PART II: STEREOSELECTIVE PALLADIUM(0)-CATALYZED FOUR-COMPONENT CASCADE SYNTHESIS OF PYRROLIDINYL ISOQUINOLINES

INTRODUCTION

Multi-component reactions (MCRs) play an important role in combinatorial chemistry because of there ability to prepare complex molecular architectures from readily available building blocks (Grigg *et al*., 1999; Ugi *et al*., 2000; Montgomery *et al*., 2000). Among the advantages of MCRs are yields that higher than almost any sequential synthesis of the same target, a single purification step and easy to adaptation to combinatorial synthesis. A MCR is defined as three or more different starting materials that react to form product, where most, if not all the atoms are incorporated in the final product.

We have demonstrated a series of novel palladium catalyzed cascade reaction which involved the synthesis of bis(2-allyl)tertiary amines. 1,2,3,4-tettrahydroisoquinolines, isoindolinones, 4-methyllene-3,4-dihydro-1(2H)-isoindolinones and triazole analogues (Grigg *et al*., 2000; Grigg *et al*., 2003). The development of these reactions involves the use of allenes as "relay switches" in palladium cascade reactions and is a very creative and significant idea for the construction of complex nitrogen heterocycles. We focus on the combination of palladium cascade reactions with other significant atom economic reactions to develop novel synthesis of complex bioactive nitrogen heterocycles. In 1999, Fruhaul *et al*. demonstrated imines can be used as nucleophiles in palladium catalyzed allene reactions to afford iminium species. As part our on going interest in the design of palladium-catalyzed allylation processes in the tactical combination with core reactions, we have explored combinations that have 1,3-dipolar cycloaddition processes as the key step in the synthesis of heterocycles (Grigg *et al*., 2001; Grigg *et al*., 2003). To our knowledge, this palladium-catalyzed four component cascade process is the first reported case which combines palladium catalyzed allene reaction with a 1,3-dipolar cycloaddition reaction in one pot.

The objective was to prepare pyrrolidinyl isoquinoline derivatives using a four component cascade with 2-iodobenzyldehyde that generates azomethine ylids *in situ* which are trapped with *N*-methyl maleimide (NMM) as the dipolarlophile.

LITERATURE REVIEW

Palladium-catalyzed reactions of allenes

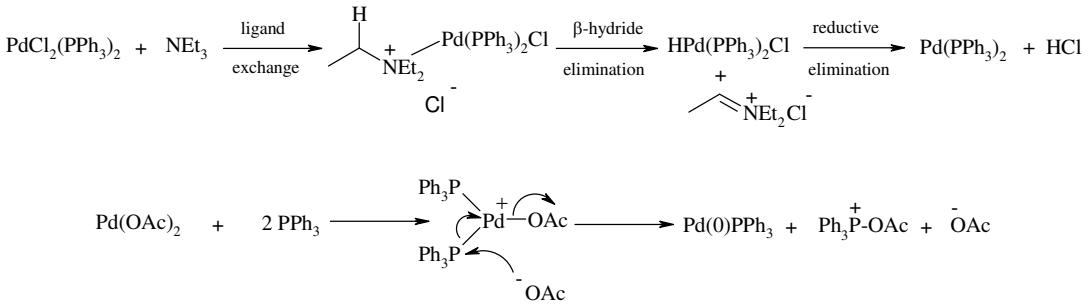
Over the last few decades, palladium-catalyzed reactions have assumed a key role in organic synthesis because they exhibit a high level of chemo-, regio-, and stereoselectivity in a wide range of transformation (de Meijere and Meyer, 1994; Mueller and Beller, 1998). Palladium catalysed reaction of allenes with carbon and heteroatom nucleophiles leading to the formation of carbon-carbon and carbon-heteroatom bonds generally proceed with the involvement of a π-allylpalladium intermediate. This combination is playing an increasing role in organic synthesis (Hiroi and Kato, 1996; Yamamoto and Radhakrishnan, 1999).

Palladium

There are several features that make reactions involving the most important transition metal, palladium, particularly useful and versatile. Palladium catalysts are the most widely used both in industrial and academic laboratories on both small and large scale because they offer many possibilities for carbon-carbon, carbon-hetroatom bond formation. The tolerance of Pd reagents to many functional groups such as carbonyl and hydroxyl groups is a further important feature. Pd-catalyzed reactions can be carried out without protection of many functional groups. Additionally the chemo- and regioselectivity of Pd catalysts has fostered an ever-increasing amount of research.

Both palladium(0) complexes and palladium(II) salts are used in organic synthesis. Palladium(0) complexes are used as catalysts and palladium(II) salts either as stoichiometric reagents or as catalysts. Tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$, and tris(dibenzylideneacetone)dipalladium(0), $Pd_2(dba)_3$, or the chloroform complex, $Pd_2(dba)_3$-$CHCl_3$, which is air-stable, are the most common sources of palladium(0). Palladium(II) salts such as $PdCl_2$ and $Pd(OAc)_2$ are commercially available, widely used and more stable. They can be used in two important ways: as unique stoichiometric oxidizing agents, and as precursors of Pd(0)

complexes (Tsuji, 1995). The reduction of palladium(II) to palladium(0) can be achieved with amines, phosphines, alkenes and organometallic reagents such as DIBAL-H, butyl lithium or trialkyl aluminium. For example, $PdCl_2(PPh_3)_2$ was reduced to palladium(0) *in situ* in the presence of phosphine ligands (Scheme 1).



Scheme 1

Allenes

The allene or 1,2-dienes serve as potential precursors of highly complex and strained target molecules of biological and industrial importance. Their unique reactivity has been successfully applied to pharmaceuticals, dyes, polymers, etc (Zimmer *et al*., 2000). Allenes comprise two adjacent double bonds with their π–orbitals perpendicular to each other, with the central atom (*sp*-hybridised) joined to two terminal (sp^2-hybridised) carbon atoms. As a consequence, allenes are chiral if both the 1- and 3- carbon centres are unsymmetrically substituted (Figure 1).

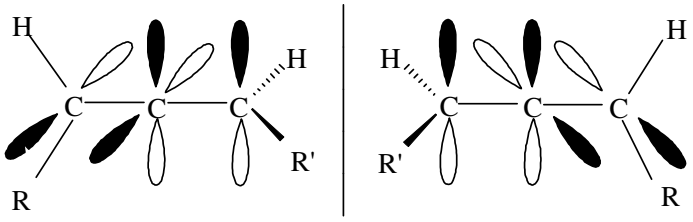


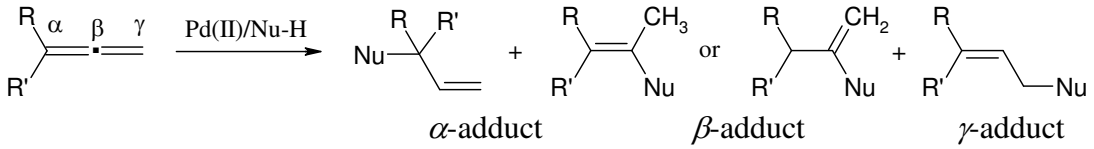
Figure 1 allene

The allene was first prepared in 1887 by Burton and von Pechmann, (1887) but the structure was not confirmed until 1954 (Jones *et al*., 1954). Up to the 1950's, allenes were considered highly unstable and difficult to prepare, (Celmer and Solomons, 1952) but recently a variety of methodologies have been developed for their synthesis (Grigg and Sridharan, 1998; Lautens *et al*., 1998). Research on the catalytic reactions of allenes started in the 1960's and since then publications, particularly those involving iron (Shiabata *et al*., 1995), cobalt (Owada *et al*., 1997) nickel (Satyanarayana *et al*., 1990), ruthenium (Yamaguchi *et al*., 1995), rhodium (Yamaguchi *et al*., 1994) and palladium (Grigg and Sridharan, 1999) have flourished.

Cascade reactions

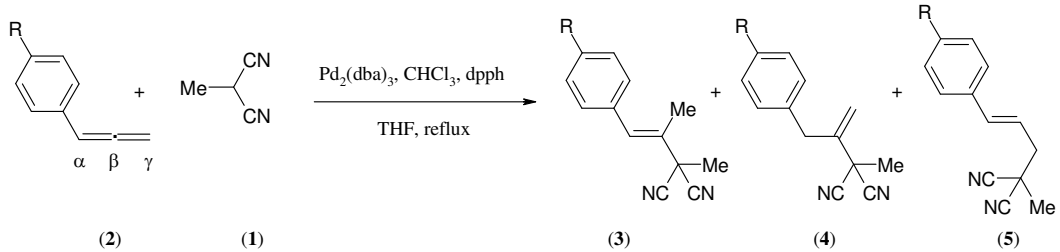
Organic synthesis is concerned with developing viable processes to useful materials by methods that minimize waste, maximize molecular complexity and are highly selective (regio-, stereo-, chiro- and chemo-specific). Cascade processes aspire to meet these criteria. A cascade reaction is a multi-step process where the functionality created in the first step allows the second step to proceed and so forth until the desired product is generated. Compared to a conventional synthesis, a cascade reaction generates a significant increase in molecular complexity much more effectively. The need for only one work-up and purification also minimises waste, making cascades environmentally friendly. Palladium has recently played a prominent role in cascade reactions due to its outstanding catalytic properties (Grigg and Sridharan, 1999).

Palladium catalysed reactions of allenes involving π–allylpalladium species, were reported in 1964 by Schultz, and recently a growing number of applications in cascade reactions have been reported (Zimmer *et al*., 2000). Nucleophilic addition to allenes coordinated by Pd(II) can give rise to three possible regioisomers depending upon the substituents on the terminal carbon atoms (Scheme 2).



Scheme 2

Yamamoto *et al*. (1999) investigated the regioselectivity of the reaction of arylallenes having different *para*-subsituents. The reaction of activated methylene and methine reactants (1) with (2) is catalysed by $Pd_2(dba)_3$/dppb in THF under reflux. When an electron withdrawing group (e.g., Br, CF_3, OCF_3) was present at the *para*-position, attack occurs at the β-position of the allene affording mixture of (3) and (4). Whereas carbon-carbon bond formation at the γ-position (5) was observed in the presence of para electron-donating groups (e.g., Me, OMe) (Scheme 3).



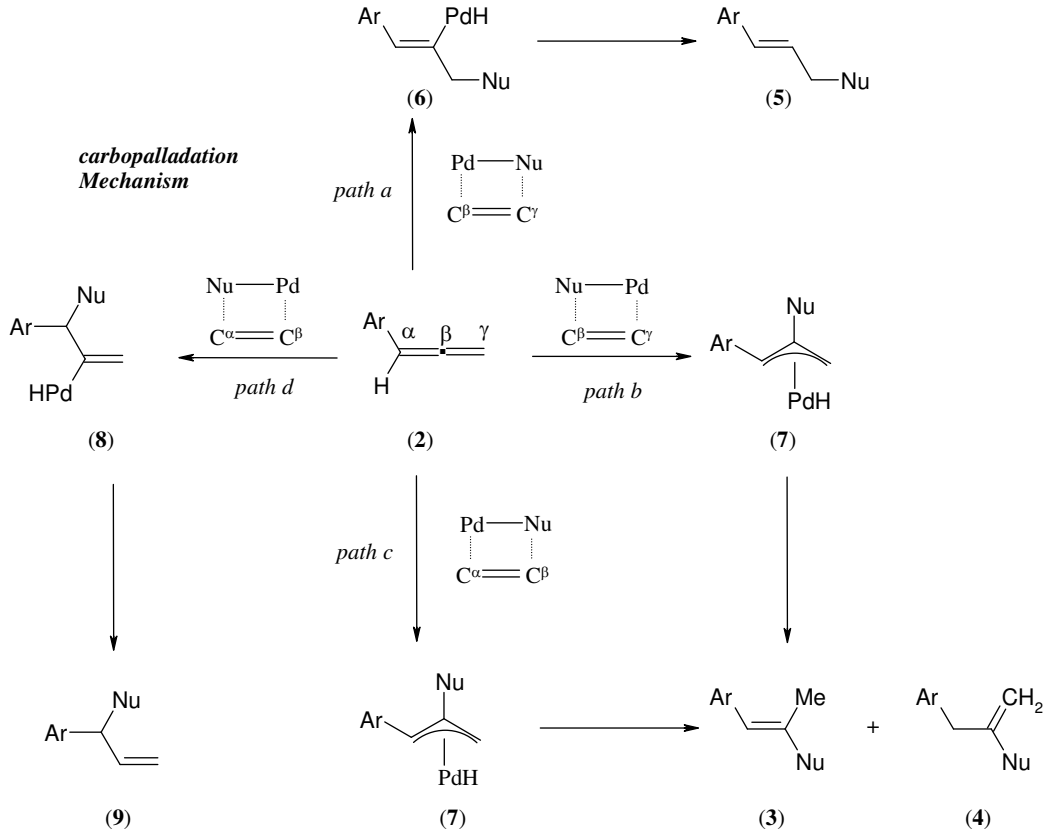
Scheme 3

Table 1 Regioselectivity of the reaction of activated methylene (1) and arylallene (2)

R	3 (%)	4 (%)	5 (%)
Br	46	14	-
CF_3	47	20	-
OCF_3	68	16	-
OMe	-	-	85

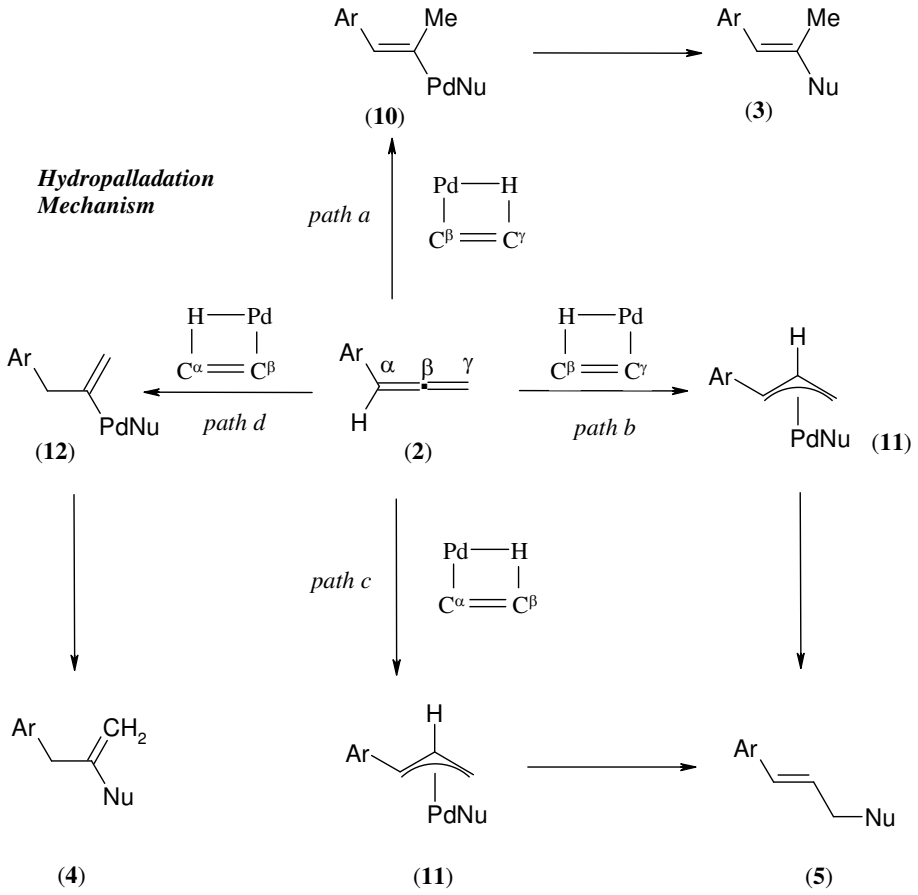
Product formation can be expained either by a carbopalladation (Scheme 4) or or by a hydropalladation mechanism (Scheme 5). Carbopalladation of the $C^{\gamma}=C^{\beta}$ bond of (2) Scheme 4, (path a) give (6), which was transformed into (5).

Carbopalladation of the C^{β}=C^{γ} bond (path b) and C^{β}=C^{α} bond (path c) produce the π-allypalladium intermediate (7) leading to the β-adducts (3) and (4). Carbopalladation of the C^{α}=C^{β} bond (path d) is a difficult pathway due to the steric hindrance at the C^{α} atom.



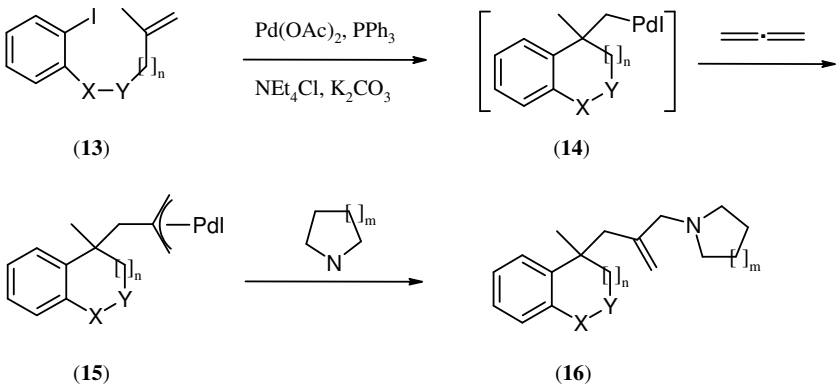
Scheme 4

Hydropalladation of the C^{γ}=C^{β} bond of (2) (Scheme 5 path a) gives (10), which affords β-adduct (3) *via* reductive elimination. Hydropalladation of C^{β}=C^{γ} bond (path b) and C^{β}=C^{α} bond (path c) produce the π-allypalladium intermediate (11). Attack of a nucleophile at the centre carbon atom of the π-allypalladium intermediate is not common. Therefore, compound 11 is unlikely to give β-adducts, but instead affords the γ-adduct (5). Hydropalladation of C^{α}=C^{β} bond (path d) provides (12), which is transformed into (4).



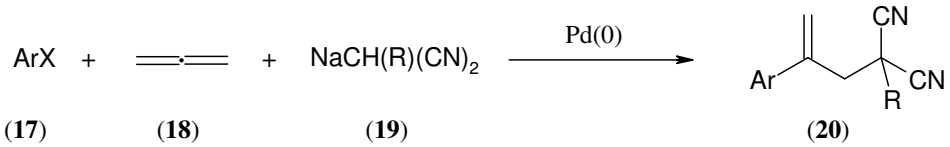
Scheme 5

In the mid-1990s, Grigg developed an extremely useful palladium-catalysed cyclization-anion capture methodology employing a 'zipper' starter species. The presence of a methallyl or similar moiety in the side chain of the aryl halides (13) prevents β-hydride elimination in intermediate (14), which permits allene insertion forming the π–allylpalladium species (15). Nucleophile attack on (15) gives heterocycles (16) (Scheme 6) (Grigg, 1994). Recently this palladium-catalysed cyclization-anion capture process has been substantially extended (Grigg and Sridharan, 1999).



Scheme 6

Malononitrile could be sequentially alkylated by conventional and/or less traditional methods to afford dialkylated products (Diez-Barra *et al*., 1991). There are many non-traditional ways of accessing dialkylated malononitriles. A typical example was shown in (Scheme 7) which employs the Pd catalysed reactions of allenes.



Scheme 7

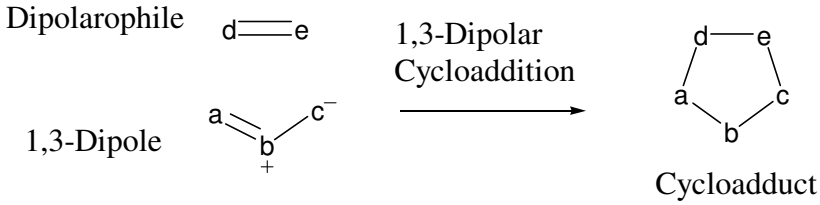
1,3-dipolar cycloaddition reactions

1,3-Dipolar cycloadditions, known as the Huisgen reaction, play a very important role in the synthesis of heterocycles (Kurt *et al*., 1998). They are the reaction between a 1,3-dipole and a dipolarophile, most of which are substituted alkenes, to form a five-membered ring. Rolf Huisgen (1963) first discovered the prospects of varying the 1,3-dipole and its high value for synthesis of 5-membered heterocycles. The history of 1,3-dipole was started in 1883 by Curtius, who discovered diazoacetic ester. Five years later, Buchner studied the reaction of

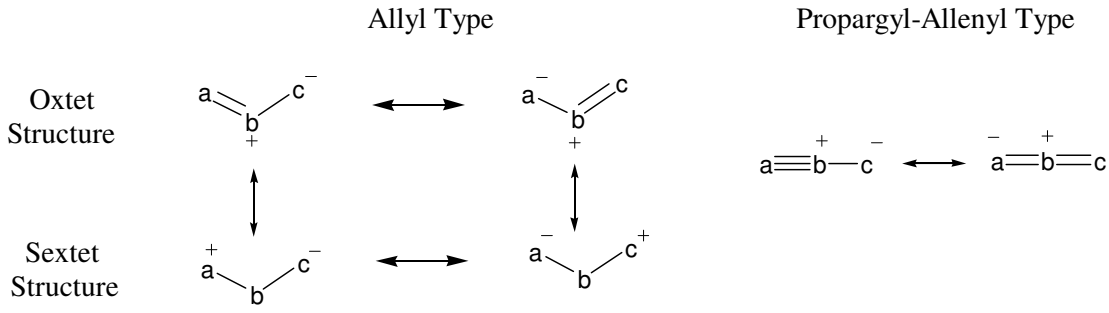
diazoacetic ester with α,β-unsaturated ester and described the first 1,3-dipolar cycloaddition reaction.

Basic aspects

A 1,3-dipole is delineated as a '**a-b-c**' structure, containing a formal positive and negative charge, which undergoes [3+2] cycloaddition with dipolarophile '**d-e**' to form a five-member ring system in which the 1,3-dipole provides three atoms and the dipolarophile provides two atoms.

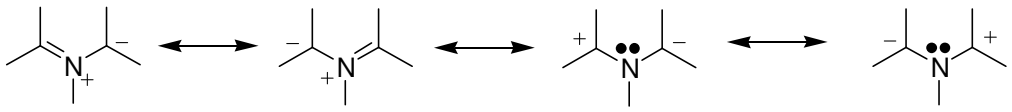


Basically, 1,3-dipoles can be classified into different types: the allyl and propargyl/allenyl type depending on nature and resonance structure of parent skeletons. In the allyl type 1,3-dipole has four-electron π-system orthogonal to the dipolar plane and can be represented by four canonical forms. Two are octet structures in which all three atoms have a complete octet and other two are sextet structures in which terminal atoms **a** and **c** both have six electrons. The central atom b can be nitrogen, oxygen or sulphur. Whilst the propargyl/allenyl type is linear and possesses extra π-orbital located in the a-b-c plane. This π-orbital is not directly involved in both of resonance structure and reaction of dipole. The central atom **b** is limit to nitrogen.



Azomethine ylides

Azomethine ylides are one of the most important class of 1,3 dipoles. They comprise a central nitrogen atom together with sp2 terminal carbon atoms. This ylide, which contains four electrons in its three p-orbitats, may be represented using a canonical form.



This ylide can be classified as non-stabilized, stabilized or stable. Non-stabilized type has no electron withdrawing groups at one or both of the ylide termini. Stabilized type has one or more electron withdrawing groups at the ylide termini. Both of these types are very common and generated *in situ*. In the case of stable type, it is stable and isolable but it is rare.

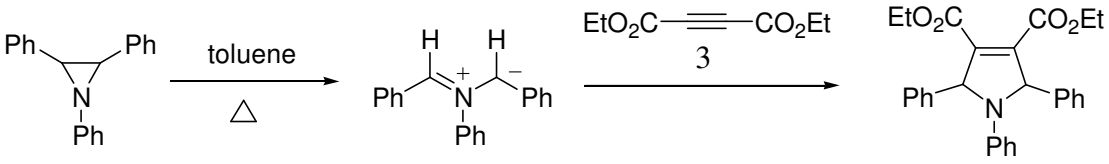
Non-stabilized azomethine ylides

Many approaches were used for the generation of non-stabilized azomethine ylides.

Aziridine pathway

In 1965, Heine and Peavy demonstrated the frist example of the ring opening of an aziridine to generate an azomethine ylide. 1,2,3-Triphenylaziridine (21) was

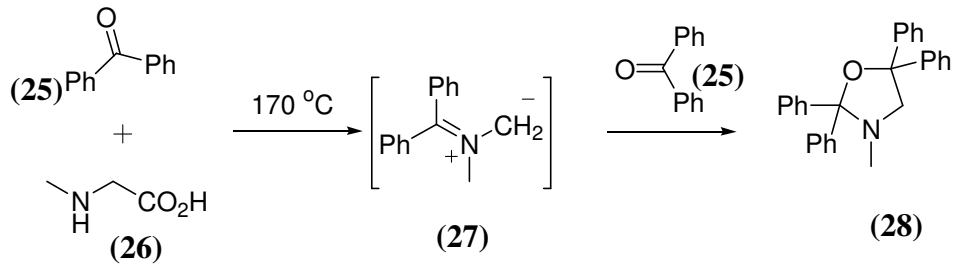
refluxed in tolulene in the presence of diethyl acetylenedicarboxyrate (23). Azomethine ylide (22) was generated *in situ* and subsequently trapped by acetylene (23) to give a quantitative yield of cycloadduct (24). Later studies, Padwa and Huisgen (1965) obtained similar results independently.



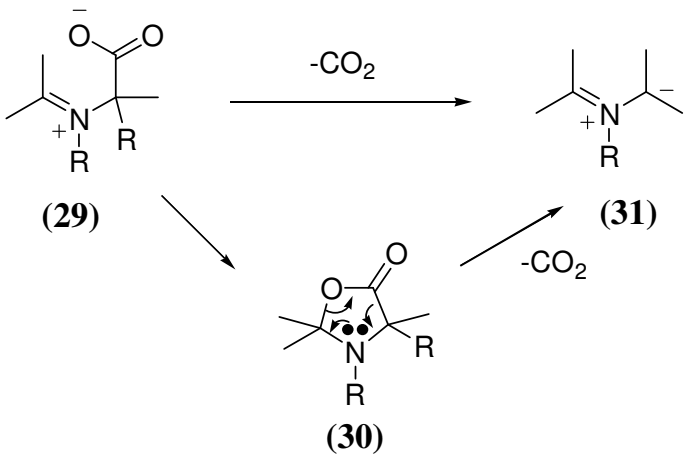
(21) (22) (24)

Decarboxylation pathway

The first example of decarboxylative route which involved heating sarcorsine (6) at 170 ^{o}C to give azomethine ylide **27** *in situ* was reported by Rizzi *et al.* in 1970. The ylide **27** was trapped with diphenylketone (25) to give cycloadduct (28).



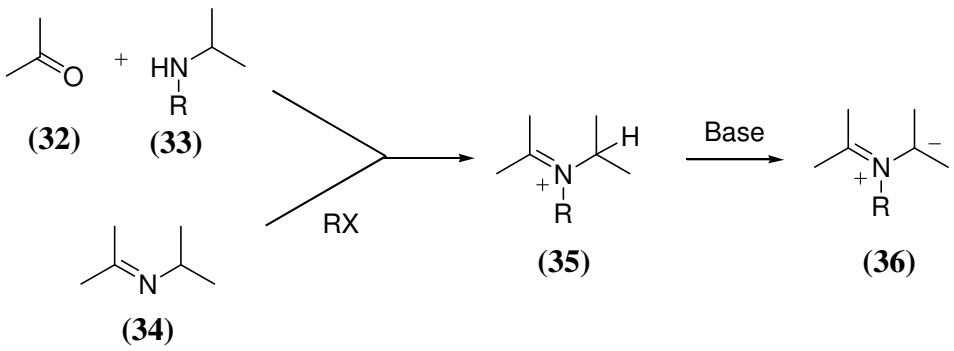
α-Amino acids were used to generate N-unsubstituted (or N-substituted) azomethine ylides (31). The formation of azomethine ylides (31) were simply explained by either direct decarboxylation of the zwitterions (29) or by cyclisation to **30** and subsequent retrocycloaddition (Joucla *et al*., 1985).



(29) **(31)** **(30)**

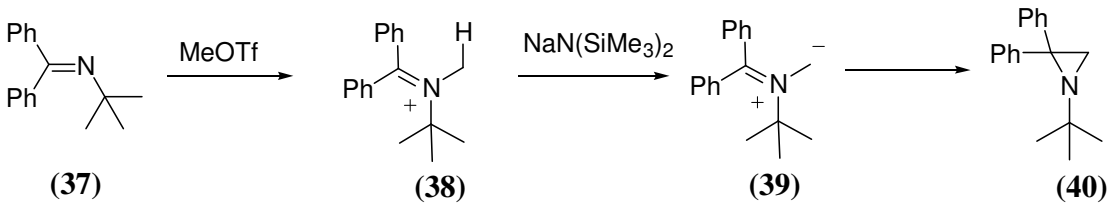
Deprotonation of iminium ions

Normally, iminium ions are prepared by condensation of carbonyl compound (32) with secondary amimes (33) or *N*-alkylation of imines (34) followed by α-deprotronation of (35) to afford (36) (Tsuge *et al*., 1989).



(32) **(33)** **(34)** **(35)** **(36)**

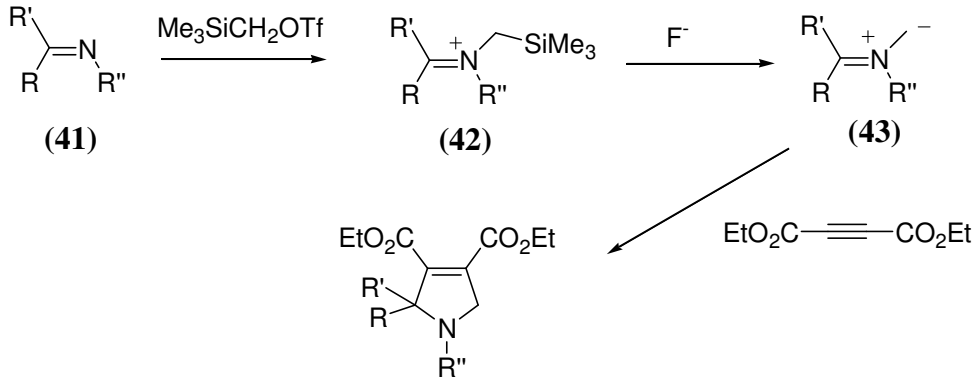
In 1975, Deyrup *et at*. reported the use of MeOTf for *N*-alkylation of imime (17) to from iminium salt (18). α-Deprotronation of (38) generated the non-stabilized azomethine ylide (39) and subsequent ring closure to give aziridine (40) in a quantitative yield.



(37) **(38)** **(39)** **(40)**

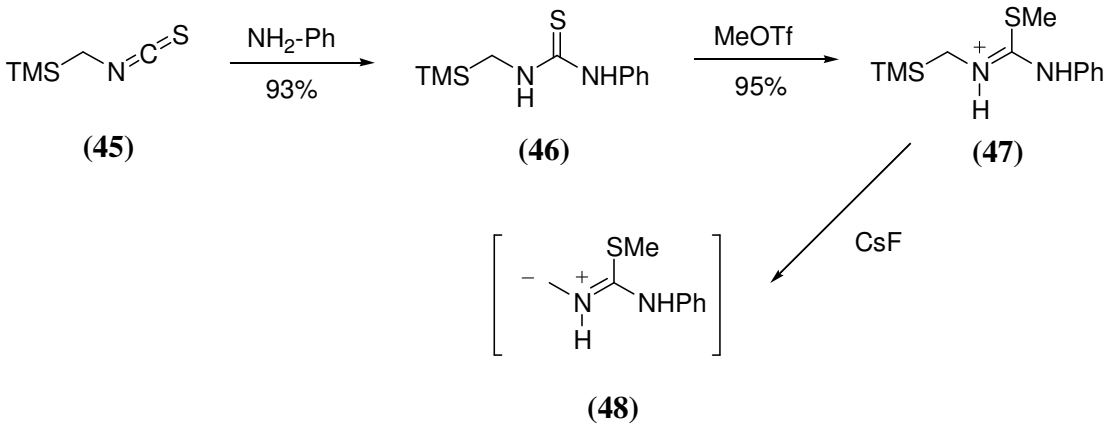
Desilylation pathway

This approach is fairly common for generation of non-stabilized azomethine ylides. In 1979, Vedejs and Martines reported the modified iminium iron route which involved alkylation of imine (41) by using trimethylsilylmethyl trifate to form the iminium salt (42). Desilylation of (42) by F^- ion gave non-stabilized azomethine ylide (43) which was trapped by dimethyl acetylenedicarboxylate (Vedejs *et al*., 1986).

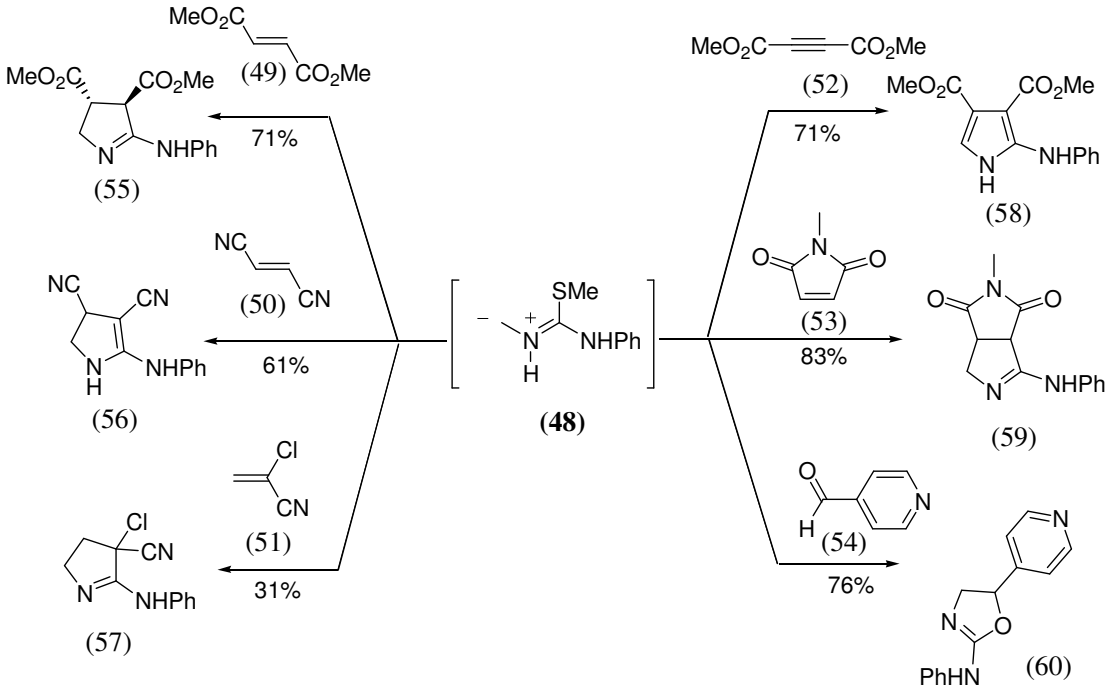


(41) **(42)** **(43)** **(44)**

Tsuge *et al*. (1984) reported the generation of azomethine ylide (48) from isothiocyanate (45) (Scheme 10)**.** Treatment of azomethine ylide (48) *in situ* with electron-deficient olefins (49), (50), (51), (52), (53) and (54) gave cycloadduct (55), (56), (57), (58), (59) and (50), respectively, after elimination of methylthio group (Scheme 8) (Tsuge *et al*., 2000).

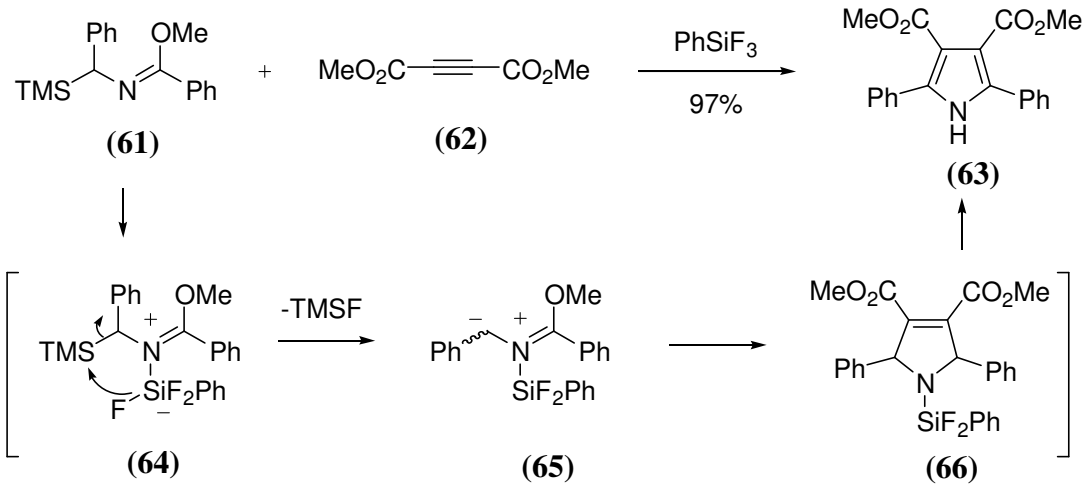


(45) **(46)** **(47)** **(48)**



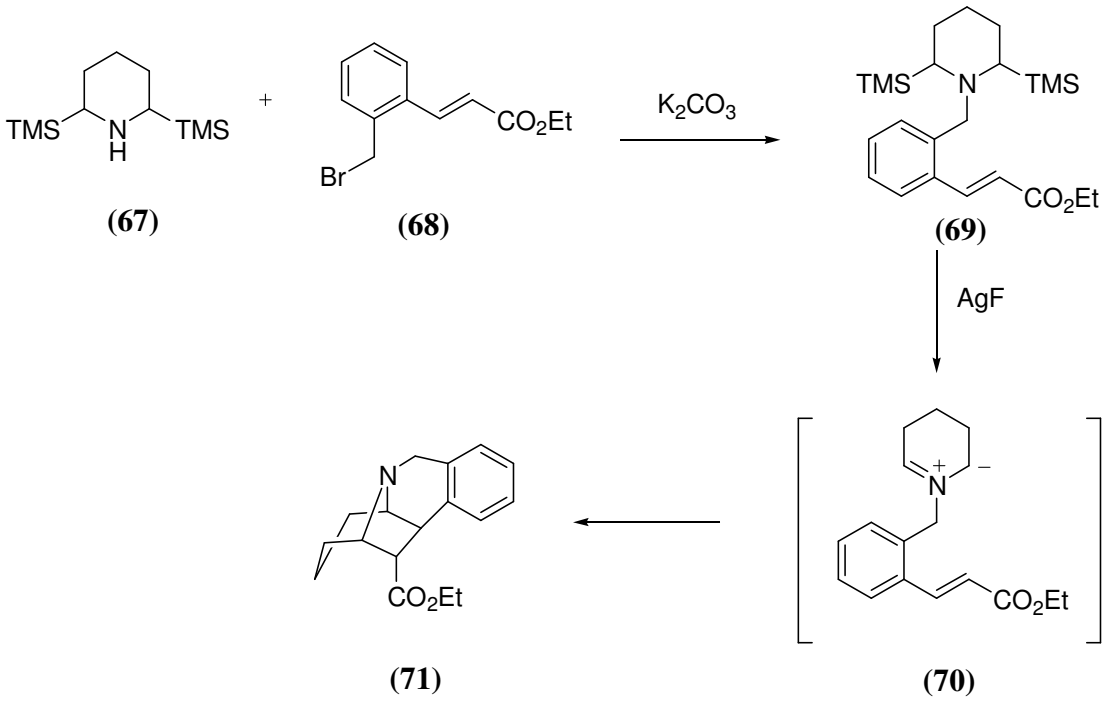
Scheme 8

The related N-silylated azomethine ylide (65) was obtained by treatment of α-silylimidate (61) with trifluorophenylsilane under relatively mild conditions. This azomethine ylide reacted with acetylenic (62) (or olefinic dipolarophiles) to give pyrroline (66) which then underwent aromatization to provide the N-unsubstitued pyrroles (63) (Damrauer *et al*., 1986).



Nitrogen bridge-heterocycle (71) was prepared in a regio- and stereospecific route via the intramolecular 1,3-dipolar cycloaddition of nonstabilized cyclic

azomethine ylide (70), which is generated by the sequential double desilyation of N-alkyl α,α'-bis(trimethylsilyl)cyclic amines (69) using AgF as a one electron oxidant. A typical example was shown in Scheme 9, whereby cycloadduct (71) was obtained regio- and stereospecifically in a good yield (Pandey *et al*., 2000).

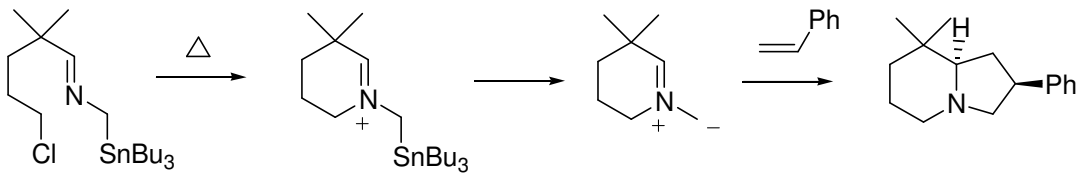


(67) **(68)** **(69)** **(70)** **(71)**

Scheme 9

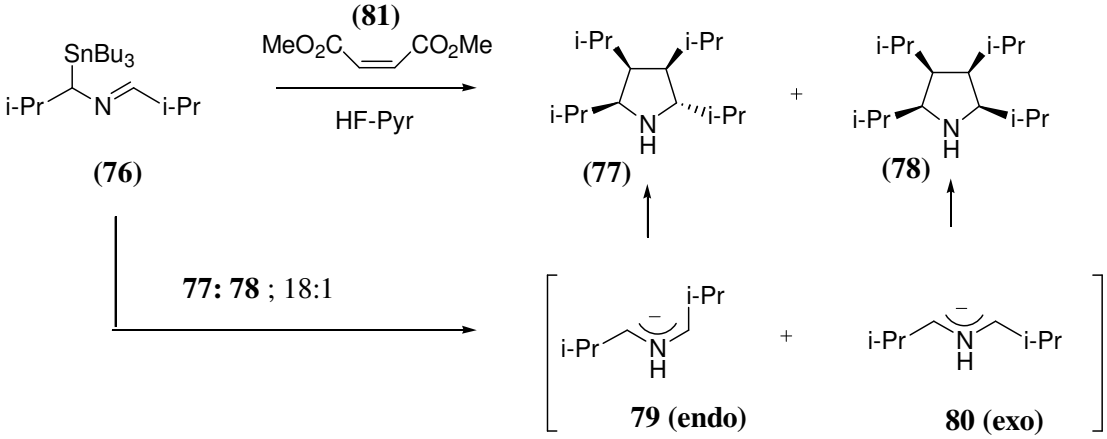
Destannylation pathway

The destannylation pathway is fairly similar to desilylation pathway and showed in below. Intramolecular cyclisation of (72) furnished (73) and subsequent destannylation generated non-stabilized azomethine ylide (74) which underwent cycloaddition to form (75) as a single diastereomer (Katrizky *et al*., 1998).



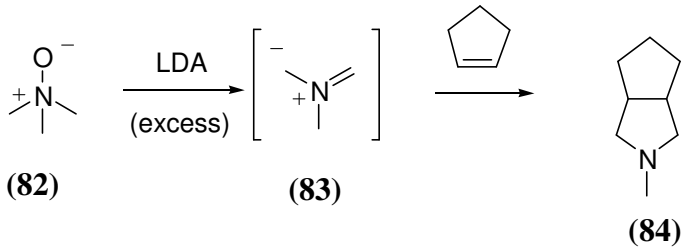
(72) **(73)** **(74)** **(75)**

The generation of non-stabilized azomethine ylides by protodestannyllation of (2-azaallyl)stannanes (76) is interesting in that cycloaddition with electron-poor alkene (81) gave trans-2,5-dialkypyrrolidine (77) as the major product with high stereoselectivity (**77 : 78** ; 18 : 1) in 68 % yield. The major product structures implicated dipole (**79**) with endo-transition states (Pearson *et al*., 1999).

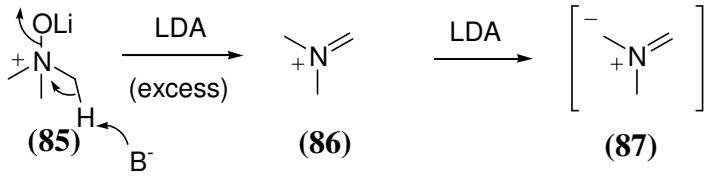


N-oxide pathway

In 1983, Roussi first reported the use of trimethylamine N-Oxide (82) with a large excess of lithium diisopropylamide (LDA) to generate the non-stabilized azomethine ylide (83).

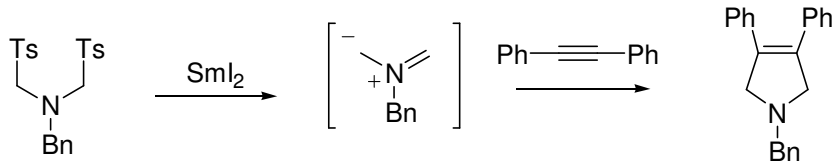


The plausible mechanism was illustrated. O-lithiation of tertiary amine N-oxide (85) followed by α-deprotonation gave an iminium intermediate (86) which was underwent α-deprotonation again to give non-stabilized azomethine ylide (87) (Roussi *et al*., 1988).



SmI_2 reduction pathway

The final approach was first reported by Roussi *et al*. The azomethine ylide (89) was generated by treatment of (88) with SmI_2 in THF/HMPA at rt for 18 h in the presence of diphenylacetylene to obtain the dihydropyrrole (90).

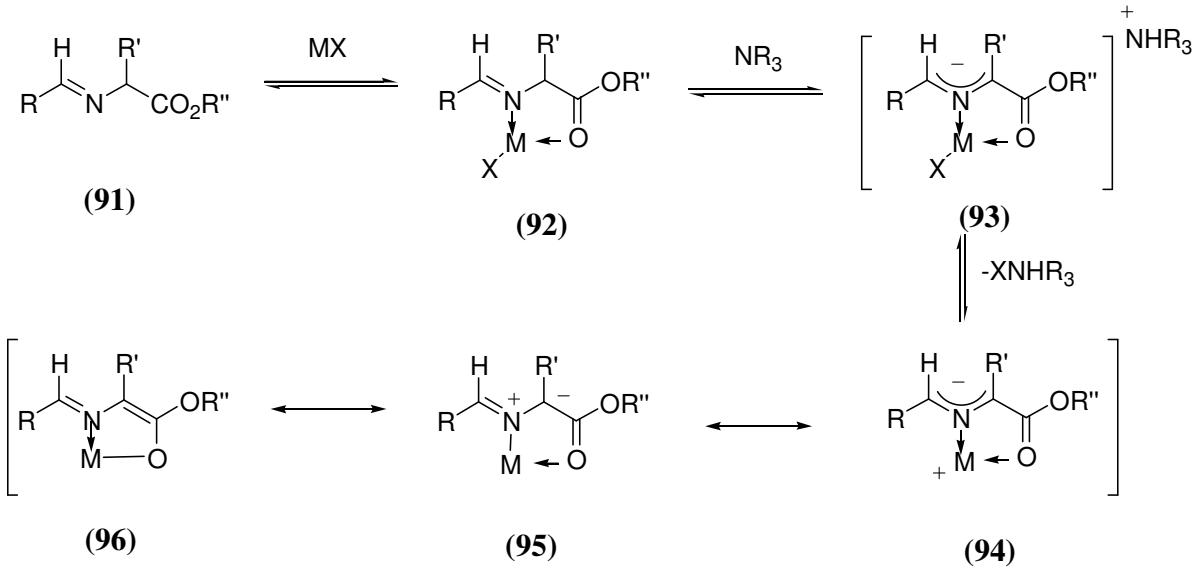


Stablised azomethine ylides

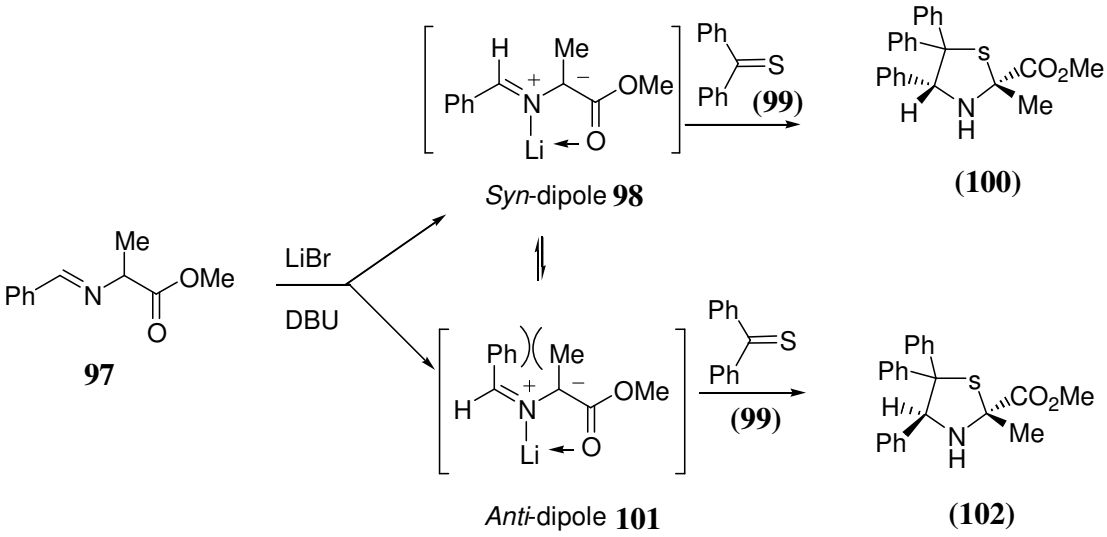
Stablised azomethine ylides can be generated by the same methods of non-stabilized azomethine ylides. The additional methods include the following:

N-metallation pathway

Coordination of an appropriate metal ion to the imine (91) afforded complexes (92) which undergoes deprotonation by base to form the (E,E)-metallo-azomethine ylide (93) It is unclear whether (93) loses the metal counter ion X to afford (94) and R_3NHX. The three canonical forms ((94), (95) and (96)) represent the relative degrees of coordination by the nitrogen and oxygen atoms. A wide range of metal salts and bases have been employed in this process. However, LiBr or AgOAc are the most used metal salts, whereas DBU or triethylamine are most frequently used bases (Grigg *et al*., 1995)

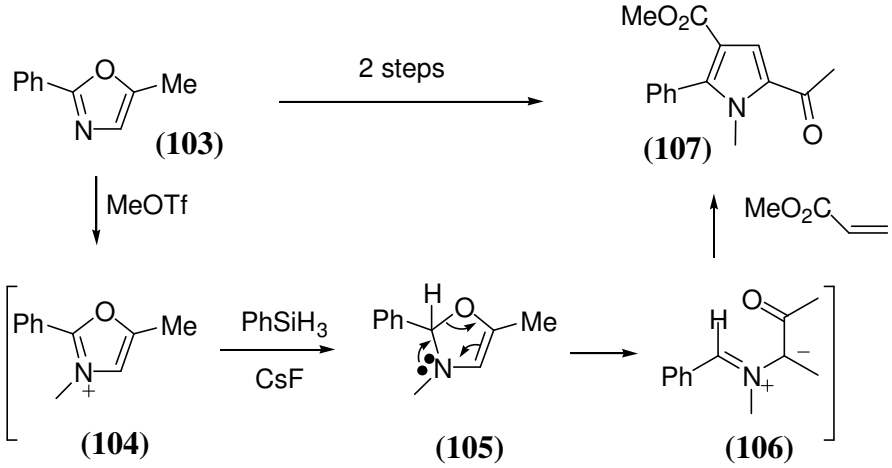


1,3-Dipolar cycloaddition of N-benzylidenalamine methyl ester (97) with thiobenzophenone (99) as a dipolarophile in the presence of LiBr and DBU gave a 4:1 mixture of diasteromers (100) and (102) in good yield. The product was formed regioselectively to generate *in situ* lithio-azomethine ylide syn-dipole (98) and anti-dipole (101), respectively (Heimgartner *et al*., 2001).



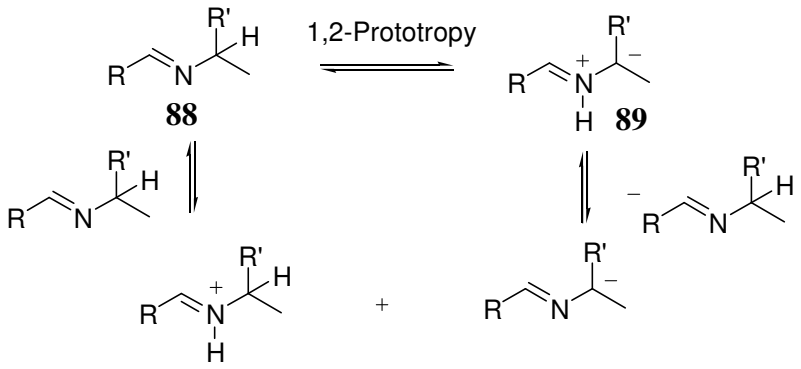
Oxazolidione pathway

In 1986, Vedejs developed the methodology to generate azomethine ylide via reduction oxazolium salt. Treatment of oxazole (103) with methyl triflate provided the oxazonium salt (104) followed by reduction by hydride transfer from $PhSiH_3$/CsF to afford the oxazoline (105) which was spontaneously open the ring to give azomethine ylide (106). The ylide was trapped with methyl acrylate to give a single diastereoisomer (107) in good yield.



Formal 1,2-prototropy in imines

The formal 1,2-prototropy of imines of α-amino acid esters was first discovered by Grigg *et al.* in 1978, who has contributed extensively in this area to both mechanism and the application (Grigg *et al.*,1980; Grigg *et al.*, 1987). The formation of (109) is a bimolecular process involving two molecules of (108) since a concerted 1,2-shift, a four-electron process, contravenes the Woodward-Hoffman rules. The pKa of the proton and the basicity of the nitrogen atom control the process with are, in turn, dependent on the activating group R and R' group respectively.



Stable azomethine ylides

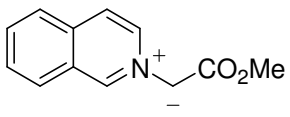
Stable azomethine ylides are comparatively rare and can be classified into three types;

(i) One C-N bond of the azomethine ylide is located within a heteroaromatic structure (Surpateanu *et al*., 1984).

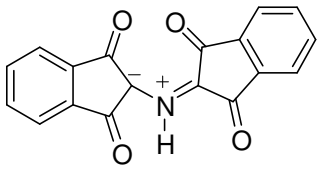
(ii) Neither C-N bond of azomethine ylide is located within a heteroaromatic structure (Grigg *et al*., 1989).

(iii) The azomethine ylide is locade within a mesoionic ring system (Huisgen *et al*., 1964).

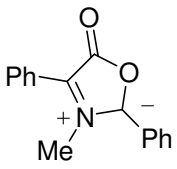
The example of each type is shown in below.



110 (i)



111 (ii)



112 (iii)