamides**

*by*

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*Submitted*

**In fulfillment of the requirements of the degree of Doctor  
of Philosophy**

*to the*



**INDIAN INSTITUTE OF TECHNOLOGY DELHI**

**February 2024**

*Dedicated*  
*To*  
*My Family and Teachers*

## **CERTIFICATE**

This is to certify that the thesis entitled “*Development of transition metal catalysts for C-H bond functionalization of aryl ketones, sulfones, and carboxamides*” being submitted by Mr. **Ashutosh Verma** 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. **Ashutosh Verma** has worked under my supervision and guidance, and he 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 a Ph.D. degree.

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

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Ashutosh Verma

## ABSTRACT

The thesis entitled "*Development of transition metal catalysts for C-H bond functionalization of aryl ketones, sulfones, and carboxamides*" presents the results obtained from the research work carried out on the development, characterization, and application of transition metal complexes and organometallic compounds as catalysts for the oxidative functionalization of ketones and sulfones using alcohols and C-H bond functionalization of aryl and ferrocene carboxamide derivatives. The accompanied research work has been divided into seven chapters.

**Chapter 1** of the thesis begins with a brief discussion of the traditional C-H bond functionalization reactions and classical organic condensation reactions for the formation of new C-C bonds. This thesis centers around the development of various transition metal complexes and organometallic compounds and their application for C-H bond alkylation of ketones and sulfones using alcohols and C-H bond arylation/alkylation of aryl/ferrocene carboxamides. The first chapter of the thesis deals with a detailed discussion on the sustainable pathways and directing group enabled C-H bond functionalization reactions. After that, various methodologies have been discussed to carry out the reactions in aqueous medium. This is followed by a detailed discussion of the previous works carried out for the synthesis of  $\alpha$ -alkylated ketones, quinolines, and directing group enabled C-H bond functionalization of ferrocene and aryl carboxamides. In the last section of this chapter, a brief background of the use of sulfones in chemical reactions and recent developments for the synthesis of branched sulfones has been portrayed. The chapter ends with the scope of the present work carried out and reported in the thesis.

**Chapter 2** describes the general experimental procedures adopted for the synthesis of new compounds and details of utilized characterization techniques. Specific synthetic details of the starting materials described in the thesis are also presented.

**Chapter 3** describes the ruthenium-catalyzed synthesis of  $\alpha$ -alkylated ketones and quinolines in an aqueous medium via a hydrogen-borrowing strategy. In this methodology, various acetophenone or secondary alcohols were used as substrates, and benzyl alcohol derivatives as the sustainable and greener alkylating agents. In the reaction, a water-soluble and air-stable [Ru(8-AQ)Cl(p-cymene)]Cl complex has been used as the catalyst, in the presence of KO<sup>t</sup>Bu base in an aqueous medium. From control experiments, it was found that the reaction follows the borrowing hydrogen strategy in synthesizing functionalized ketones and quinolines. Our methodology is also applicable for the large-scale synthesis of target products and it generated H<sub>2</sub>O molecules and H<sub>2</sub> gas as side products during the reaction.

**Chapter 4** describes a directing group-enabled ‘on-water’ methodology for the bis C-H bond functionalization of ferrocene carboxamide derivatives. In this work, 8-aminoquinoline and picolinamide were used as bidentate directing groups and Pd(OAc)<sub>2</sub> as a catalyst in an aqueous medium. The substrate scope showed the applicability of this reaction in the presence of electron-donating as well as electron-withdrawing substrates. The insoluble nature of the substrates, reagents, and products, helped us to explore the reusability of the solvent i.e. water, and the catalyst for further reaction cycles. Due to the ‘on-water’ reaction conditions, our methodology requires less catalyst loading to carry out the reaction compared to previous reports which makes our procedure greener and more efficient as compared to reported methodologies. Control experiments were carried out to

understand the mechanistic pathway which suggests the *in situ* formation of palladacycle during the reaction.

**Chapter 5** describes the C-H bond functionalization of aryl acids and benzyl/naphthyl amine derivatives using bidentate directing groups under the ‘on-water’ reaction conditions. In this methodology, selective mono and bis C-H bond functionalization was achieved using suitable directing groups. To show the applicability of this methodology, late-stage functionalization of pharmaceutically important molecules and large-scale synthesis of products were also shown. The reusability experiments of catalysts and solvents make this methodology more sustainable and efficient compared to the previous reports. For further derivatization of the functionalized products, directing group removal reactions were also successfully attempted. In addition to substrate scope, control experiments have also been carried out to find out the possible palladacycle intermediate and the reaction pathway.

**Chapter 6** deals with the reactions involving an earth-abundant manganese catalyst for the  $\alpha$ -C-H bond alkylation of sulfones using alcohols as sustainable alkylating agents. A (NNN)Mn(II)Cl<sub>2</sub> catalytic system has been developed by using an inexpensive metal precursor and commercially available ligands for the synthesis of branched sulfones. Control experiments suggested that the Mn-catalyst follows the hydrogen borrowing pathway in synthesizing branched sulfones.

**Chapter 7** gives the overall conclusions of the entire work carried out in the present study.

## सारांश

शोध प्रबंध जिसका शीर्षक है, "**एरिल केटोन्स, सल्फोन्स और कार्बोक्सामाइड्स के कार्बन-हाइड्रोजन बंध के कार्यात्मककरण के लिए संक्रमण धातु उत्प्रेरक का विकास**" जिसमें अल्कोहल का उपयोग करके कीटोन्स और सल्फोन्स का ऑक्सीकृत कार्यात्मककरण तथा एरिल और फेरोसीन कार्बोक्सामाइड यौगिक का कार्बन-हाइड्रोजन बंध के कार्यात्मककरण करने के लिए उत्प्रेरक के रूप में उपयोग हुए संक्रमण धातु यौगिकों और कार्ब-धात्विक यौगिकों के विकास, लक्षण वर्णन और अनुप्रयोग पर किए गए शोध कार्यों से परिणामों को प्रस्तुत किया गया है। संलग्न शोध कार्य को सात अध्यायों में विभाजित किया गया है।

इस शोध प्रबंध का **अध्याय 1**, पारंपरिक कार्बन-हाइड्रोजन बंध की कार्यात्मकता प्रतिक्रियाओं और नए कार्बन-कार्बन बंध के निर्माण के लिए प्रतिष्ठित कार्बनिक संघनन प्रतिक्रियाओं की संक्षिप्त चर्चा के साथ शुरू होता है। यह शोध प्रबंध अल्कोहल का उपयोग करके कीटोन्स और सल्फोन्स का ऑक्सीकृत कार्यात्मककरण तथा एरिल और फेरोसीन कार्बोक्सामाइड यौगिक का कार्बन-हाइड्रोजन बंध के एरीलेशन/एल्काइलेशन करने के लिए उत्प्रेरक के रूप में उपयोग हुए संक्रमण धातु यौगिकों और कार्ब-धात्विक यौगिकों के विकास, लक्षण वर्णन और अनुप्रयोग पर केन्द्रित है। इस शोध प्रबंध का पहला अध्याय धारणीय मार्गों और निर्देशन समूहों के उपयोग से कार्बन-हाइड्रोजन बंध के कार्यात्मककरण की विस्तृत चर्चा करता है। इसके बाद जलीय माध्यम में प्रतिक्रियाओं को पूरा करने के लिए विभिन्न तरीकों पर चर्चा की गई है। इसके बाद  $\alpha$ -अल्काइलेटेड कीटोन्स, क्विनोलिन्स संश्लेषण और निर्देशन समूह के उपयोग द्वारा फेरोसीन और एरिल कार्बोक्सामाइड्स के कार्बन-हाइड्रोजन बंध के कार्यात्मककरण के पिछले कार्यों का विस्तृत वर्णन किया गया है। इस अध्याय के अंतिम भाग में, सल्फोन्स की रासायनिक अभिक्रियों की संक्षिप्त पृष्ठभूमि को और शाखित सल्फोन्स के संश्लेषण के लिए आधुनिक गतिविधियों को चित्रित किया गया है। यह अध्याय, शोध प्रबंध में प्रस्तुत किए गए वर्तमान कार्यों एवं उनके भविष्य में होने वाले विस्तार के साथ समाप्त होता है।

इस शोध प्रबंध का **अध्याय 2**, नये यौगिकों के संश्लेषण में अपनाई सामान्य प्रायोगिक अभिक्रियाओं और उपयोग किए गये तकनीकों का विवरण करता है। शोध प्रबंध में वर्णित शुरूआती सामग्रियों के विशिष्ट संश्लेषण का विवरण भी प्रस्तुत किया गया है।

इस शोध प्रबंध का **अध्याय 3**, ruthenium-उत्प्रेरित  $\alpha$ -अल्काइलेटेड कीटोन्स और क्विनोलिन्स की हाइड्रोजन-बॉरोविंग प्रक्रिया द्वारा जलीय माध्यम में संश्लेषण को वर्णित करता है। इस कार्यप्रणाली में, विभिन्न प्रकार के एसिटोफेनॉस और सेकेंडरी-अल्कोहोल्स को अभिक्रमक के रूप में और बेंजाइल अल्कोहोल्स को धारणीय, हरित एल्काइलेटिंग प्रतिनिधियों के रूप में प्रयोग किया गया है। अभिक्रिया करने के लिए, पानी में घुलनशील तथा हवा में स्थिर [Ru(8-AQ)Cl(p-cymene)]Cl यौगिक को उत्प्रेरक के रूप में, क्षार KO<sup>t</sup>Bu की उपस्थिति में जलीय माध्यम में उपयोग किया गया है। नियंत्रण प्रयोगों से यह पाया गया कि  $\alpha$ -अल्काइलेटेड कीटोन्स और क्विनोलिन्स के संश्लेषण के लिए उत्प्रेरक हाइड्रोजन-बॉरोविंग प्रक्रिया का अनुसरण करता है। हमारी पद्धति लक्ष्य उत्पादों के बड़े पैमाने पर संश्लेषण के लिए भी लागू है और यह प्रतिक्रिया के दौरान सह उत्पादों के रूप में H<sub>2</sub>O अणु और H<sub>2</sub> गैस उत्पन्न करती है।

इस शोध प्रबंध का **अध्याय 4**, फेरोसीन कार्बोक्सामाइड व्युत्पन्न के बिस कार्बन-हाइड्रोजन बंध की कार्यात्मकता प्रतिक्रियाओं के लिए निर्देशन समूह सक्षम 'ऑन-वॉटर' पद्धति का विवरण करता है। इस प्रक्रिया में 8-अमीनोक्विनलिन और पिकोलिनामिड को निर्देशन समूह के रूप में और Pd(OAc)<sub>2</sub> को उत्प्रेरक के रूप में जलीय माध्यम में उपयोग किया गया है। सबस्ट्रेट स्कोप इस अभिक्रिया की विभिन्न इलेक्ट्रान-दाता और इलेक्ट्रान-निकाशी अभिक्रमकों के उपयोगिता को दर्शाता है। सबस्ट्रेट्स, अभिक्रमकों और उत्पादों की अघुलनशील प्रकृति, हमें विलायक यानी पानी और उत्प्रेरक की आगे की प्रतिक्रिया चक्रों के लिए पुनः प्रयोज्यता का पता लगाने में मदद करता है। 'ऑन-वॉटर' पद्धति के कारण, हमारी अभिक्रिया में उपयोग होने वाले उत्प्रेरक की मात्रा पिछली रिपोर्ट्स की तुलना में कम है, जो हमारी पद्धति को अन्य पद्धतियों से हरित और कार्यक्षम बनाता है। यंत्रवत मार्ग को समझने के लिए नियंत्रण प्रयोग किए गए जो यह बताते हैं कि, अभिक्रिया के दौरान *इन सीटू* मध्यवर्ती पैलेडासाइकिल बनता है।

इस शोध प्रबंध का **अध्याय 5**, एरिल एसिड्स और बेंजाइल/नाफ्थाइल एमीन्स व्युत्पन्न के कार्बन-हाइड्रोजन बंध की कार्यात्मकता प्रतिक्रियाओं के लिए निर्देशन समूह सक्षम 'ऑन-वॉटर' पद्धति का विवरण करता है। इस प्रक्रिया में उपर्युक्त निर्देशन समूह के उपयोग से चयनात्मक मोनो और बिस कार्बन-हाइड्रोजन बंध की कार्यात्मकता प्रतिक्रियाओं को प्राप्त किया गया। इस पद्धति की प्रयोज्यता दर्शाने के लिए महत्वपूर्ण योगिकों का लेट-स्टेज कार्यात्मकता और उत्पादों का बड़े पैमाने पर संश्लेषण को दर्शाया गया है। विलायक और उत्प्रेरक की आगे की प्रतिक्रिया चक्रों के लिए पुनः प्रयोज्यता हमारी पद्धति को अन्य पद्धतियों से हरित और कार्यक्षम बनाता है। कार्यात्म उत्पादों की पुनः व्युत्पत्ति करने के लिए निर्देशन समूह का निष्कासन भी सफलतापूर्वक दिखाया

गया है। सब्सट्रेट स्कोप के साथ अभिक्रिया के दौरान बनने वाले मध्यवर्ती पैलेडासाइकिल को जानने के लिए नियंत्रण प्रयोग भी किये गये हैं।

इस शोध प्रबंध का **अध्याय 6**, पृथ्वी में प्रचुर मात्रा में उपलब्ध मैंगनीज उत्प्रेरक द्वारा अल्कोहोल्स को एक धारणीय, हरित एल्काइलेटिंग प्रतिनिधियों के रूप में प्रयोग करके सल्फोन्स के  $\alpha$ -कार्बन-हाइड्रोजन बंध के अल्कीलेशन को वर्णित करता है। शाखित सल्फोन्स के संश्लेषण के लिए एक सुलभ और व्यावसायिक रूप से उपलब्ध लिगैंड का उपयोग करके (NNN)Mn(II)Cl<sub>2</sub> उत्प्रेरक प्रणाली को विकसित किया गया है। नियंत्रण प्रयोगों से यह पाया गया कि शाखित सल्फोन्स के संश्लेषण के लिए (NNN)Mn(II)Cl<sub>2</sub> उत्प्रेरक हाइड्रोजन-बॉरोविंग प्रक्रिया का अनुसरण करता है।

इस शोध प्रबंध का **अध्याय 7**, वर्तमान अध्ययन में किए गए संपूर्ण कार्य का समग्र निष्कर्ष देता है।

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## List of Abbreviations Used

Anal.	Analysis
<i>i</i> Pr	Isopropyl
Calcd.	Calculated
Cp	Cyclopentadiene
Me	Methyl
Et	Ethyl
Ph	Phenyl
Fc	Ferrocene
Mp	Melting point
RT	Room Temperature
h	Hour(s)
min	Minutes
THF	Tetrahydrofuran
UV	Ultraviolet Spectroscopy
TLC	Thin Layer Chromatography
NMR	Nuclear Magnetic Resonance Spectroscopy
HRMS	High Resolution Mass Spectroscopy
PyO	Pyridine- <i>N</i> -oxide
TDG	Transient directing group
DG	Directing group
DMSO	Dimethyl sulfoxide
SCXRD	Single crystal X-ray diffraction

DCM	Dichloromethane
DMF	<i>N, N</i> -dimethyl formamide
Aq.	Aqueous
TON	Turn Over Number
DCE	1, 2-dichloroethane
GC-MS	Gas Chromatography-Mass Spectrometry
NNN	<i>N</i> -((1 <i>H</i> -benzo[ <i>d</i> ]imidazol-2-yl)methyl)quinolin-8-amine
8-AQ	8-Aminoquinoline
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
COD	Cyclooctadiene
NMP	<i>N</i> -Methyl pyrrolidone
HFIP	Hexafluoro-2-propanol
GVL	$\gamma$ -Valerolactone
PEG	Polyethylene glycol
DMS	Dimethyl sulfide
DMAP	4-Dimethylaminopyridine
NHC	<i>N</i> -Heterocyclic carbene
DMA	Dimethylacetamide
NBS	<i>N</i> -Bromosuccinimide
KHMDS	Potassium hexamethyl disilazide
NaHMDS	Sodium hexamethyl disilazide