# DEVELOPMENT OF LEWIS ACID-PROMOTED METHODOLOGIES FOR C-N AND C-S BOND FORMATION: UNLOCKING THE SYNTHESIS OF AMINES, THIOETHERS AND N-HETEROCYCLES

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*by*

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**Doctor of Philosophy**

*to the*


**INDIAN INSTITUTE OF TECHNOLOGY DELHI**

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*"I would like to dedicate this work to my mother,* ***Mrs Janawati Devi,*** *her love, strength, and constant belief in me have been my guiding light. Though she is no longer with me, her memory and the lessons she taught me will forever remain a part of who I am. I am deeply grateful for her support and the inspiration she continues to provide. "*

# CERTIFICATE

This is to certify that the thesis entitled ***"Development of Lewis Acid-Promoted Methodologies for C-N and C-S Bond Formation; Unlocking the Synthesis of Amines, Thioethers and N-Heterocycles"*** being submitted by Mr. **Rahul Vishwakarma** to the *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. **Rahul Vishwakarma** 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 a 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.*

**Dr. Chinmoy Kumar Hazra**

Research Supervisor,

Associate Professor,

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Rahul Vishwak:arma

## Abstract

The thesis titled ***"Development of Lewis Acid-Promoted Methodologies for C-N and C-S Bond Formation: Unlocking the Synthesis of Amines, Thioethers, and N-Heterocycles"*** offers a detailed exploration of Lewis acid-promoted strategies for synthesizing C-N and C-S bonds. It emphasizes the identification of innovative pathways for preparing homoallylic amines, aryl thioethers, substituted quinolines, tetrahydroquinolines, and N-alkylated amines, applicable to both small and large-scale synthesis. By combining mechanistic insights with an expanded substrate scope and meticulous optimization of reaction conditions, this research seeks to establish versatile and sustainable methodologies for organic synthesis. These methodologies are also applied for the late-stage functionalization of natural products and pharmaceutical compounds. The strategies presented in this thesis contribute significantly to the advancement of bond-forming reactions and can substantially impact the synthesis of valuable compounds across diverse chemical disciplines.

**Chapter 1** explores the strategic application of acid catalysis in the formation of carbon-nitrogen (C-N) and carbon-sulfur (C-S) bonds-transformations that are central to the synthesis of pharmaceuticals, agrochemicals, and advanced functional materials. Emphasis is placed on both Br0nsted and Lewis acid catalysis, highlighting their mechanistic roles and advantages in promoting efficient, selective, and atom-economical reactions. Particular focus is given to trimethylsilyl trifluoromethanesulfonate (TMSOTf), a powerful Lewis acid catalyst that enables a variety of transformations, including glycosidation, 0- and C-silylation, and dipolar cycloadditions. This work also discusses the mechanistic versatility of TMSOTf in activating diverse functional groups and facilitating multicomponent reaction strategies. The studies presented herein provide a foundation for the development of new acid-catalysed protocols and underscore the continuing relevance of acid catalysis in modem synthetic organic chemistry.

**Chapter 2** demonstrates the synthesis of homoallylic amines, quinolines, and tetrahydroquinolines. The domino one-pot multi-component approach has been accomplished using Lewis acid-catalyzed conditions. A useful scaffold construction strategy can be achieved by controlling the electronic effect of aniline rather than relying on reaction conditions. The described method applies to a wide variety of substrates embedded with diverse functional groups and can be extended toward the synthesis of natural products. Suitable control experiments, real-time NMR studies, and DFT calculations have validated the reported process.

The protocol outlines a strategy for synthesizing homoallylic amines and quinolines, controlled by the electronic properties of anilines.

**Chapter 3** describes the development of a one-pot, organocatalytic approach for the synthesis of N-alkylated secondary and tertiary amines. The reaction proceeds *via* the reduction of *in-situ* generated imines, where the solvent acts as a hydride surrogate in the presence of TMSOTf, thereby facilitating the alkylation process. Mechanistic insights, derived from control experiments and deuterium labeling studies, reveal a solvent-mediated hydride transfer pathway, underscoring the efficiency of this approach. This methodology offers a streamlined approach to amine alkylation, eliminating the need for metal catalysts and providing a potentially more sustainable alternative to traditional protocols.

**Chapter 4** describes the development of an efficient catalytic system employing TMSOTf for the regioselective thiolation of electron-rich arenes with sulfonyl hydrazides. The reaction occurs in a solvent mixture of dichloroethane and trifluoroethanol under mild conditions, with the addition of water. This method furnishes a range of para-thio-substituted arenes and 3-sulfenyl-indoles in good to excellent yields, marking a significant advancement in organic synthesis.

**Chapter 5** gives the overall conclusions of the entire work carried out in the present study and future outline.

# सारांश


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aik''lFJ-iiJ-B/fibffl ' **J;** -B°'<d'lJ'OJ' qJJ-Jjrjfflip ¯ifiRT"

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ti !JW JfR "CR 'S<cilSlOl'' $ ffl1]_ '-11QRIR!c.t,' ' ' ''QJ-11'1',

''-1TRi-1,' 'e'1t;1' ,T..:l1Ri-1 ' ' JrR lFf-'q' 8e'6' ' ''QJ-11-1'ffiq)B$

m-rif '4'6'il'H'' ti ' ' «'11'Ra' ''tl c:' ' '3fR ''1.1Rlfihi11'' $

31jif? H'$ mtf "ct,T'utl'9c.t,-{, !JW "5<tt' c.t,lc.t,' ' S<cilSlOl'' $ 'at§Jffifl' **'3fR**

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''c.t,'1qfc.t,c.t,-{Ol''' iftffl1J_f<Pmuf@Ttl **ll** '-{Ol4lffiqifi-

'q,'frnJl''s.iffifihq1"3if **ll** J-1t;cc1q:of' 'q"1T1&1-1 **mttW** JfR '-{1-t'11qPlc.t,' **ll**

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'c.t,'lqMc.t,''t!1J-l ql'' 'S<cilSlOl''$ WI JfR 'c.t,'Rl't!' ' "CR

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urrq s 11qcfJ-1H 3f 11f npnr t cfTT4 * lSr.t,t{ dfR ¥4 1cft i1

# Table of Contents

## List of Abbreviations Used

| | |
|---|---|
| lPr | Isopropyl |
| *tBu* | Tert-butyl |
| TMB | 1,3,5-Trimethoxy benzene |
| Me | Methyl |
| Et | Ethyl |
| Ph | Phenyl |
| MP | Melting point |
| RT | Room Temperature |
| h | Hours |
| min | Minutes |
| THF | Tetrahydrofuran |
| UV | Ultraviolet Spectroscopy |
| TLC | Thin Layer Chromatography |
| HFIP | Hexafluoroisopropanol |
| TFE | 2,2,2-Trifluoroethanol |
| IPA | Isopropyl alcohol |
| EtOAc | Ethyl acetate |
| NMR | Nuclear Magnetic Resonance Spectroscopy |
| HRMS | High Resolution Mass Spectroscopy |
| NOESY | Nuclear Overhauser Effect Spectroscopy |
| DG | Directing Group |
| DMSO | Dimethyl sulfoxide |
| DMF | *N,* N-Dimethylformamide |
| DCM | Dichloromethane |
| Aq. | Aqueous |
| SCXRD | Single Crystal X-ray Diffraction |
| TON | Tum Over Number |
| DCE | 1,2-Dichloroethane |
| DDQ | 2,3-Dichloro-5,6-Dicyanobenzoquinone |

| | |
|---|---|
| GC-MS | Gas Chromatography Mass Spectrometry |
| Boe | tert-butyloxycarbonyl |
| Cbz | benzyloxycarbonyl |
| Dq | doublet of a quartet |
| dr | diastereomeric ratio |
| dt | doublet of a triplet |
| equiv | equivalents |
| Hz | Hertz |
| Ppm | parts per million |
| t | triplet |
| td | triplet of a doublet |
| m | multiplet |
| tert | tertiary |
| pTSA•H20 | para-toluenesulfonic acid monohydrate |
| TMS | trimethylsilyl |
| TMSOTf | Trimethylsilyl trifluoromethanesulfonate |
| TLC | thin-layer chromatography |
| BzOH | Benzoic acid |
| TfDH | Triflic Acid |
| Cbz | benzyloxycarbonyl |