Abstract

The contents of the thesis entitled "**Metal and Oxidant Free Direct C(sp^3)-H Arylation of *N*-heterocycles**" have been divided into six chapters based on the results of experimental works performed during the complete course of the research period. Carbon–hydrogen bonds are abundant in most organic molecules. Methods for their direct and selective functionalization are attractive as an efficient means to access more complex molecular structure. The first chapter of the thesis presents a review on different aspects of C-H arylation of secondary amines. Chapters 2-4 describes the studies on the metal and oxidant free direct C(sp^3)-H arylation of *N*-heterocycles (e.g. pyrrolidine, substituted pyrrolidines, 1,2,3,4-tetrahydroisoquinoline and *β*-carbolines). Chapter 2 describes metal and oxidant free route to direct C(sp^3)-H arylation of pyrrolidine. In Chapter 3, a regio-, diastereo and enantiospecific metal free C(sp^3)-H arylation of 2-substitued pyrrolidines has been described. The method was found to be efficient for the synthesis of optically active 5-aryl-2,5-disubstituted pyrrolidine. Chapter 4 describes direct C-H arylation of 1,2,3,4-tetrahydroisoquinoline and *β*-carbolines under metal, oxidant, and solvent free conditions. C-H functionalization enabled stereoselective Ugi-azide reaction of *N*-heterocycles to *α*-tetrazolyl alicyclic amines has been described in chapter 5. Finally, Chapter 6 contain the copies of ^{1}H, ^{13}C NMR spectra, and HPLC chromatogram, of selected new compounds respectively.

Chapter 1: C(sp^3)-H Arylation of Secondary Amines

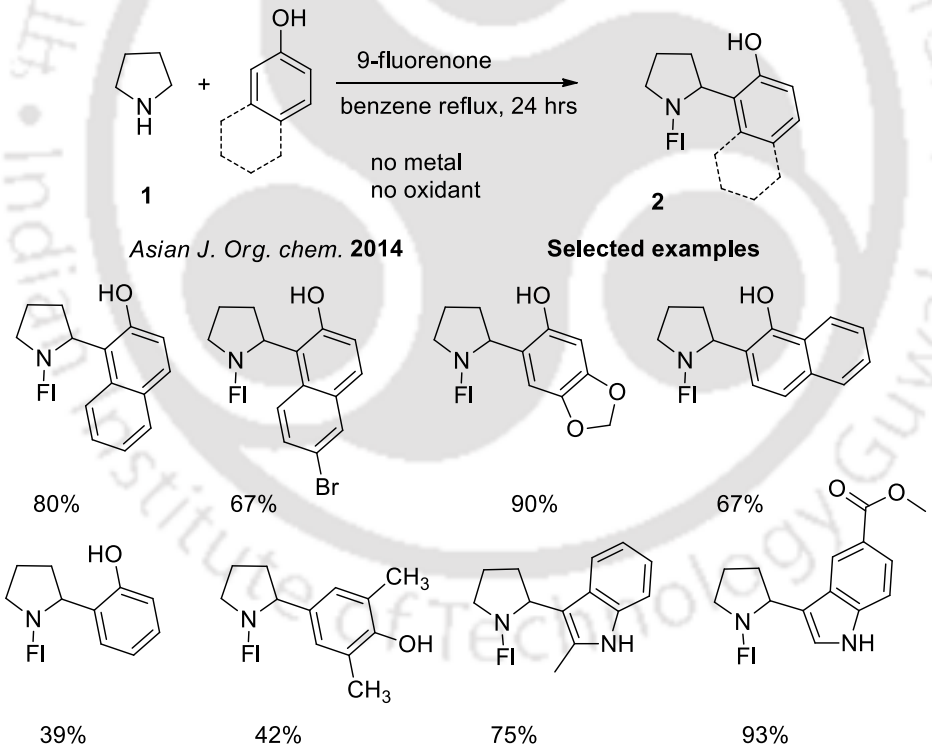
An aryl group at the *α*-position of an amine is frequently observed in drug molecules, natural products and auxiliaries/or catalyst for asymmetric transformations. This chapter summarizes the known strategies for the synthesis of arylated *N*-heterocycles. Sometimes, *N*-cycloalkyalation strategies involving chiral amines were adopted for the synthesis of arylated *N*-heterocycles. *α*-deprotonation of *N*-Boc-protected pyrrolidine with a strong base followed by transmetallation and subsequent coupling with arene based substrates has been widely used for the preparation of *α*-arylated pyrrolidine. One of the approaches involves transition metal catalyzed directed arylation of *N*-heterocycles. Metal and photo catalyzed Cross-Dehydrogenative- Coupling (CDC) reaction of arene and *N*-heterocycles have been popular for the synthesis of arylated *N*-heterocycles. Arylated *N*-heterocycles were also synthesised from pre-functionalized and pre-oxidized *N*-heterocycles. However the practical applications of these are limited due to involvement of toxic and expensive metal catalyst, oxidants and harsh reaction

conditions. Therefore the main aim of the thesis is to develop of novel synthetic methodologies, which are environment friendly and free from the aforementioned difficulties.

Chapter 2: Metal and Oxidant Free Direct C(sp^3)-H Arylation of Pyrrolidine

All of the known protocol for direct arylation of saturated *N*-heterocycles generally involve the use of organometallic reactants either in stoichiometric and/or catalytic amount in the presence of toxic oxidants. In another approach preoxidized starting materials were used for the arylation with or without metal-based reagents. Therefore, all of these known processes produce toxic chemical wastes, which are a burden to the environment.

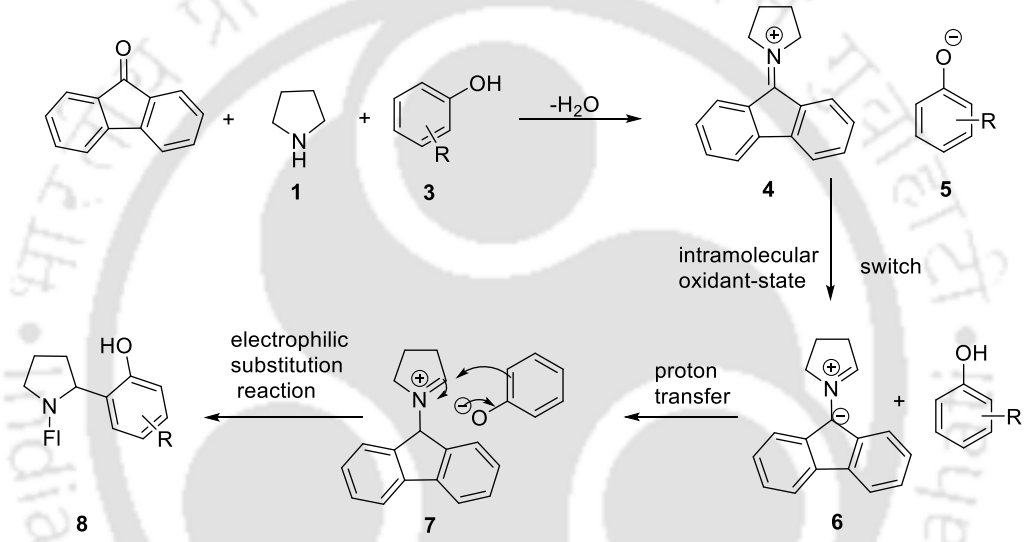
A metal-free, oxidant-free, atom-economic and operationally simple method for direct α-C-H arylation of pyrrolidine via a three component reaction, without any additional aid has been developed. Arylated pyrrolidines were formed from the reaction of pyrrolidine and electron rich arene in the presence of 9-fluorenone under reflux in benzene with excellent yield. The method is highly regioselective and very efficient even on a gram scale.



Scheme 1: Direct C-H arylation of pyrrolidine by electron rich nucleophiles, phenols napthols and indoles.

Based on the experimental findings a mechanistic proposal for the metal- and oxidant-free atom-economic α-C-H arylation of pyrrolidine is presented in Scheme **2**. Pyrrolidine condenses with 9-fluorenone with the assistance of the phenolic OH group (**3** as a proton source) to form the corresponding iminium cation **4**, which is accompanied by phenolate

anion **5**. Base-(pyrrolidine or phenolate) aided isomerization of parent iminium ion **4** occurs to produce the azomethine ylide **6**, which has a fluorenyl anion moiety that is stabilized by its aromaticity. A secondary iminium ion **7** is probably formed through protonation of azomethine ylide **6**. The oxidation state switch from the fluorenone carbon in **4** to the C2 position of pyrrolidine in **7** eliminates the possibility of Mannich or Betti product formation. Then, the secondary iminium ion **7** reacts with the phenolic compound by an aromatic electrophilic substitution reaction to provide the α-arylated product **8**. The close association (as shown in Scheme **2**) of the electrophilic iminium ion **7** with the nucleophilic phenolate anion probably directs the reaction entirely through the *ortho* position and consequently brings the exclusive regioselectivity.

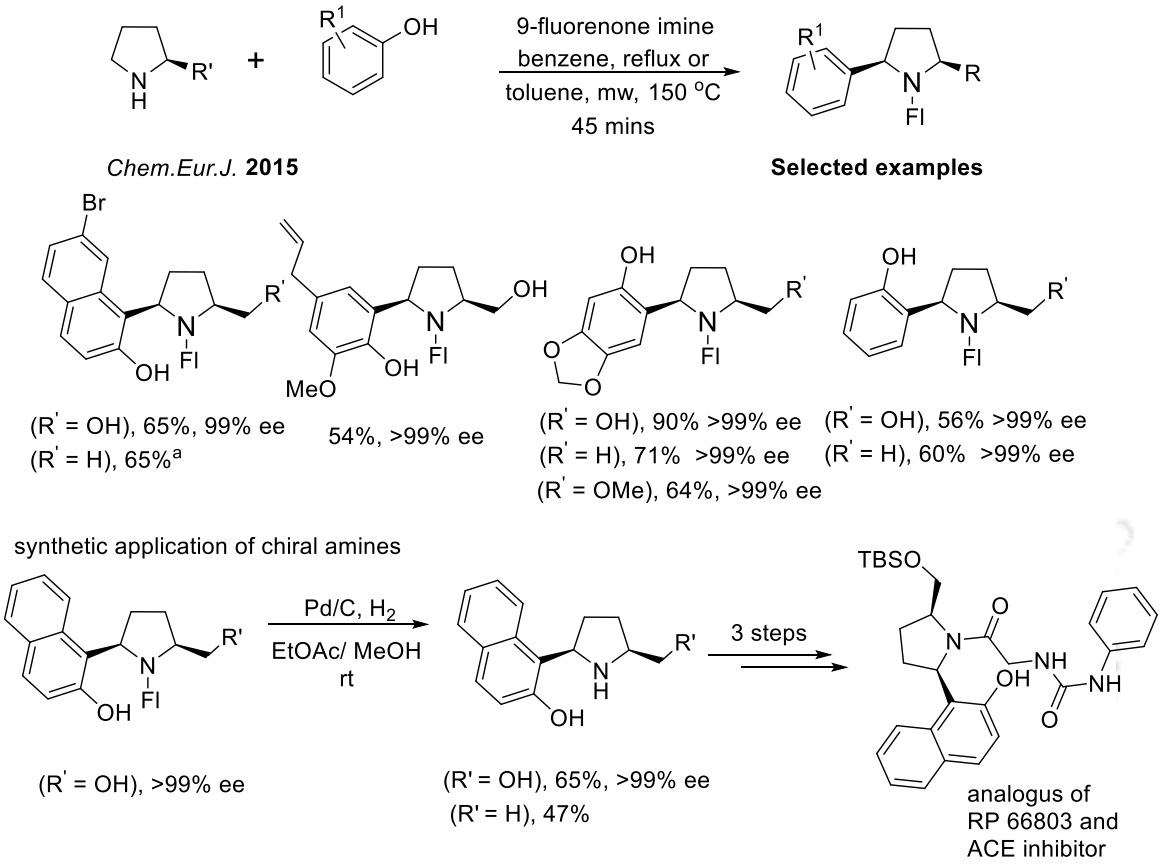


Scheme 2: Proposed reaction mechanism for metal free arylation of pyrrolidine.

Chapter 3: Regio-, Diastereo-selective and Enantiospecific Metal Free C(sp^3)-H Arylation: A Facile Access To Optically Active 5-aryl 2,5-Disubstituted Pyrrolidine

Optically active 5-aryl-2,5-disubstituted pyrrolidines are the principal structural moieties of many bioactive compounds including natural products and catalysts for asymmetric synthesis. Various methods have been reported for the synthesis of the arylated pyrrolidines. However, strategies for syntheses of these molecules in enantiomerically pure form are limited. A highly regio- and diastereo-selective and enantiospecific method for direct α-CH arylation of substituted pyrrolidine has been developed under metal and oxidant free conditions. Structurally diverse enantiopure arylated pyrrolidines were synthesized from commercially available starting materials, through a single-step three-component reaction under metal- and oxidant-free

conditions. Optically active arylated pyrrolidine was shown to be useful for the easy and efficient synthesis of structural analogues of RP 66803 and ACE inhibitors. Furthermore, DFT studies were performed to explore the mechanistic route for the selective C-H arylation reaction.

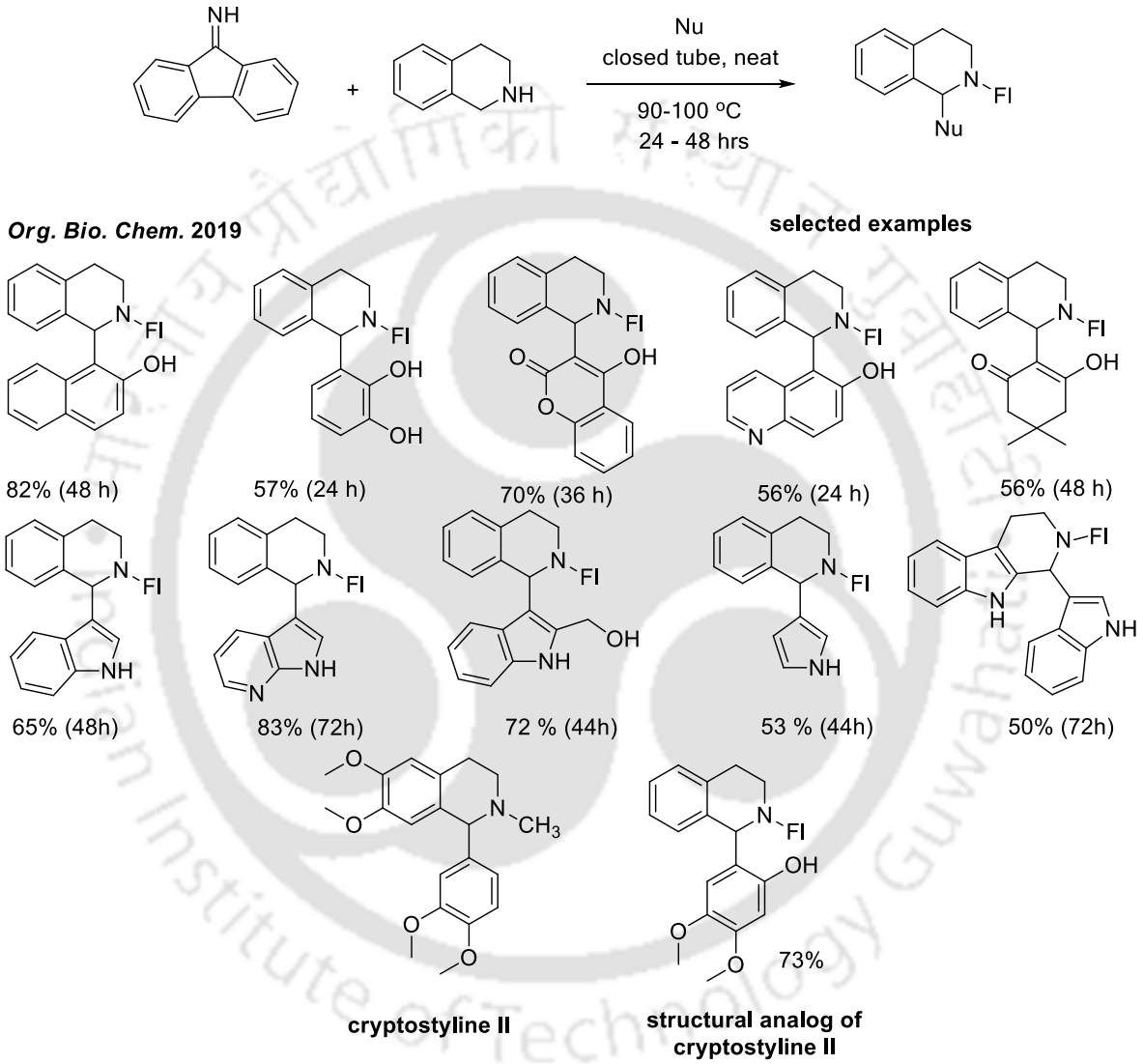


Scheme 3: Direct stereoselective C-H arylation of substituted pyrrolidines and synthetic application of chiral amines. [a] The reaction were carried out with racemic amine.

Chapter 4: Metal, Oxidant and Solvent Free Direct C(sp^3)-H Arylation of 1,2,3,4-Tetrahydroisoqunolines and *β*-Carbolines

Tetrahydroisoquinoline is a privileged heterocyclic skeleton and a variety of its natural and unnatural derivatives exhibit wide range of biological activities. Therefore, a number of methodologies for the efficient preparation of such compounds have been developed. Pictet−Spengler condensation and the Bischler−Napieralski cyclization/reduction sequence were mostly used. *α*-C−H arylation of THIQs presents a novel synthetic strategy for direct access to this molecules. Toxic and expensive transition metal catalysts, oxidants and harsh conditions, which limit their practical application, were mainly used in most of the known strategies. An operationally simple, highly atom economic three component reaction for

efficient and high yielding C(sp^3)-H bond functionalization of 1,2,3,4-tetrahydroisoquinolines and β-carbolines have been developed under metal, oxidant and solvent free condition. The method also allowed the synthesis of the structural analogues of cryptostyline II.

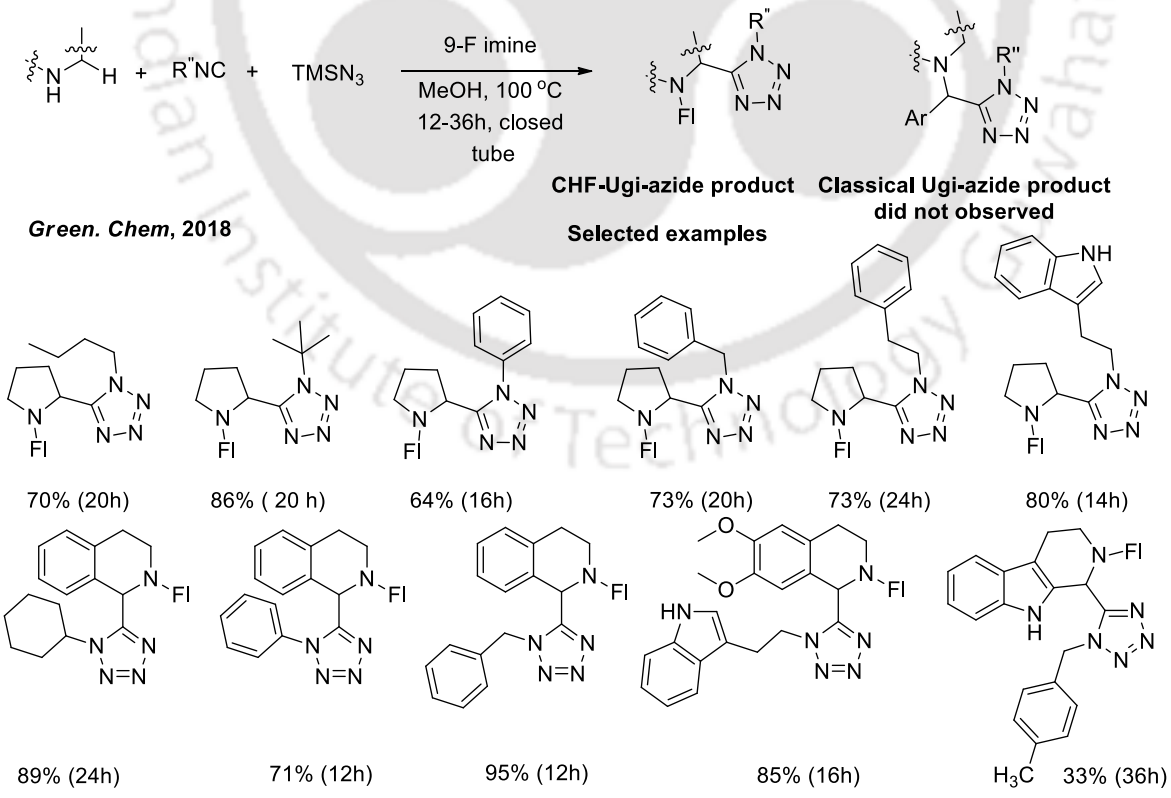


Scheme 4: Direct C-H Arylation of 1,2,3,4-tetrahydroisoquinoline and β- carboline.

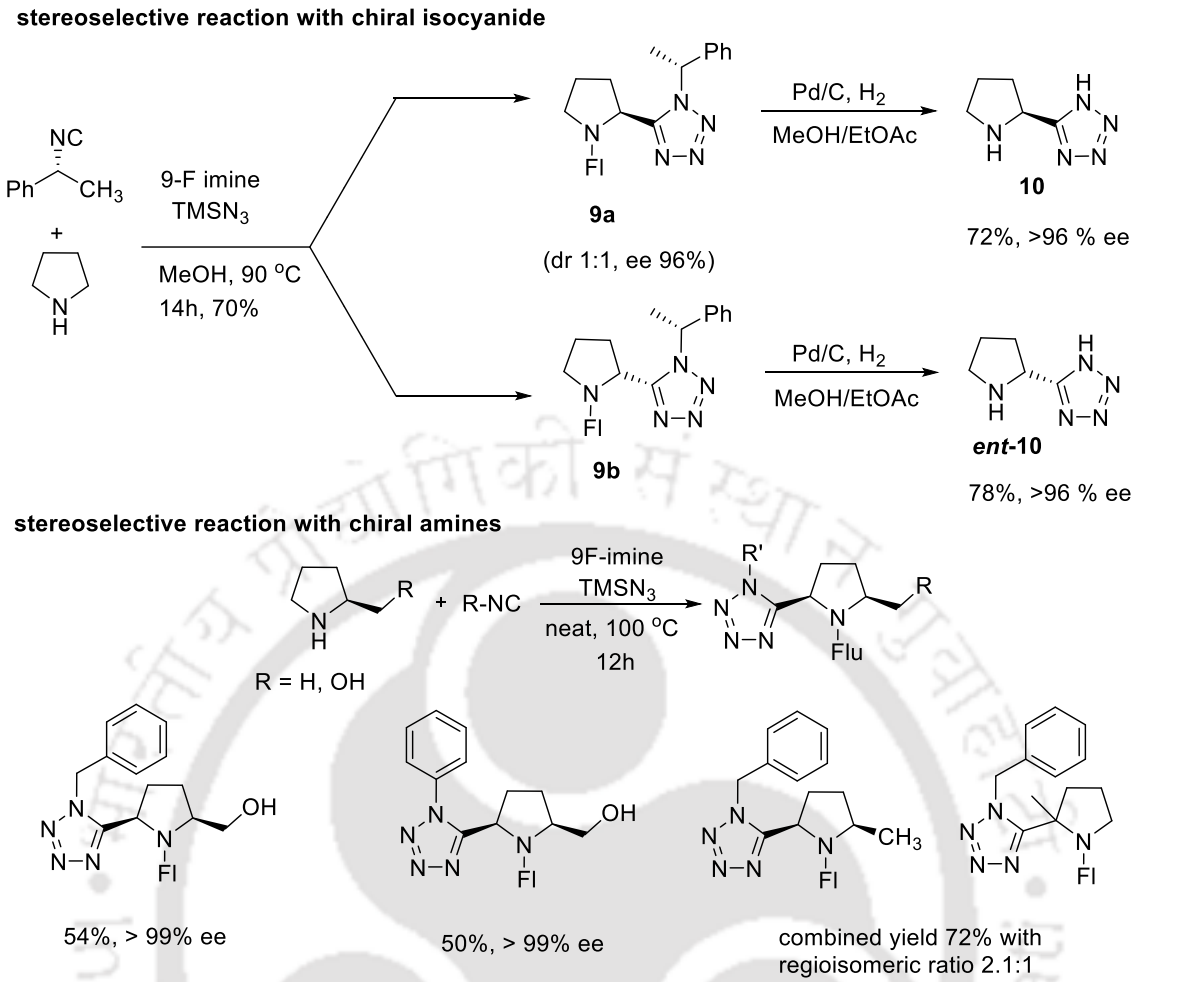
Chapter 5: C-H Functionalization Enabled Stereoselective Ugi-azide reaction to α-tetrazoyl Alicyclic Amines

In recent years multicomponent reactions are one of the most powerful synthetic tools for the chemist to produce simple organic molecules to diverse complex molecules. As large variety of C-H bonds are present in organic molecules, the integration of C-H functionalization into multicomponent reaction would provide an opportunity to greatly expand the scope and

product diversity. Among these multicomponent reactions, isocyanides based four component (Ugi-4CR) Ugi-azide reactions is well- known for its efficiency in preparation of tetrazole derivative. Tetrazoles are important class of compounds because of their wide range of application as the medicinal drug, ligand for metal ion, imaging agent precursors for metal-organic frame work and highly energetic compounds. In particular, *α*-tetrazoyl amines, which are tetrazole analogs of amino acids, have been recognized as the interesting scaffolds in peptidomimetics and medicinal chemistry. Additionally, enantiopure *α*-tetrazoyl pyrrolidine is widely used as organocatalyst in asymmetric organic synthesis. Related tetrazoyl pyrrolidine derivative also utilized for the synthesis of aza-sugar containing nucleoside analogs. The known synthesis of aza-sugar containing nucleoside analogs required multistep reaction sequences. The first example of a metal and oxidant free C-H functionalization enabled azido-Ugi reaction (CHF-Ugi-azide) is developed (scheme **5**). The reaction enables direct conversion of *N*-heterocycles to α-terazoyl *N*-heterocycles instead of tetrazoyl methyl amines that generally are formed through calassical Ugi-azide reactions. Importantly, the stereoselective reaction involving chiral amines or chiral isocyanides allowed the expeditious syntheses of aza-sugar containing nucleoside analogs and *α*-tetrazoyl pyrrolidine in enantiopure form.

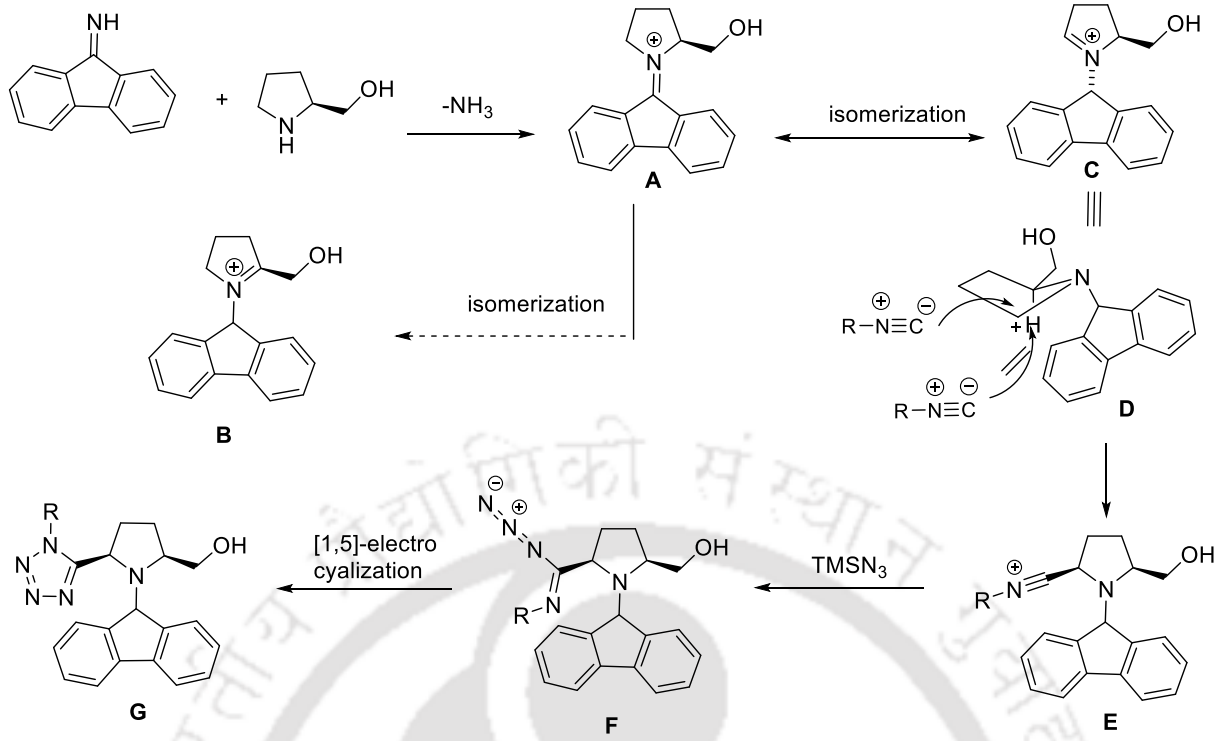


Scheme 5: C-H functionalization of enabled via Ugi-azide reaction.



Scheme 6: Streoselective CHF-Ugi-azide reaction with chiral isocyanides and chiral amines.

A plausible reaction mechanism has been proposed for the CHF-Ugi-azide reaction (**scheme 7**). Activator (9F-imine) reacts with prolinol to produce iminium ion **A**. Isomerization of the initially formed iminium ion **A** could be preferentially drawn towards **C** probably due to the unfavourable allylic strain in its regioisomer **B**. Then, the isocyanide approached from the less hindered side of **D** where the fluorenyl group prefers to remain in the opposite side of $–CH_2OH$ group to avoid the steric interaction. The nitrilium ion **E** with *syn* geometry reacted with $TMSN_3$ to give the corresponding adduct **F**. Finally, [1, 5] electrocyclization of **F** provided the desired product **G** with observed *syn* stereochemistry.



Scheme 7: Plausible reaction mechanism for the synthesis of tetrazole substituted cyclic amines.