AMINO-CLAISEN REARRANGMENT OF N-ALLYL ARYL AMINES: A VERSATILE PRECURSOR IN THE PALLADIUM CATALYZED HETROANNULTATION TO INDOLES

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ABSTRACT

The [3,3]-sigmatropic shift of vinyl and aryl allyl ether is known as claisen rearrangement. It has been extensively studied and exploited as an expeditious approach to carbon-carbon bond formation in organic synthesis[1-3]. Similarly, the nitrogen[4] analogues of Claisen rearrangement are of importance in view of synthetic and mechanistic aspects.

The nitrogen analogue of the simple Claisen rearrangement with N-allylaniline and related derivatives is called the amino-Claisen rearrangement (or aza-Claisen rearrangement)[5]. (It is the [3,3]-sigmatropic shift of N- alkenyl-N-arylamine to furnish 2-alkenylarylamine, which is known as the amino-Claisen rearrangement). Anilines substituted at 2-position are valuable materials for the construction of a number of different classes of compounds. In particular, 2-alkenylanilines are converted to indoles by means of a palladium-catalyzed cyclization process[6]. They also serve as precursors for the preparation of quinolines and cinnolines[7].

Key words: Amino-claisen rearrangement, N-allyl aryl amine, Palladium catalyzed.

INTRODUCTION

Several approaches have been made for the amino-Claisen rearrangement in the literature which may be broadly divided in to two categories.

(i) Amino-Claisen rearrangement of N-allylarylamine derivatives.

(ii) Amino-Claisen rearrangement of N-allylindole derivatives.

(i) Amino-Claisen rearrangement of N-allylarylamine derivatives

Thermal rearrangement

Thermal rearrangement of N-allyl arylamines has until recently received much less attention than its oxygen counterpart, probably because of the most drastic condition required and the concomitant tendency towards side reactions. Jolidon and Hansen[8] convincingly characterized the thermal reaction as a [3,3]-sigmatropic process of N-allylarylamines (**1**) to give o-allylarylamines (**2**) (**Scheme 1**)[9]. It occurred at 200°C -350°C forcing the cleavage of the allyl group from the ring to give arylamines, as a significant side product.
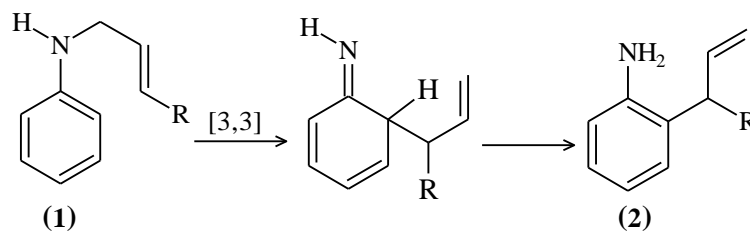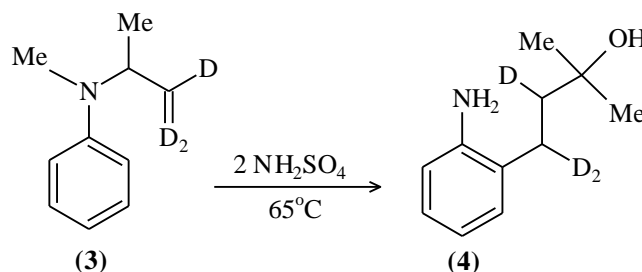
Scheme 1

## Bronsted acid induced rearrangement

Acid catalysis is found to be especially useful on these systems[10] and often permits the occurrence of a reaction that is thermally inaccessible. Bronsted acid catalysis is the most thoroughly investigated reaction, largely due to an exemplary systematic study carried out by Jolidan and Hensen[8], who observed rate acceleration by factors of 10^5-10^7 with protonated amines compared to neutral substrates in 0.1-2.0 N H_2SO_4 or in $CF_3.CO_2H/H_2O$ /dioxane (TWD) 2/1/1 (V/V) system. For example, the deuterated substrate (**3**) in 2 N H_2SO_4 at 65°C for 2 h yielded alcohol 4 (36%) (**Scheme 2**).

Several examples have been reported in the literature for the rearrangement using 2 N H_2SO_4.

Scheme 2

A high yield of [3,3]-sigmatropic rearranged products (**6**) were obtained when N-allylated (**5**) were refluxed in a mixture of concentrated HCl[11] and ethanol for 12 h (90%) (**Scheme 3**).
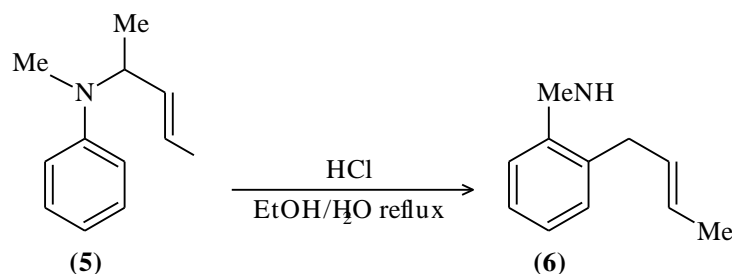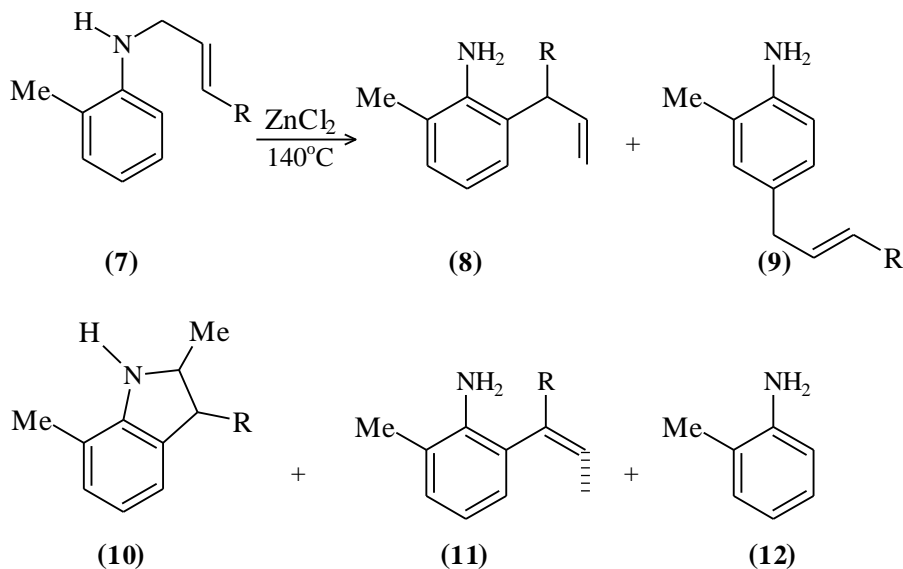

Scheme 3

Comparable results were obtained with the following ring substituted derivative under the same condition, (p-Me (95%), p-OMe (92%), m-Me (90%) and m-OMe rearranged in 80% yield). Roughly, comparable results were observed in TWD. However, the reaction medium of HCl/EtOH appeared to give better yields than H_2SO_4 or TWD[11].

Lewis acid induced rearrangement

Among the lewis acid catalyzed, anhydrous $ZnCl_2$ has received the most attention[10]. Rearrangements are usually carried out in refluxing xylene, followed by work up with aqueous sodium hydroxide. An

example[4] of the Lewis acid catalyzed rearrangement reaction for the conversion of (7) to give (8) along with the products (9-12) is given in the (Scheme 4).

ZnCl$_2$ catalyzed amino-Claisen rearrangement has been used in the synthesis of 2-allyl anilines having a variety of functional groups in the benzene ring (4-Me, 3,5-dimethyl, 4-tBu, 4-F, 4-Cl) in a moderate to good yield[12].

Scheme 4

Aromatic N-allyamines (13) is rearranged in BF$_3$.OEt$_2$ to give the products (14) in yields ranging from 50 to 60 % (Scheme 5). The use of this catalyst shortened the reaction time by 2 h. and reduced the formation of by- products[13].

Although this rearrangement tolerated the electron-rich as well as the electron deficient substituents present in N-ally arylamines but N-allyl arylamines having electron deficient substituents underwent rearrangement at lower temperature than electron-rich ones. This is consistent to the proposed mechanism of the amino-Claisen rearrangement. As BF$_3$.OEt$_2$ Catalyzed amino-Claisen rearrangement[13] provide a mild and one pot entry to the allylarylamines, therefore this method may find a wide spread application to the synthesis of complex 2-ally arylamines (14) from N-allylarylamines (13) (Scheme 5).

(13)   (14)
R = 2CH$_3$, 2-OCH$_3$,   R = 6-CH$_3$, 6-OCH$_3$,
    2-CONH$_2$ 6-CONH$_2$
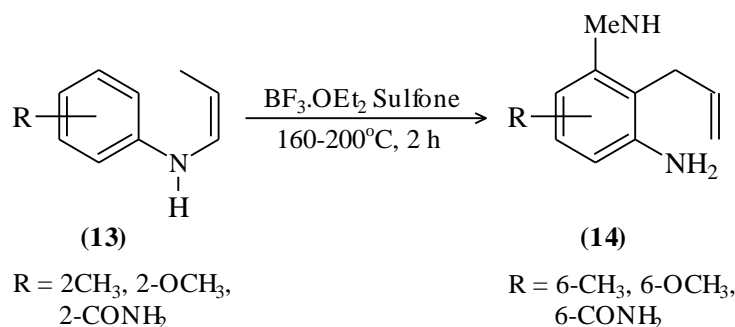
Scheme 5

**Miscellaneous approaches for the rearrangement**

Amino-Claisen rearrangements of N-allyl quaternary anilinium salts[14] have been well studied. Schmid et al.[15] briefly described the charge induced aromatic amino-Claisen rearrangement of quaternary

anilinium salts such as N-allyl-N,N-dimethylanilinium tetraphenyl borates (BPh$_4$) (**15**) to give (**16**) along with the product (**17**) as shown below in (**Scheme 6**)[4].
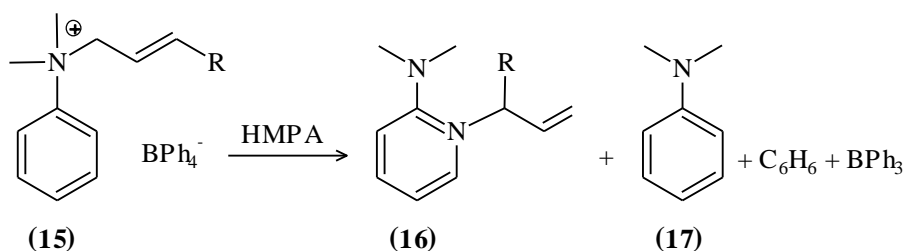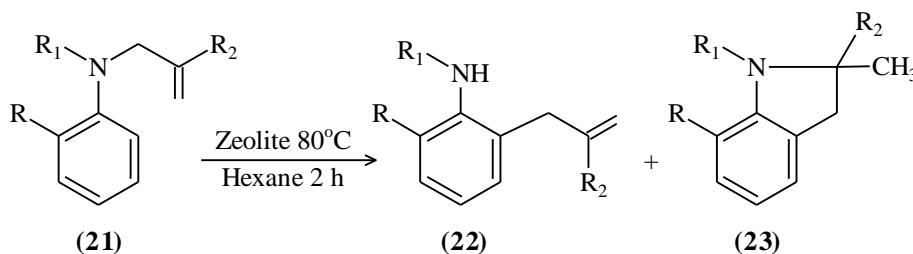

Scheme 6

Recently, it was observed that the benzyl group in N-benzyl-N,N-dimethylanilinium hexafluoroantimonates (SbF$_6^-$) migrated to the ortho or para position of aniline when heated neat[14]. (without any solvent). Similarly, N-allyl-N,N-dimethylanilinium hexafluoroantimonate (**18**) rearranged to give 2-allylanilinium salt (**19**) with the formation of N,N-dimethylindolinium salts (**20**) (**Scheme 7**)[15(a)].
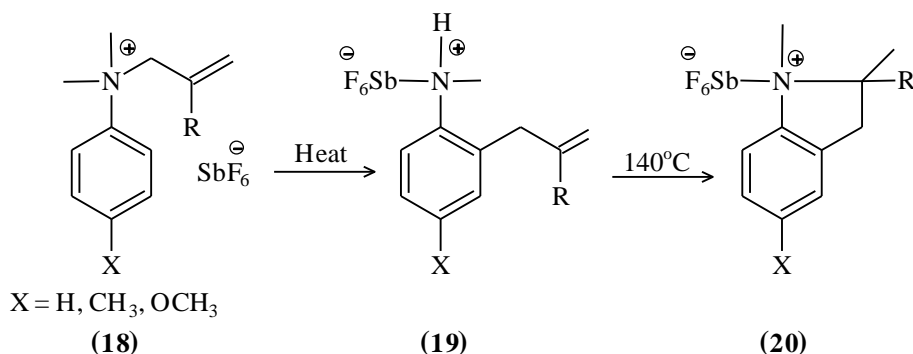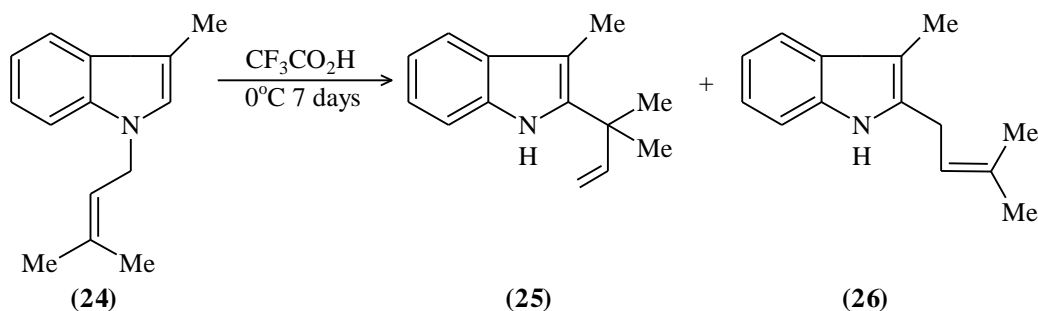

Scheme 7

Recently zeolites have been employed to effect the amino-Claisen rearrangement of N-allylarylamines (**21**) to give (**22**) along with (**23**). However, their applications in this process have not been fully explored. An example of this reaction is shown below (**Scheme 8**)[15(b)].

Scheme 8

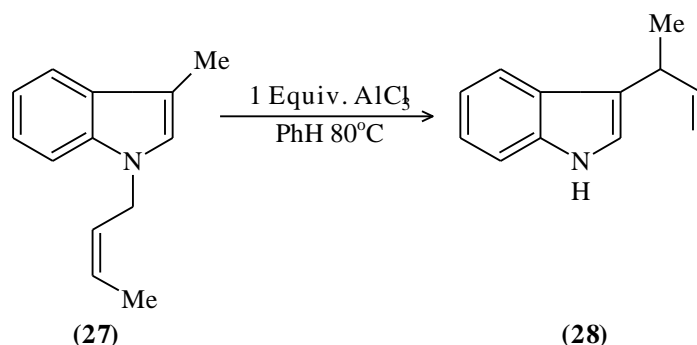## (ii) Amino-Claisen rearrangement of N-allylindole derivatives

Flash vacuum pyrolysis of N-crotylindole (**24**) at 450°C -470°C caused (3,3)-rearrangement to take place to give 3-(1-methylallyl) indoles but this compound was readily converted in to 2-(1-Methylallyl) indole (**25**) and (**26**) on heating in a condensed phase[16] (**Scheme 9**).

(24)   **(25)**   **(26)**

Scheme 9

The trifluoroacetic acid mediated rearrangement of a series of 3-alkyl-1-allylindoles **27** yielded 3-alkyl-2-allyl indoles with inverted **(25)** as well as non-inverted **(26)** allyl groups **(Scheme 9)**[17].

Inversion of the allyl moiety was also seen in the $AlCl_3$ catalyzed rearrangement of trans-1-crotylindole from **(26)** to **(27)** **(Scheme 10)**[18].

(27)   **(28)**

Scheme 10

Mechanism of the amino-Claisen rearrangement

The mechanism of the amino-Claisen rearrangement shown in Figs. 1 and 2, is consistent to the mechanism proposed for the traditional claisen-rearrangement of allyl phenyl ethers (Fig. 1a)[18]. It is quite likely that when arylamine is treated with 3 equiv. of $ZnCl_2$ it gives a complex 29 (Fig. 2a). This complexation tends to reduce the electron density at nitrogen by forming a cationic quaternary nitrogen center and makes the reaction facile through charge acceleration process. On the basis of the known composition of $ZnCl_2$-aniline complex, the amine undergoing rearrangement could be presumed to possess two amines co-ordinated to the zinc. The formation of aniline-$ZnCl_2$ complex is slow and rate determining. In the subsequent step the aniline-$ZnCl_2$ complex tautomerizes to give **(30)**, which with the loss of $ZnCl_2$ on treatment with NaOH forms the final product **(31)**.

These predictions are consistent for the mechanism of charge induced sigmatropic rearrangement by $BF_3.OEt_2$ (Fig. 2b) as well as by protic acids (Fig. 1b).

## (3) Amino-Claisen rearrangement of N-allyl-1 H-indole

A survey of literature reveals that allyl group in allylindole has a tendency to migrate to 3-position of the indole ring[19]. When the 3-position is blocked then it migrate to 2-position. However, no migration of the allyl group to the 7-position of the indole ring has ever been observed.

Therefore for the preparation of 2-allylated product, the 3-position of indole was blocked by a piperidinomethyl group. This group was introduced at 3-position by Mannich reaction of N-allylindole **(32)**
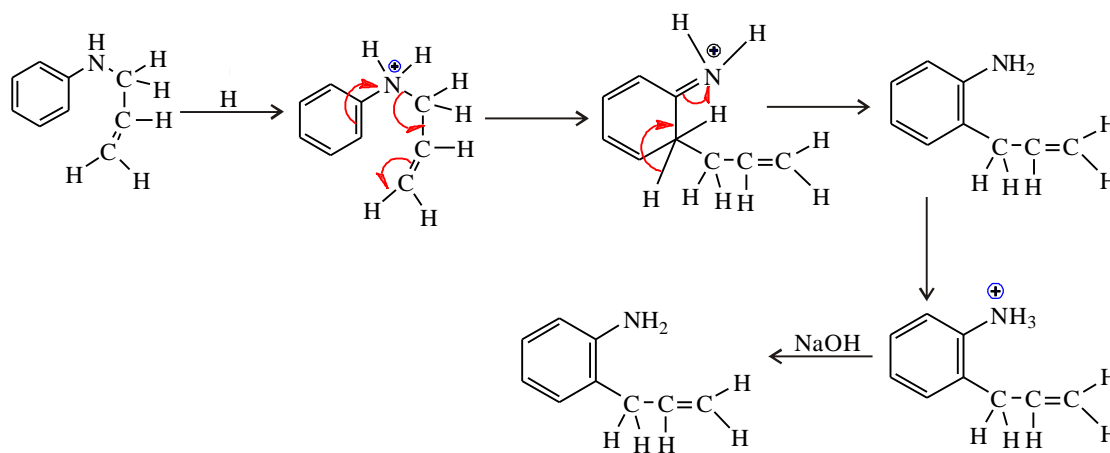
with formaldehyde and piperidine. The 3-subsituted N-allylindole **(33)** cleanly rearranged to 2-allylated analogues **(34)** in presence of BF$_3$.OEt$_2$ **(Scheme 11)**.
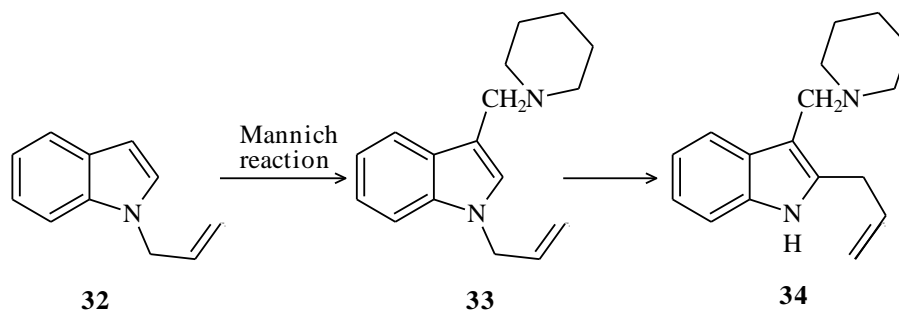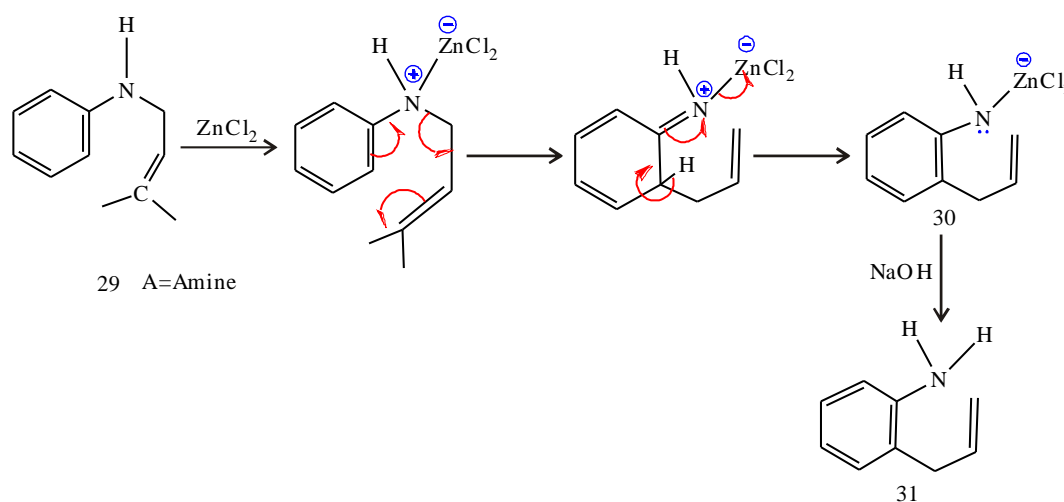

Scheme 11
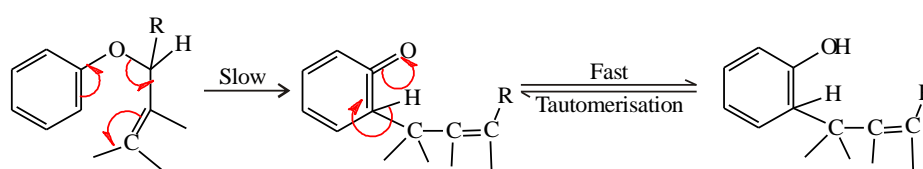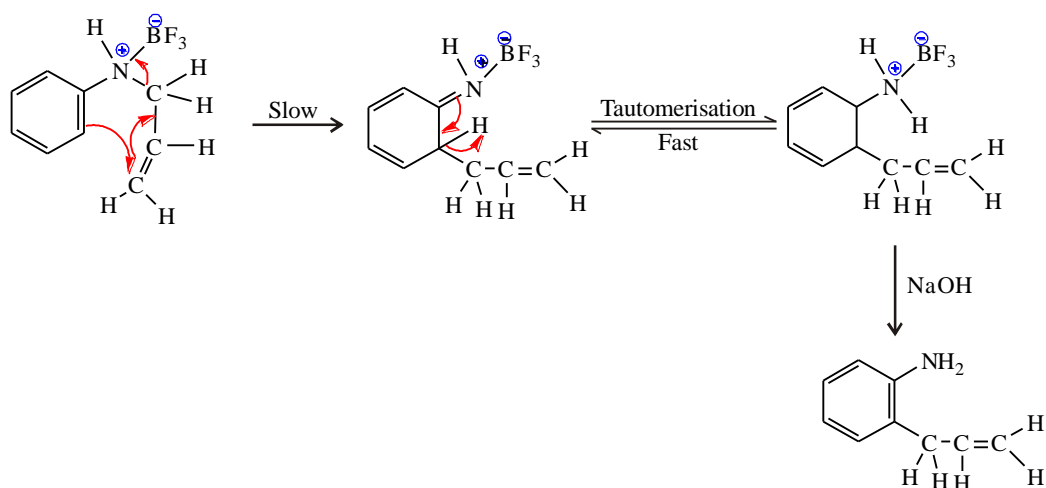

(a) Mechanism of Claisen rearrangement

(b) Mechanism of charge induced amino-Claisen rearrangement in presence of acid

Fig. 1

(a) Mechanism of charge induced Amino-Claisen rearrangement in the presence of Zinc Chloride

(b) Mechanism of charge induced amino-Claisen rearrangement in the presence of boron trifluoride etherate

Fig. 2

Amino-Claisen rearrangements of N-vinyl isoquinuclidenium salts, generated in situ from the corresponding tertiary amines, serve as mild and efficient methods for preparation of cis-fused hydroisoquinolines[20]. Our continuing studies in this area are focused on the development of another general hydroisoquinoline synthetic methodology based upon amino-Claisen rearrangements of zwitterionic N-vinylisoquinuclidenes **(36)**. The zwitterionic version of the amino-Claisen rearrangement shown in **Scheme 12** is a viable process and that Wenkert cyclization of β-enamino esters like **(39)** is applicable to the construction of systems having the pentacyclic reserpine skeleton[21].
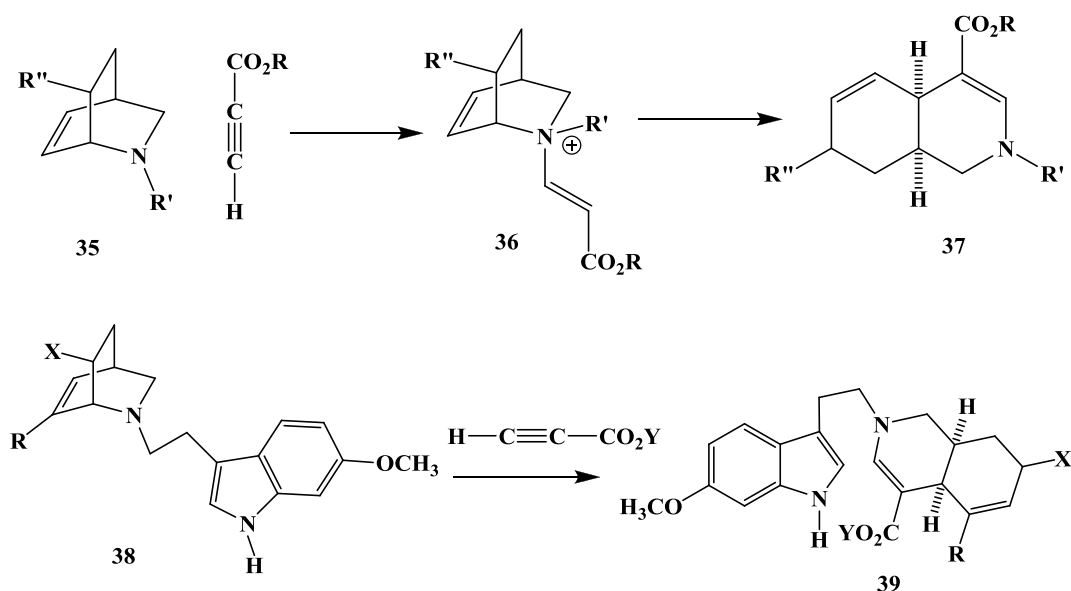
Scheme-12

Amino-Claisen rearrangements[22,23] of N-propargyl aniline derivatives, which open up an alternative route to quinoline ring systems, proceed via o-allenylaniline under thermal[24] or copper-promoted condition[25,26] (path a', **(Scheme 13)**. Although a few indoles have been synthesized by the thermal rearrangement of N-propargyl anilines, these procedures require extremely high temperatures (240–260^{0}C)

and products were only obtained in low yield[24]. Herein, we describe the mild formation of indoles by an amino-Claisen rearrangement of N-propargyl anilines catalyzed by cationic RhI complexes[27].
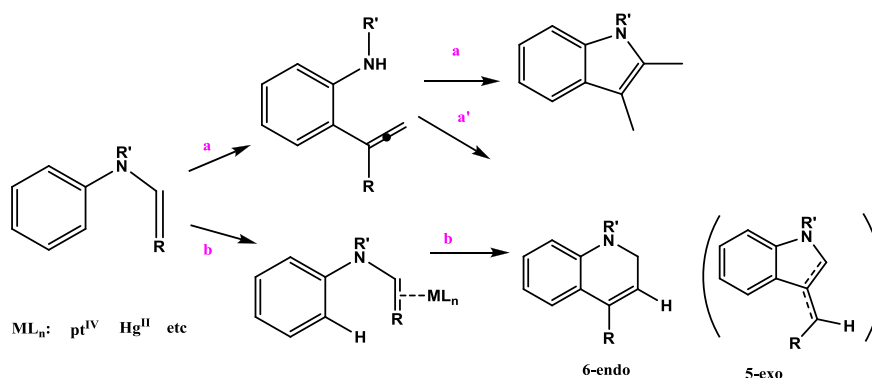
**Scheme 13: Possible routes for the cyclization of N-propargyl anilines**

We have reported the facile formation of indoles by an aromatic amino-Claisen rearrangement of N-propargyl aniline derivatives in the presence of a [Rh- (cod)$_2$]OTf/dppp catalyst in HFIP in (**Scheme-14**)[28].
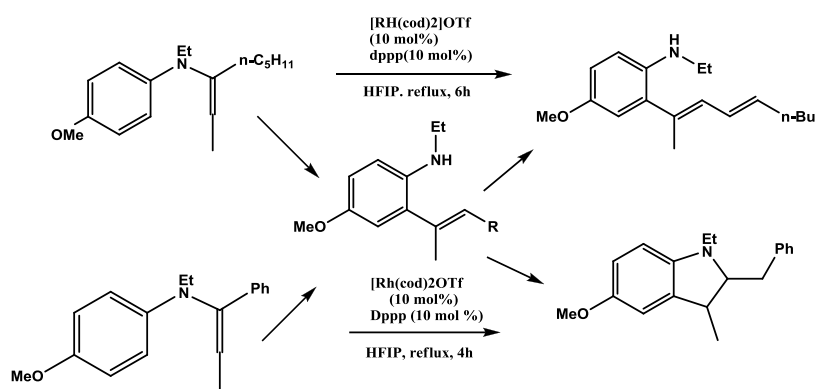
**Scheme 14: Formation of diene or an indole**

The substrates (**40 a–f**) possess two potential sites for Claisen rearrangement. The aryloxypropargyl ether moiety may undergo an oxy-Claisen rearrangement, while the vinylpropargyl-*N*-methylamine fragment may undergo an amino-Claisen rearrangement. Hence these substrates provide scope for studying the competition between oxygen Claisen and amino-Claisen rearrangements. It is well known that the amino-Claisen rearrangement[29] requires higher activation energies than the oxygen Claisen rearrangement. However, the activation energy required for the arylpropargyl ether rearrangement[30] is much higher than that of propargylvinyl ether rearrangement[31].

The amino-Claisen rearrangement leads to the exclusive formation of unusual products containing exocyclic double bonds (**41 a-f**), instead of the normal products containing a endocyclic double bond (**42**)[32].

R₁=(a)H, (b)2-Me,(C) 4-Me,(d)3,5-Me,(e)4Cl,(f)2-NO₂
R=(a)H,(b)H,(c)H,(d)Me,(e)Me,(f)H
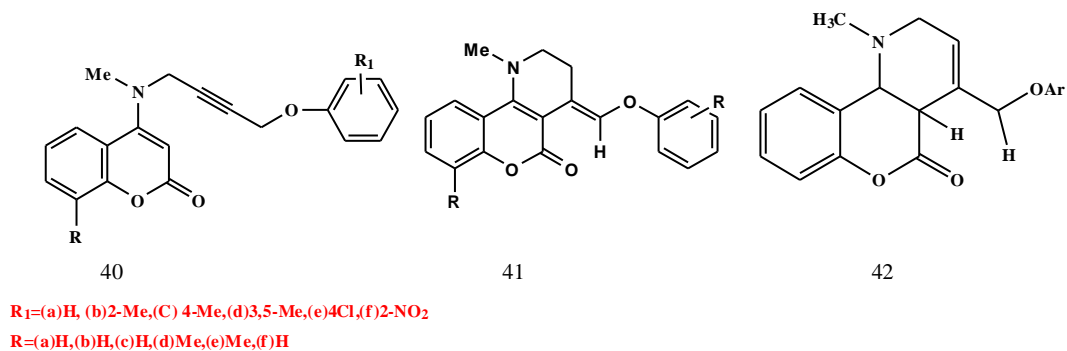
Scheme 15

A novel type of a amino (N)-Claisen rearrangement[33] as shown in **(Scheme-15)**. As a continuation of this work, the effects of ortho substituents upon this quaternary N-Claisen rearrangement[34] and therefore prepared a series of ortho-substituted N-allylanilinium compounds and also synthesized the corresponding N-allyated tertiary anilines in order to compare the quaternary and tertiary N-Claisen rearrangements.
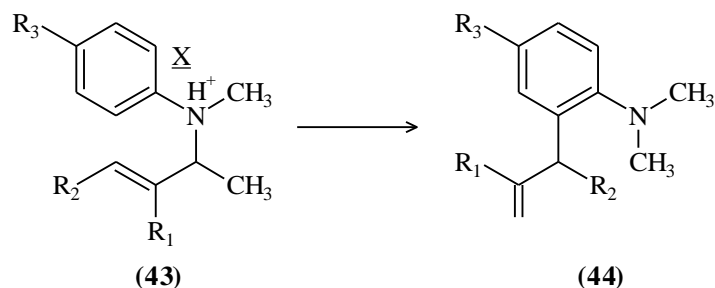
Scheme 16

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