Chapter 1: General Introduction

1.1. Cascade Reactions in Organic Synthesis

Multi-bond forming processes that generate two or more new covalent bonds in a single synthetic operation have attracted considerable attention of synthetic organic chemists and the versatility of this strategy has been exploited for the synthesis of diverse range of compounds of biological interest and natural products.\(^1\) The two major classes of multi-bond forming reactions include cascade or domino or tandem reactions and multicomponent reactions. In cascade reactions, several sequential transformations take place in one synthetic operation for the formation of two or more bonds under identical conditions, in which the functionalities obtained in the first reaction undergo the subsequent reaction (Scheme 1.1). Cascade reactions that occur in one-pot, require only a single reaction solvent, workup procedure and purification step, fall under green chemistry owing to the accepted benefits including step and atom economy, reduction of waste production, creation of molecular complexity, cost effectiveness etc.\(^2,3\) The another class of multi-bond forming process include multicomponent reactions, where three or more reactants combine to form a single product having considerable portions of all the reactants.\(^4\) All the multicomponent reactions can be considered as cascade reactions and substantial number of one- and two-component cascade reactions has also been developed.

Robinson’s one-pot, three-component synthesis of tropinone \(1.4\) starting from succinaldehyde \(1.1\), methylamine \(1.2\) and acetonedicarboxylic acid \(1.3\) remains one of the earliest examples of cascade/domino reactions.\(^5\) Initial reaction between succinaldehyde \(1.1\) and methylamine \(1.2\) generates iminium cation \(A\) with two new C–N bonds, which
subsequently reacts with compound 1.3 to generate the second intermediate B. Final intramolecular iminium ion cyclization followed by decarboxylation affords tropinone 1.4 via the intermediacy of dicarboxylic acid C. In this one-pot cascade reaction, four new bonds (two C–N and two C–C) and two rings were created in a single synthetic operation involving three intermediates (Scheme 1.1).

![Scheme 1.1](image_url)

**Scheme 1.1.** Representative example of three-component cascade reaction: Robinson’s tropinone synthesis

### 1.2. Nucleopalladation-Initiated Cascade Reactions

Palladium-catalyzed cascade process has emerged as promising approach for the construction of complex molecules by creating several carbon–carbon, carbon–heteroatom bonds and rings through a single synthetic operation. These sequential one-pot reactions including cascade, domino or tandem processes, in general, are considered
to be an alternative, often superior to the classical multistep syntheses. Indeed, on several occasions, molecules that cannot be accessed through conventional methods could be synthesized by means of cascade reactions. Although a large number of strategies including palladium catalysis were employed to initiate these sequential processes, over the past three decades, nucleopalladation-initiated cascade reactions were found to be expedient to achieve diverse products elegantly. In particular, intramolecular nucleophilic cyclization of alkynes in the presence of palladium catalysts and the subsequent domino reactions were considered to be a prominent strategy to access complex molecules.

The nucleopalladation of alkynes, both inter and intramolecular versions, generate σ-vinylpalladium intermediates A and B, which undergo various cascade transformations including olefin insertion (Heck-type coupling), 1,2-addition to carbonyl, nucleophilic addition to CN, alkoxy carbonylation, arylation, alkyne, carbene, isocyanide, isocyanate insertion etc. for the generation of diverse products in a single operation (Scheme 1.2). The most common nucleopalladation-initiated reactions including aminopalladation, oxypalladation, carboxypalladation, halopalladation, carbopalladation and hydropalladation-initiated cascade reactions have been explored for the synthesis of a wide range of products. Herein, we summarize the recent literature that covers the above-mentioned nucleopalladation-initiated cascade reactions to access compounds of biological interest. The mechanisms of these cascade reactions have also been discussed in the respective sections.
1.2.1. Aminopalladation-Initiated Cascade Reactions

The intramolecular aminopalladation of alkynes and the subsequent cascade reactions were recognized as one of the simplest approaches to access highly functionalized nitrogen heterocycles including indoles, pyrroles, carbazoles etc.\textsuperscript{10} For instance, the first example of aminopalladation-triggered carbene insertion of alkynes \textsuperscript{1.5} in the presence of PdCl\textsubscript{2} under basic conditions furnished the C-3 alkylated indoles \textsuperscript{1.7} (Scheme 1.3).\textsuperscript{11} The intramolecular aminopalladation of the deprotonated species A generates σ-indolylpalladium intermediate B and the successive insertion of carbene \textsuperscript{1.6} delivers the desired product \textsuperscript{1.7} via the intermediacy of species C. In this reaction, migratory insertion of the carbene into the σ-indolylpalladium intermediate was favored over the competitive N–H insertion.
Scheme 1.3. Intramolecular aminopalladation-carbene insertion cascade

The synthesis of benzo[α]carbazole derivatives was achieved via intramolecular aminopalladation-initiated cascade process. As demonstrated in Scheme 1.4, alkynes 1.8 undergo palladium-catalyzed aminopalladation followed by intramolecular nucleophilic addition to cyano or aldehyde moiety to furnish the benzo[α]carbazole derivatives 1.9 and
The formation of compound 1.9 could be visualized via \( \sigma \)-indolylpalladium intermediate B and the palladium species C.

Recently, Lu and co-workers reported the diastereoselective synthesis of pentaleno[2,1-b]indoles 1.12 starting from alkynes 1.11 involving an aminopalladation-initiated cascade process (Scheme 1.5).\(^{13}\) The mechanism of the reaction comprises initial palladium-triggered intramolecular aminopalladation of intermediate A to deliver \( \sigma \)-indolylpalladium species B. Successive intramolecular nucleophilic addition of the C–Pd bond to the carbonyl group followed by hydrolysis furnish the desired products 1.12 via intermediate C.

![Scheme 1.5. Intramolecular aminopalladation-carbonyl addition sequence](image)

The synthesis of pyrrole/furan-3-carboxamides was achieved via aminopalladation/oxy palladation-isocyanate insertion cascade.\(^{14}\) 1-Amino-3-alkyn-2-ols and 3-alkyne-1,2-diols 1.13 reacted with PdCl\(_2\) under basic conditions to generate
intermediate A, which undergoes successive isocyanate insertion to furnish the desired pyrrole and furan derivatives \textbf{1.14} \textit{via} species B (Scheme 1.6).

![Scheme 1.6. Aminopalladation/oxypalladation-isocyanate insertion cascade](image)

Palladium-catalyzed oxidative coupling between 2-alkynyl anilines \textbf{1.15} and allylic alcohols \textbf{1.16} was established for the synthesis of β-indole ketones \textbf{1.17} (Scheme 1.7).\textsuperscript{15} Initial intramolecular aminopalladation of alkyne \textbf{1.15} furnishes vinylpalladium intermediate A, which undergoes insertion of allyl alcohol to C–Pd bond to yield the desired products through intermediate B.

![Scheme 1.7. Aminopalladation-initiated oxidative Heck reaction](image)

\textbf{1.2.2. Oxypalladation-Initiated Cascade Reactions}

Oxypalladation-initiated cascade process was recognized as an efficient strategy for the synthesis of biologically significant oxygen heterocycles including benzofurans, isoxazoles, pyrones, furans and isocoumarins.\textsuperscript{16} Cyclohexane fused isocoumarins \textbf{1.19}
were synthesized in high yields involving a cationic Pd(II)-catalyzed cascade cyclization reaction of alkynes 1.18 (Scheme 1.8). Initial intramolecular oxypalladation of alkyne A with ester group generates intermediate B with loss of isobutene. Next, intramolecular 1,2-addition of C–Pd bond to the carbonyl group affords intermediate C, which upon protonation yields the expected products 1.19. In some cases, protonolysis of intermediate B furnishes compounds 1.20.

**Scheme 1.8.** Intramolecular oxypalladation of ester oxygen-initiated cascade synthesis of isocoumarins

The synthesis of heterocycle-fused β-naphthylamines 1.22 was established involving intramolecular oxy/aminopalladation of alkynes 1.21 followed by nucleophilic addition of C–Pd bond to the intramolecular cyano group via intermediates A–C (Scheme 1.9).
Scheme 1.9. Intramolecular oxy/aminopalladation-nucleophilic addition sequence

Jiang and co-workers reported a highly regioselective intramolecular oxypalladation (6-endo-dig cyclization) of alkynes \( \text{1.23} \) followed by Mizoroki-Heck reaction with allyl alcohol \( \text{1.24} \) for the synthesis of isocoumarin derivatives \( \text{1.25} \) (Scheme 1.10).\(^{19}\) The desired product \( \text{1.25} \) was obtained from intermediate \( \text{C} \) involving β-hydride elimination, reinsertion of the hydrated palladium species and the second β-hydride elimination steps.

Scheme 1.10. Oxypalladation-Mizoroki-Heck reaction cascade
1.2.3. Halopalladation-Initiated Cascade Reactions

Halopalladation of alkynes in the presence of LiX or CuX₂ and the subsequent cascade reactions allowed the simultaneous construction of C–C and C–halogen bonds.²⁰ Wang and Lu reported a trans halopalladation-olefin insertion cascade for synthesis of δ-halo-γ,δ-unsaturated carbonyl compounds (Scheme 1.11).²¹ Treatment of alkynes 1.26 with palladium acetate and excess of lithium halides delivers the vinylpalladium intermediate A, which undergoes olefin insertion followed by protonation to furnish the desired products 1.28 via palladium species B.

![Scheme 1.1](image)

**Scheme 1.11.** Synthesis of δ-halo-γ,δ-unsaturated carbonyls via halopalladation-olefin insertion cascade

The synthesis of 3-chloro- or 3-bromo-1-methyleneindenenes 1.30 were achieved involving halopalladation of 2-alkenylphenylacetylenes 1.29 followed by intramolecular olefin insertion and β-hydride elimination steps (Scheme 1.12).²²
Peng and Liu demonstrated a fluoropalladation-initiated cascade process for the synthesis of fluorinated lactams.\textsuperscript{23} Enynes 1.31 were treated with palladium catalyst, bathocuproine, \textit{p}-nitrophenol and \textit{N}-fluorobenzenesulfonimide (NFSI) as the fluoride source to obtain the vinylpalladium intermediate \textit{B} \textit{via} \textit{cis} fluoropalladation. Subsequent intramolecular alkene insertion-protonation steps afford fluorinated lactams 1.32 (Scheme 1.13).
The first example of chloropalladation-initiated asymmetric intermolecular carboesterification of alkenes with alkynes was achieved using chiral amine auxiliaries.\textsuperscript{24} As shown in Scheme 1.14, (1S,2S)-\(N^1,N^1\)-dimethylcyclohexane-1,2-diamine was employed as a chiral auxiliary for the synthesis of \(\alpha\)-methylene-\(\gamma\)-lactones 1.35 starting from alkynes 1.33 and a large number of styrene derivatives 1.34 in moderate to good yields with excellent enantioselectivities.

\begin{center}
\textbf{Scheme 1.14.} Chloropalladation-initiated asymmetric intermolecular carboesterification of alkenes with alkynes
\end{center}

\textbf{1.2.4. Carboxypalladation-Initiated Cascade Reactions}

Intramolecular carboxypalladation of alkynoic acids followed by insertion of \(\alpha,\beta\)-unsaturated carbonyl compounds were achieved in the presence of palladium acetate and LiBr under mild conditions to access furan-2(3\(H\))-one derivatives.\textsuperscript{25} Palladium triggered 5-\textit{endo-dig} cyclization of alkynoic acid 1.36 delivers vinylpalladium intermediate B, which undergoes olefin insertion with compound 1.37 to furnish the final products 1.38 after the protonation step. Here, the role of LiBr is to suppress the competitive \(\beta\)-hydride elimination reaction over protonation. A related acetoxypalladation-intramolecular olefin insertion cascade was also developed for the synthesis of indene derivatives.\textsuperscript{26}
1.2.5. Carbo- and Hydropalladation-Initiated Cascade Reactions

In addition to the above-mentioned nucleopalladation-initiated reactions, carbopalladation and hydropalladation-initiated cascade reactions were also reported in the literature. As shown in Scheme 1.16, 1-(arylethynyl)-2-vinylbenzenes 1.39 undergo palladium-triggered intramolecular carbopalladation reaction to generate carbocation intermediate B. Subsequently, deprotonation of species B followed by olefin insertion furnishes the PdII intermediate D, which undergoes β-hydride elimination to afford the naphthalene derivatives 1.41.27

Scheme 1.16. Intramolecular carbopalladation-olefin insertion cascade for the synthesis of naphthalenes

A cationic PdII catalyzed hydropalladation-initiated cascade reaction was developed for the synthesis of 1,2,3,4-tetrahydroquinolines.28 The active palladium hydride complex A
was generated from Pd(dppp)(H$_2$O)(BF$_4$)$_2$ and ethanol. Hydropalladation of alkyne 1.42 with catalyst A furnishes intermediate B, which successively undergoes intramolecular carbonyl addition to generate intermediate C. Final protonation of species C delivers the desired tetrahydroquinolines 1.43.

Scheme 1.17. Synthesis of tetrahydroquinolines via hydropalladation-intramolecular carbonyl addition cascade

As demonstrated in this section, nucleopalladation of alkynes and the subsequent cascade reactions continue to be an active and fascinating field of research owing to their high efficiency in constructing several new bonds, thus leading to various complex molecules in a single synthetic operation. Consequently, in the present thesis we envisioned to develop a set of nucleopalladation-initiated cascade reactions for the synthesis of biologically relevant indeno[1,2-b]furan-2-ones, 2,3-dihydro-1H-inden-1-ones, isoquinolines and tetrahydroquinolines.
1.3. Objectives

Within the general framework of the development of palladium–catalyzed cascade reactions for the synthesis of biologically relevant compounds involving nucleopalladation of alkynes as the key step, we propose the following as the specific objectives of the present thesis:

1. Development of a palladium–catalyzed intramolecular carboxypalladation (5-endo-dig)–olefin insertion cascade for the synthesis of indeno[1,2-b]furan-2-ones starting from alkynoic acids tethered with α,β-unsaturated carbonyl moiety.
2. Exploration of a palladium–catalyzed internal nucleophile–assisted hydration–olefin insertion cascade for the diastereoselective synthesis of 2,3-dihydro-1H-inden-1-ones. Alkynes with pendant nucleophiles such as hydroxyl and tosylamino groups will be investigated for the nucleophile–assisted hydration process.


5. The mechanisms of the above-mentioned palladium–catalyzed nucleopalladation-initiated cascade processes will be investigated.
1.4. References


7. For selected recent examples of palladium-catalyzed cascade reactions, see:


