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REVIEW ARTICLE

Recent advances in synthesis of ketenimines

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KEYWORDS

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Rearrangement;
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Abstract Ketenimines are a kind of reactive species that can be used as synthetic intermediates. In the last two decades, there has been a surge of interest in this class of building blocks and their applications, which has led to extensive research on ketenimine derivatives such as fluorine ketenimine, metal complexes of ketenimines, and the various methods of their preparation. Ketenimines have been prepared by a variety of methods, including photolysis, elimination, or rearrangement reactions. As well as, ketenimines can be prepared using a variety of useful reagents, including isocyanates, copper acetylide, amides, organometallic compounds, and metal complexes. An overview of these achievements is presented here.

1. Introduction

In more than 180 years, chemists have made significant advances in the development of chemical reactions and methods for the selective and efficient conversion of organic compounds. Thanks to these discoveries, many of the most complicated products can now be produced by organic synthesis (Corey and Cheng, 1995; Nicolaou and Sorensen, 1996; Nicolaou and Snyder, 2003; Nicolaou et al., 2000). Yet, it was not so long ago that the possibilities in this field were not well developed. For example, chemical research has shown that the fluorine atom and fluorine-containing motifs have a significant impact on the composition, reactivity, and function of organic and inorganic molecules (Kirsch, 2004; Groult et al., 2017; Haufe and Leroux, 2019). Since ketenimines are extremely versatile intermediates and can be used in a wide range of reactions, including nucleophilic additions and pericyclic reactions (Krow, 1971; Gambaryan, 1976; Aumann, 1988a,b). However, fluorinated ketenimines are understudied, possibly because there are few synthetic methods for their preparation. On the other hand, ketenimine complexes are used as versatile synthetic building blocks, but due to the lack of suitable methods for their preparation, they have received less attention. These shortcomings have challenged the synthesis initiatives of chemists and stimulated innovative methods for their synthesis, constantly updating the creativity of chemists involved in the Synthesize topologically complex molecules. Literature survey shows that most of the papers about the chemistry of ketenimines were published in the Journals of the American Chemical Society (www.scopus.com). In the last decade, scientists have developed a variety of methods for the Synthesize ketenimines, such as the Wittig reagent, alkane nitriles, amides, metal complexes as "non-classical" building blocks, cleavage of heterocyclic compounds, elimination reactions, isocyanide and rearrangement reactions, and pericyclic processes. Although three reviews on the chemistry of ketenimines have been published, none of them provides a comprehensive evaluation of the synthetic methods for these compounds (Lu et al., 2012; Dodd and Cariou, 2018; Alajarin et al., 2012). Therefore, in this review paper, we have detailed and explained various methods for the preparation of ketenimines, which serve as important intermediates for

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[2 + 2]-cycloaddition reactions (Alajarin et al., 1996) or for the formation of five-or six-membered ring systems (Aumann, 1988a,b). The review paper is roughly chronological in its development.

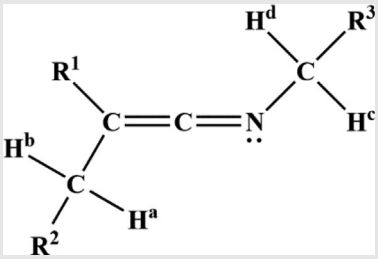
2. Background

2.1. Chemistry

In chemistry, ketenimines (IUPAC name: 1-alkenylideneamines) are considered a main category of compounds as valuable synthetic intermediates or reactive species. The ketenimine system contains an axial dissymmetry that is parallel to the allenes. Due to their special properties, such as a C—C double bond of the ethylene type and a C—N double bond of the azomethine type, they can be chiral. Nevertheless, the ability to perceive axial disharmony depends on the structural constancy of ketenimine, which is likely to reverse its formation either by turning around the imine or inversion of the nitrogen lone pair. The calculated barrier to interconversion is $\leq$ 10kcal/mol [Simon et al., 1968], which is consistent with available experimental data. Another reason that causes ketenimines to be chiral is that they have a linear nitrilium resonance form that leads to very fast epimerization with all carbon-substituted groups, and this barrier is only 9 – 12kcal/mol [Moss et al., 1995]. For ketenimines, resonance structures 1 – 1″ are the most crucial ones. As shown in Scheme 1, describing ketenimine as a structure 1 may in fact oversimplify the situation. Other potential canonical forms include a zwitterionic form **1′**, which emphasizes the nucleophilicity of the β-carbon atom, and an alternative zwitterion **1″** which emphasizes the electrophilicity of the central carbon atom.

Ketenimines' structure is almost linear (170 – 176°) and has a triad CCN bond, according to single-crystal X-ray diffraction studies, but there are a few examples ("e.g., with (R^1 = R^2 = $MeSO_2$, R^3 = Me") that prove that with a strong electron-withdrawing sulfone group on the ketene portion and a methyl group on the imine portion of ketenimine **1** the CH_3-N-C bond angle is 180°. The large contribution of the resonance structure **1′** can account for the linearity in the crystalline state. However, when the *N*-methyl group is replaced by an *N*-ethyl group, the CH_2-N-C bond angle is 144°. The development of the ketenimine was confirmed by observing the absorption band of the C═C═N in FT-IR spectra, which showed a very robust absorption around 2000 cm^{-1}. The strong shielding of the terminal allenic carbon ($\delta_C = 37 - 38$ *ppm* for various methyl- and phenyl- substituted ketenimines) also suggests the conjugative interaction between the C═C bond and the lone nitrogen pair implicit in the canonical form **1′**, and the up field ^{15}N chemical shift support this conclusion. An attempt to observe the effects of the barrier to interconversion of ketenimines on the chemical shifts of the diastereotopic methylene hydrogens in ketenimines **I** to **IV**, shown in Table 1, was unsuccessful. The protons

Table 1 Ketenimines were used in an attempt to observe diastereotopic hydrogens.



	R^1	R^2	R^3
I	Ph	CH_3	*tert*-C_4H_9
II	Ph	Ph	*tert*-C_4H_9
III	Ph	CH_3	Ph
IV	H	$C(CH_3)_2Cl$	*tert*-C_4H_9

H^a, H^b or H^c, H^d appeared magnetically equivalent over a temperature range of −60 to +80 °C (Krow, 1971).

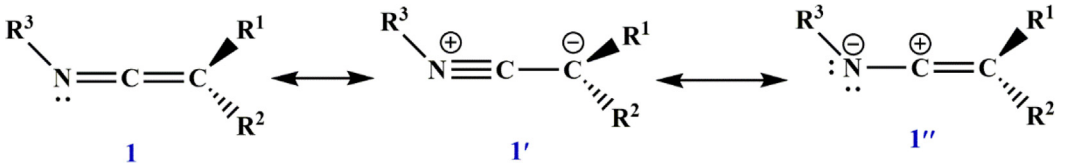
Table 1**.** Ketenimines were used in an attempt to observe diastereotopic hydrogens.

Jochims et al. (Jochims and Anet, 1970) used the NMR method to determine the barriers to racemization of 3-methyl-*N*,2-diphenylbut-1-en-1-imine **V** and 2,3-dimethyl-*N*-phenylbut-1-en-1-imine **VI** (Scheme 2). At −113 °C, the methyl protons of the isopropyl group of 3-methyl-*N*,2-diphenylbut-1-en-1-imine **V** separated into a double pair with a 4Hz chemical shift difference, corresponding to a free activation energy for racemization of 9.1 ± 0.2 kcal/mol. The barrier in 410 was raised to 12.2 ± 0.3 kcal/mol.

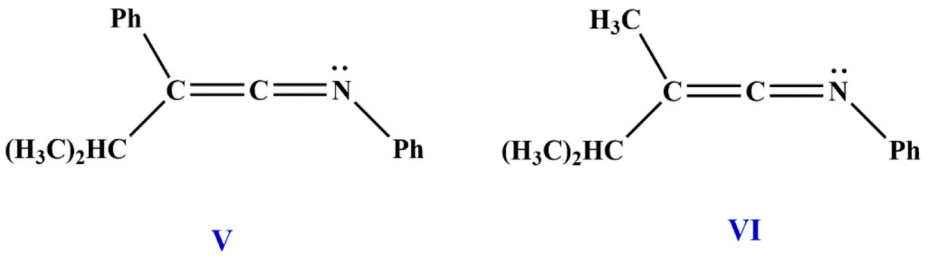
In general, ketenimines possess a higher stability level than ketenes and can reach even higher stability through bulky groups or heteroatoms such as phosphorus and silicon, and likewise through mesmeric groups (Kim et al., 2011). Their C═C═N cumulenic system contributes a high potential for reactions to the members of this class of organic complexes (Kirsch, 2004; Groult et al., 2017; Haufe and Leroux, 2019; Borrmann, 1968), which have the potential to undergo a wide variety of modifications which are particularly significant in the structure of nitrogen heterocycles (Molina et al., 1991; Alajarin et al., 2000). It is believed that ketenimines, as tautomers of aliphatic nitriles, can contribute as intermediates in some important chemical reactions. In modern organic synthesis, ketenimines with high stability levels are absorbed elements (Kaneti and Nguyen, 1982).

2.2. History

The first stable member of the group was described by Staudinger et al. in 1920 (Staudinger and Meyer, 1919). Although no



Scheme 1 Resonance structures of ketenimines.



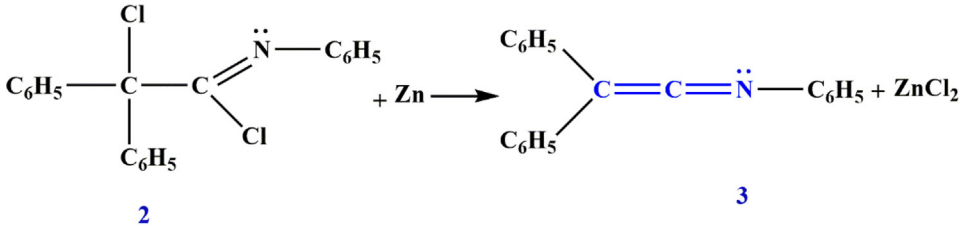
Scheme 2 Structure of ketenimines.

yield was given and no attempts were made to extend the synthesis to other ketenimines, they discovered that the reaction of (*Z*)-2-choro-*N*,2,2-triphenylacetimidoyl chloride **2** with zinc leads to the preparation of ketenimine **3** (Scheme 3).

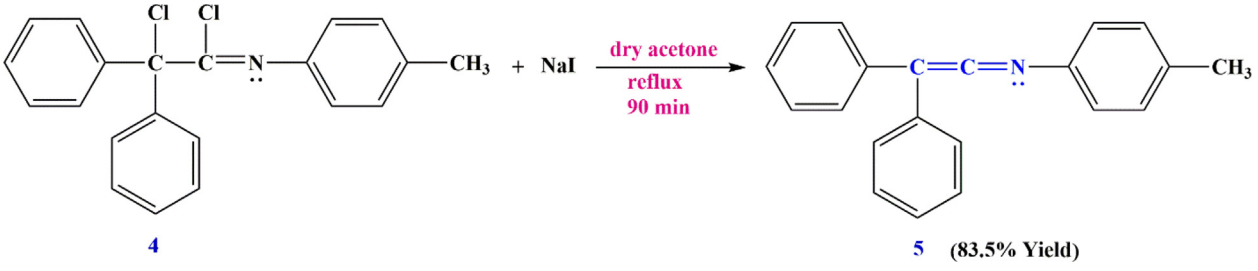
Their results showed that the C═C═N unit is very susceptible to decomposition by hydrolysis, dimerization, polymerization, and other reactions. They actually developed a new class of highly reactive compounds containing C—C and C—N double bonds. Another successful method for the preparation of ketenimine was proposed by Stevens et al. in 1953 (Stevens and French, 1953). They showed that 2-chloro-2,2-diphenyl-*N*-(*p*-tolyl)acetimidoyl chloride **4** was readily dehalogenated with sodium iodide, resulting in the formation of 2,2-diphenyl-*N*-(*p*-tolyl)ethen-1-imine **5** as a ketenimine derivative (Scheme 4).

Continuing the work of other researchers, Dijkstra et al. (Dijkstra and Backer, 1954) have shown that the reaction between diazomethane **7** and bis-methylsulphonylacetonitrile **6** can produce *N*,2-dimethylprop-1-en-1-imine-sulfur (IV) oxide **8** in a medium yield (Scheme 5).

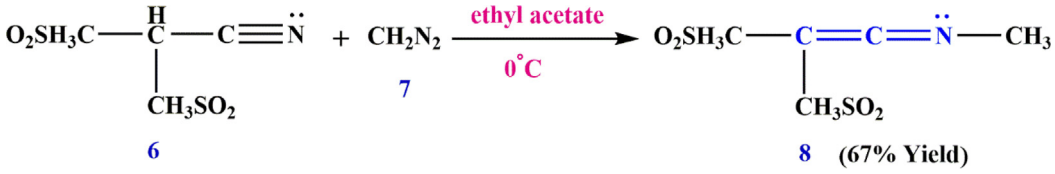
Due to the unique properties and high reactivity of ketenimines, the chemistry of these compounds was first studied by Krow (Corey and Cheng, 1995). By 1971, the methods for the preparation of ketenimines had been further developed, and despite substitution reactions in ketenes, isocyanates, and carbodiimides, other addition reactions of isocyanides with carbenes or cyclopropenones, alkynes, as well as elimination and rearrangement reactions, were proposed by other scientists. But the methods he proposed for the synthesis of ketenimine were very limited. In 1976, Gambaryan (Nicolaou and Sorensen, 1996) dealt with



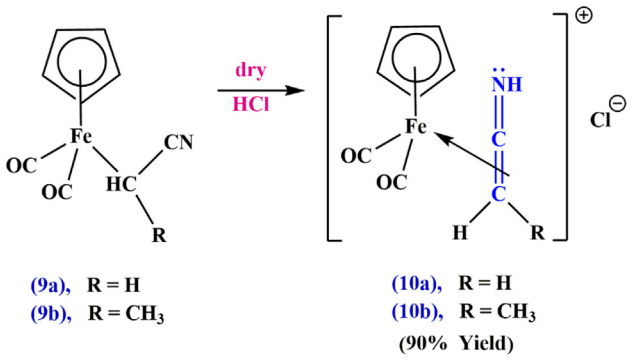
Scheme 3 Structure of the first ketenimine **3**.



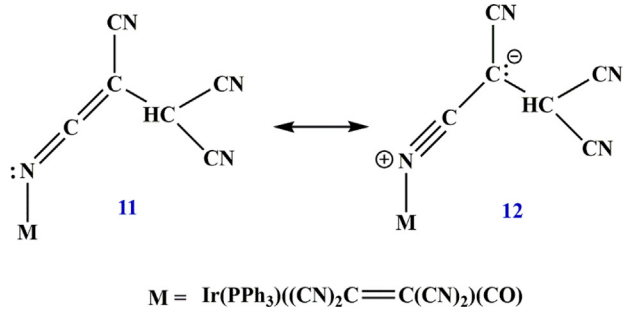
Scheme 4 Synthesizing 2,2-diphenyl-*N*-(*p*-tolyl)ethen-1-imine **5**.



Scheme 5 Synthesize *N*,2-dimethylprop-1-en-1-imine-sulfur (IV) oxide **8**.



Scheme 6 Synthesize the ketenimin-iron complex **10**.

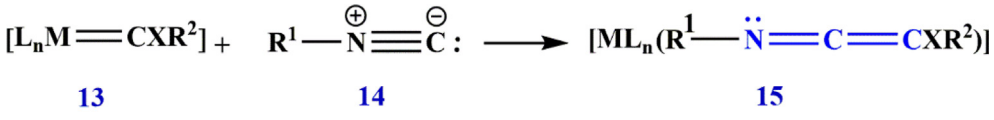


Scheme 7 Resonance structures of the metal complex ketenimine.

the subject of fluorinated ketenimines in a specialized review paper and investigated the methods used for obtaining imines of fluorinated ketenes as well as their dimerization and nucleophilic addition. Other scientists have shown that metal complexes of ketenimines are of particular importance for synthesis. Namely, they have shown how the reactivity of these compounds changes upon complexation and how ketenimine complexes can be used as versatile synthetic building blocks. To further evaluate the generality and scope of the reaction, Ariyaratne et al. (Ariyaratne and Green, 1963) indicated that the metal-π complex of ketenimin-iron **10** can be synthesized by proton-catalyzed isomerization of the σ-complex **9** (Scheme 6). The un-complexed imine function can be identified by the characteristic infrared bands at 1554 cm^{-1}.

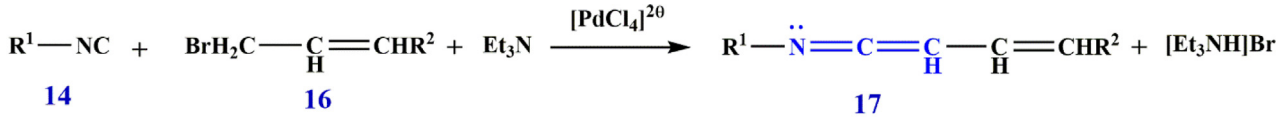
Beck et al. (Beck et al., 1966; Beck et al., 1967) showed another method for the preparation of metal complexes ketenimine using a nitrogen transition metal compound. Using X-ray experiments, they demonstrated that the iridium-tetracyanoethylene complex should be the ((2,3,3-tricyano prop-1-en-1-ylidene) amino) iridium-tetracyanoethylene complex **11**, and that the iridium N—C bond angle of 162° is a good indicator of the relative importance of the resonance structure **12** (Scheme 7).

Also in 1988, Aumann (Aumann, 1988a,b) showed that metal complexes of ketenimines are of particular importance in synthesis. As a matter of fact, he showed that ketenimine complexes **15** are formed by the insertion of a 1,2-bond N=C to the bond M=C carbon **13**, the complexes being bonded to isocyanide **14** (Scheme 8). The insertion of iso-

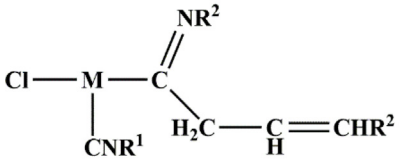


X = O-alkyl, S-alkyl, N=CR_2, PR_3
R^1, R^2 = alkyl, aryl, alkenyl, alkynyl
M = Cr, Mo, W, Mn, Fe, Os, Th, U
L = CO, PR_3, η^5-$CH_3C_5H_4$, η^5-C_5H_5

Scheme 8 The reaction between carbon complex and isocyanide.



R^1 = *cyclo*-C_6H_{11}, C_6H_5, *p*-NO_2—C_6H_4
R^2 = CH_3, H



18 M = Pd

Scheme 9 Synthesize ketenimine **17**.

cyanides into M=C bonds is not specific to any particular metal, and complexes **15** with M=V, Cr, Fe, Ni, Th, Ir, Mg, Li, U, Au, Cu, Co, and Pd have been crystallographically characterized. It is possible to build up palladium-ketenimine complexes catalytically from isocyanides **14**, allyl bromides **16**, and triethylamine. Catalysis involves the *N*-substituted alkenimidoyl complexes **18** as intermediates (**18**, R^2=CH_3, H, has been isolated) which are probably formed by the insertion of R^1-NC into a Pd=C δ bond. However, coupling *via* Pd=C bonds cannot be excluded. Coupling reactions of carbenes (dichloride-, diphenyl-, dimethoxycarbonylcarbene) or with isocyanides to form ketenimines are also known (Scheme 9).

2.3. Mechanism

The reaction to produce ketenimines was developed by Staudinger et al., but they did not describe the mechanism of the reaction. It appears that organometallic reagents, including zinc, tend to act as strong reducing agents in the preparation of ketenimines. In fact, the reactions leading to the preparation of ketenimines must follow one of the proposed mechanisms, such as: substitution in heterocumulene, elimination reactions, rearrangement reactions, elimination-rearrangement, metal complexes, or transition metal complexes.

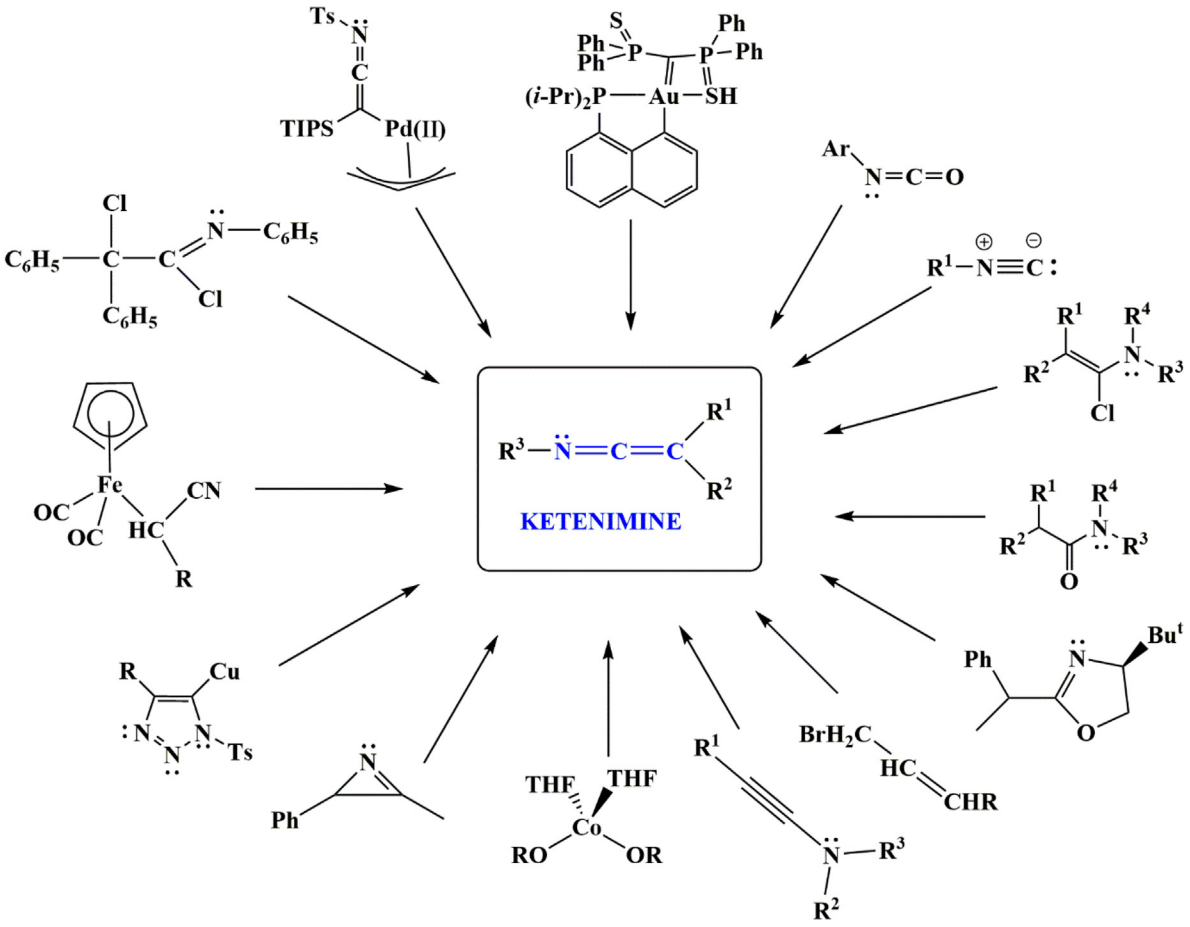
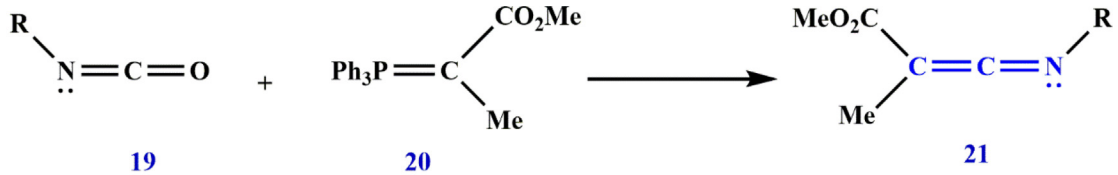


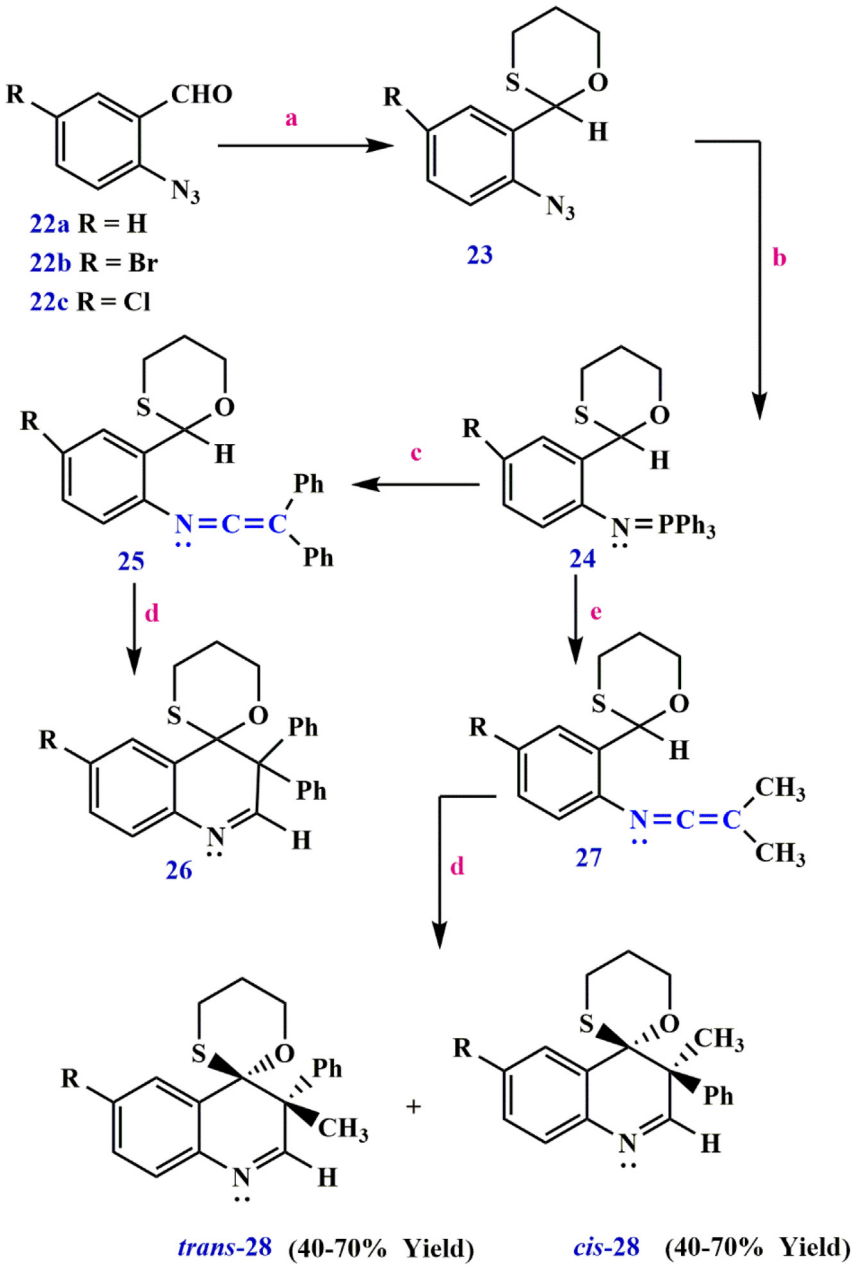
Fig. 1 All precursors for the preparation of ketenimines-based intermediates.



Scheme 10 Synthesize ketenimine **21**.

2.4. Precursors

The reaction of isocyanides with electron-deficient groups such as acetylenic ester, acetylenedicarboxylate, acid chlorides, and diethyl (bromo (phenyl) methyl) phosphonate are the most commonly used reagents for the preparation of ketenimines. These ketenimines can also be synthesized by various reagents, such as isocyanates, copper acetylides, amides, or organometallic or metal complexes of ketenimines by a variety of methods, including cleavage of compounds, photolysis, or elimination or rearrangement reactions. However, as shown in Fig. 1, there are several other ketenimine precursors. All methods for the preparation of ketenimines have been thoroughly investigated in this review paper. As we know, ketenimines are very reactive, and only sterically hindered or inductively stabilized ketenimines can be isolated. Therefore, ketenimines are almost always prepared in *situ* and trapped with species already in solution. The following sections show how ketenimines are used in organic synthesis to speed up the process of making molecules with many different parts.

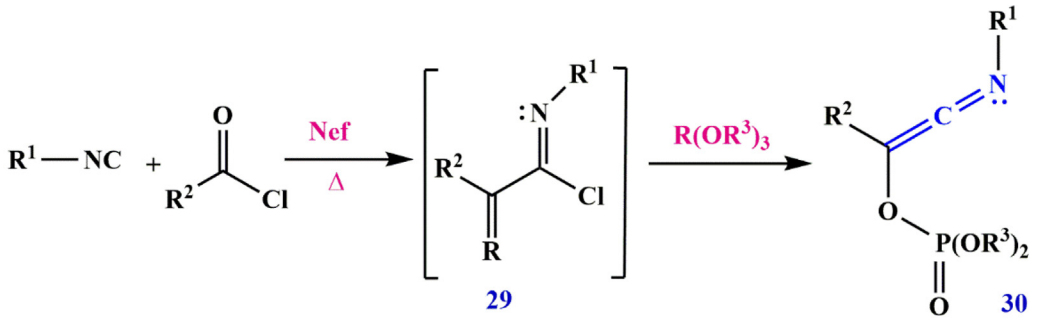


Reagents and conditions: (a) 3-mercaptopropanol, *p*-TsOH, benzene, reflux, 3h (b) PPh_3, Et_2O, rt,12 h (c) $Ph_2C{=}C{=}O$, *o*-xylene, rt, 30 min (d) *o*-xylene, reflux, 12 h (e) $PhCH_3C{=}C{=}O$, DCM, rt, 30 min.

Scheme 11 Synthesize spiroquinolines **28** *via* ketenimine.

3. Ketenimines preparation

Ketenimines are flexible intermediates capable of going through different organic reactions, and therefore their construction and potential for reactions have been the subject of extensive research (Jochims and Anet, 1970). Ketenimines belong to the group of heterocumulenes and are considered as imine equivalents of ketenes (Yoo and Chang, 2009). No wonder that they are mostly used as starting materials in chemical reactions for the synthesis of open-chain and heterocyclic compounds (Denmark and Wilson, 2012; Barker and Rosamond, 1972; Kaufman, 1970) and also peptides (Stevens and Munk, 1958). This is due to their high reactivity. However, this high reactivity and the difficult reaction conditions required for their building can sometimes cause problems in the preparation of functionalized ketenimines. Ketenimines stabilized by heteroatoms such as silicon, phosphorus, and sulfur, as well as those conjugated with vinyl, aryl, and carbonyl functional groups, can be synthesized and separated as active intermediates.

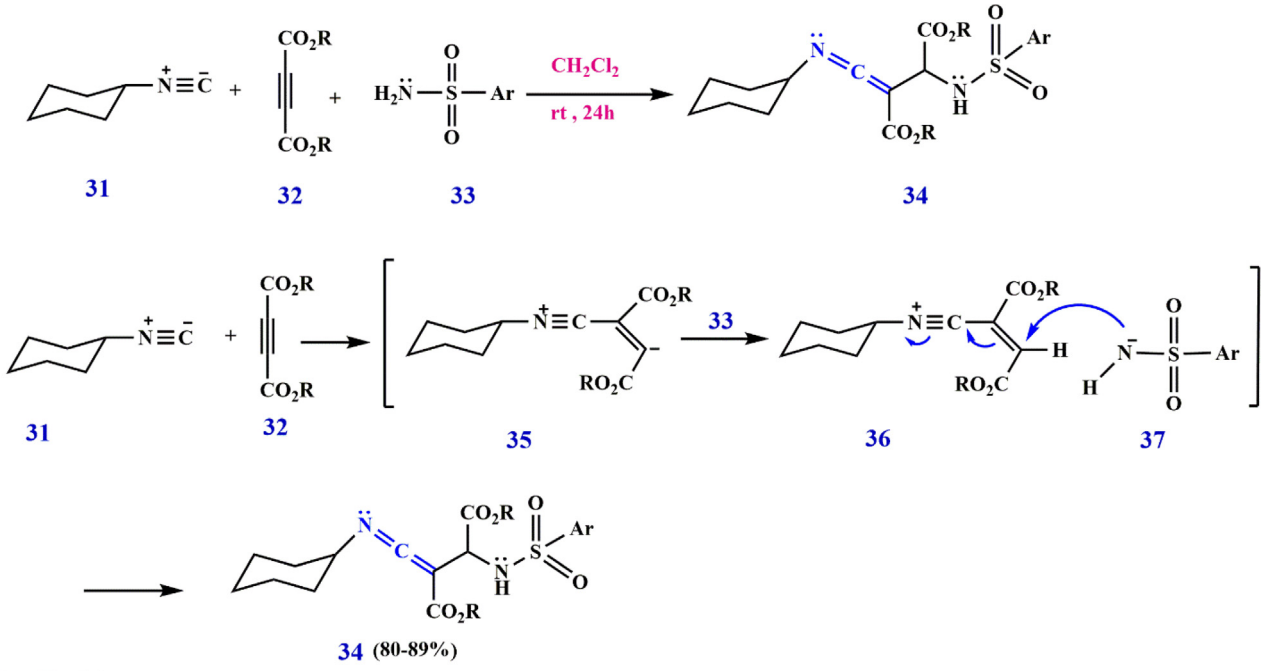


R^1= Cy, 4-ethyl-1,2-dimethoxybenzene, 3-ethoxyprop-1-ene, isobutane

R^2= CO_2Et

R^3= *i*-Pr, Et

Scheme 12 Synthesize ketenimines *via* a Nef/Perkow sequence.



R = Et, Me

Ar = *p*-CH_3-phenyl, *p*-NO_2-phenyl, phenyl

Scheme 13 Synthesize ketenimines **34** by cyclohexyl isocyanide.

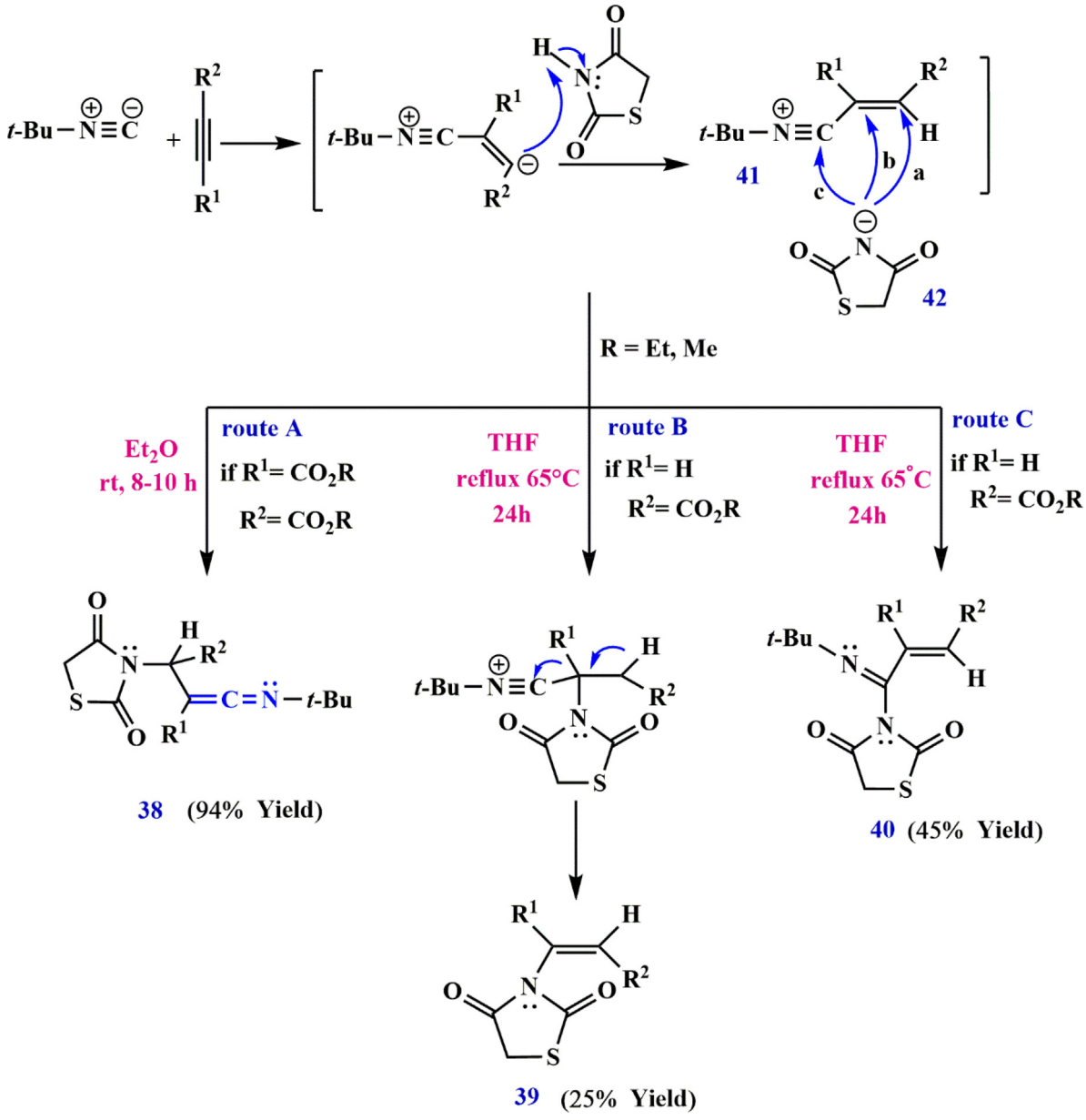
3.1. Ketenimine preparation via coupling reactions

The Wittig reaction is a commonly used method for the preparation of C═C or C═N bonds of ketenimines (Guan et al., 2019; Xiong et al., 2021). Aryl isocyanate **19** and methyl 2-(triphenylphosphoranylidene) propanoate **20** can be utilized to prepare methyl 3-(arylimino)-2-methylacrylate **21,** a highly electrophilic ketenimine (Cheng et al., 2009). In such a reaction, the Wittig reagent serves as an equivalent to the nucleophilic attack of the electron-deficient isocyanates. Since the ester group at the *C*-terminus stabilizes the ketenimines, they can be isolated (Scheme 10).

Alternatively, the coupling reaction between the Wittig reagent **24** and diphenylketene can be carried out in anhydrous *ortho*-xylene at room temperature to give the 1,3-oxathiane ketenimine **25**, which under the reaction conditions converts to the 3',3'-diphenylspiro[1,3-oxathiane-2,4'(3'*H*)-quinoline] **26** and spiroquinolines **28** in *cis* and *trans* (*via* 1,3-oxathianeketenimines [1,5]-*H*-shift followed by 6-electrocyclisation) in moderate yield (Scheme 11) (Alajarin et al., 2012).

3.2. Ketenimine preparation via isocyanide-based multicomponent reactions

Many methods based on multicomponent reactions (MCRs) have gained increasing attention (Zhu and Bienaymé, 2005; Domling, 2006; Orru and Greef, 2003). Imidoyl chloride **29** can be prepared in *situ via* the Nef reaction between isocyanide and acid chloride. When trialkyl phosphites are used to trap the α-keto imidoyl chloride, chloride through a phosphite, a



Scheme 14 Synthesize ketenimines **38**.

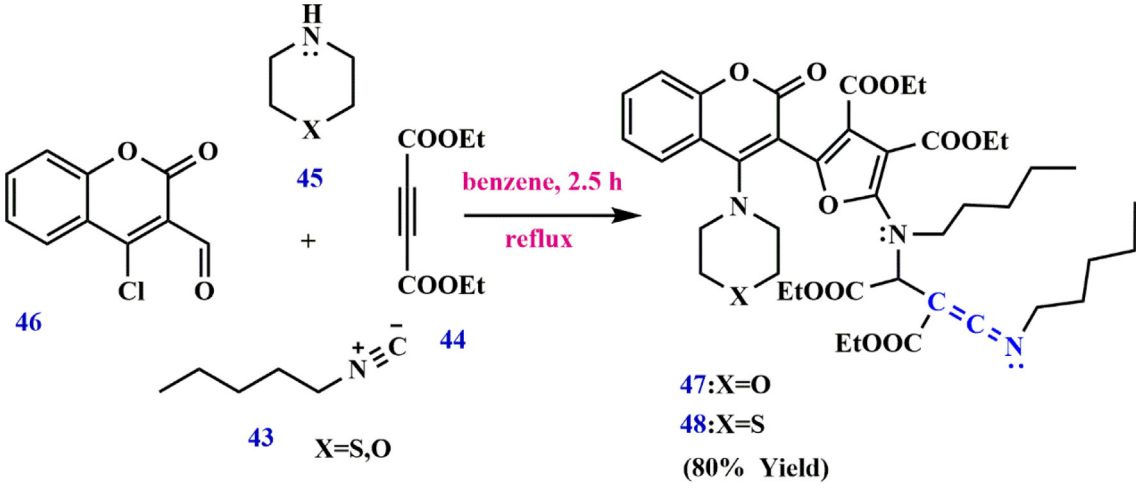
Perkow-type reaction can take place to form ethyl 3-(substitu tedimino)-2-((dialkoxyphosphoryl)oxy) acrylate **30** (Scheme 12) (Coffinier et al., 2011).

A parallel reaction model is also detected in the reaction of cyclohexyl isocyanide **31** with dialkyl acetylenedicarboxylate **32** in the presence of aryl sulfonamide **33**, which proceeds with a soft reaction in dichloromethane at room temperature to obtain dialkyl 2-cyclohexyliminomethylene-3-arylsulfonyla mino succinates **34** in good yield. Despite the lack of a feasible mechanism for the reaction between isocyanides and acetylene esters in the presence of aryl sulfonamide, a plausible mechanism has been presented (Scheme 13). A logical assumption, according to the deep-rooted chemistry of isocyanides, is that the functionalized ketenimine **34** obviously comes from the primary addition of the cyclohexyl isocyanide **31** to the acetylenic ester **32** and the subsequent protonation of the 1:1 adduct **35** by aryl sulfonamide **33**. Then the positively charged ion **36** is attacked by anion **37,** and finally, product **34** is formed (Anaraki-Ardakani et al., 2011).

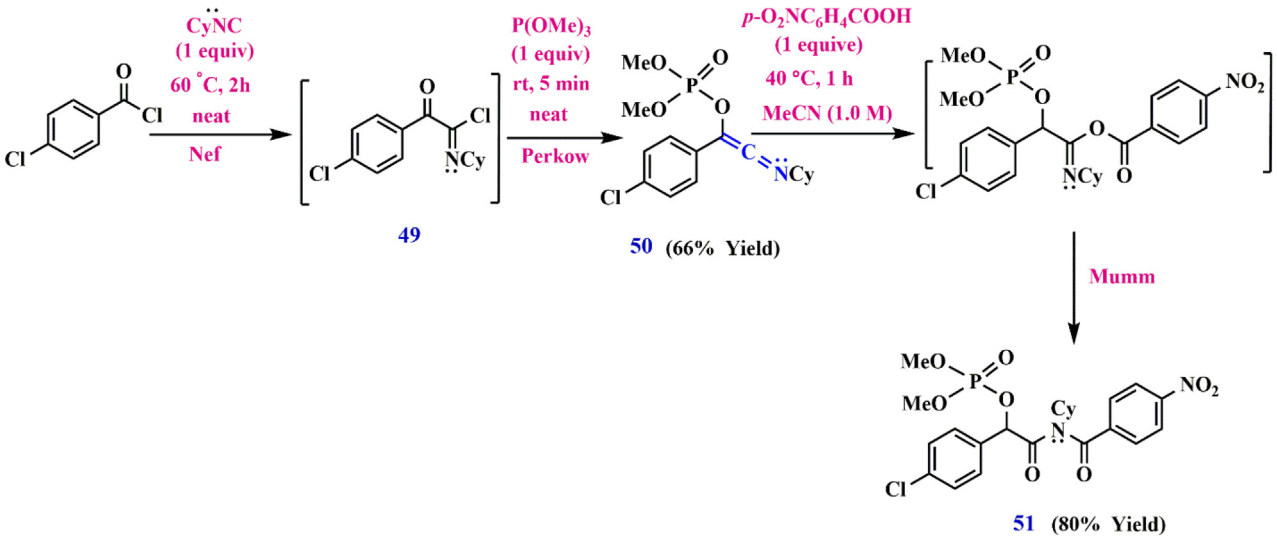
In 2013, Asghari et al. (Asghari et al., 2013) described a three-component reaction for the synthesis of ketenimines. The reaction starts with the Michael addition of *tert*-butyl isocyanide to the electron-deficient acetylenic ester, and finally the cationic intermediate, (Z)-*N*-(4-methoxy-2-(methoxycarbo nyl)-4-oxobut-2-en-1-ylidyne)-2-methylpropan-2-aminium **41** is formed (Scheme 14). Subsequently, 2,4-dioxothiazolidin-3-ide, the negatively charged ion **42** can attack the cationic intermediate **41** *via* routes A and B, and dialkyl-2-((*tert*-butylimino) methylene)-3-(2,4-dioxothiazolidin-3-yl) succinate **38** is produced by the Michael addition of the intermediate **42** to the cationic intermediate **41**.

Jalli et al.)Jalli et al., 2015) reported the reaction performed using pentyl isocyanide **43**, diethyl acetylene dicarboxylate **44**, morpholine **45** (or) thiomorpholine and 4-chloro-3-formyl coumarin **46** to give the corresponding ketenimine furyl coumarin **47** and **48**, respectively (Scheme 15).

Santos et al.)Dos Santos et al., 2017) have shown that imidoyl chloride **49** causes the formation of 1-(4-chlorophenyl)-2-



Scheme 15 Synthesize ketenimine furyl coumarin **47, 48**.

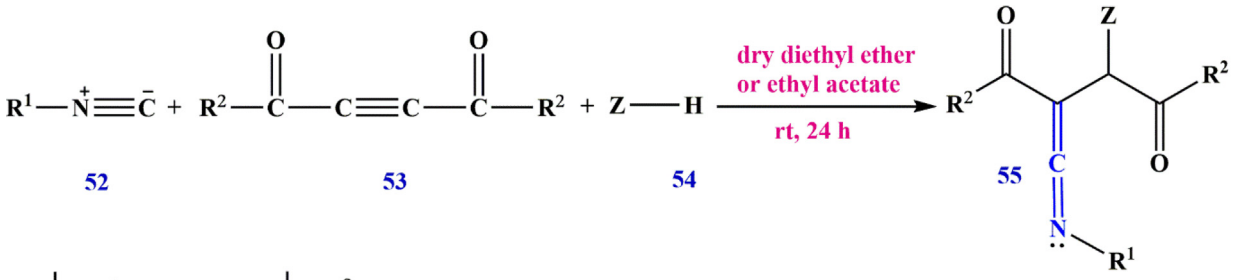


Scheme 16 Nef-Perkow-Mumm rearrangement cascade towards imido phosphate **51**.

(cyclohexylimino) vinyl dimethyl phosphate **50** in the Nef-Perkow sequence, whereupon the intermediate imidate ester undergoes a Mumm rearrangement, leading to imido phosphate **51**(Scheme 16).

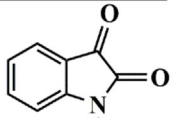
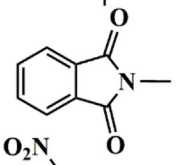
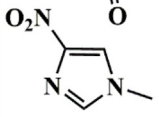
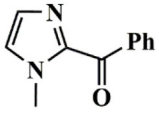
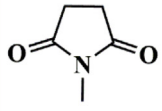
Bayat et al.)Bayat et al., 2008) described a modern and effective approach to the synthesis of ketenimines **55** using alkyl isocyanide **52** with dibenzoylacetylene or dialkyl acetylenedicarboxylate **53** in the presence of NH-acid **54**, prepared at ambient temperature in dry diethyl ether or ethyl acetate (Scheme 17).

Recently, Zhang et al. (Zhang et al., 2019) studied the reaction of difluorocarbene with isocyanide to produce



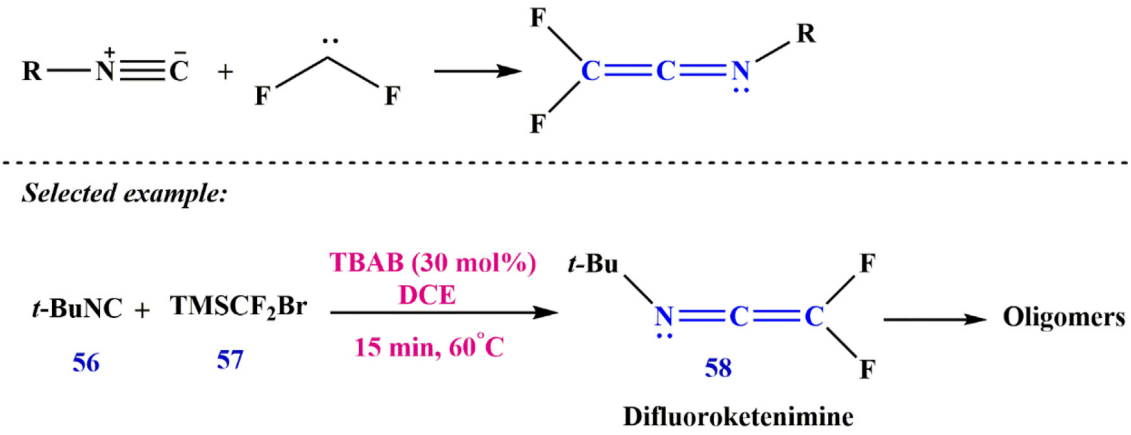
52	R^1
a	*t*-Bu
b	*c*-Hexyl

53	R^2
a	OMe
b	OEt
c	Ph
d	O*t*-Bu

54	Z
a	
b	
c	
d	
e	

55	Z	R^1	R^2	%Yield
a	Isatin	*t*-Bu	OMe	93
b	Isatin	*t*-Bu	OEt	95
c	Isatin	*c*-Hexyl	OEt	90
d	Phthalimide	*t*-Bu	OMe	87
e	4-Nitroimidazole	*t*-Bu	Ph	95
f	2-benzoylimidazole	*t*-Bu	Ph	92
g	Succinimide	*c*-Hexyl	O*t*-Bu	85

Scheme 17 Synthesize ketenimine **55**.



Scheme 18 Synthesize difluoroketenimine **58**.

difluoroketenimine **58.** They showed that the addition of fluorine substituents at the *C*-terminus leads to the activation of the ketenimines (Scheme 18).

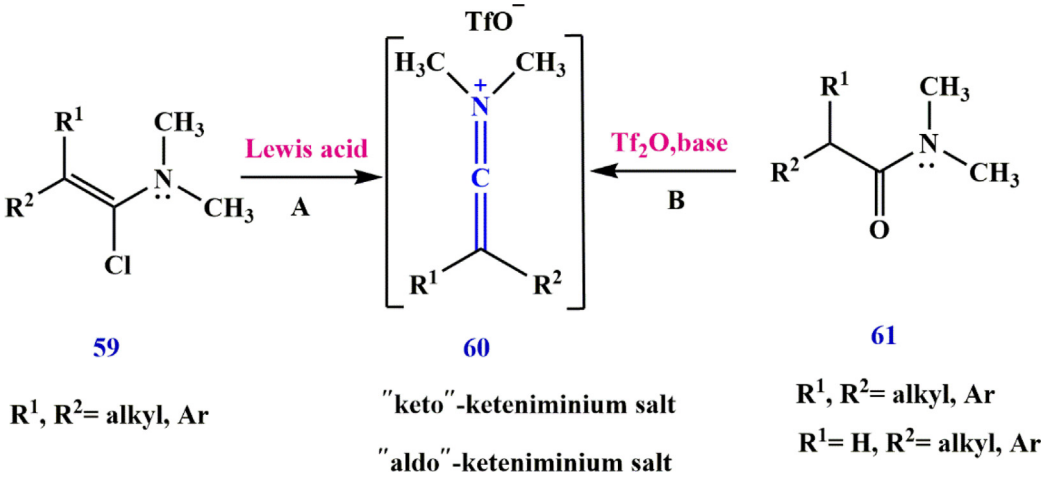
3.3. Ketenimine preparation via α-chloroenamine and tertiary amide

In 1972, Ghosez (Marchand-Brynaert and Ghosez, 1972) reported that 'keto'-keteniminium salts **60** (R^1, $R^2 \neq H$) can be prepared from the corresponding α-chloroenamine **59**, route A in (Scheme 19), or tertiary amide **61** (Falmagne et al., 1981), route B in (Scheme 19). Since the reactivity of the aldo-keteneiminium salts **60** ($R^1 = H$) is very high, they are only prepared *via* route B and lead to the formation of cyclobuteniminium salt **62** by the reaction [2 + 2] of the keto-keteneiminium salts **60** (R^1, R^2 = alkyl, *c*-alkyl). The iminium salt **60** was then used as dienophiles in Diels–Alder reactions with various functionalized dienes, giving compound **64** (Scheme 20).

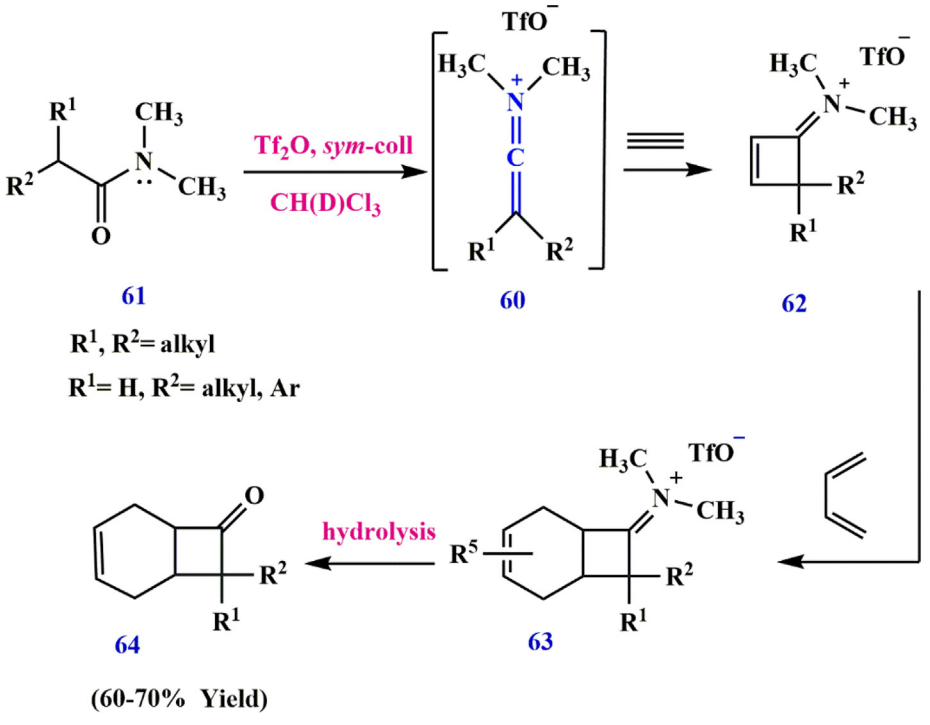
3.4. Ketenimine preparation via cleavage of heterocyclic compounds

3.4.1. Cleavage of azirines

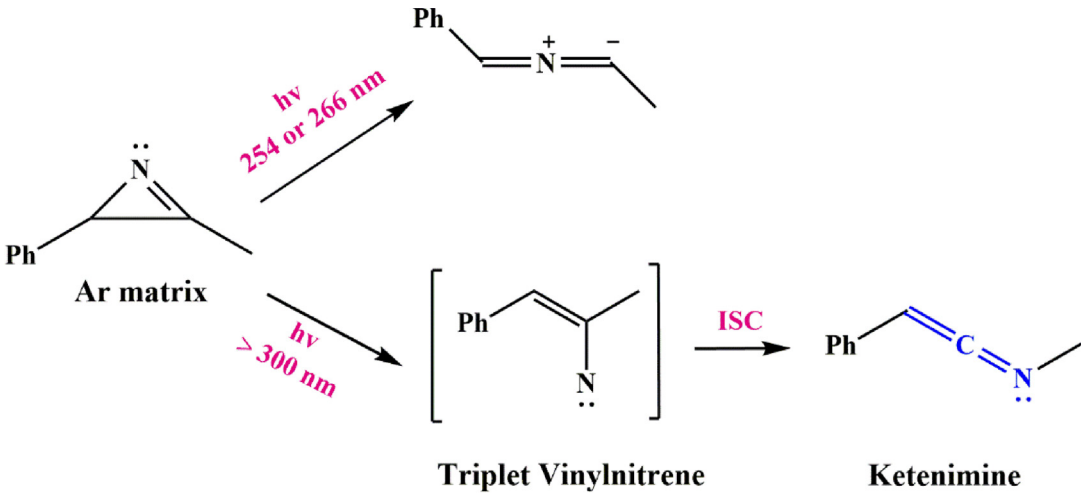
Irradiation with a short wavelength of 3-methyl-2-phenyl-*2H*-azirine in an argon matrix leads to the ylide, while irradiation with a longer wavelength forms the ketenimine (Scheme 21)



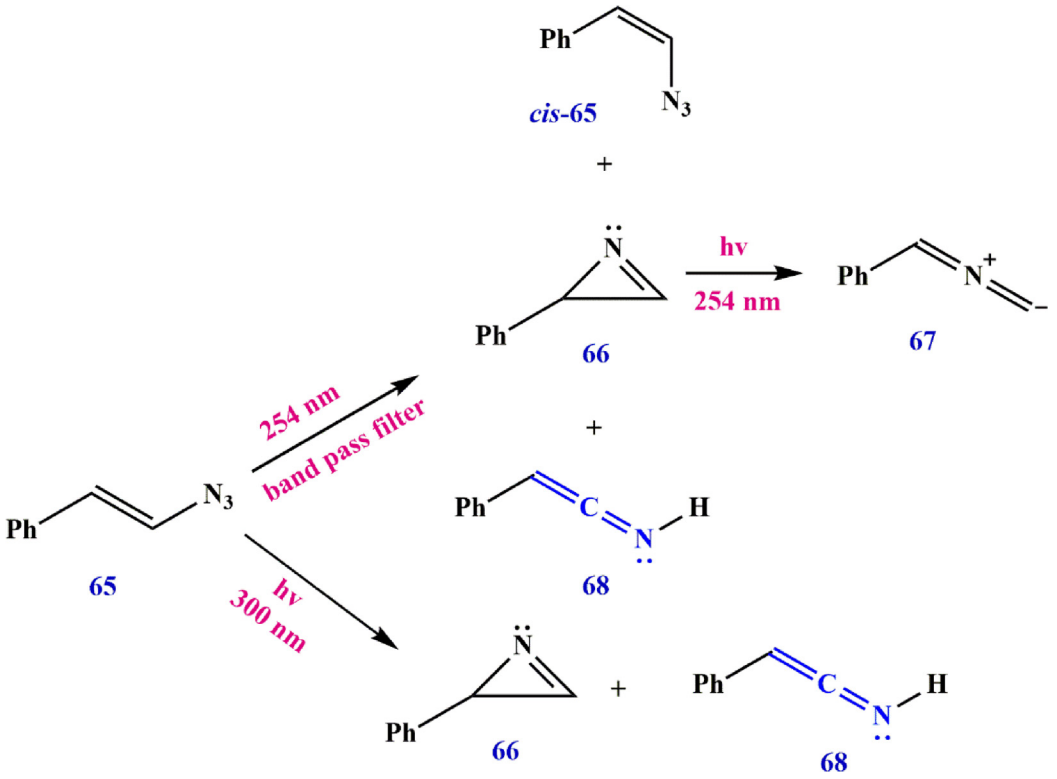
Scheme 19 Synthesize keteniminium salt **60**.



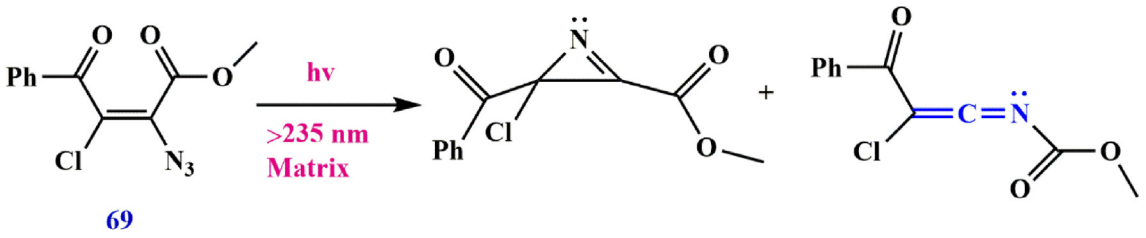
Scheme 20 Synthesize cyclobuteniminium salt **62** from keteniminium salt.



Scheme 21 Cleavage of 3-methyl-2-phenyl-2*H*-azirine.

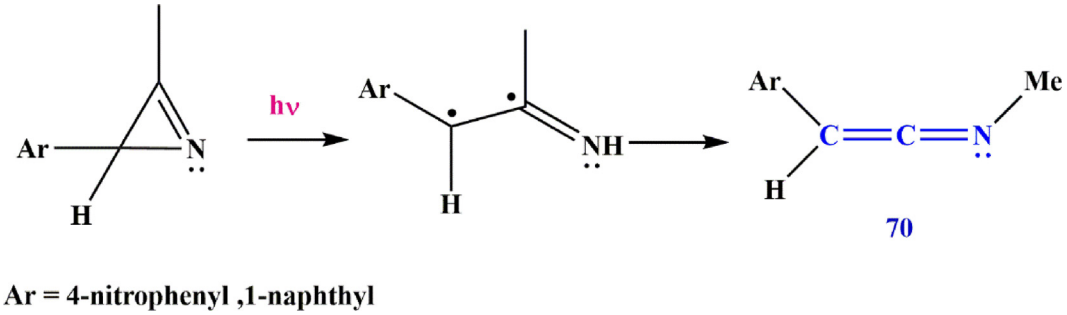


Scheme 22 Cleavage of azirine **66**.

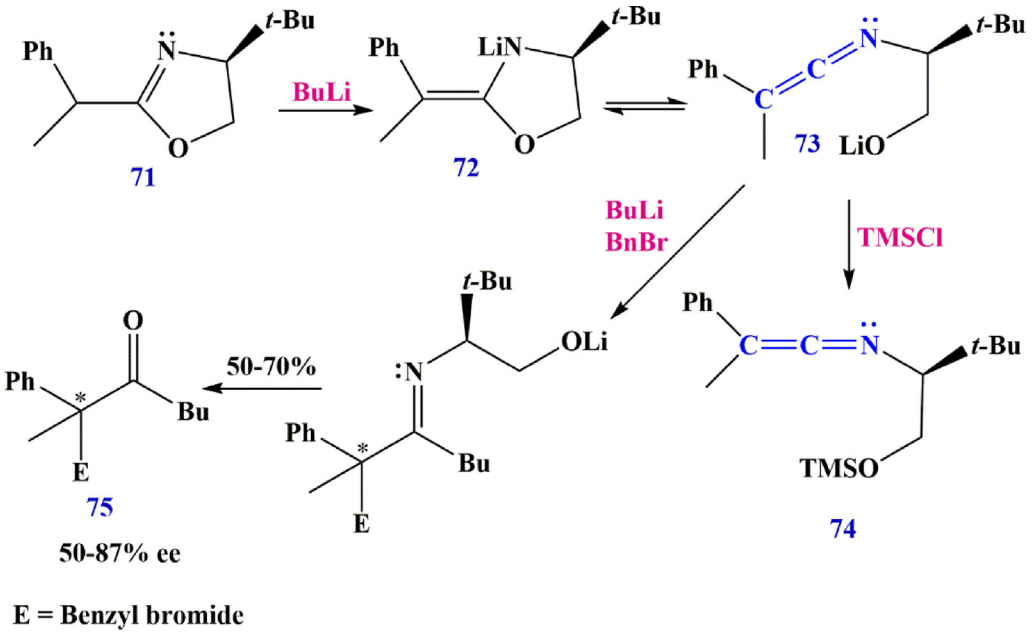


Scheme 23 Cleavage of vinyl azide.

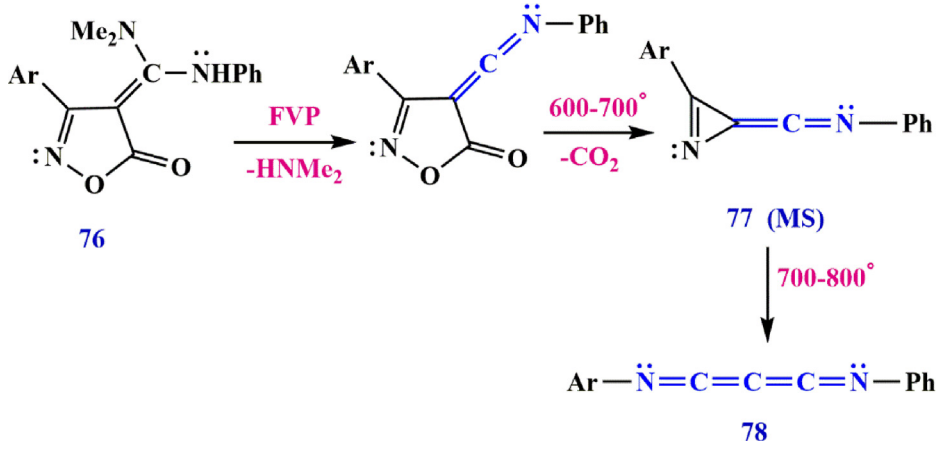
(Zhang et al., 2014; Weragoda et al., 2017). Irradiation of 2-azidovinylbenzene **65** under reaction conditions leads to 2-phenyl-2*H*-azirine **66** as the main product, some ketenimine **68**, and a small amount of *cis*-**65**, while irradiation of vinyl azide **65** under reaction conditions produces only2-phenyl-2*H*-azirine **66** and 2-phenylethen-1-imine **68** (Scheme 22).



Scheme 24 Cleavage of 2*H*-azirines **70**.



Scheme 25 Synthesize ketenimine **74**.



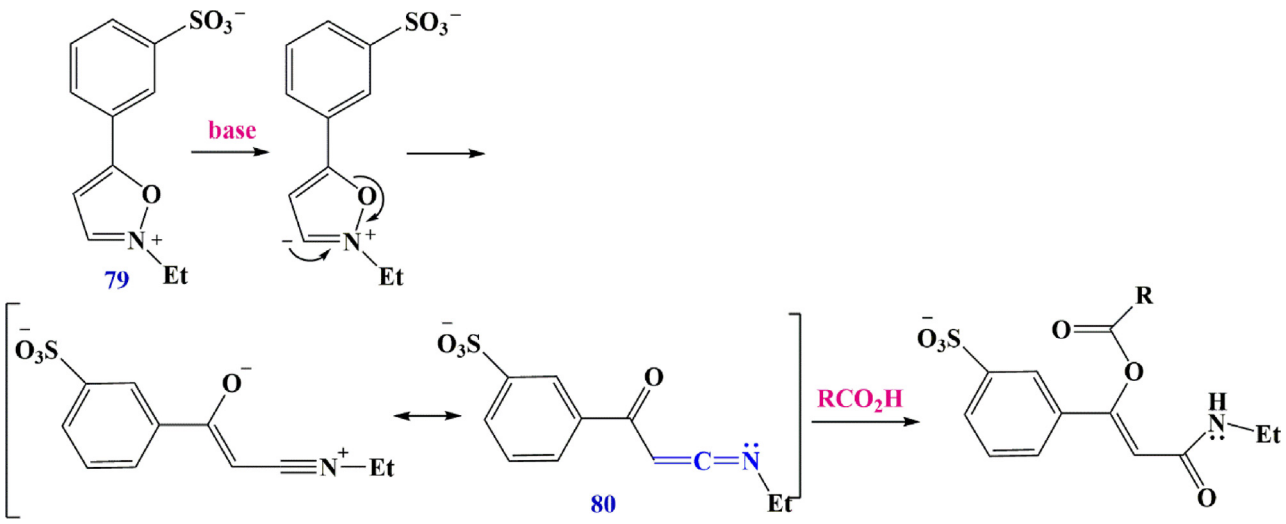
Scheme 26 Cleavage of isoxazolone

Osisioma et al. (Osisioma et al., 2018) showed that irradiation of vinyl azide **69** led to the simultaneous preparation of the parallel azirine (methyl 2-benzoyl-2-chloro-2*H*-azirine-3-carboxylate) and ketenimine (methyl (2-chloro-3-oxo-3-phenyl prop-1-en-1-ylidene) carbamate) derivatives (Scheme 23).

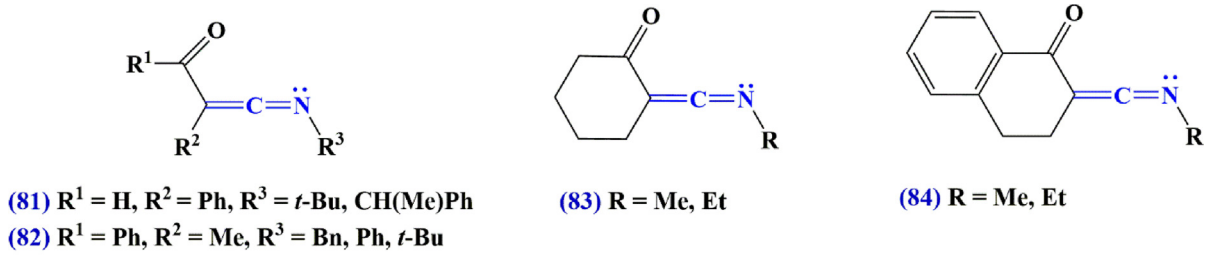
Another method of producing ketenimines reported by Inui et al. (Inui and Murata, 2001). In their method, matrix isolation/IR at low temperature leads to the formation of the diradical (2-aryl-3-methyl-2*H*-azirine), which is used as an intermediate for the synthesis of 2-aryl-*N*-methylethen-1-imine **70** (Scheme 24).

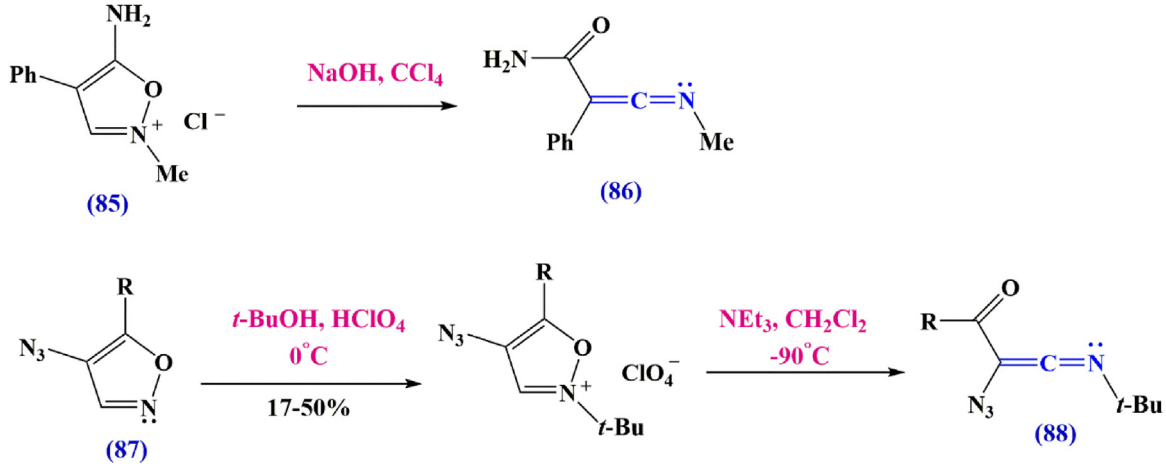
3.4.2. Cleavage of oxazolines and isoxazolium salts

The ring cleavage observed in achiral oxazolines during lithiation has now been extended to chiral oxazolines. For example, treatment of oxazoline **71** with BuLi gives lithium (*S,E*)-4-(*tert*-butyl)-2-(1-phenylethylidene)oxazolidin-3-ide **72**, which is mainly in the ketenimine form **73** (Scheme 25). This



Scheme 27 Synthesize ketenimines with Woodward's reagent.

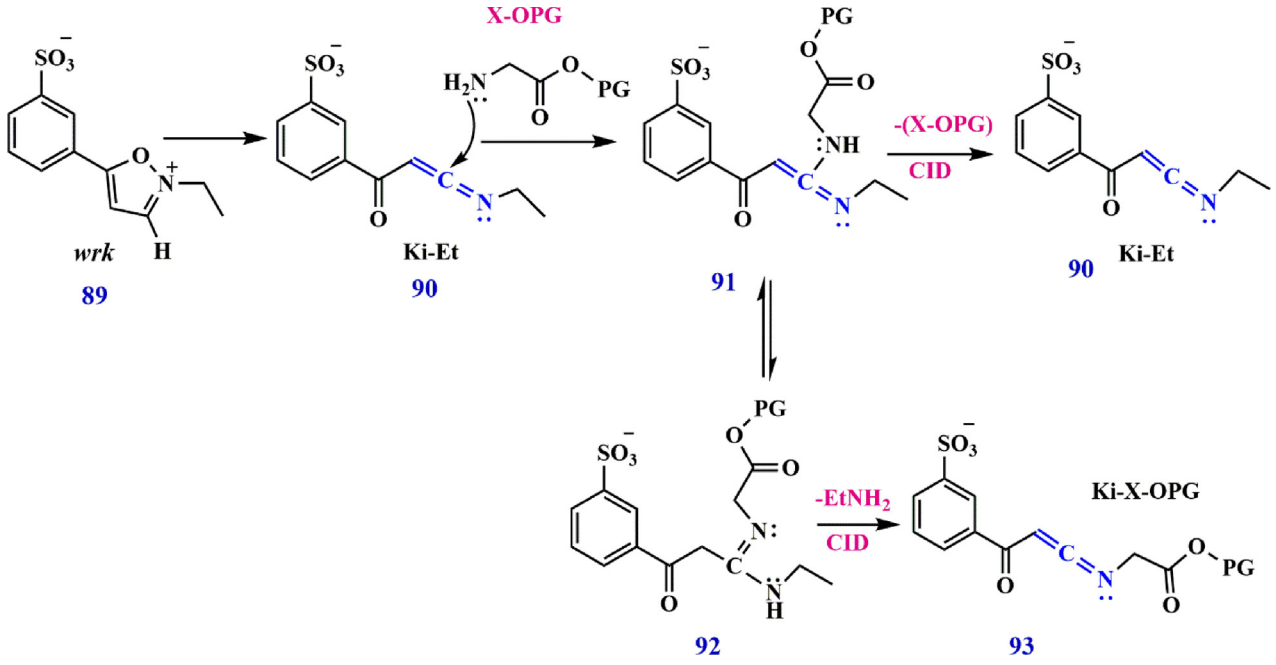




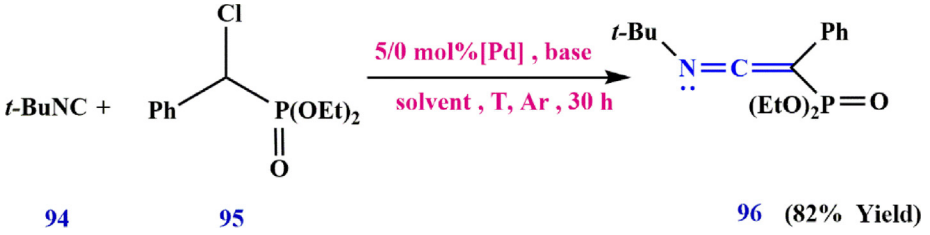
Scheme 28 Synthesize ketenimines from 4-azido isoxazolium salts.

ketenimine can be trapped with TMSCl to give 3-(((3*R*)-4,4-dimethyl-3-((2-phenylprop-1-en-1-ylidene) amino) pentyl) dimethylsilyl) oxazolidin-2-one **74**, but it is more useful to react with second equivalents of BuLi and a benzyl bromide to give chiral ketones such as 2-methyl-1,2-diphenylheptan-3-one **75** in 50–70% yield and 50–87% ee after work-up (Dwyer et al., 1999).

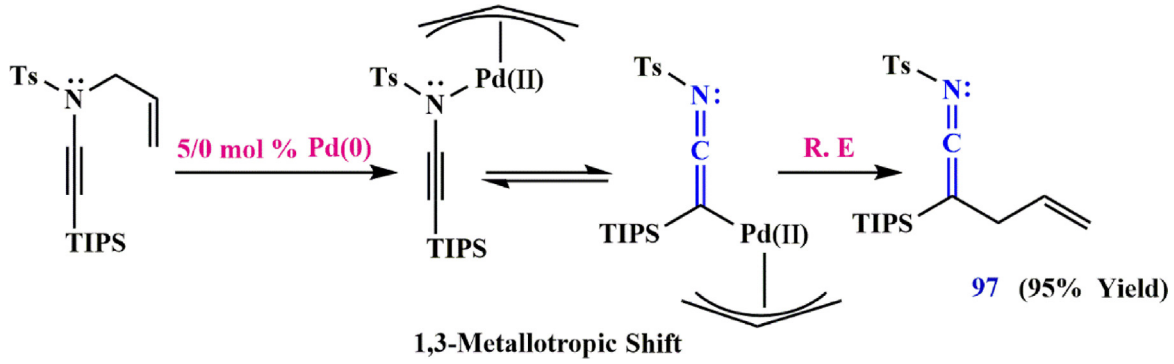
Flash vacuum pyrolysis (FVP) of 3-aryl-4-[(dimethylamino (alkyl(aryl)amino methylene] isoxazol-5(*4H*)-ones **76** gives 1-(3-aryl-*2H*-azirin-2-ylidene)-*N*-phenylmethanimine **77** and bisiminopropadiene ArN═C═C═C═NR **78** with the elimination of dimethylamine and CO_2 and rearrangement of the 3-aryl-4-((phenylimino) methylene) isoxazol-5(4*H*)-one (Scheme 26) (Wolf et al., 1996).



Scheme 29 Reaction of amidine synthesis between keto-ketenimine (Ki-Et) and Woodward's reagent K.

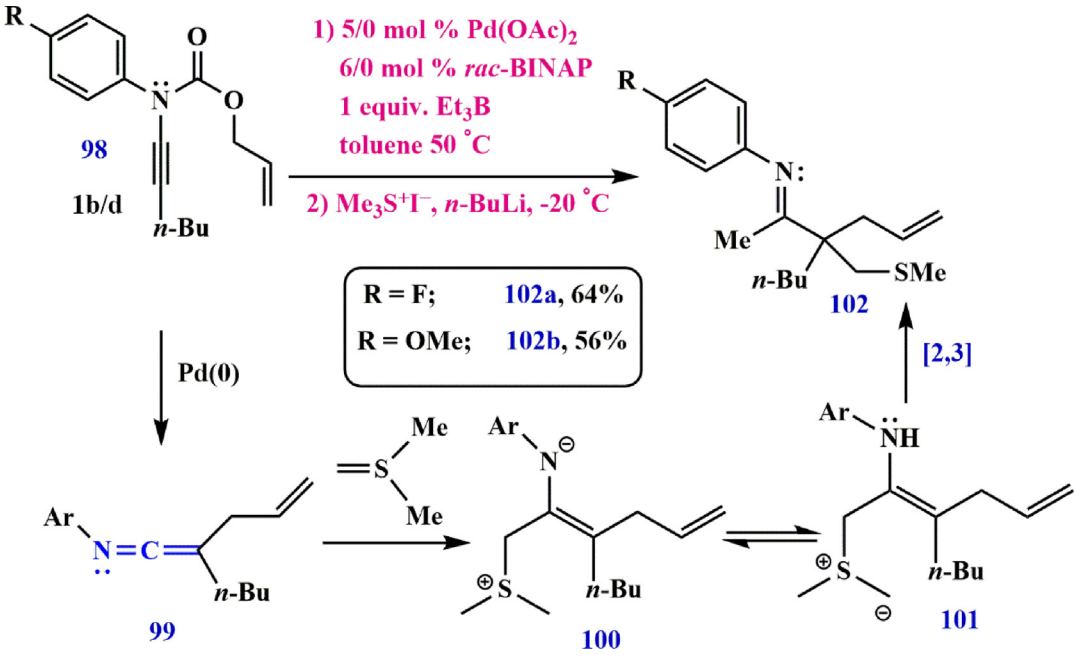


Scheme 30 Synthesis diethyl (2-(*tert*-butylimino)-1-phenylvinyl) phosphonate **96**.

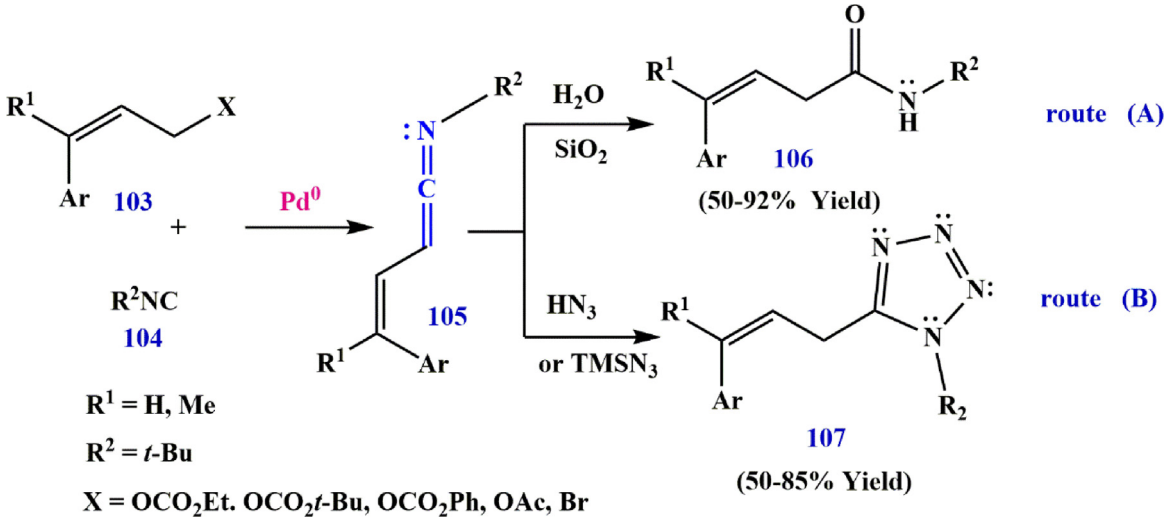


Scheme 31 Recommended mechanism to the synthesis of ketenimine **97**.

Woodward's reagent K79 was introduced as a prototype for a class of peptide synthesis reagents in 1961. (Woodward and Olofson, 1961). They showed that the initial deprotonation at the unsubstituted 3-position has been attributed to the reactivity of these isoxazolium salts, accompanied by ring cleavage to form *C*-acyl ketenimine **80**, which was intercepted by a carboxylate to afford enol esters suitable for further attack (Scheme 27). Spectroscopic evidence for acyl intermediates of ketenimine was provided by Woodward et al.in later studies. This route is limited to relatively stable compounds such as *N*-(*t*-butyl)-benzoylketenimine and the related acetyl compound, which are prepared in 60% and 70–80% yields from isoxazolium perchlorates and triethylamine, respectively, for preparative purposes. 4,5-disubstituted isoxazolium perchlorates or tetrafluoroborates have also been used to isolate *C*-acyl ketenimines **80-84**. By reacting the salt with triethylamine in an acetonitrile solution, the comparatively unstable *C*-acyl ketenimine **80** can be prepared from reagent K itself. With the addition of cuprate, other susceptible acyl ketenimines can be intercepted (Scheme 28). Several isoxazolium salts with heteroatomic substituents were also found to produce ketenimines when treated with a base. The 5-aminoisoxazolium precursor **85** of ketenimine-amide **86** and the 4-azido isoxazolium salt **87** were used to prepare the special *C*-azido ketenimine **88**, which is stable only below −60 °C.

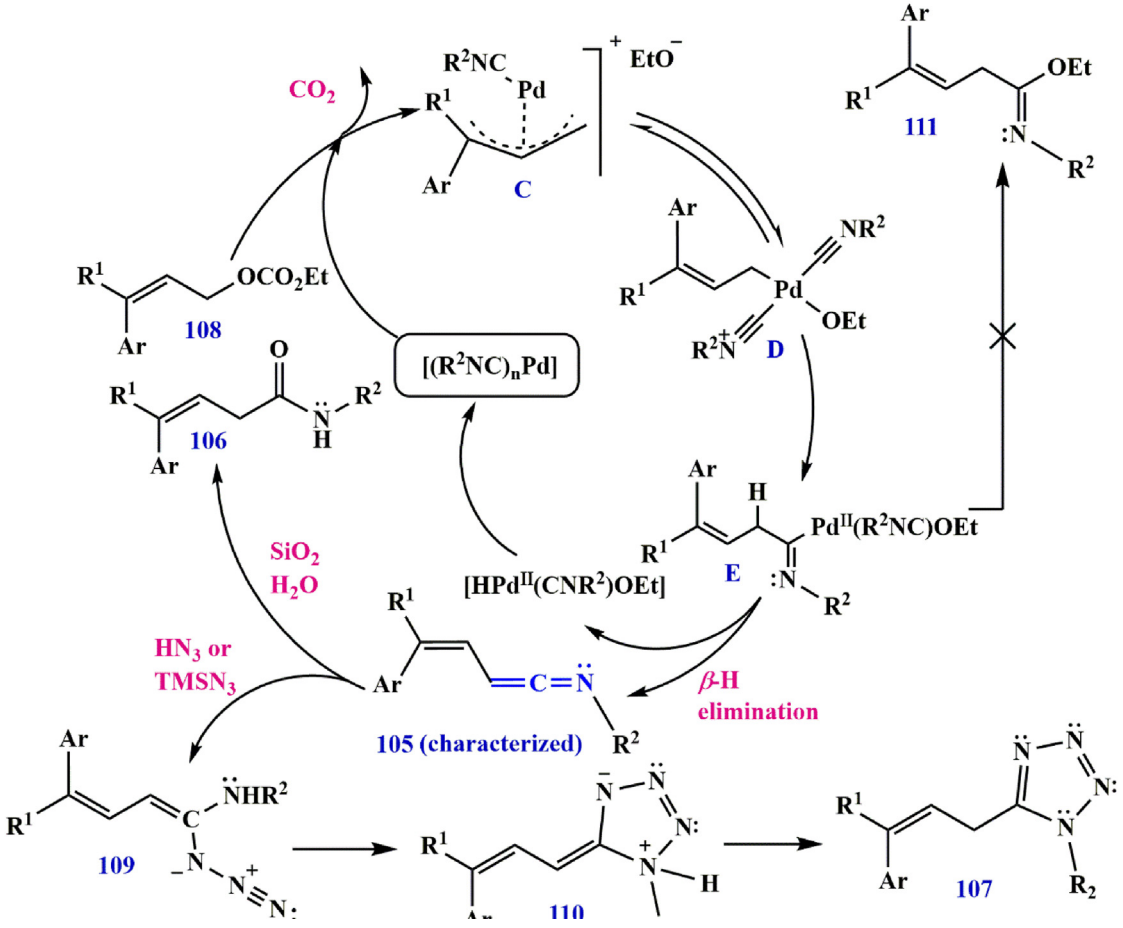


Scheme 32 Synthesize ketenimine **99**.

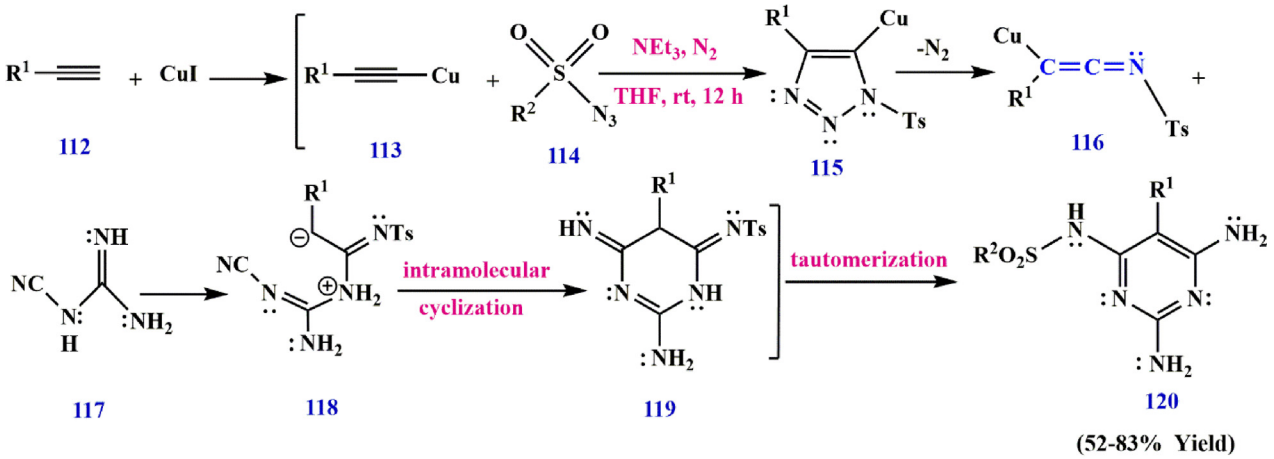


Scheme 33 Synthesize ketenimine **105.**

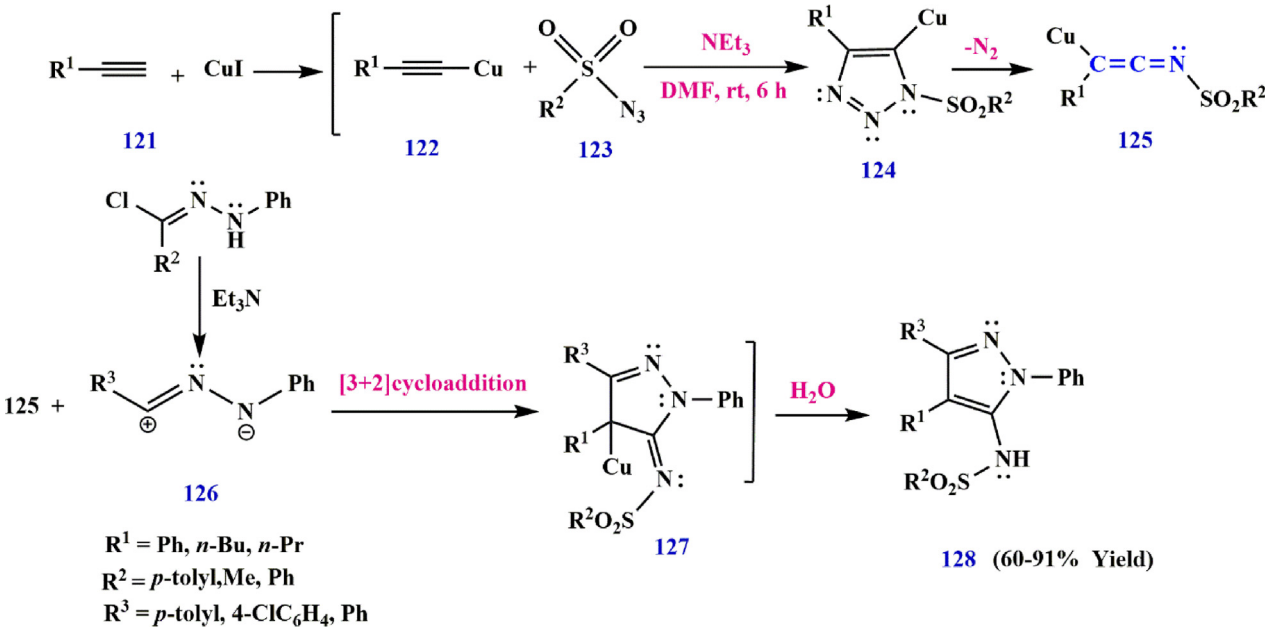
The K reagents were developed in another study by Peng et al. *via* a solution-phase nucleophilic addition reaction accompanied by a gas-phase elimination reaction. The reaction pathway for reagent ion preparation which involves the irreversible conversion of the *wrk* **89** to a reactive *N*-ethyl keto-ketenimine (Ki-Et) **90** by proton abstraction from the 3 isoxa-zole positions (Scheme 29). The intermediate **91**, termed amidine, has the potential to be converted by tautomerism to



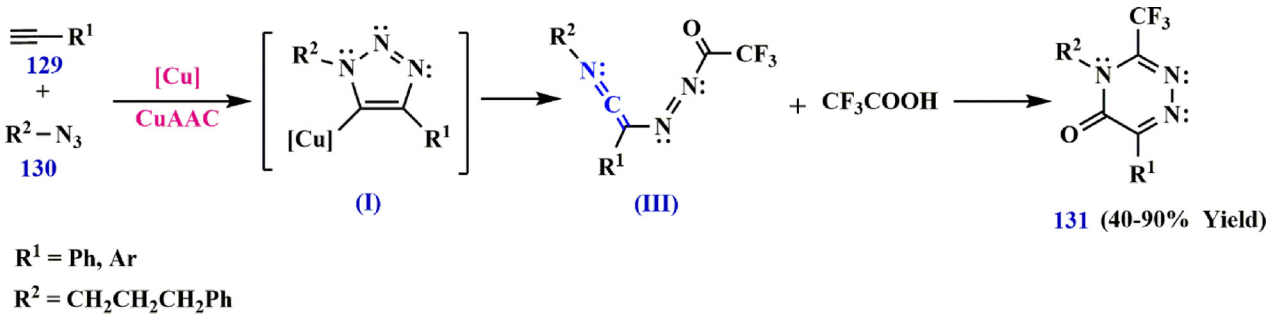
Scheme 34 Recommended mechanism for the synthesis of ketenimine **105**.



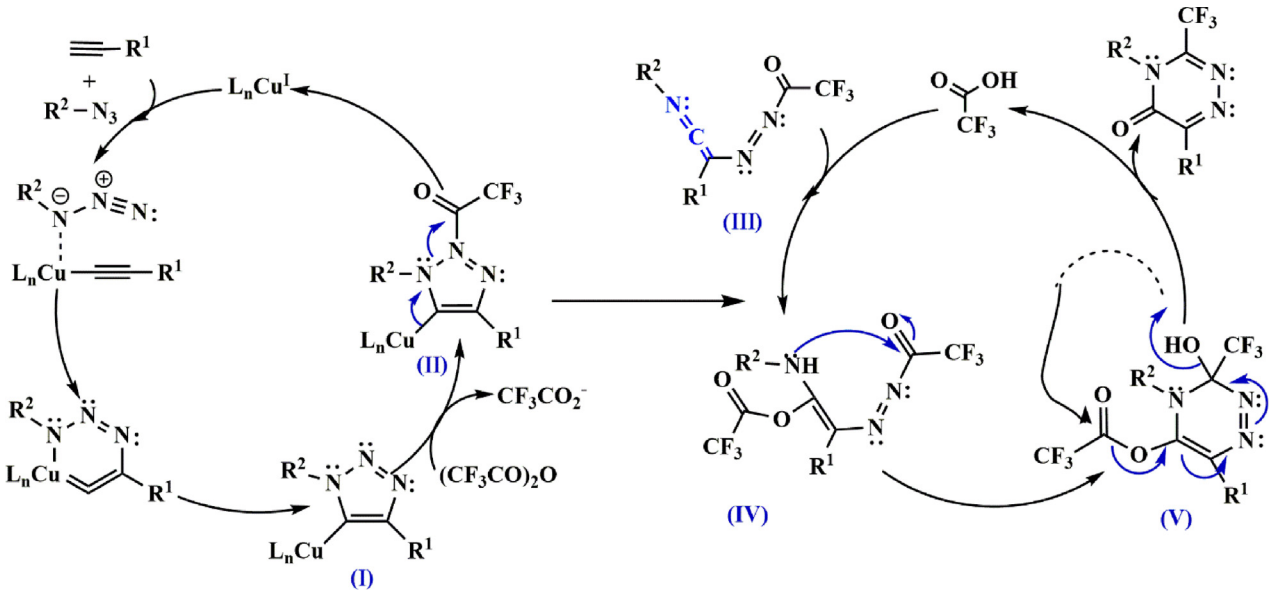
Scheme 35 Recommended mechanism for the synthesis of diaminopyrimidine derivatives **120**.



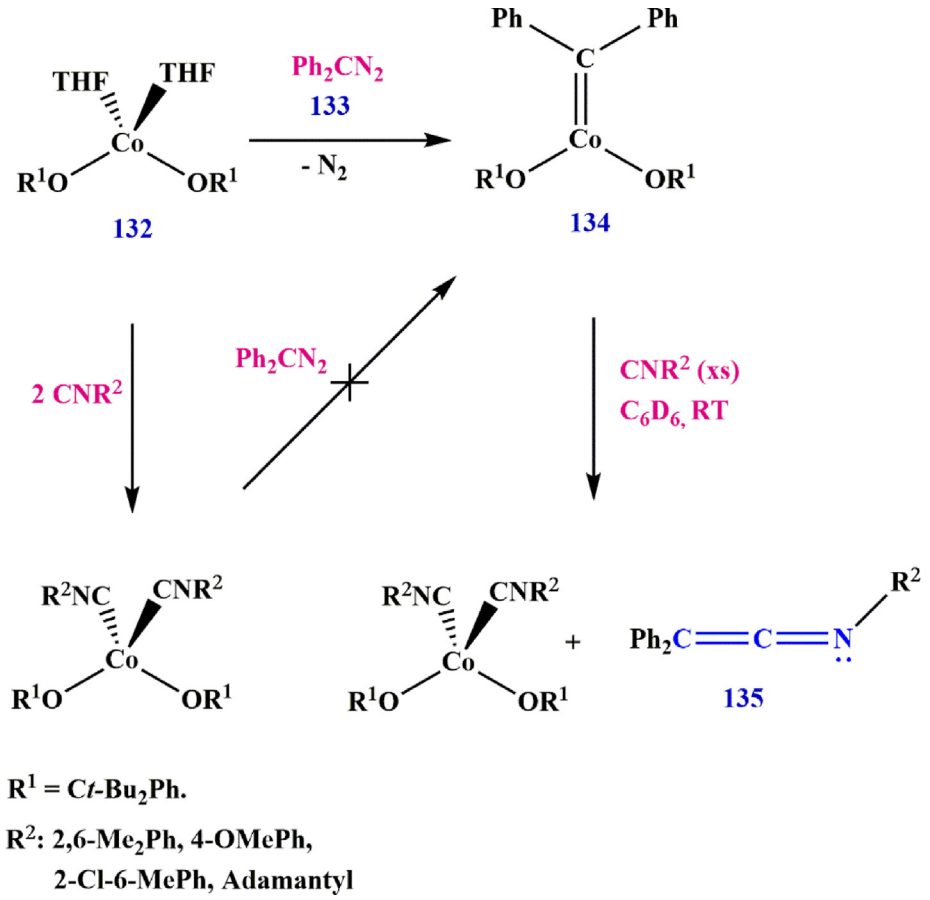
Scheme 36 A possible mechanism for the synthesis of pyrazole derivatives **128.**



Scheme 37 Synthesize 3-trifluoromethyl-substituted 1,2,4-triazinone **131**.



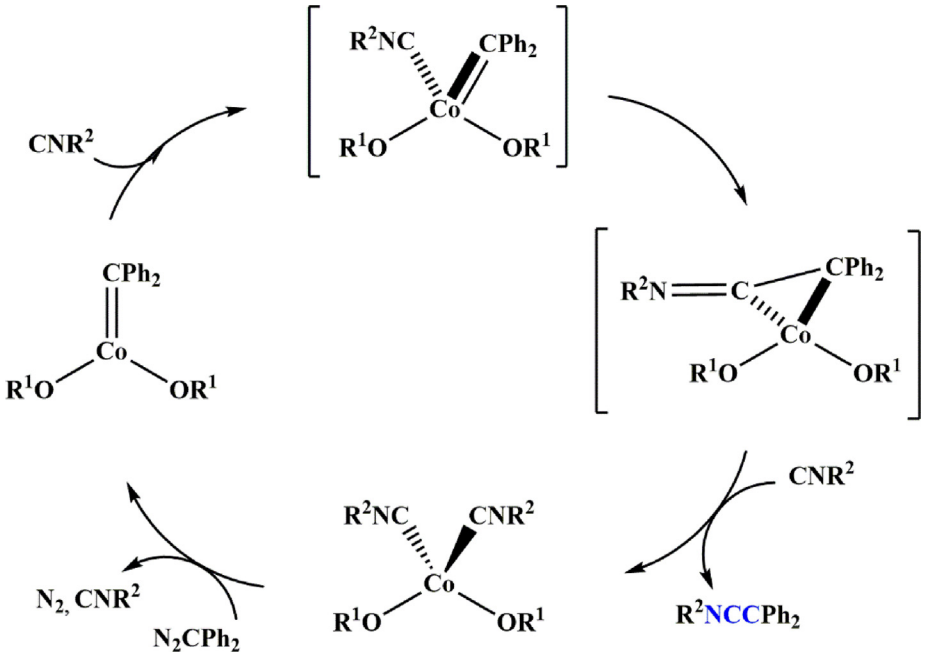
Scheme 38 Recommended mechanism for the synthesis of 3-trifluoromethyl-substituted 1,2,4-triazinone **131.**



R^1 = C*t*-Bu_2Ph.

R^2: 2,6-Me_2Ph, 4-OMePh,
2-Cl-6-MePh, Adamantyl

Scheme 39 Synthesize ketenimine **135**.



Scheme 40 Recommended mechanism for the synthesis of ketenimines **135**.

compound **92**, which in turn reacts with a primary amine of an amino acid. The C—N bonds of both amidines, **91** and **92**, are easily cleavable upon collisional activation in the gas phase, which either generates the *N*-amino acid keto-ketenimine (Ki-X-OPG) **93** with the loss of an ethylamine, or reproduces the Ki-Et **90** at the loss of the NH_2-X-OPG (Peng and McLuckey, 2015).

3.5. Transition Metal-Catalyzed Synthesis of Ketenimine

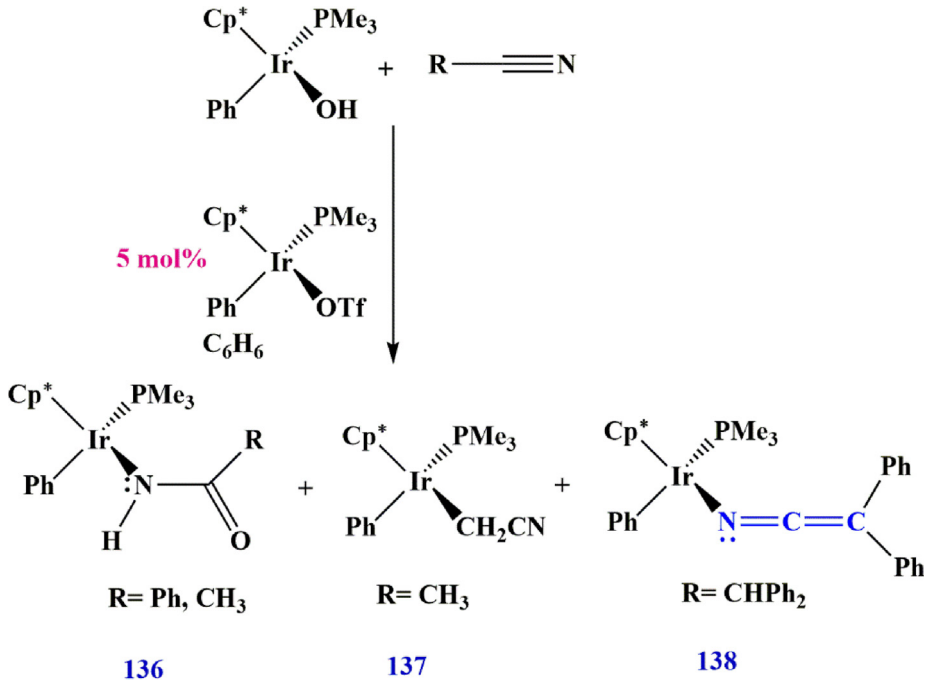
3.5.1. Pd -Catalyzed synthesis of ketenimine

For the first time in the history of chemistry, scientists have developed an effective method for the synthesis of *C*-phosphonoketenimines using palladium-catalyzed migratory insertion of isocyanides (Qian et al., 2016). The peculiarity of this method is that it involves a large number of functional groups and has good atomic economy. In this method, *tert*-butylisocyanide **94** was reacted with diethyl(bromo(phenyl) methyl) phosphonate **95** to synthesis of diethyl (2-(*tert*-butylimino)-1-phenylvinyl) phosphonate **96** (Scheme 30).

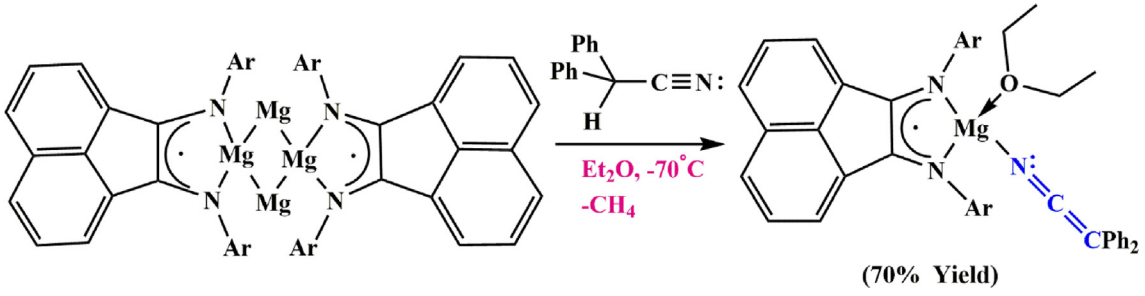
Interestingly, ketenimines can be prepared very rapidly using rearrangement of *N*-allocynamides and a functional group-tolerant Pd catalyst under neutral conditions. Hsung et al. (Zhang et al., 2009; De Korver et al., 2010; De Korver et al., 2011) previously described the heat and palladium catalyzed rearrangement of *N*-allyl-*N*-tosyl ynamides to obtain 4-methyl-*N*-(2-(triisopropylsilyl)penta-1,4-dien-1-ylidene)ben zenesulfonamide **97** as ketenimine, which can be trapped by an exogenous nucleophile such as an amine or an alcohol (Scheme 31).

Another method for the preparation of ketenimine in the presence of Pd is the substitution reaction (Hiroi and Sato, 1985; Alexander and Cook, 2017). Although various heteroatom nucleophiles have been used to prepare amidine and imidate compounds, the use of carbon nucleophiles is much less common. The imine **102** with a fully substituted α-carbon results from the reaction of 2-allyl-*N*-arylhex-1-en-1-imine **99** with sulfur (Scheme 32).

Hydrolysis of ketenimine **105** results in the formation of an β, γ-unsaturated carboxamide **106**, which is produced by the reaction of allyl ethyl carbonate **103** with isocyanide **104** in



Scheme 41 Synthesize the Ir-ketenimine complex **138**.



Scheme 42 Synthesize Mg-ketenimine complex.

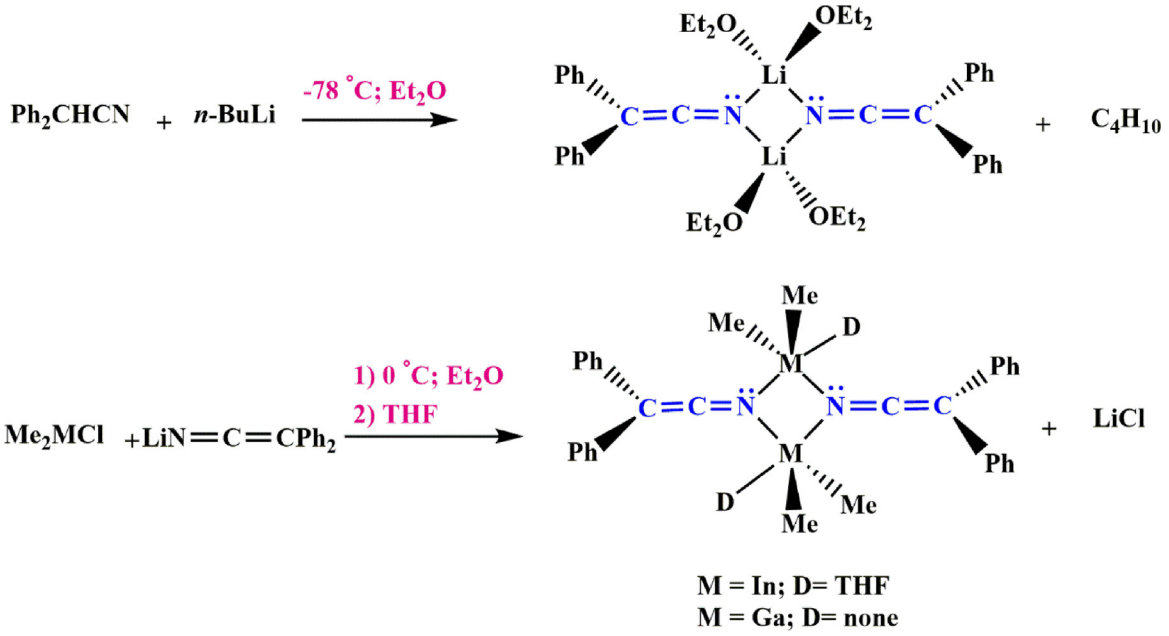
the presence of Pd $(OAc)_2$ as a catalyst (route A in Scheme 33). Moreover, a three-component synthesis of 1,5-disubstituted tetrazole **107** can be achieved by [3 + 2]-cycloaddition with hydrazoic acid (HN_3) or $TMSN_3$ in *situ* trapping of ketenimine **105** (route B in Scheme 33). The oxidative addition of an allyl carbonate **108** to Pd^0 give an π-allyl Pd complex **C** that is symmetric to the η^1-allyl Pd species **D** (Qiu et al., 2016). Migratory insertion of **D** would produce an imidoylpalladium intermediate **E**, which upon β-hydride elimination would furnish a ketenimine **105** with the concurrent rearrangement of the Pd^0 catalyst (Scheme 34).

3.5.2. Cu -Catalyzed synthesis of ketenimine

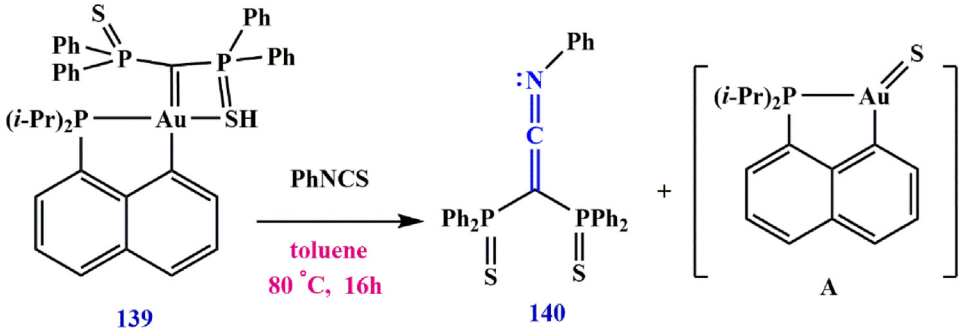
Ketenimine **116** can be prepared *via* the coupling reaction between copper acetylide **113**, formed from phenylacetylene **112** and CuI (undergoes a 1,3-dipolar cycloaddition) reaction with sulfonyl azide **114**, to give the triazole derivative **115** (Yoo et al., 2007). This intermediate can be converted to the ketenimine derivative **116**, which is attacked by cyanoguanidine **117** to afford **118**. This intermediate undergoes intramolecular cyclization and tautomerization to diaminopyrimidine derivatives **120** (Yavari et al., 2012) (Scheme 35).

Similarly, copper acetylide **122** undergoes 1,3-dipolar cycloaddition with sulfonyl azide **123** to form triazole **124**. This intermediate is converted to the ketenimine derivative **125**, which is then cycloaddition with the nitrile imine **126**, which is prepared from hydrazonoyl chloride and Et_3N, to afford **127**. Finally, the intermediate **127** is converted to the product tetrasubstituted pyrazole **128** *via* a 1,3-*H* shift (Yavari et al., 2012) (Scheme 36).

Based on the above results, a reaction pathway for the synthesis of ketenimine **III** was developed leading to the preparation of 3-trifluoromethyl-substituted 1,2,4-triazinone **131** (Scheme 37). First, ring-opening of **II** leads to the formation of ketenimine **III**, which can be converted to **IV** by nucleophilic addition with CF_3CO_2H. Subsequently, the amine moiety is cyclized with the ketone C═O bond to form **V**, which then undergoes condensation and aromatization to produce the 3-trifluoromethyl-substituted 1,2,4-triazinone as the major product (Scheme 38) (Wu et al., 2017).



Scheme 43 Synthesize Li, In and Ga-ketenimine complex.



Scheme 44 Synthesize (2-(phenylimino) ethene-1,1-diyl) bis (diphenylphosphine sulfide) **140**.

3.5.3. Co -Catalyzed synthesis of ketenimine

The high-valent cobalt carbene $Co(OR)_2(=CPh_2)$ (OR=OC′-Bu_2Ph) reacts with various isocyanides CNR′ to form ketenimine. While spectroscopic and theoretical studies reveal a significant radical characteristic in carbene functionality, only sluggish cyclopropanation reactivity with styrene was observed. The carbene complex, (diphenylmethylene)bis((2,2,4,4-tetramethyl-3-phenylpentan-3-yl)oxy)cobalt **134** is obtained by treating the cobalt bis (alkoxide) complex **132** with diphenyldiazomethane **133**. Subsequent, ^{1}H-NMR investigation revealed that treatment of **134** with **132** in the presence of 2,6-dimethylphenyl isocyanide **133** (CN(2,6-Me_2Ph) resulted in the formation of ketenimine **135** in around 30% yield. The preparation of ketenimine **135** was confirmed by GC-MS, and the results, unlike previous reports (Grass et al., 2019), showed that the process produced ketenimine **135** without photolysis or heating (Scheme 39).

According to a possible mechanism, carbene complex 134, formed from complex **132** and diazoalkane, undergoes an intramolecular reaction with an isocyanide, resulting in the formation of ketenimine. In the presence of excess isocyanide, the isocyanides replace the ketenimine to form $Co(OR^1)_2(CNR^2)_2Co(OR^1)_2(CNR^2)_2$, which then reacts with the diazoesters to restore carbene functionality, releasing two equivalents of isocyanide and dinitrogen molecules (Scheme 40).

3.6. Ketenimine preparation via organometallic

3.6.1. Ketenimine preparation via Ir complexes

The use of Ir-OH or Ir-OTF complexes, which was introduced by Bissember et al. (Bissember et al., 2018) in 2018, is another method for the preparation of ketenimines. They showed that the carboxamide product **136** is produced exclusively when R is an aromatic group. However, when R = methyl, a mixture of hydration product **136** and α-deprotonated product **137** is formed, and when R = $CHPh_2$, ketenimine complex **138** was the only product (Scheme 41).

3.6.2. Ketenimine preparation via Mg complexes

More basic ligands, such as alkyl ligands, can generate α-cyanocarbanion complexes when they react with a suitable nitrile. Indeed, an Mg complex with methyl-bridged ligands was reacted with diphenyl acetonitrile to produce the desired ketenimine complex (Fedushkin et al., 2009) with loss of methane (Scheme 42).

3.6.3. Ketenimine preparation via Li complexes

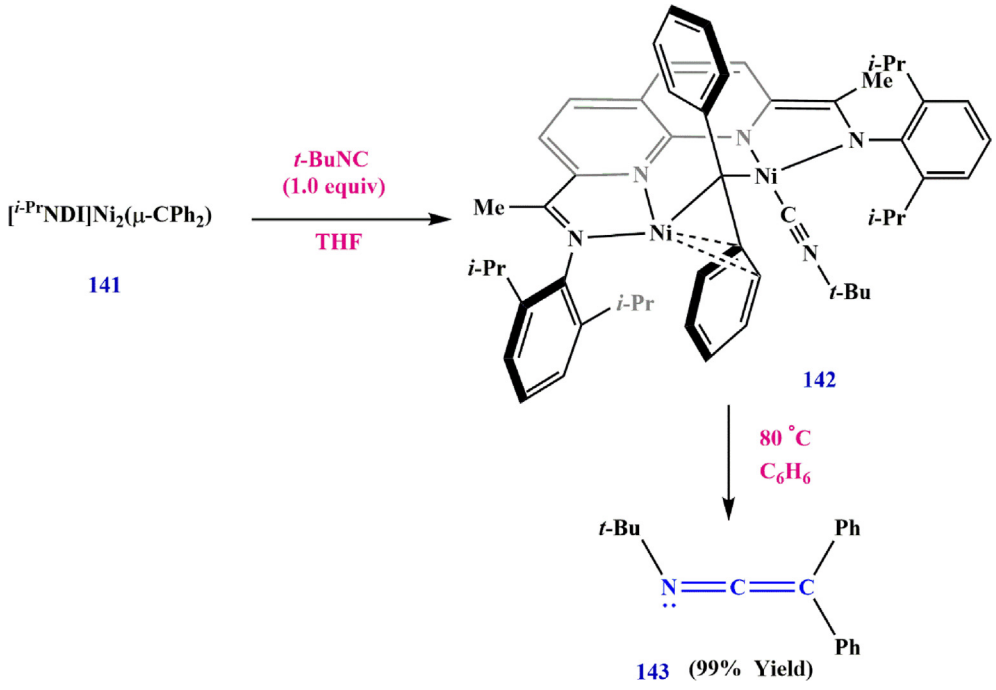
Iravani et al. (Iravani and Neumüller, 2003) showed that lithium ketenimine salts were prepared by reacting diphenyl acetonitrile with *n*-butyl lithium then salt metathesis with indium (III) and gallium (III) halide complexes (Scheme 43).

3.6.4. Ketenimine preparation via Au complexes

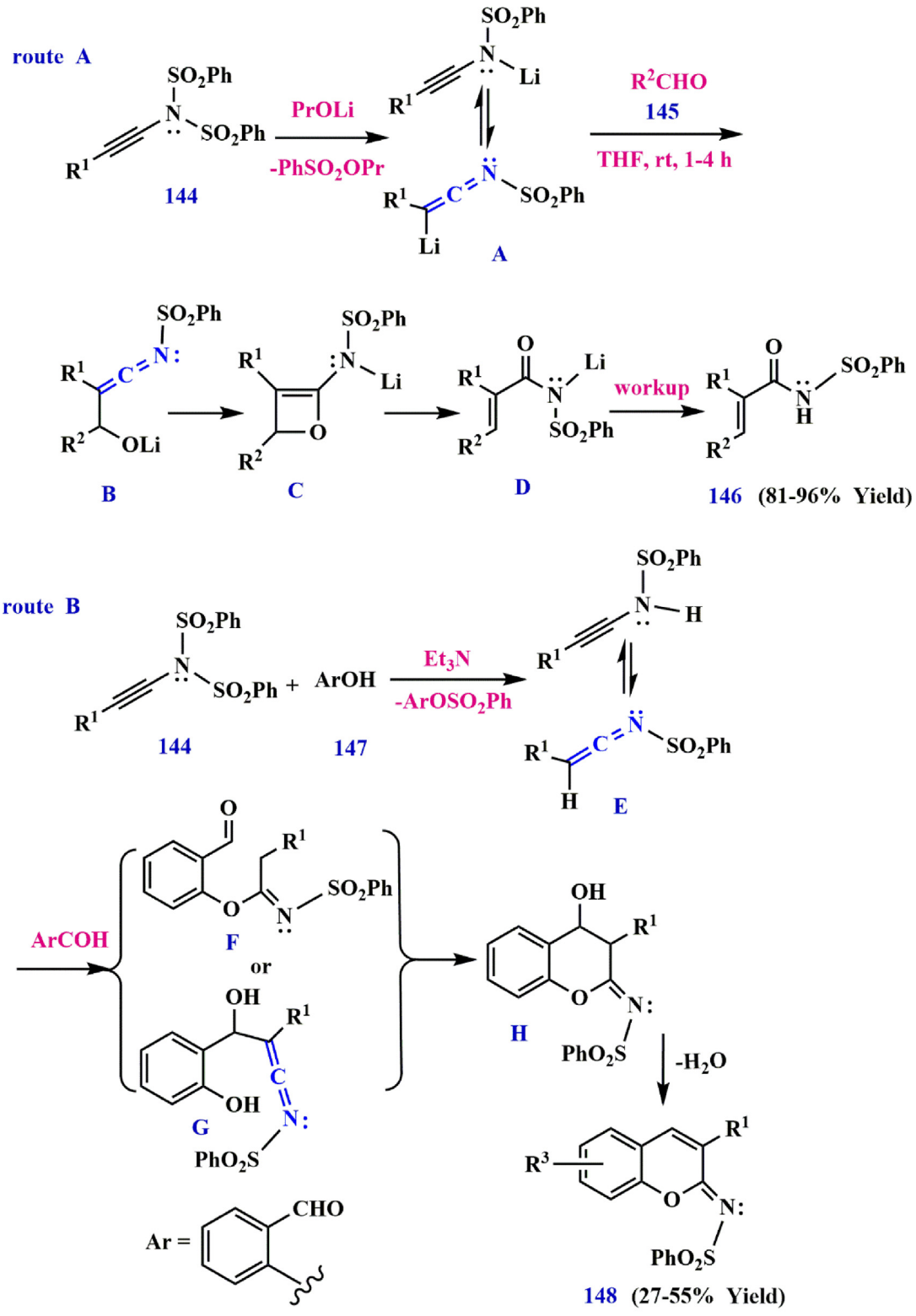
The first gold (III) carbene complex was generated by the reaction of a geminal di-anion with a (P, C) cyclometallated gold (III) precursor that can react with a variety of electrophiles. Heterocumulenes have been shown to be the reagent of choice to test the nucleophilicity of carbene complexes, while another method was proposed by Pujol et al. (Pujol et al., 2017) *via* isocyanate. They showed that complex **139** reacts with PhNCS to form (2-(phenylimino)ethene-1,1-diyl)bis(diphenylphosphine sulfide) **140** and the monomeric "Au=S" complex **A**, which is formed by an Aura-Wittig reaction (Scheme 44).

3.6.5. Ketenimine preparation via Ni complexes

Nickel complexes are also used for the preparation of ketenimines. In this reaction, the $Ni_2(CPh_2)$ complex **141** reacted



Scheme 45 Synthesize ketenimine **143**.



R^1 = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *p*-PrC_6H_4

R^2 = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *o*-BrC_6H_4, *α*-Furyl

R^3 = H, Me, Cl, Br, diethylamine

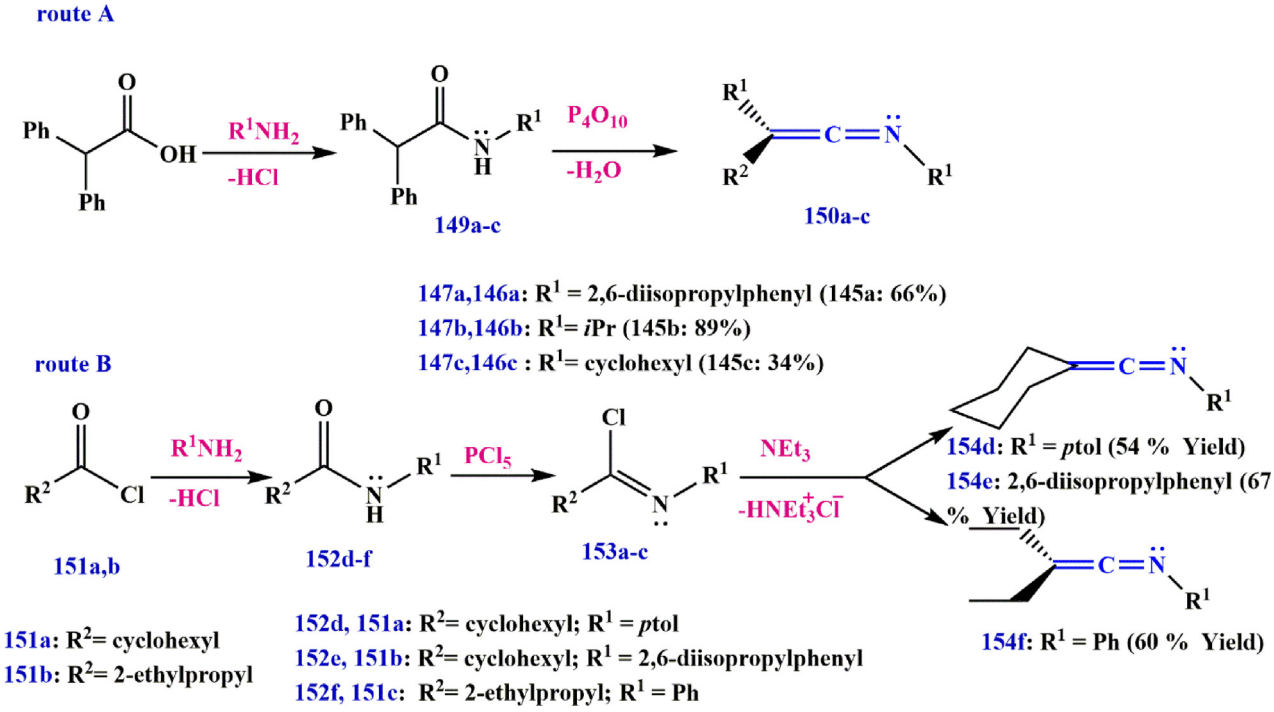
Scheme 46 Synthesize ketenimine from *N*, *N*-disulfonyl ynamide.

with *t*-BuNC, leading to the formation of isonitrile **142**.When the $Ni_2(\mu\text{-}CPh_2)(CN\ t\text{-}Bu)$ complex **142** is subsequently dissolved in C_6H_6, *N*-(*tert*-butyl)-2,2-diphenylethen-1-imine **143** is formed (Maity et al., 2018) (Scheme 45).

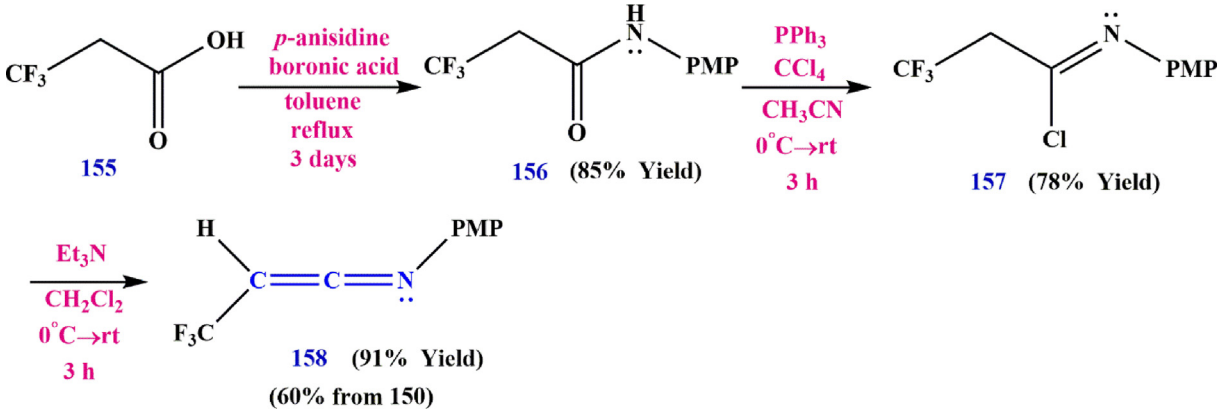
3.7. Ketenimine preparation via elimination reactions

Ketenimine **A**, formed from *N, N*-disulfonyl ynamide **141** and *n*-PrOLi reacts with aldehyde **142** to form oxetene **C**. Ring-opening of oxetene **C** gives amide **D**, which is protonated to produce the *α*, *β*-unsaturated **143** after work-up (route A in Scheme 46). On the other hand, *N*, *N*-disulfonyl ynamide **141** may be reacted with salicylaldehyde **144** in the presence of Et_3N to produce the ketenimine intermediate **E**. Subsequently, after addition of the second molecule **144**, followed by intramolecular nucleophilic addition and dehydration, iminocoumarin **145** is generated (route B in Scheme 46) (Yu and Cao, 2014).

Jin et al. have described another method for the synthesis of ketenimines using amides. The *C*-diaromatic ketenimine derivatives of **150a-c** are prepared by the elimination of water from secondary amides **149** using P_4O_{10} of anhydrous pyridine or triethylamine. Route B also shows that *C*-dialiphatic ketenimines **154d-f** can be readily prepared by chlorination of secondary amides **152** with phosphoryl chloride *via* established procedures to give imidoyl chloride **153**, followed by their dehydrochlorination with an excess of trimethylamine (route A in Scheme 47) (Stevens and Singhal, 1964; Jin et al., 2015).



Scheme 47 Synthesize ketenimines **150** and **154**.



Scheme 48 Synthesis trifluoromethylketenimine (*N*- polymethylpentene -3,3,3-trifluoroprop-1-en-1-imine) **158**.

In 2009, Katagiri et al. (Katagiri et al., 2009) reported the first example of the effective synthesis of 2-trifluoromethylketenimines. In fact, imidyl chlorides **157** play a significant role in this synthesis because they engage in the elimination process, which is catalyzed by a triethylamine chloride, and leads to the generation of trifluoromethylketenimine (*N*- polymethylpentene -3,3,3-trifluoroprop-1-en-1-imine) **158** (Scheme 48).

3.8. Ketenimine via rearrangement reactions

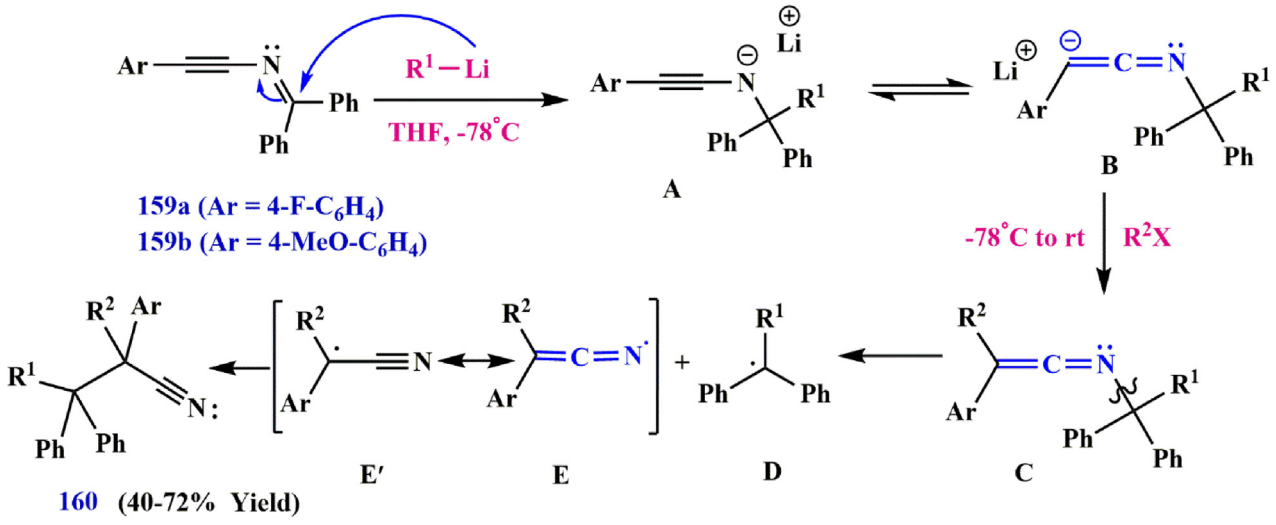
3.8.1. Rearrangement of enolizable nitriles

Due to the strong electron-withdrawing ability of the nitrile group, the reactivity of the ynimines under anionic conditions investigated by examining the result of the reaction between non-enolizable benzophenone-derived ynimines **159a** and 159**b** and organolithium reagents. The addition of the organolithium reagent to the starting ynimine **159** produces a lithiated ynamine **A** which is in equilibrium with the lithiated ketenimine form. Using the electrophile to trap this intermediate would lead to the formation of a transient, unstable ketenimine **C**, which then rearranges, as seen previously with comparable ketenimines (Clarke et al., 1992; Alajarin et al., 2004; Khlebnikov et al., 2003). Subsequently, rapid rearrangement of **C** leads to the formation of a stable benzhydryl radical **D**, which is then reacted with radicals **D** and **E**/**E**′ to form nitrile **160** (Bendikov et al., 2005; Laouiti et al., 2014) (Scheme 49).

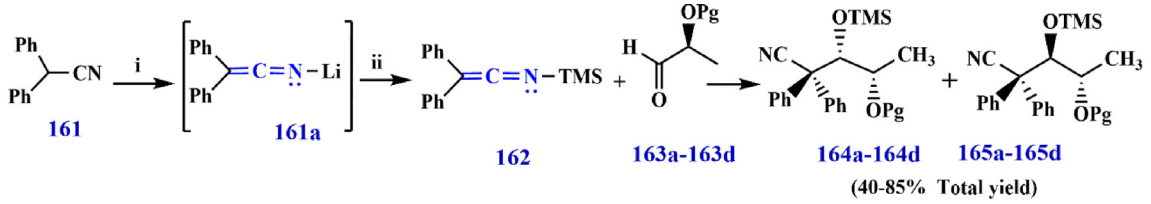
Based on the synthesis of TMS-ketenimine **162** by the reaction of diphenylacetonitrile **161** with LDA, leading to the formation of compounds **164** and **165** (Long et al., 2013), the Li-stabilized ketenimine 161a also exhibits a parallel reaction pattern (Scheme 50).

3.8.2. [1,3]-Brook rearrangement

In 2014, Evano et al. (Laouiti et al., 2014) investigated the possibility of trapping intermediate lithiated-silylketenimine **167** with aromatic aldehydes. They showed that the nucleophilic



Scheme 49 Recommended mechanism for the transformation of ynimine to alkanenitril.



Scheme 50 Synthesize *N*-TBDMS- keteneimine **162**.

addition of **167** to these aldehydes should allow the formation of alkoxysilylketenimine **168**, which could be formed *via* a [1,3]-Brook rearrangement, a nucleophilic addition of the alkoxide to the central carbon atom of the ketenimine moiety, or a Peterson-type olefination. Finally, [3]-azacumulene hydrolysis (*E*)-3-aryl-*N*-(1,1-diphenylethyl)propa-1,2-dien-1-imine **169** leads to the formation of the α, β-unsaturated amide **170** (Doney et al., 1983) (Scheme 51).

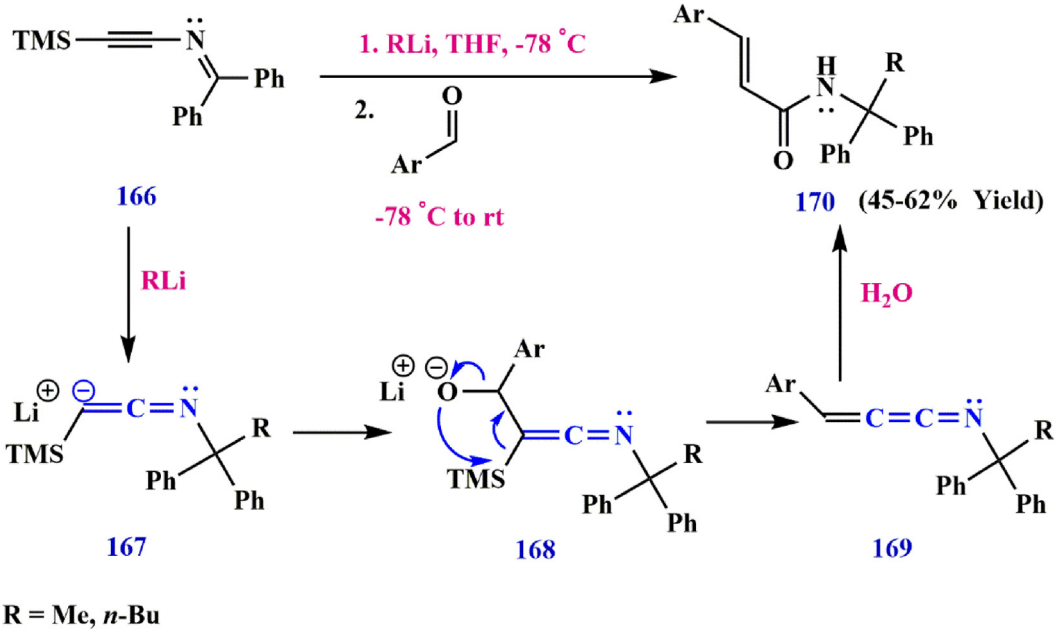
3.8.3. Aza-Claisen rearrangement of ynamides derivatives

The first thermal conversion of an ynamide to a ketenimine was reported by Bendikov et al. (Bendikov et al., 2005). They showed that the *p*-tosyl group of compounds **171** migrates from N to C under reaction conditions, leading to the formation of ethyl 3-((4-methoxybenzyl)imino)-2-tosylacrylate **172** (Scheme 52).

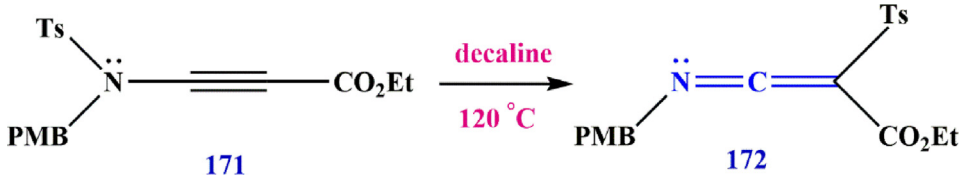
Dekorver et al. (Dekorver et al., 2010) obtained similar results for the thermal rearrangement of *N*-allylsulfonylynamide **173**, although in this case the allyl group first migrates through an Aza-Claisen rearrangement. Their results showed that the nature of the R group has a significant effect on the outcome of the process and the phenyl group **173a** or a protected primary alcohol **173b**, the intermediate ketenimine **174**, eventually migrates to the corresponding tertiary nitrile **175** by a 1,3-sulfonyl shift (route A in Scheme 53). On the other hand, the substituent a TIPS brings sufficient stabilization to allow isolation of the ketenimine **174** or its trapping by nucleophilic addition with pyrrolidine to give the amidine **176**. Prolonged heating, results in desilylation of the ketenimine and triggers its rearrangement into the 2-tosylpent-4-enenitrile (secondary nitrile) **175d** (route B in Scheme 53).

In addition, thermal Aza-Claisen rearrangement of *N*-phosphoryl ynamide **177** can generate allyl ketenimines (5,5-dimethyl-2-((2-phenylpenta-1,4-dien-1-ylidene)amino)-1,3,2-dioxaphosphinane 2-oxide) **180**, which subsequently undergo a 1,3-phosphoryl shift from nitrogen to carbon to generate nitriles **178** or cyclopentenimine **179**. On the other hand, heating *N*-phosphoryl ynamide **177** in toluene in the absence of a competing 1,3-phosphoryl shift leads to the formation of cyclopentenimine **179** in an isolated yield of 50%. (Dekorver et al., 2010) (Scheme 54).

In 2012,continuing their studies, Dekorver et al. demonstrated that *N*-phosphorylyl ynamide **182e** leads to the formation of compounds **183e** and TIPS-ketenimine **184e** under reaction conditions. They showed that in the presence of Pd as a catalyst, *N*-phosphoryl ynamide **185** can undergo the Rautenstrauch rearrangement, yielding Pd-π-allyl ketenimines **186b** as an intermediate (Rautenstrauch, 1984; Shi et al., 2005), leading to the formation of compound **187**. On the other hand,

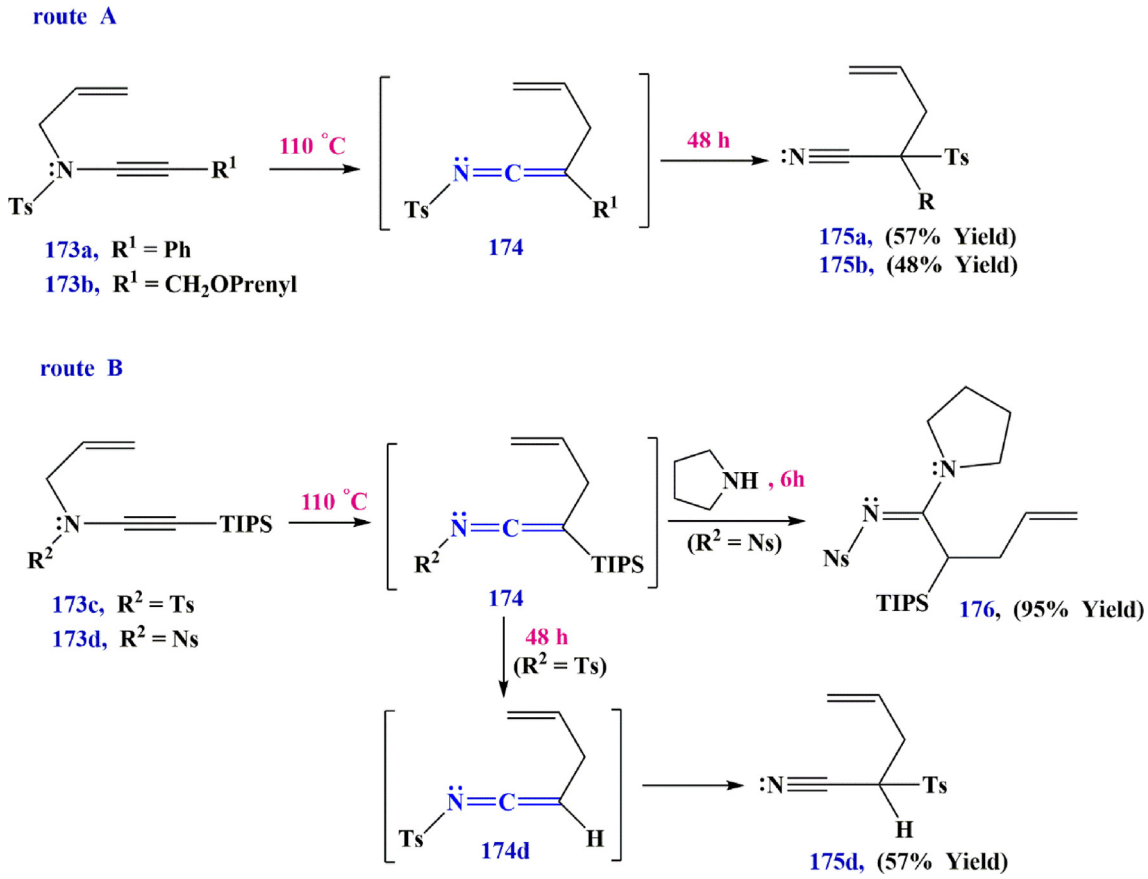


Scheme 51 Synthesize ketenimine **169**.

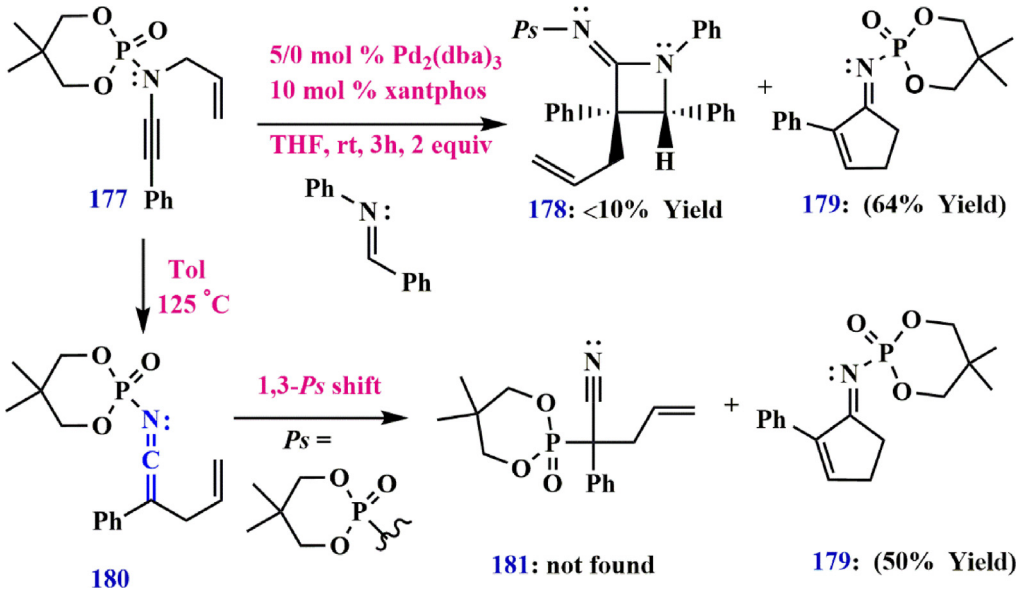


Scheme 52 Synthesize ketenimines **172**.

the carbocyclization of *N*-phosphoryl ynamide **188** by ketenimine **189** appears to be accelerated under both palladium-catalyzed and thermal conditions in the absence of a competing 1,3-phosphoryl shift. Subsequently, carbocyclization of ketenimine **189** (Hanessian et al., 2005; Sosa et al., 2008) gives an intermediate **190**, which undergoes a 1,2-*H* shift to provide



Scheme 53 Synthesize compounds 175 and 176 *via* Aza-Claisen rearrangement.



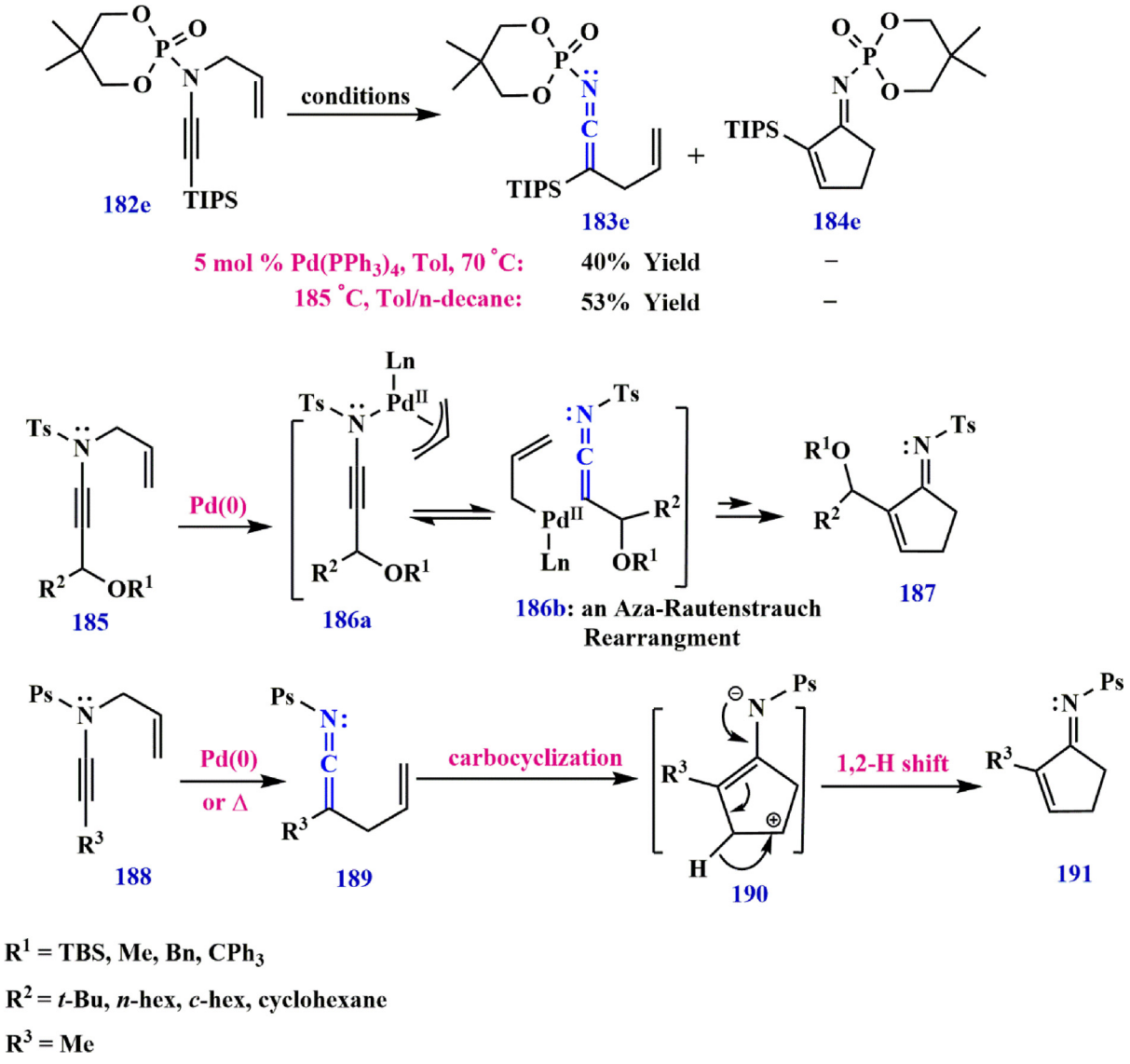
Scheme 54 Synthesize *N*-phosphoryl ynamide from allyl ketenimines.

cyclopentenimine **191**. Carbocyclization of ketenimine **193** without the use of a palladium catalyst leads to the formation of **194a**– **194c**, avoiding possible scrambling (Scheme 55). Also, the possibility of trapping intermediates with bound nucleophiles to produce bicyclic scaffolds such as **195a**–**195c** is predictable (Scheme 56). Furthermore, when ynamide **196** is heated to 135 °C in toluene with a bound benzene ring, only cyclopentenemine **200** is formed, resulting from a 1,2-*H* shift in **199**. In contrast, the *m*-methoxy group, which is an electron-donating group, can enrich the benzene ring in yanmide **197** with electrons, and 2-((7-methoxy-3a-methyl-3-phenyl-3a,4,5,9b-tetrahydro-1*H*-cyclopenta[α]naphthalen-2-yl) amino)-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide **202** is immediately synthesized in 85% yield in a combination of *cis* and *trans* isomers *via* the Aza-Claisen/Friedel-Craft electrophilic aromatic substitution process (Dekorver et al., 2012; Wang et al., 2013) (Scheme 57).

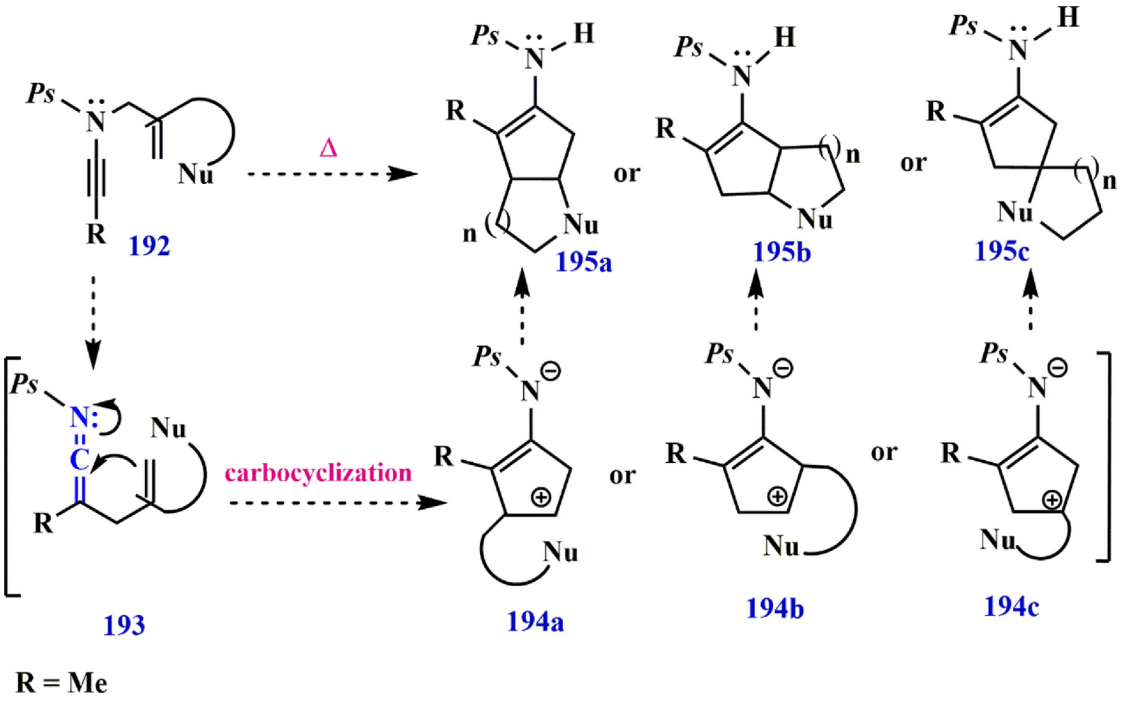
3.8.4. Beckmann rearrangement of oxime derivatives

The SCF_3 substituent has attracted much attention in recent years, and various methods for its direct introduction using electrophilic, nucleophilic, and radical sources have been investigated. (Tlili and Billard, 2013; Toulgoat et al., 2014). The Beckmann rearrangement of ketoxime **204** is one of the simplest methods to obtain fluorinated ketenimines. Treatment of (*Z*)-1-phenyl-2-((trifluoromethyl)thio)ethan-1-one oxime **203** under the reaction conditions led to the preparation of ketoxime **204**. Monitoring of, GC-MS showed that a solution of **204** was stable under argon for several days (Scheme 58).

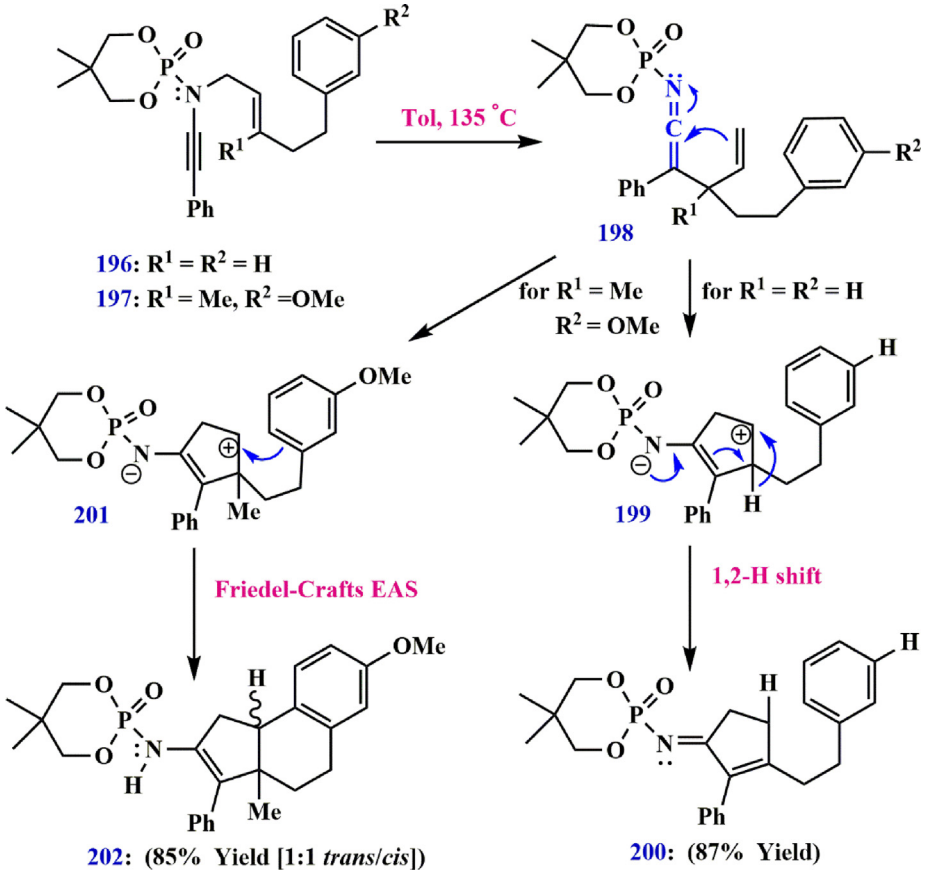
According to the plausible mechanism, the oxime is first converted to its triflic ether derivative **I**, as (*Z*)-1-phenyl-2-((trifluoromethyl)thio)ethan-1-one *O*-((trifluoromethyl)sulfonyl) oxime (Guérin et al., 2020), then the phenyl group migrates to the nitrogen as the triflate anion leaves, resulting in the synthesis of intermadiate **II**, a mesomeric form of nitrilium **III**.



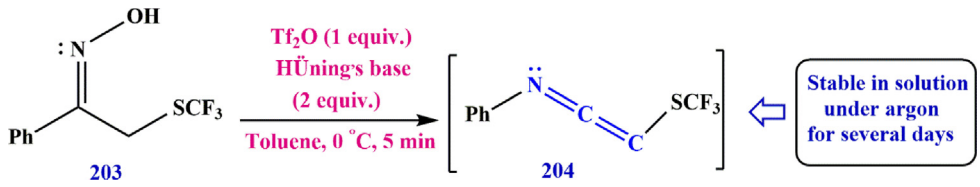
Scheme 55 Synthesize ketenimine from ynamide.



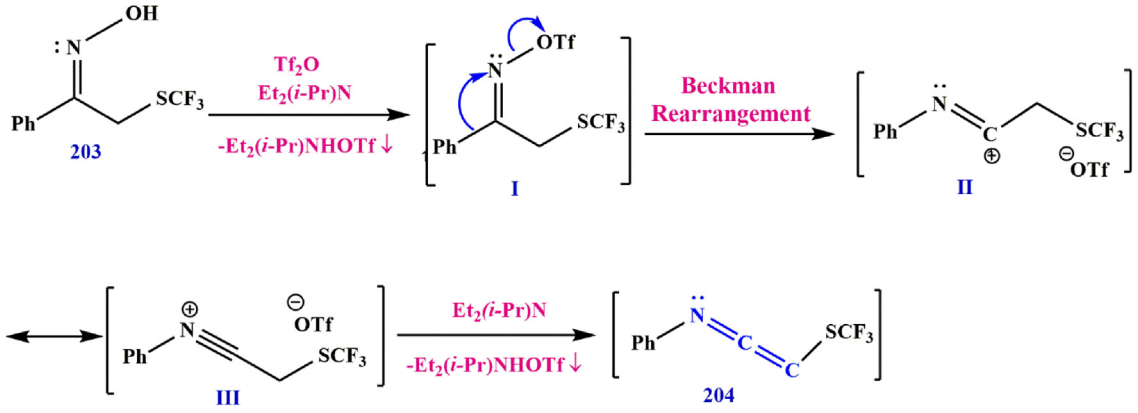
Scheme 56 Various pathways of *N*-phosphoryl ynamide synthesis.



Scheme 57 Synthesis routes of compounds **200** and **202**.



Scheme 58 Synthesize ketoxime **204**.



Scheme 59 Synthesize ketenimine **204**.

The remainder of the base deprotonates II or III to generate ketoxime **204** (Scheme 59).

4. Summary and outlook

The chemistry of ketenimines is interesting. Because of their excellent lability, ketenimines are often prepared in *situ* as reactive intermediates and used in one-pot processes. In the last decade, stabilizing substituents have also been used to create a variety of isolable ketenimines. In this review, we have presented a summary of the latest developments in the chemistry of ketenimines, which are a significant category of structural units with a significant application in biological synthesis. Despite the tremendous progress that has been made in this area, developing new methods for the generation of ketenimines and applying them in modern organic synthesis continues to be a time-consuming task. It's worth noting that the chirality transfers and preparation of chiral ketenimines have yet to be reported. However, since the chemistry of ketenimines is much more complex than that summarized in this study, this is most likely just the tip of the iceberg. The application of asymmetric variations of these transformations, a problem that has yet to be tackled, would most likely be of special importance for future research in the area. We hope that this study will encourage chemists to examine the flourishing field of ketenimine chemistry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Aumann, R., 1988a. Ketenimine Complexes from Carbene Complexes and Isocyanides: Versatile Building Blocks for Carbocycles and N-Heterocycles [New Synthetic Methods. Angew. Chem. Int. Ed. Engl. 27, 1456–1467.

Alajarin, M., Marin-Luna, M., Vidal, A., 2012. Recent Highlights in Ketenimine Chemistry. Eur. J. Org. Chem. 29, 5637–5653.

Alajarin, M., Molina, P., Vidal, A., 1996. Intramolecular [2 + 2] cycloaddition of ketenimines with imines. Tetrahedron Lett. 37, 8945–8948.

Aumann, R., 1988b. Keteniminkomplexe aus Carbenkomplexen und Isocyaniden – vielseitige Bausteine für Carbocyclen und N-Heterocyclen. Angew Chem. 100, 1512–1524.

Alajarin, M., Vidal, A., Tovar, F., 2000. Periselective intramolecular [4 + 2] cycloadditions of ketenimines: synthesis of pyrido[1,2-*a*] benzimidazoles. Tetrahedron Lett. 41, 7029–7032. https://doi.org/10.1016/S0040-4039(00)01197-7.

Ariyaratne, J., Green, M., 1963. Some ketenimine complexes of iron. J. Chem. Soc., 2976–2983 https://doi.org/10.1039/JR9630002976.

Alajarin, M., Bonillo, Luna, M.M., Andrada, P.S., Vidal, A., Orenes, R.A., 2012. Tandem [1,5]-H shift/6p-electrocyclizations of ketenimines bearing 1,3-oxathiane units. Computational assessment of the experimental diastereoselection. Tetrahedron Lett. 68, 4672–4681. https://doi.org/10.1016/j.tet.2012.04.021.

Anaraki-Ardakani, H., Mosslemin, M.H., Sadoughi, H., Makvandi, N., 2011. Three-component synthesis of dialkyl 2-(cyclohexyliminomethylene)-3-arylsulfonylamino succinate. J. Chem. Res. 35, 98–100. https://doi.org/10.3184/174751911X12964930076881.

Asghari, S., Haghdadi, M., Momeni, A.S., Monatsh, S.R., 2013. One-pot synthesis of N-substituted 2,4-thiazolidinediones and computational investigation of the products. Monatsh. Chem. 144, 337–343. https://doi.org/10.1007/s00706-012-0815-4.

Alexander, G.R., Cook, M.J., 2017. Formation of Ketenimines via the Palladium-Catalyzed Decarboxylative π–Allylic Rearrangement of *N*-Alloc Ynamides. Org. Lett. 19, 5822–5825. https://doi.org/10.1021/acs.orglett.7b02780.

Alajarin, M., Vidal, A., Tovar, F., 2004. Imino-Ketenimines on an Ortho-Benzylic Scaffold. Nitrogen to Carbon [1,3] Shift of an Ortho-Functionalized Benzyl Group. Lett. Org. Chem. 1, 340–342. https://doi.org/10.2174/1570178043400398.

Borrmann, D., 1968. Methoden der Organischen Chemie. (Houben-Weyl).

Beck, W., Hieber, W., Neumair, G., 1966. Über Metall-Stickoxid-Komplexe. XXI. Tricyanomethanido–Nitrosyl-Komplexe von Kobalt und Nickel. Z. Anorg. Allg. Chem. 344, 285–291. https://doi.org/10.1002/zaac.19663440508.

Beck, W., Nitzschmann, R.E., Smedal, H.S., 1967. Pseudohalogeno—Metallverbindungen XVIII. Anionische (Tricyanomethanido)pentacarbonyl-Komplexe von Chrom, Molybdän und Wolfram. J. Organometal. Chem. 8, 547–550. https://doi.org/10.1016/S0022-328X(00)83678-5.

Barker, M.W., Rosamond, J.D., 1972. Heterocycles from ketenimines. V. 2-Iminoazetidines through thermolysis. J. Heterocyclic Chem. 9, 1147–1148. https://doi.org/10.1002/jhet.5570090535.

Bayat, M., Imanieh, H., Hossieninejad, E., 2008. Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry. Synth. Commun. 38, 2567–2574. https://doi.org/10.1080/00397910802219213.

Bissember, A.C., Gardiner, M.G., Wierenga, T.S., 2018. α-Cyanocarbanion complexes and their application in synthesis. J. Organomet. Chem. 869, 213–226. https://doi.org/10.1016/j.jorganchem.2018.04.010.

Bendikov, M., Duong, H.M., Bolanos, E., Wudl, F., 2005. An Unexpected Two-Group Migration Involving a Sulfonynamide to Nitrile Rearrangement. Mechanistic Studies of a Thermal N → C Tosyl Rearrangement. Org. Lett 7, 783–786. https://doi.org/10.1021/ol0477327.

Corey, E.J., Cheng, X., 1995. The Logic of Chemical Synthesis. John Wiley & Sons.

Cheng, Y., Ma, Y., Wang, X., Mo, J., 2009. An Unprecedented Chemospecific and Stereoselective Tandem Nucleophilic Addition/Cycloaddition Reaction of Nucleophilic Carbenes with Ketenimines. J. Org. Chem. 74, 850–855. https://doi.org/10.1021/jo802289s.

Coffinier, D., Kaim, L.E., Grimaud, L., Ruijter, E., Orru, R.V.A., 2011. A new multicomponent reaction for the synthesis of pyridines via cycloaddition of azadienes and ketenimines. Tetrahedron Lett. 52, 3023–3025. https://doi.org/10.1016/j.tetlet.2011.04.007.

Clarke, L.F., Hegarty, A.F., O'Neill, P.J., 1992. Relatively Stable N-Benzhydryl- and N-Benzyldiarylketene Imines and Their Conversion to Cyanodiarylmet hanes via an Isolable Radical. Org. Chem. 57, 362–366. https://doi.org/10.1021/jo00027a062.

Dodd, R.H., Cariou, K., 2018. Ketenimines Generated from Ynamides: Versatile Building Blocks for Nitrogen-Containing Scaffolds. Chem. Eur. J. 24, 2297–2304.

Dijkstra, R., Backer, H.J., 1954. Imenes derived from methylsulphonyl-acetonitrile: (Properties of the sulphonyl group XLIII). Recl. Trav. Chim. Pays-Bas. 73, 575–581. https://doi.org/10.1002/recl.19540730710.

Denmark, S.E., Wilson, T.W., 2012. Silyl Ketene Imines: Highly Versatile Nucleophiles for Catalytic, Asymmetric Synthesis. Angew. Chem. Int. Ed. 51, 9980–9992. https://doi.org/10.1002/anie.201202139.

Domling, A., 2006. Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry. Chem. Rev. 106, 17–89. https://doi.org/10.1021/cr0505728.

Dos Santos, A., Cordierb, M., El Kaïm, L., 2017. Nef–Perkow–Mumm Cascade towards Imido Phosphate Derivatives. Synlett 28, 2637–2641. https://doi.org/10.1055/s-0036-1590856.

Dwyer, M.P., Price, D.A., Lamar, J.E., Meyers, A.L., 1999. An asymmetric oxazoline ketenimine rearrangement. Construction of chiral o -quaternary carbon ketones. Tetrahedron Lett. 40, 4765–4768. https://doi.org/10.1016/S0040-4039(99)00729-7.

De Korver, K.A., Hsung, R.P., Lohse, A.G., Zhang, Y., 2010. A Divergent Mechanistic Course of Pd(0)-Catalyzed Aza-Claisen Rearrangement and Aza-Rautenstrauch-Type Cyclization of *N*-Allyl Ynamides. Org. Lett. 12, 1840–1843. https://doi.org/10.1021/ol100446p.

De Korver, K.A., Johnson, W.L., Zhang, Y., Hsung, R.P., Dai, H., Deng, J., Lohse, A.G., Zhang, Y.S., 2011. *N*-Allyl-*N*-sulfonyl Ynamides as Synthetic Precursors to Amidines and Vinylogous Amidines. An Unexpected N-to-C 1,3-Sulfonyl Shift in Nitrile Synthesis. J. Org. Chem 76, 5092–5103. https://doi.org/10.1021/jo200780x.

Doney, J.J., Chen, C.H., George, A.R., Franklin, D.S., 1983. New Donors with Two-Electron Oxidation. Synthesis and Electrochemical Properties of Highly Conjugated Bis(4H-pyrans), Bis(4H-thiopyrans), and Bis(flavenes). J. Org. Chem. 4, 2757–2761. https://doi.org/10.1021/jo00164a024.

Dekorver, K.A., Hsung, R.P., Lohse, A.G., Zhang, Y., 2010. A Divergent Mechanistic Course of Pd $^{(0)}$-Catalyzed Aza-Claisen Rearrangement and Aza-Rautenstrauch-Type Cyclization of *N*-Allyl Ynamides. Org. Lett. 12, 1840–1843. https://doi.org/10.1021/ol100446p.

Dekorver, K.A., Wang, X.N., Walton, M.C., Hsung, R.P., 2012. Carbocyclization Cascades of Allyl Ketenimines via Aza-Claisen Rearrangements of N-Phosphoryl-N-allyl-ynamide. Org. Lett. 14, 1768–1771. https://doi.org/10.1021/ol300366e.

Falmagne, J.B., Escudero, J., Taleb-Sahraoui, S., Ghosez, L., 1981. Cyclobutanone and Cyclobutenone Derivatives by Reaction of Tertiary Amides with Alkenes or Alkynes. Angew. Chem. Int. 20, 879–880. https://doi.org/10.1002/anie.198108791.

Fedushkin, I.L., Morozov, A.G., Chudakova, V.A., Fukin, G.K., Cherkasov, V.K., 2009. Magnesium (II) Complexes of the dpp-BIAN Radical-Anion: Synthesis, Molecular Structure, and Catalytic Activity in Lactide Polymerization. Eur. J. Inorg. Chem. 2009, 4995–5003. https://doi.org/10.1002/ejic.200900710.

Groult, H., Leroux, F.R., Tressaud, A., 2017. Modern Synthesis Processes and Reactivity of Fluorinated Compounds. Elsevier Science.

Gambaryan, N.P., 1976. Fluorinated Ketenimines. Russ. Chem. Rev. 45, 630–638.

Guan, Z.R., Liu, S., Liu, Z.M., Ding, M.W., 2019. One-Pot Three-Component Synthesis of Pyrrolidin-2-ones via a Sequential Wittig/Nucleophilic Addition/Cyclization Reaction. Synth. 51, 2402–2408. https://doi.org/10.1055/s-0037-1612279.

Grass, A., Dewey, N.S., Lord, R.L., Groysman, S., 2019. Ketenimine Formation Catalyzed by a High-Valent Cobalt Carbene in Bulky Alkoxide Ligand Environment. J. Organomet. Chem. 38, 962–972. https://doi.org/10.1021/acs.organomet.8b00911.

Guérin, T., Pikun, N.V., Morioka, R., Panossian, A., Hanquet, G., Leroux, F.R., 2020. Synthesis and use of trifluoromethylthiolated ketenimines. Chem. Eur. J. 26, 14852–14855. https://doi.org/10.1002/chem.202002723.

Haufe, G., Leroux, F.R., 2019. Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals. Academic Press.

Hiroi, K., Sato, S., 1985. Asymmetric Induction Reactions. I. Asymmetric [2, 3] Sigmatropic Rearrangements of Sulfur Ylides Derived from Chiral Ketenimines and Trimethylsulfonium Ylide-Chem. Pharm. Bull. 33, 2331–2338. https://doi.org/10.1248/cpb.33.2331.

Hanessian, S., Tremblay, M., Marzi, M., Del Valle, J.R.J., 2005. Synthetic Studies in the Intramolecular Carbocyclization of N-Acyloxyiminium Ions. Stereoelectronic and Steric Implications of Nucleophilic Alkene, Alkyne, and Allene Tethers. Org. Chem. 70, 5070–5085. https://doi.org/10.1021/jo050326w.

Inui, H., Murata, S., 2001. Control of C-C and C–N Bond Cleavage of *2H*-Azirine by Means of the Excitation Wavelength: Studies in Matrices and in Solutions. Chem. Commun. 2001, 1036–1037. https://doi.org/10.1246/cl.2001.832.

Iravani, E., Neumüller, B., 2003. Trimerization of Phenylacetonitrile. InMe3 as a Base for C-H Acidic Nitriles. Organometallics 22, 4129–4135. https://doi.org/10.1021/om0303956.

Jochims, J.C., Anet, F.A.L., 1970. Ketenimines. Geometry and barriers to racemization. J. Am. Chem. *Soc* 92, 5524–5525. https://doi.org/10.1021/ja00721a044.

Jalli, V.P., Krishnamurthy, S., Moriguchi, T., Tsuge, A., 2015. One-pot four component synthesis of novel 3-furyl coumarin derivatives. J. Chem. Sci. 128, 217–226. https://doi.org/10.1007/s12039-015-1014-8.

Jin, X., Willeke, M., Lucchesi, R., Daniliuc, C.G., Fröhlich, R., Wibbeling, B., Würthwein, E.U., 2015. Hydroalumination of Ketenimines and Subsequent Reactions with Heterocumulenes: Synthesis of Unsaturated Amide Derivatives and 1,3-Diimines. J. Org. Chem. 80, 6062–6075. https://doi.org/10.1021/acs.joc.5b00466.

Kirsch, P., 2004. Modern Fluoroorganic Chemistry. Wiley-VCH.

Krow, G.R., 1971. Synthesis and Reactions of Ketenimines. Angew. Chem. Ed 10, 435–449.

Kim, S.H., Park, H.S., Choi, J.H., Chang, S., 2011. Sulfonyl and Phosphoryl Azides: Going Further Beyond the Click Realm of Alkyl and Aryl Azides. Chem. Asian. J. 6, 2618–2634. https://doi.org/10.1002/asia.201100340.

Kaneti, J., Nguyen, M., 1982. Theoretical study of ketenimine: Geometry, electronic properties, force constants and barriers to inversion and rotation. J. Mol. Struct. 87, 205–210. https://doi.org/10.1016/0166-1280(82)80054-7.

Kaufman, W.J., 1970. Reaction of ethyl azidoformate with dimethyl- and diethylketen-*N*-(p-tolyl) imine. J. Org. Chem. 35, 4244–4245. https://doi.org/10.1021/jo00837a011.

Katagiri, T., Handa, M., Asano, H., Asanuma, T., Mori, T., Jukurogi, T., Uneyama, K., 2009. Preparations and reactions of 2-trifluoromethylketenimines. J. Fluor. Chem 130, 714–717. https://doi.org/10.1016/j.jfluchem.2009.05.020.

Khlebnikov, A.F., Novikov, M.S., Kusei, E.Y., Kopf, J., Kostikov, R. R., 2003. Cascade Transformations of (2,2-Diaryl-3,3-dichloroaziridin-1-yl) acetates. Russ. J. Org. Chem 39, 559–573. https://doi.org/10.1023/A:1026068020111.

Lu, P., Wang, Y., 2012. The thriving chemistry of ketenimines. Chem. Soc. Rev. 41,5687–5705. Chem. Soc. Rev. 41, 5687–5705.

Laouiti, A., Couty, F., Marrot, J., Boubaker, T., Rammah, M.M., Rammah, M.B., Evano, G., 2014. Exploring the Anionic Reactivity of Ynimines, Useful Precursors of Metalated Ketenimines. Org. Lett. 16, 2252–2255. https://doi.org/10.1021/ol500749h.

Long, S., Panunzio, M., Qin, W., Bongini, A., Monari, M., 2013. Efficient Aldol-Type Reaction of O-Protected α-Hydroxy Aldehydes and N-Trimethylsilyl Ketene Imines: Synthesis of *β,* γ-Dihydroxy-Nitriles. Eur. J. Org. Chem 2013, 5127–5142. https://doi.org/10.1002/ejoc.201300430.

Moss, G.P., Smith, P.A., Tavernier, D., 1995. Glossary of class names of organic compounds and reactivity intermediates based on structure (IUPAC Recommendations 1995). Pure. Appl. Chem. 67, 1307–1375. https://doi.org/10.1351/pac199567081307.

Molina, P., Alajarin, M., Vidal, A., Feneau, D.J., Declerq, J.P., 1991. Domino reactions. One-pot preparation of fluoreno[2,3,4-ij] isoquinoline derivatives from conjugated ketene imines. J. Org. Chem. 56, 4008–4016. https://doi.org/10.1021/jo00012a039.

Marchand-Brynaert, J., Ghosez, L., 1972. Cycloadditions of keteneimmonium cations to olefins and dienes. New synthesis of four-membered rings. J. Am. Chem. Soc. 94, 2870–2872. https://doi.org/10.1021/ja00763a062.

Maity, A.K., Zeller, M., Uyeda, C., 2018. Carbene Formation and Transfer at a Dinickel Active Site. J. Organomet. Chem. 37, 2437–2441. https://doi.org/10.1021/acs.organomet.8b00261.

Nicolaou, K.C., Sorensen, E.J., 1996. Classics in Total Synthesis. Wiley-VCH.

Nicolaou, K., Snyder, S.A., 2003. Classics in Total Synthesis II. Wiley-VCH.

Nicolaou, K.C., Vourloumis, D., Winssinger, N., Baran, P.S., 2000. The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century. Angew. Chem. Int. Ed. 39, 44–122.

Orru, R.V.A., Greef, M.D., 2003. Recent Advances in Solution-Phase Multicomponent Methodology for the Synthesis of Heterocyclic Compounds. Synth. 10, 1471–1499. https://doi.org/10.1055/s-2003-40507.

Osisioma, O., Chakraborty, M., Ault, B.S., Gudmundsdottir, A.D., 2018. Wavelength-dependent photochemistry of 2-azidovinylbenzene and 2-phenyl-*2H*-azirine. J. Mol. Struct. 1172, 94–101. https://doi.org/10.1016/j.molstruc.2018.04.042.

Peng, Z., McLuckey, S.A., 2015. C-terminal peptide extension via gas-phase ion/ion reactions. Int. J. Mass Spectrom. 391, 17–23. https://doi.org/10.1016/j.ijms.2015.07.027.

Pujol, A., Lafage, M., Rekhroukh, F., Merceron, N.S., Amgoune, A., Bourissou, D., Nebra, N., Boutignon, M.F., Mézailles, N., 2017. A Nucleophilic Gold (III) Carbene Complex. Angew. Chem. Int. Ed. 56, 12264–12267. https://doi.org/10.1002/anie.201706197.

Qian, Y., Chong, L., Cheng, M.X., Yang, S.D., 2016. Palladium-Catalyzed Migratory Insertion of Isocyanides for Synthesis of C-Phosphonoketenimines. ACS Catal 6, 4715–4719. https://doi.org/10.1021/acscatal.6b01253.

Qiu, G., Mamboury, M., Wang, Q., Zhu, J., 2016. Ketenimines from Isocyanides and Allyl Carbonates: PalladiumCatalyzed Synthesis of *β,* γ-Unsaturated Amides and Tetrazoles. Angew. Chem. 128, 15603–15607. https://doi.org/10.1002/ange.201609034.

Rautenstrauch, V.J., 1984. 2-Cyclopentenones from 1-ethynyl-2-propenyl acetates Org. Chem. 49, 950–952. https://doi.org/10.1021/jo00179a044.

Simon, Z., Kerek, F., Ostrogouich, G., 1968. Stereochemistry of carbodiimides and ketenimines. Rev. Roum. Chim. 13, 381.

Staudinger, H., Meyer, J., 1919. Uber neue organische Phosphorverbindungen III. Phosphinmethylenderivate und Phosphinimine. Helv. Chim. Acta. 2, 635–646. https://doi.org/10.1002/hlca.19190020164.

Stevens, C.L., French, J.C., 1953. Nitrogen Analogs of Ketenes. A New Method of Preparation. J. Am. Chem. Soc. 75, 657–660. https://doi.org/10.1021/ja01099a043.

Stevens, C.L., Munk, M.M., 1958. Nitrogen Analogs of Ketenes. V. Formation of the Peptide Bond. J. Am. Chem. Soc. 80, 4065–4071. https://doi.org/10.1021/ja01548a060.

Stevens, C.L., Singhal, G.H.J., 1964. Nitrogen Analogs of Ketenes. VI.[1] Dehydration of Amides. Org. Chem. 29, 34–37. https://doi.org/10.1021/jo01024a007.

Shi, X., Gorin, D.J., Toste, F.D., 2005. Synthesis of 2-Cyclopentenones by Gold(I)-Catalyzed Rautenstrauch Rearrangement. J. Am. Chem. Soc. 127, 5802–5803. https://doi.org/10.1021/ja051689g.

Sosa, J.R., Tudjarian, A.A., Minehan, T.G., 2008. Synthesis of Alkynyl Ethers and Low-Temperature Sigmatropic Rearrangement of Allyl and Benzyl Alkynyl Ethers. Org. Lett. 10, 5091–5094. https://doi.org/10.1021/ol802147h.

Tlili, A., Billard, T., 2013. Formation of C-SCF3 Bonds through Direct TrifluoromethylthiolationAngew. Chem. Int. 52, 6818–6819. https://doi.org/10.1002/anie.201301438.

Toulgoat, F., Alazet, S., Billard, T., 2014. Direct Trifluoromethylthiolation Reactions: The "Renaissance" of an Old Concept. Eur. J. Org. Chem. 2014, 2415–2428. https://doi.org/10.1002/anie.201301438.

Weragoda, G.K., Das, A., Sarkar, S.K., Sriyarathne, H.D.M., Zhang, X., Ault, B.S., Gudmundsdottir, A.D., 2017. Singlet Photoreactivity of 3-Methyl-2-phenyl-*2H*-azirine. J. Chem. 70, 413–420. https://doi.org/10.1071/CH16604.

Wolf, R., Stadtmüller, S., Wong, M.W., Flammang, R., Barbieux-Flammang, M., Wentrup, C., 1996. Novel Heterocumulenes: Bisiminopropadienes and Linear Ketenimines. Chem. Eur. J. 2, 1318–1329. https://doi.org/10.1002/chem.19960021020.

Woodward, R.B., Olofson, R.A., 1961. A NEW SYNTHESIS OF PEPTIDES. Am. Chem. Soc. 4, 1007–1009. https://doi.org/10.1021/ja01465a072.

Wu, W., Wang, J., Wang, Y., Huang, Y., Tan, Y., Weng, Z., 2017. Trifluoroacetic Anhydride-Promoted Copper(I)-Catalyzed Interrupted Click Reaction: From 1,2,3-Triazoles to 3- Trifluoromethyl-Substituted 1,2,4-Triazinones. Angew. Chem Int. 56, 10476–10480. https://doi.org/10.1002/anie.201705620.

Wang, X.N., Winston-McPherson, G.N., Walton, M.C., Zhang, Y., Hsung, R.P., Dekorver, K.A., 2013. J. Org. Chem. 78, 6233–6244. https://doi.org/10.1021/jo400960e.

Xiong, J., Mu, Z.-Y., Yao, G., Zhang, J.A., Feng, Q.X., He, H.T., Pang, Y.L., Shi, H., Ding, M.W., 2021. One-Pot Synthesis of Polysubstituted Pyrroles via Sequential Ketenimine Formation/Ag (I)-Catalyzed Alkyne Cycloisomerisation Starting from Ylide Adducts. Chin. Chem. Lett. 39, 1553–1557. https://doi.org/10.1002/cjoc.202000639.

Yoo, E.J., Chang, S., 2009. Copper-Catalyzed Multicomponent Reactions: Securing a Catalytic Route to Ketenimine Intermediates and their Reactivities. Curr. Org. Chem. 13, 1766–1776. https://doi.org/10.2174/138527209789630497.

Yoo, E.J., Ahlquist, M., Kim, S.H., Bae, I., Fokin, V.V., Sharpless, K. B., Chang, S., 2007. Copper-Catalyzed Synthesis of *N*-Sulfonyl-1,2,3-triazoles: Controlling SelectivityAngew. Chem. Int. 46, 1730–1733. https://doi.org/10.1002/anie.200604241.

Yavari, I., Nematpour, M., Ghazanfarpour-Darjani, M., 2012a. One-pot synthesis of 2,6-diamino-4-sulfonamidopyrimidines from sulfonyl azides, terminal alkynes and cyanoguanidine. Tetrahedron Lett. 53, 942–943. https://doi.org/10.1016/j.tetlet.2011.12.041.

Yavari, I., Nematpour, M., Yavari, S., Sadeghizadeh, F., 2012b. Copper-catalyzed one-pot synthesis of tetrasubstituted pyrazoles from sulfonyl azides, terminal alkynes, and hydrazonoyl chloride. Tetrahedron Lett. 53, 1889–1890. https://doi.org/10.1016/j.tetlet.2012.01.083.

Yu, L., Cao, J., 2014. Synthesis of α, β-unsaturated amides and iminocoumarins from N, N-disulfonyl ynamides with aldehydes via the ketenimine intermediate. Org Biomol. Chem. 12, 3986–3990. https://doi.org/10.1039/C4OB00513A.

Zhu, J., Bienaymé, H., 2005. Multicomponent Reactions. France: Eds. Wiley: Weinheim.

Zhang, R., Zhang, Z., Zhou, Q., Yu, L., Wang, J., 2019. The Generation of Difluoroketenimine and Its Application in the Synthesis of α, α-Difluoro-β-amino Amides. Angew. Chem. 131, 5800–5804. https://doi.org/10.1002/anie.201901591.

Zhang, X., Sarkar, S.K., Weragoda, G.K., Rajam, S., Ault, B.S., Gudmundsdottir, A.D., 2014. Comparison of the Photochemistry of 3–Methyl-2-phenyl–*2H*–azirine and 2–Methyl-3-phenyl–*2H*–azirine. J. Org. Chem. 79, 653–663. https://doi.org/10.1021/jo402443w.

Zhang, Y., De Korver, K.A., Lohse, A.G., Zhang, Y.S., Huang, J., Hsung, R.P., 2009. Synthesis of Amidines Using N-Allyl Ynamides. A Palladium-Catalyzed Allyl Transfer through an Ynamido-π-Allyl Complex. Org. Lett. 11, 899–902. https://doi.org/10.1021/ol802844z.