Pergamon

TETRAHEDRON

Tetrahedron 57 (2001) 7575–7606

Tetrahedron report number 583

Recent advances in the chemistry of ynamines and ynamides

Craig A. Zificsak, Jason A. Mulder,[†] Richard P. Hsung,[*] C. Rameshkumar and Lin-Li Wei

Department of Chemistry, University of Minnesota, 207 Pleasant Street S.E., Minneapolis, MN 55455-0431, USA

Received 13 March 2001

Contents

1. Introduction 7576
2. Part I—Ynamines 7578
    - 2.1. Synthesis of ynamines 7578
        - 2.1.1. Synthesis of chiral ynamines 7578
        - 2.1.2. Synthesis of achiral ynamines 7579
            - 2.1.2.1. Elimination protocols 7579
                - 2.1.2.1.1. From haloalkenes and haloalkynes 7579
                - 2.1.2.1.2. From non-haloalkenes 7580
            - 2.1.2.2. Alkynyliodonium salts 7580
            - 2.1.2.3. Other methods 7581
    - 2.2. Reactions of ynamines 7581
        - 2.2.1. Addition reactions 7581
        - 2.2.2. Cycloaddition reactions 7583
            - 2.2.2.1. [2+1] Cycloadditions 7583
                - 2.2.2.1.1. Formation of carbocycles 7583
                - 2.2.2.1.2. Formation of phosphorus heterocycles 7584
            - 2.2.2.2. [2+2] Cycloadditions 7584
                - 2.2.2.2.1. Formation of carbocycles 7584
                - 2.2.2.2.2. Formation of N- and P-heterocycles 7585
                - 2.2.2.2.3. O-, S-, and Se-heterocycles 7586
            - 2.2.2.3. [2+4] Cycloadditions 7588
                - 2.2.2.3.1. Formation of carbocycles 7588
                - 2.2.2.3.2. Formation of N- and P-heterocycles 7588
                - 2.2.2.3.3. Formation of oxygen heterocycles 7590
            - 2.2.2.4. [3+n] Cycloadditions 7591
            - 2.2.2.5. Metal mediated cycloadditions 7592
                - 2.2.2.5.1. [2+2+1] Cycloadditions 7592
                - 2.2.2.5.2. [2+2+2] Cycloadditions 7593
                - 2.2.2.5.3. Other cycloadditions 7593
        - 2.2.3. Functionalizations 7593
3. Part II—Ynamides 7594
    - 3.1. Synthesis of ynamides 7594
        - 3.1.1. Synthesis of chiral ynamides 7594
        - 3.1.2. Synthesis of achiral ynamides 7595
            - 3.1.2.1. Elimination protocols 7595
            - 3.1.2.2. Alkynyliodonium salts 7597
            - 3.1.2.3. Other methods 7597

---

[*] Corresponding author. Tel.: +1-612-625-3045; fax: +1-612-626-7541; e-mail: hsung@chem.umn.edu

[†] Recipient of 2000–2001 University of Minnesota Graduate Dissertation Fellowship.

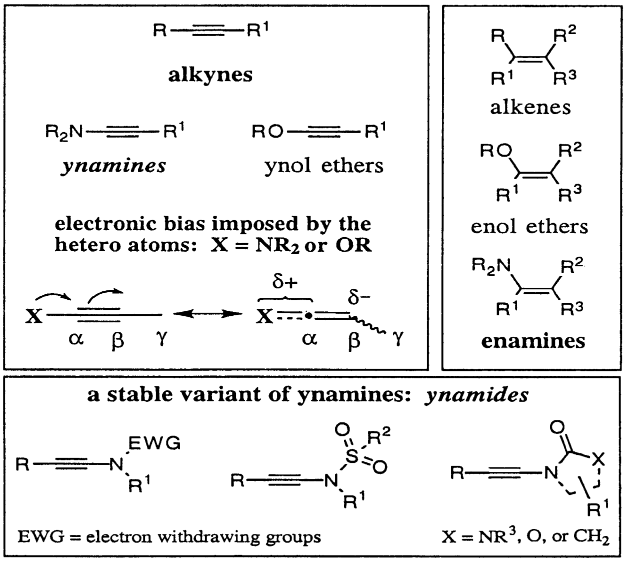
PII: S0040-4020(01)00681-0

3.2. Reactions of ynamides 7598
  3.2.1. Addition reactions 7598
  3.2.2. Cycloaddition reactions 7598
    3.2.2.1. [2+2] and [4+2] Cycloadditions 7598
    3.2.2.2. Metal mediated cycloadditions 7598
      3.2.2.2.1. [2+2+1] Cycloadditions 7598
      3.2.2.2.2. [2+2+2] Cycloadditions 7601

1. Introduction

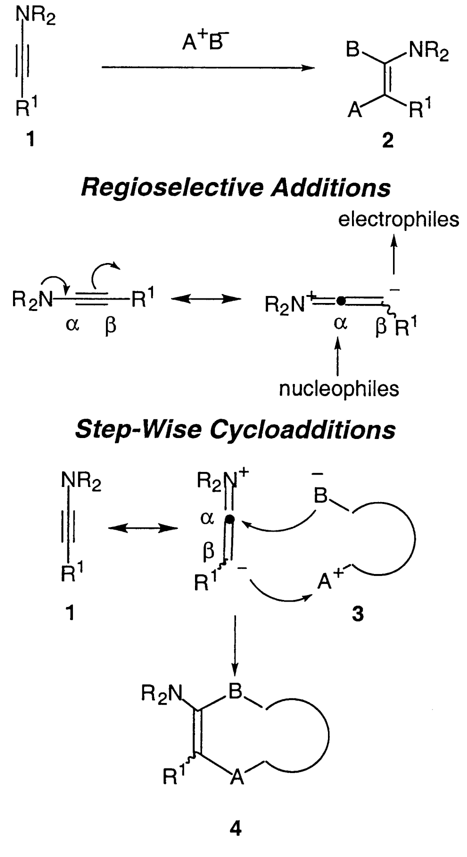
Alkynes are among the most important building blocks in organic synthesis. The richness of this functional group renders it extremely versatile as a synthon for a diverse array of modern synthetic methods. Useful subgroups of alkynes are those containing heteroatom substitution, specifically ynamines. The electron donating ability of the nitrogen atom renders ynamines even more synthetically effective because of the electronic bias imposed by the heteroatom, allowing highly regioselective transformation of these molecules.

The first attempt at preparation of an ynamine was reported by Bode in 1892.[1,2] While well characterized ynamines were reported in 1958[3] and 1960,[4] a practical synthesis was not achieved until the effort led by Viehe in 1963.[5] For the twenty years thereafter, the synthetic utility of ynamines in organic and organometallic chemistry was firmly established by the work of many creative synthetic chemists, and reactivities of 1-aminoalkynes were thoroughly explored. These elegant pioneer works have been informatively and carefully reviewed by Viehe in 1967[6] and 1969,[7] Ficini in 1976,[8] Pitacco and Valentin in 1979,[9] Collard-Motte and Janousek in 1985,[10] and most recently, Himbert in 1993.[11]



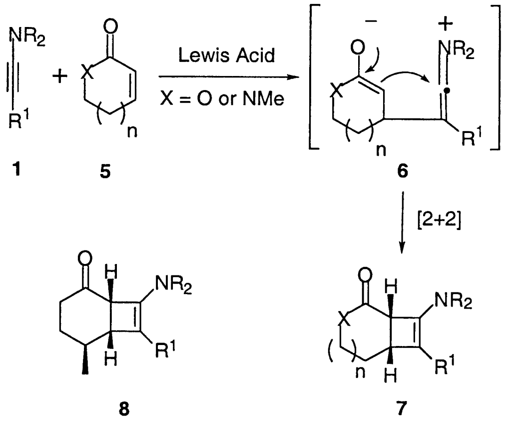
Unlike enamines, the widespread synthetic use of ynamines has remained relatively limited, especially during the last 15 years. Reasons in part for the limited synthetic application of ynamines include the difficulty in preparation and handling of ynamines due to their sensitivity toward hydrolysis and their high reactivity—unlike its counterpart, the ynol ethers which are less reactive, owing to the stabilizing effect of the electronegative oxygen atom. Therefore, the focus of this particular review is to survey the development in the chemistry of *ynamines* since 1993 in Section 2, and particularly highlight the new advances that have occurred in employing a more stable variant of ynamines—*ynamides* in Section 3, which should bring an exciting future to the chemistry of ynamines.

During the last eight years, there have been limited new approaches to ynamine synthesis, although there are over 30 accounts on preparations of ynamines. The most notable approach would be the use of hypervalent iodine reagents. On the other hand, there are over 120 accounts citing various reactions involving ynamines, 10–12 of which published in very recent years are devoted to reactivities of ynamides. Although fewer in number than the accounts reported 15 years ago, many of these recent reactions remain elegant and demonstrate that ynamines have synthetic potential in various applications. The reactions of ynamines can be categorized, as in previous reviews, into two classes: Addition reactions of ynamines and cycloaddition reactions of ynamines.



Scheme 1.

A Step-wise Thermal [2+2] Cycloaddition Reaction

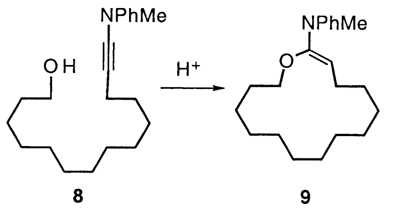


Scheme 2.

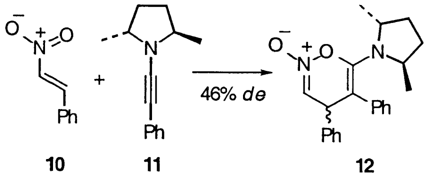
As illustrated in Scheme 1, addition reactions of ynamines **1** typically involve the addition of reagents such as A^+B^- across the triple bond in the presence of promoters such as Lewis acids or protic acids to give products such as **2**. These addition reactions are highly regioselective as demonstrated in previous reviews.[6–11] The sense of the regioselectivity may be readily predicted by the well-known electronic nature of ynamines (Scheme 1).[8] By far, cycloaddition reactions of ynamines, [2+2], [4+2], and [3+*n*], have received the greatest attention, leading to unique heterocycles such as **4** that have synthetic potential. Mechanistically these cycloadditions follow mostly a step-wise pathway, joining appropriate atoms to match the electronic demand. There are also accounts on transition metal-mediated cycloadditions.[11]

One of the most interesting and synthetically useful cycloaddition is Ficini's thermal [2+2] cycloaddition reaction of ynamines with electron deficient alkenes **5**, leading to cyclobutenamines such as **7** (Scheme 2).[8] Ficini has demonstrated that these [2+2] cycloaddition reactions can be carried out diastereoselectively to give cyclobutenamines such as **8** as the major isomers.[8] Although limited, there are attractive applications of this highly useful reaction.

Intramolecular Reactions



Stereoselective Reactions



Scheme 3.

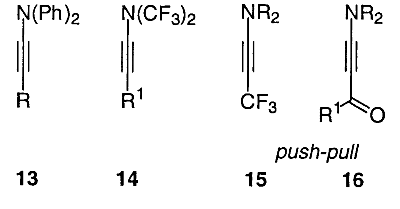
Given the versatility of ynamines in organic synthesis, it is surprising that besides Genet's example of an intramolecular reaction involving addition of a hydroxyl group to an ynamine reported in 1980 (**8**→**9** in Scheme 3),[12] there are no other intramolecular reactions involving ynamines. In addition, there was only one account of stereoselective reaction with modest diastereomeric excess (*de*) involving chiral ynamines reported by Reinhoudt in 1987 (**10**+**11**→**12**)[13] before another example appeared in 2000 [see Section 2].

The lack of attention that ynamines have received over the last 15–20 years can be attributed to their synthetic inaccessibility and sensitivity. The high reactivity and sensitivity toward hydrolysis are due to the ability of the nitrogen to donate its lone pair to the alkynyl moiety. Therefore, efforts aimed at improving the stability of ynamines without significantly diminishing their reactivity may be key to the future of this chemistry.

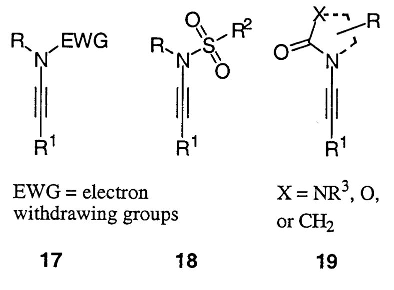
Reactivities and stabilities of a range of relatively electron-deficient ynamines such as **13**–**16** are known in literature. During the last 20 years, some very interesting chemistry has been described for the 'push–pull' ynamines **15** and **16** (Scheme 4).[6–11] Unfortunately, however, little has been gained in terms of stability. One can stabilize the ynamine to the point of being unreactive as in bis-trifluoromethyl substituted ynamine **14**.

Toward the purpose of balancing reactivity and stability, some advances have been made very recently in exploring another class of electron-deficient ynamines, ynamides, in which the nitrogen atom is substituted with an electron withdrawing group such as a sulfonamide, an imidazolidinone, an oxazolidinone, or a lactam systems (**17**–**19**). The electron-withdrawing group serves to diminish the electron-donating ability of the nitrogen atom, thereby offering stability superior to traditional ynamines. These investigations have led to the development of highly stereoselective intermolecular as well as intramolecular reactions using a stable variant of ynamines [Section 3].

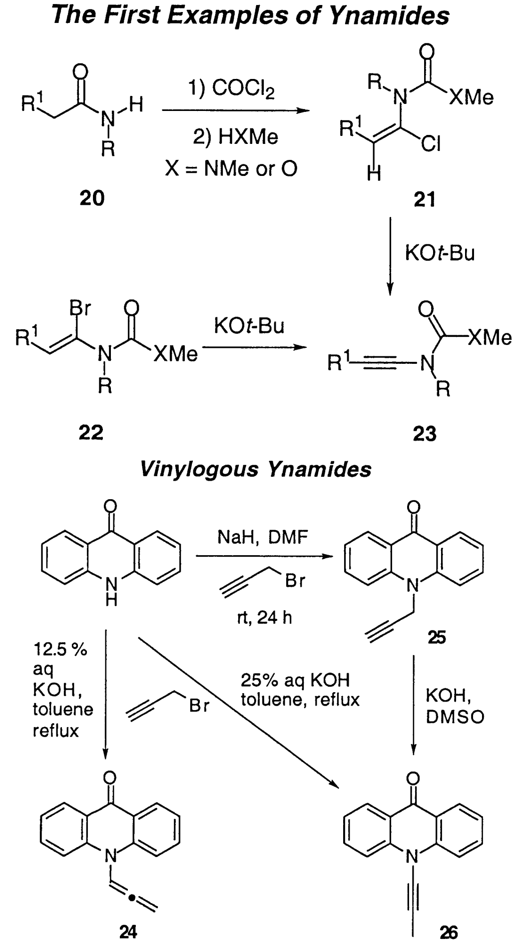
Electron Deficient Ynamines



ynamides

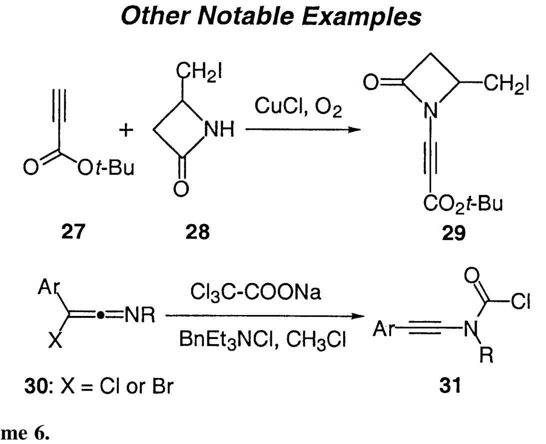


Scheme 4.

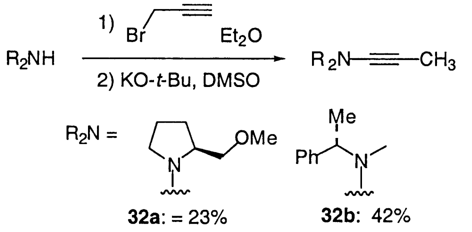


Scheme 5.

Although reactivities of ynamides are almost unknown, preparations and thermal stability of ynamides have been documented.[11] The very first synthesis of ynamides was reported by Viehe in 1972 as shown in Scheme 5.[14] Ynamides **23** could be attained from halogenated enamides such as **21** and **22** via base induced elimination, and were reported to possess much improved thermal stability and stabilities toward hydrolytic conditions.[14] Zaugg's ynamine[3] **26** (Scheme 5, or vinylogous ynamide) was prepared by Galy et al. in 1979.[15a] A number of other reports have described its synthesis through the use of base-induced isomerization protocols.[15,16]



Scheme 6.



Scheme 7.

More recently, preparations of two other ynamides were reported in 1985[17] and 1991.[18] For example, a Cu(I) mediated oxidative process that was intended for coupling *t*-butyl propiolate **27** to the alkyl halide **28** (Scheme 6) furnished instead an ynamide **29**.[17] Another involves the transformation of C-halogen substituted ketenimines **30** using a phase transfer agent.[18]

It is only recently that the reactivity of ynamides have begun to be examined. Research in this area could prove to be a fertile ground for developing useful synthetic methods because *ynamides possess enhanced stability relative to ynamines by reducing the electron density on the nitrogen atom. This allows them to be prepared, isolated, and subjected to a variety of interesting reactions including intramolecular reactions. They possess more conformational rigidity than any other heteroatom-substituted alkynes. They can coordinate to metals and can be chiral, leading to the potential for the development of stereoselective methodologies.* The investigations reviewed here and those that will appear in the future should help facilitate and revitalize interest in the chemistry of ynamines.

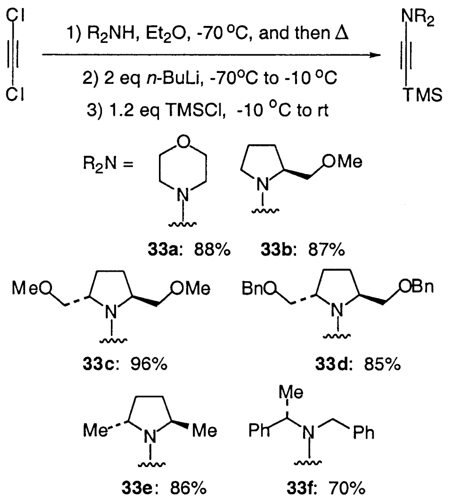
As this review is intended to examine chemistry that is of interest to the synthetic organic community, studies related to physical and spectroscopic properties of ynamines are not reviewed here.[19] In addition, any reports of the use of ynamines as ligands for transition metals are also not included here.

2. Part I—Ynamines

2.1. Synthesis of ynamines

2.1.1. Synthesis of chiral ynamines. The first synthesis of chiral ynamines since Reinhoudt's work[13] was accomplished by Fischer et al. using an isomerization protocol in 1997.[20] Beginning with chiral secondary amines (Scheme 7), ynamines **32** were obtained in moderate yields upon reaction with propargyl bromide and isomerization with potassium *tert*-butoxide.

The only other report of chiral ynamines since 1987 is the work of Pericàs[21] wherein dichloroacetylene is reacted with a variety of chiral amines and *n*-BuLi, and the resulting lithium acetylide is trapped as the silylated ynamine **33** (Scheme 8). Although these silylated ynamines exhibited improved stability over their H-substituted counterparts, they were converted into even more stable adducts upon treatment with dicobalt octacarbonyl (See Section 2.2.2.5.1). Although only two chiral ynamine reports have



Scheme 8.

occurred in the past decade,[20,21] electron-deficient ynamines have been synthesized in chiral form; these will be discussed in Section 3.

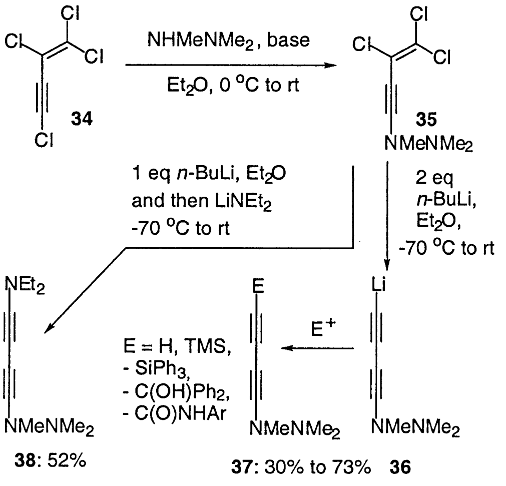
2.1.2. Synthesis of achiral ynamines

2.1.2.1. Elimination protocols

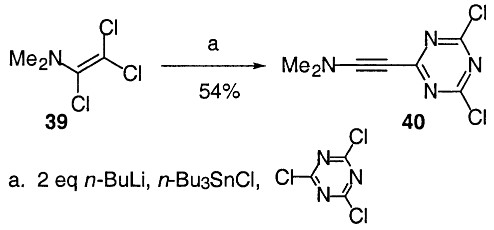
2.1.2.1.1. From haloalkenes and haloalkynes. Halogenated alkenes have long been utilized as precursors for ynamine synthesis.[6–11] Himbert[22] has continued his work into the synthesis of ynamines **38** and ynehydrazines **37** from trichloroalkenes (Scheme 9).

Likewise, dimethyl ynamine **40** has been reported by the groups of Hauser[23] and Neuenschwander[24] from the coupling a transient stannylated ynamine with cyanuric chloride (Scheme 10).

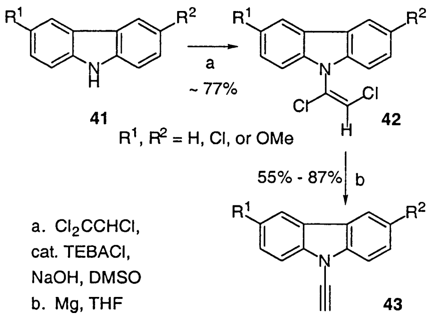
9-Ethynylcarbazoles **43** were synthesized via a phase transfer alkylation (Scheme 11) and subsequent reductive dehalogenation protocol.[25] In a similar manner, Brandsma has reported[26] the synthesis of N-ethynylpyrrole.



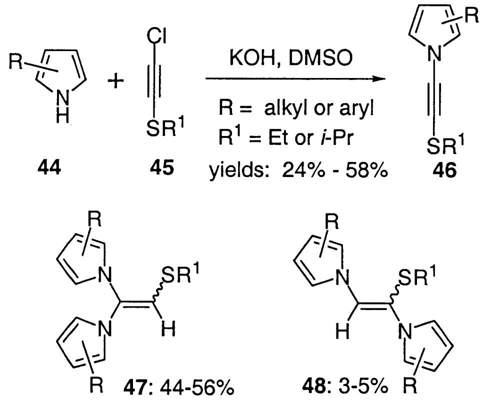
Scheme 9.



Scheme 10.



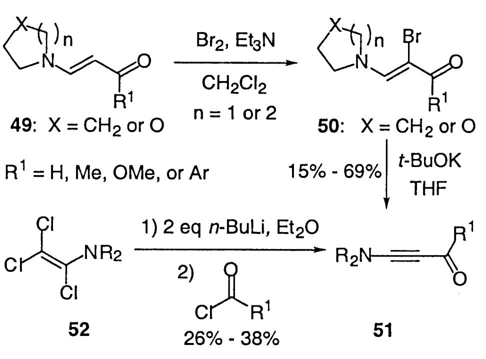
Scheme 11.



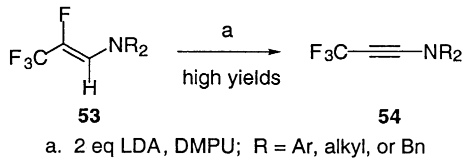
Scheme 12.

Thioynamines **46** (Scheme 12) have been constructed[27] from a variety of pyrroles and alkylthiochloroacetylenes (**45**). Unfortunately, bis-pyrrole adducts (**47** and **48**) were found to be formed competitively, leading to only moderate yields of the ynamines **46**.

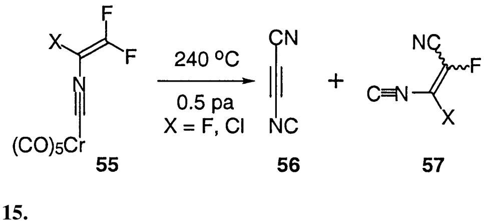
Push–pull ynamines such as **51** (Scheme 13) have found considerable interest due to the stabilizing effects of the



Scheme 13.



Scheme 14.

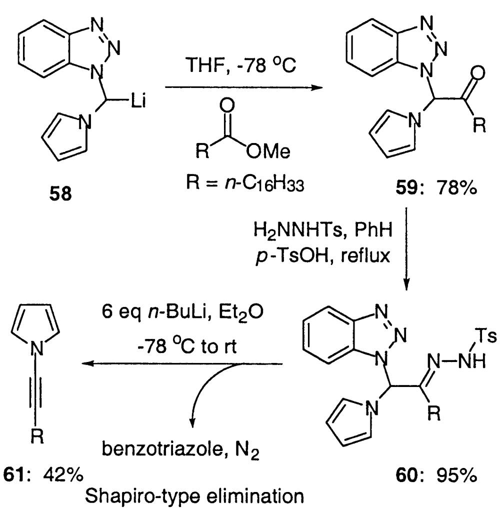


Scheme 15.

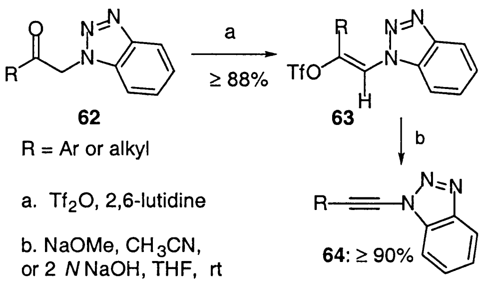
electron-withdrawing substituent on the acetylide. Dell[28] has utilized the elimination of (*Z*)-β-bromoenamines **50** to access the push–pull ynamines **51**. Neuenschwander has trapped the lithium acetylide of ynamines with acid chlorides to afford push–pull ynamines in moderate yield.[24,29] The trifluoromethyl analogue (Scheme 14) of Ficini's ynamine has also been synthesized by an elimination protocol of the (*Z*)-β-fluoroenamines **53** by Yamanaka and Ishihara.[30]

Finally as shown in Scheme 15, the pyrolysis[31] of trihaloethenyl isocyanide complex **55** affords a mixture of cyanoisocyanoacetylene (**56**) and alkene **57**, along with a significant amount of recovered metal complex **55**. Acetylide **56** and related polyynes are of interest due to the observation of similar compounds in interstellar space.[31]

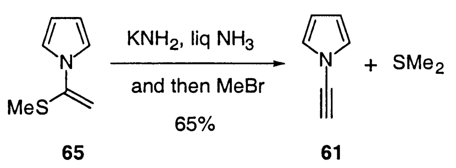
2.1.2.1.2. From non-haloalkenes. The synthesis of ynamines from non-halogenated alkenes has also been of interest. Katritzky has developed a convenient method for the construction of various alkynes from aromatic and aliphatic esters.[32] Acylation[32] of lithium ion **58** and tosylhydrazone formation gives **60** (Scheme 16). Hydrazone **60** can then undergo Shapiro-type elimination,[32] with subsequent loss of benzotriazole and molecular nitrogen, to afford pyrrolic ynamine **61**.



Scheme 16.



Scheme 17.



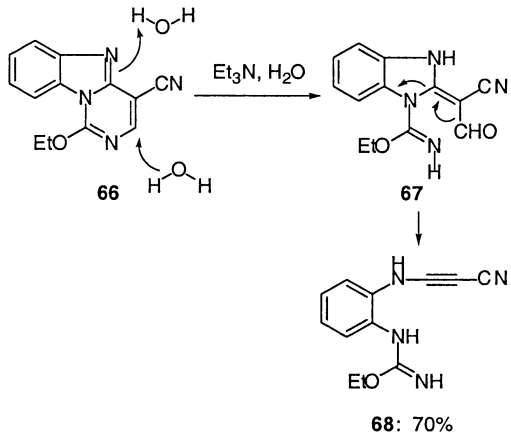
Scheme 18.

Katritzky[33] has also demonstrated (Scheme 17) that ynamines can be generated from enol triflates **63** by treatment with either sodium methoxide or aq. sodium hydroxide.

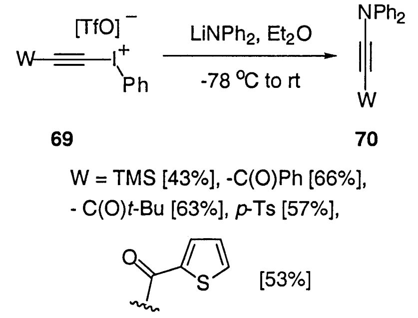
An additional synthesis of *N*-ethynylpyrrole[26] (Scheme 18) has been reported by Trofimov,[34] wherein methyl vinyl thioether **65** is treated with potassium amide in ammonia, and ynamine **61** is obtained in good yield and >95% purity. Methanethiolate is trapped during the workup of the reaction by the addition of one equivalent of methyl bromide, to generate dimethylsulfide.

Okamoto et al.[35] (Scheme 19) have synthesized ynamine **68** using the basic hydrolysis of pyrimido[1,6-*a*]benzoimidazole **66** and rearrangement by way of intermediate **67**.[35] The nitrile-substituted ynamine **68** is obtained in a 70% overall yield.

2.1.2.2. Alkynyliodonium salts. In the early 1990s, a new method for the synthesis of ynamines was discovered by Stang and co-workers,[36] which involved reaction of alkynyliodonium salts[37] **69** with lithium amides.



Scheme 19.



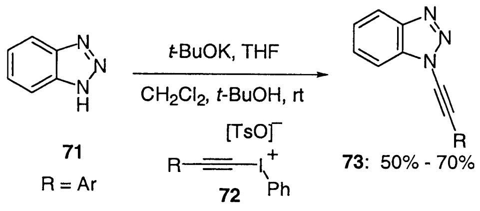
Scheme 20.

A variety of push–pull ynamines **70** (Scheme 20) could thus be obtained in yields ranging from 43 to 66%. This alkyne formation is believed to proceed via addition β to the iodine to generate iodobenzene and a vinylcarbene, which then undergoes a 1,2-shift to form the acetylide.[37] Triflate salts[36] as well as tosylate salts[38] (Scheme 21) have been used in these conversions, the latter having been used for the synthesis of benzotriazole ynamines **73**.[38]

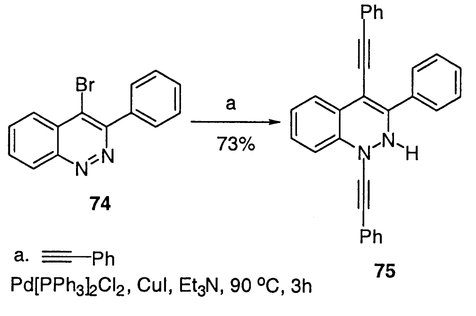
2.1.2.3. Other methods. Bromocinnoline derivatives[39] were found to undergo palladium catalyzed amination (Scheme 22) when treated with phenylacetylene in the presence of palladium catalysts and copper (I) salts, analogous[40] to the formation of *N*-aryl amines.

As shown in Scheme 23, when arylisonitrile **76** was treated with a lithiosilane and TMEDA, it formed the unique heterocycle **79** containing both nitrogen and silicon atoms in a four-membered ring, and incorporating two molecules of isonitrile **76**.[41] Thermolysis of **79** afforded the crystalline lithioynamine **80** as a dimeric complex, where TMEDA serves as a linker for the two ynamine components.[41]

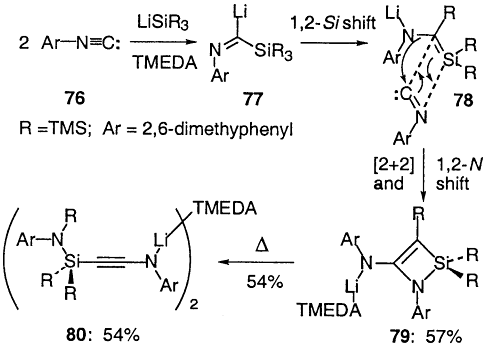
Brown[42] was able to detect the pyrazolo ynamine **83** as a minor component when subjecting amide **81** to flash vacuum pyrolysis (Scheme 24). This product is believed to be formed by rearrangement of the propynoyl amide **81** with migration from N1 to N2. Loss of CO from the resultant propadienone and 1,2-*H* shift would then be reasonable.[42]



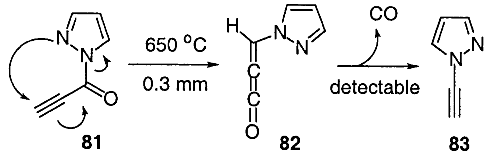
Scheme 21.



Scheme 22.



Scheme 23.



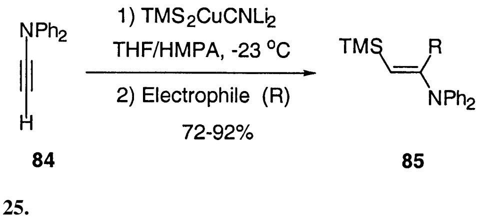
Scheme 24.

2.2. Reactions of ynamines

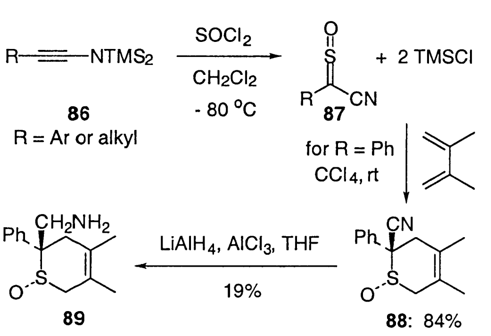
2.2.1. Addition reactions. The addition of various reagents to ynamines has been studied. One recent, intriguing study was the addition of silylcuprates to the ynamine **84** by Reginato (Scheme 25).[43]The addition of the silylcuprate resulted in a β-silyl-α-amino vinyl cuprate,[43] which is then quenched with a variety of reagents to generate the β-silylenamines **85**.

Hanack and co-workers[44] have studied the addition of thionyl chloride to ynamines **86** (Scheme 26). In this study, cyanosulfines **87** were the unexpected product of addition to the β-carbon of the ynamine, with subsequent loss of two moles of chlorotrimethylsilane. The structure of cyanosulfines **87** (R=Ph) was confirmed by cycloaddition with 2,3-dimethyl-1,3-butadiene,[44] and X-ray analysis of the adducts.

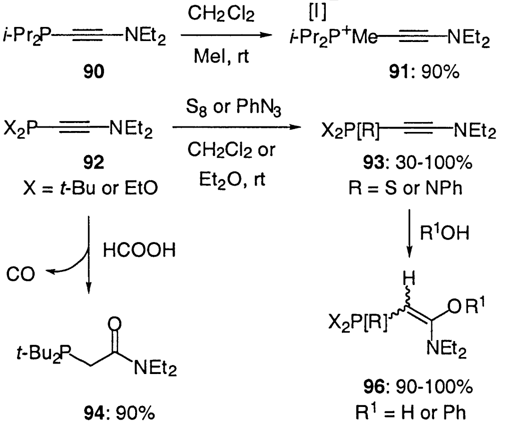
Lukashev et al. have studied the addition of various electrophiles to phosphorus substituted ynamines.[45] Functionalization of the phosphorus atom was found to occur upon treatment with methyl iodide, elemental sulfur, and phenyl azide (Scheme 27). Also, the addition of formic acid or alcohols was found to proceed by protonation of the



Scheme 25.



Scheme 26.



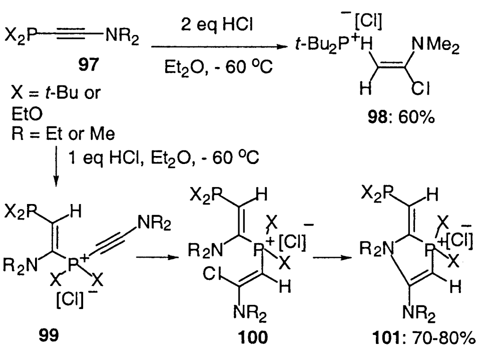
Scheme 27.

β-carbon and addition of the nucleophile to the α-carbon of the ynamine.

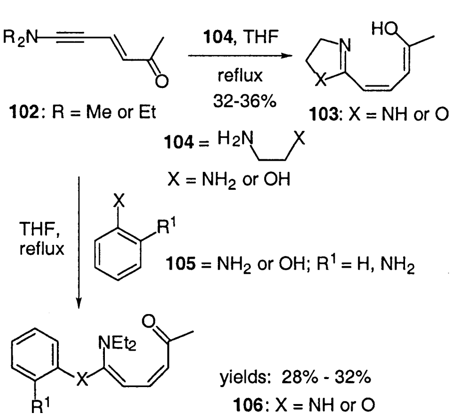
As seen in Scheme 28, the result of addition of HCl was dependent upon the stoichiometry used.[45] When two equivalents were used, chloroenamine salt **98** was isolated in 60% yield.

However, when only one equivalent was added, protonation was followed by attack of a phosphorus ynamine **97** to generate **99**, which underwent further addition of HCl and final cyclization to afford 1,3-azaphospholinium chlorides **101**.[45]

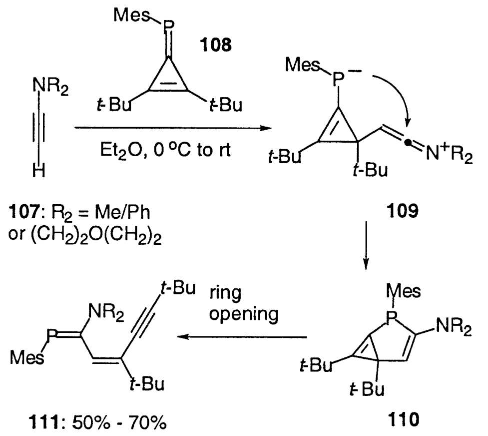
The addition of bifunctional[46] reagents to ynamines **102** was studied by Sukhova et al. and found to result in heterocycles **103** when alkyl diamines or aminoalcohols were utilized (Scheme 29). These enolic heterocycles are the result of loss of the ynamine nitrogen and alkyl substituents. The addition of anilines[46] **105** to ynamine **102** also resulted in addition across the acetylenic bond, but bis-addition was not observed in the case of *o*-hydroxy aniline.



Scheme 28.



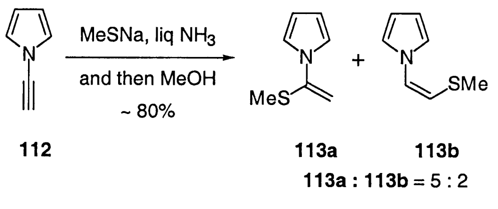
Scheme 29.



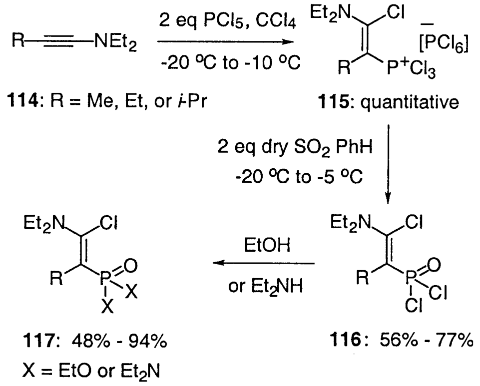
Scheme 30.

Reactions of ynamines with phosphatriafulvenes **108** has been studied by Regitz.[47] Ynamines **107** form the acyclic dienynes **111** in good yield when treated with phosphatriafulvenes (Scheme 30). Following sequential addition across the ynamine triple bond, bicycle **110** undergoes ring opening to afford the dienyne **111**.

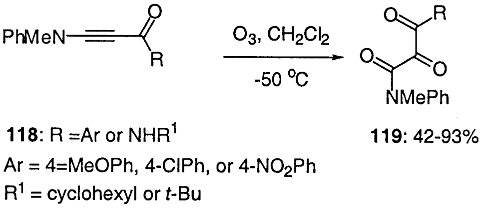
Trofimov's studies[34] for the synthesis of ethynylpyrrole demonstrated that sodium methanethiolate could effectively add to **112** (Scheme 31), which had been an undesired side reaction in the synthesis of **112**. Alkyl ynamines **114** were found to undergo quantitative addition reactions[48] when



Scheme 31.



Scheme 32.

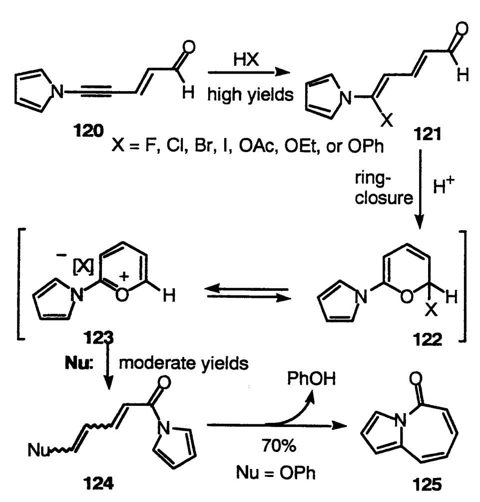


Scheme 33.

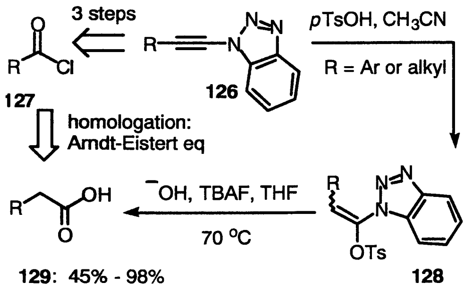
treated with phosphorus pentachloride (Scheme 32). Phosphonium salts **115** were then treated with sulfur dioxide to generate phosphonic dichlorides **116**.[48] Reaction with ethanol or diethylamine allowed for isolation of the corresponding phosphonates or phosphonamides **117**.

Push–pull ynamines **118** were used by Himbert[49] for the construction of tricarbonyl compounds **119** in moderate to excellent yields (Scheme 33). Under ozonolysis conditions, **119** is isolated as the exclusive product without the formation of peroxidic intermediates or C–C bond cleavage.[49]

Neuenschwander has thoroughly investigated the reactivity of conjugated push–pull ynamines[50] such as **120** and found that upon treatment with hydrogen halides or acids and alcohols dienes **121** were formed in high yield (Scheme 34). Further treatment of dienes **121** with acid allowed for rearrangement to 2-aminopyrylium salts **123**.[50] These salts were found to undergo reopening upon nucleophilic attack to generate amides **124**.



Scheme 34.



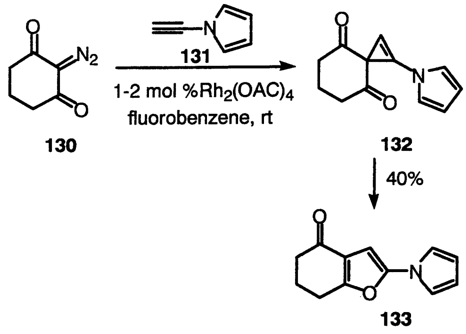
Scheme 35.

Finally, Katritzky[33] has developed an efficient one-carbon homologation protocol for carboxylic acids (Scheme 35). Synthesis of the benzotriazole ynamine from the acid chloride (Scheme 16) is followed by reaction with *p*-toluenesulfonic acid followed by treatment of the tosylenamine with base. This Arndt–Eistert equivalent is applicable for both aromatic and aliphatic carboxylic acids.[33]

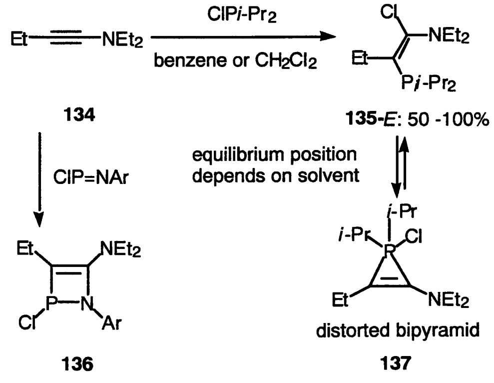
2.2.2. Cycloaddition reactions

2.2.2.1. [2+1] Cycloadditions

2.2.2.1.1. Formation of carbocycles. Pirrung[51] has found that ynamine **131** can serve as a 2 electron component in [2+1] cycloadditions (Scheme 36) with the rhodium carbenoid generated from **130**. The intermediate cyclopropene is not isolated, but instead undergoes ring



Scheme 36.



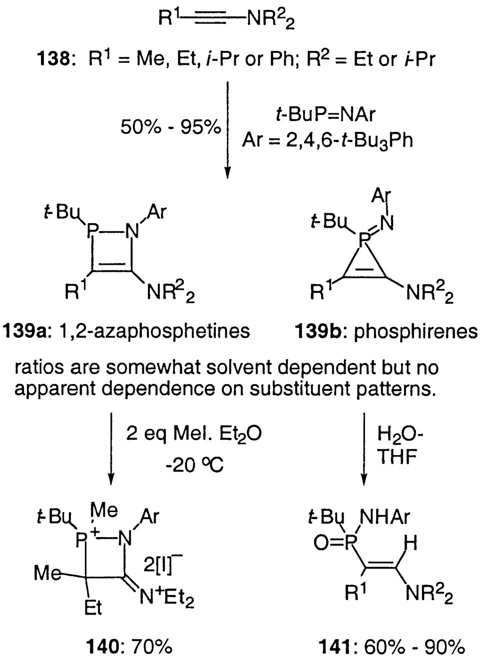
Scheme 37.

opening and recyclization onto the ketone carbonyl, to generate furan **133**.[51]

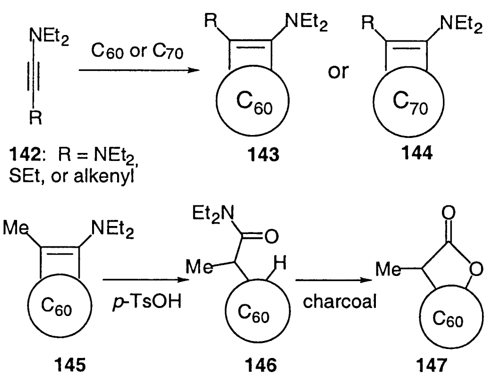
2.2.2.1.2. Formation of phosphorus heterocycles. Lukashev has demonstrated[52] the formation of a reversible mixture of alkene **135** and phosphirene **137** from the addition and cylcization of chlorophosphines with ynamine **134** (Scheme 37).

In pentane and dichloromethane **135** is favored, but a 1:1 mixture is found in benzene. The corresponding reaction with chloroimino-phosphines however generates the P–N-heterocycle **136** in favor of the three-membered ring product.[52]

In other studies,[53] the same authors have shown that *tert*-butyliminophosphines undergo similar cyclizations (Scheme 38) but generate a mixture of 1,2-azaphosphitenes **139a** and phosphirenes **139b**. The ratio of **139a** to **139b** was dependent upon the solvent that was used but it was only mildly dependent on the steric bulk of ynamine **138**. To aid in characterization,[53] **139a** and **139b** could be alkylated or hydrolyzed to give **140** and **141** respectively.



Scheme 38.



Scheme 39.

2.2.2.2. [2+2] Cycloadditions

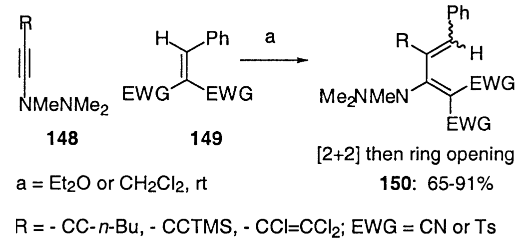
2.2.2.2.1. Formation of carbocycles. The [2+2] cycloaddition of ynamines onto fullerenes[54] has been investigated by Foote. Fullerenes can undergo a non-photochemical cycloaddition to furnish the stable cyclobutenes **143** and **144** with C_{60} and C_{70}, respectively (Scheme 39). In addition, the fullerene cycloadducts may be opened under a variety of conditions to yield amides, amide/ketones, and amide/thioesters.[54]

Himbert has demonstrated[22a] the utility of ynehydrazines **148** in cycloaddition reactions (Scheme 40) to furnish the corresponding butadienes **150**. [2+2] Cycloaddition with electron-deficient alkenes **149** is followed by ring opening, to furnish the butadienes in good yields.

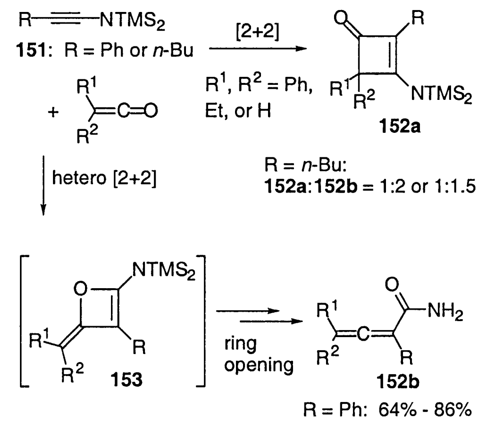
Bis-TMS ynamine **151** reacts with ketenes (Scheme 41) to generate a mixture of cyclobutene **152a** or oxetene **153** products, wherein oxetene **153** undergoes ring opening to afford allene products **152b**.[55] Competitive cyclization is observed for butyl-substituted ynamines, but selective heterocyclic [2+2] cyclization is observed for phenyl ynamine **151**.[55]

Viehe[56] has investigated the reactivity of the halogenated cyclobutene **154** (Scheme 42) toward ynamine and found that cycloadducts **155a** and **155b** are formed in excellent combined yield, with **155b** derived from elimination under basic work-up conditions.

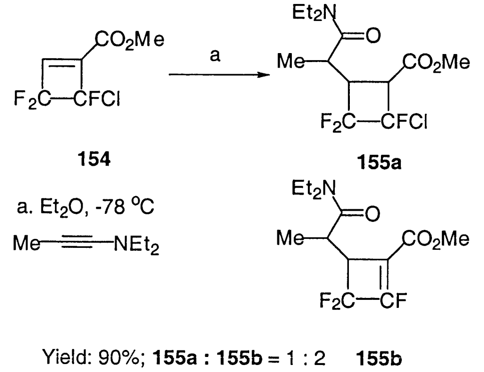
Schaumann[57] demonstrated that alkynylsilylsulfides **156** and ynamines **157** could undergo coupling to afford cyclobutenethiones **160** by stepwise silyl-transfer and addition



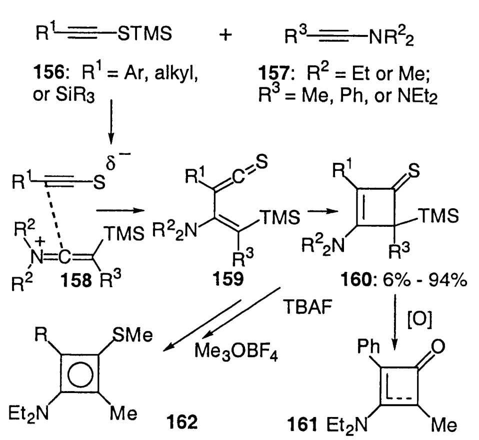
Scheme 40.



Scheme 41.



Scheme 42.



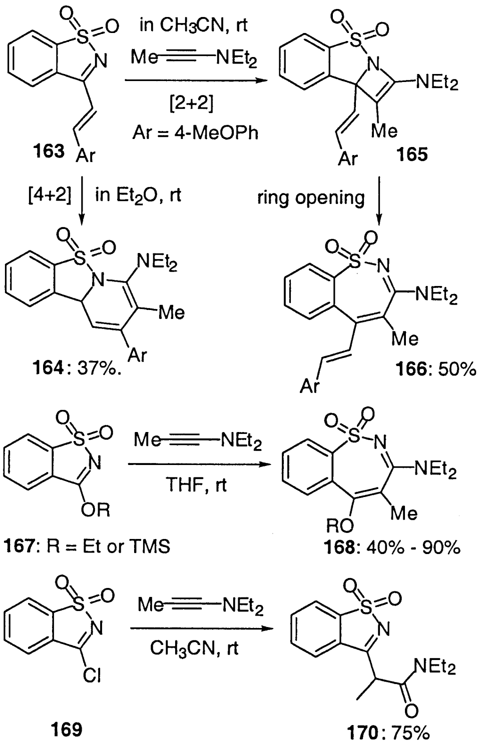
Scheme 43.

followed by cyclization (Scheme 43). Yields were generally good although poor yields were observed with sulfides having bulky substituents on the alkyne. Thiones **160** were then utilized for the generation of cyclobutadienes **162**.[57]

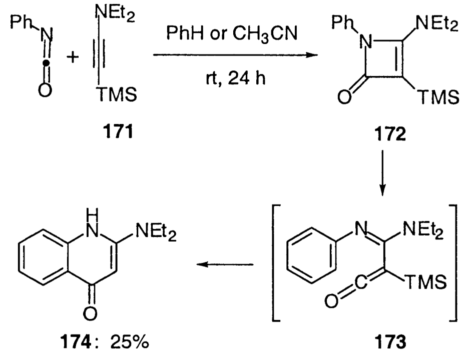
2.2.2.2.2. Formation of N- and P-heterocycles. When benzisothiazole[58] **163** was reacted with ynamine (Scheme 44), competitive cylization lead to azacyclobutene **165** or dihydropyridine **164**. The azacyclobutene was found to undergo ring opening to afford thiazepine **166** in moderate yield. Dihydropyridine **164** is the result of 1,4-addition to the conjugated imine of **163**, followed by cyclization and double bond migration.

When the styrene fragment of **163** was replaced with an alkyl or silyl ether **167**, the ring expansion products **168** were formed. Abramovitch also demonstrated that chlorobenzisothiazole **169** under similar conditions lead to addition product **170**, where the amide is formed by 1,3-Cl shift to generate a chloroenamine, followed by hydrolysis with water.[58]

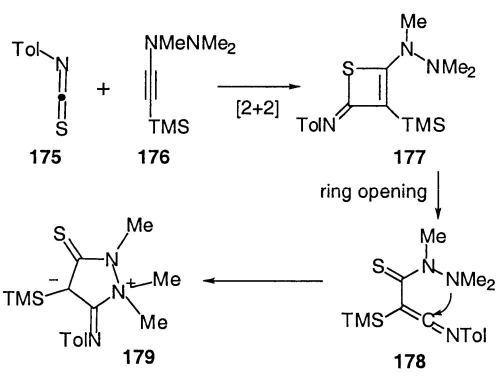
Wentrup and co-workers[59] have investigated the ynamine-isocyanate reaction (Scheme 45) using Himbert's ynamine **171**. For the formation of quinolone **174**, cycloaddition of ynamine **171** with phenyl isocyanate yielded azetinone **172**, which underwent ring opening to ketene **173**, which recyclized. The trimethylsilyl functionality was detectable by GC–MS, but was lost upon purification.[59] When Himbert explored the reactivity of ynamines toward aryl isothiocyanates,[59] he found that contrary to the regiochemical selectivity of isocyanates, isothiocyanates react with ynamines via cycloaddition across the C–S double bond (versus the N–C double bond) (Scheme 46). Ring opening of **177**



Scheme 44.



Scheme 45.



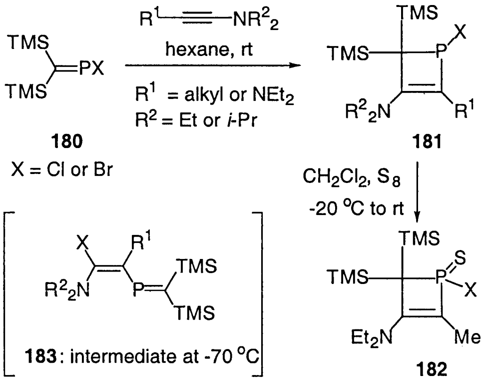
Scheme 46.

generates ketenimine **178**, which cyclizes to furnish the stable betaine **179**.[60]

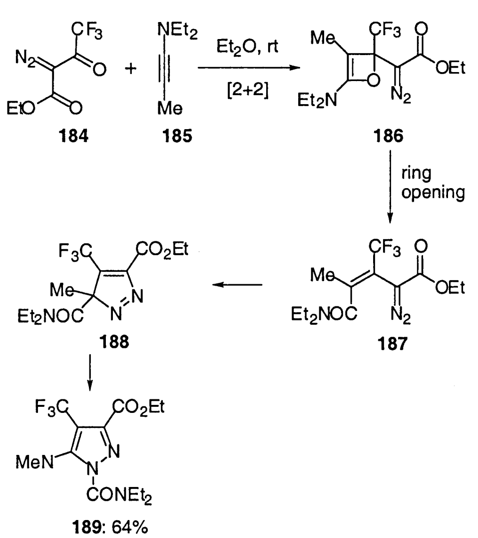
Cyclization studies[61] of halophosphaalkenes **180** with ynamines (Scheme 47) by Averin et al. demonstrated that ynamines could be utilized in the formation of phosphates **181** in near quantitative yields. The monitoring of the reaction at low temperature by NMR experiments revealed phosphabutadiene **183** to be an intermediate,[61] as a result of addition across the ynamine triple bond. The treatment of **181** with sulfur yielded **182**, a derivative more suitable for characterization.

2.2.2.2.3. O-, S-, and Se-heterocycles. Guillaume has studied[62] the reactivity of diazo compound **184** toward ynamine **185** (Scheme 48) and found that the two undergo hetero [2+2] cycloaddition/ring opening followed by addition of the vinyldiazomethane **187** into the alkene. Pyrazole **188** undergoes an allowed 1,5-carbamoyl shift to furnish the stable pyrazole **189** in good yield. The cycloaddition is limited to trifluoromethyl activated carbonyls.[62]

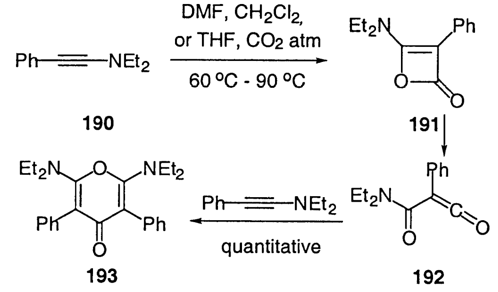
Polymerization studies[63] of 1,4- and 1,3-bis(ynamino)-benzenes with carbon dioxide was undertaken by Tsuda, and as shown in Scheme 49, a model study supported the formation of poly(4-pyrones). In the model study, phenyl ynamine **190** was found to quantitatively cyclize to form 4-pyrone **193**, incorporating two equivalents of **190** and one equivalent of CO_2.[63]



Scheme 47.



Scheme 48.

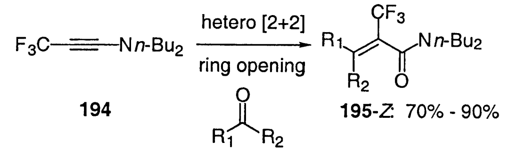


Scheme 49.

For the polymerization of bis(ynamino)benzenes, quantitative conversion was also observed, and the 1:1 copolymer had an average molecular mass ranging between 4400 and 8100 Da, dependent upon solvent used for the polymerization.[63] Another C=O hetero [2+2] cycloaddition of ynamines[64] was the reaction of novel trifluoromethyl ynamine **194** with a variety of aryl, vinyl and alkyl aldehydes and ketones (Scheme 50). Ynamine **194** undergoes Lewis acid-catalyzed hetero [2+2] cycloaddition to generate the trifluoromethyl acrylamides **195** with high (*Z*)-selectivity.

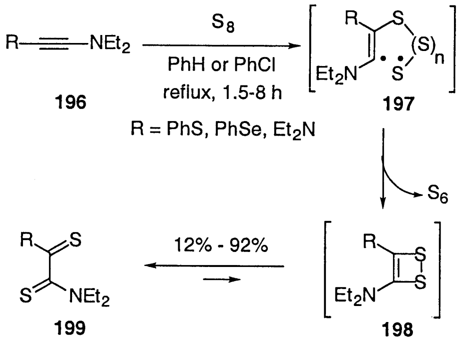
Nakayama[65] has demonstrated the cyclization of ynamines **196** with elemental sulfur to provide the dithioxo amide **199** (Scheme 51). This formation is believed to proceed via addition of diradical sulfur to **196**, followed by expulsion of sulfur to form dithiete **198**. Ring opening of **198** affords the thermodynamically favored dithioxo amide **199**.

For the selenium substituted ynamine **196**, competitive expulsion of PhSe˙ from **197** is observed, leading to

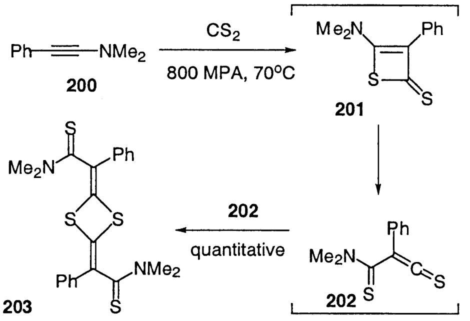


Lewis acid: BF_3-Et_2O, $TiCl_4$, $SnCl_4$, $ZnBr_2$, or $La(OTf)_3$; 5-30mol%; CH_2Cl_2, rt, MS4A

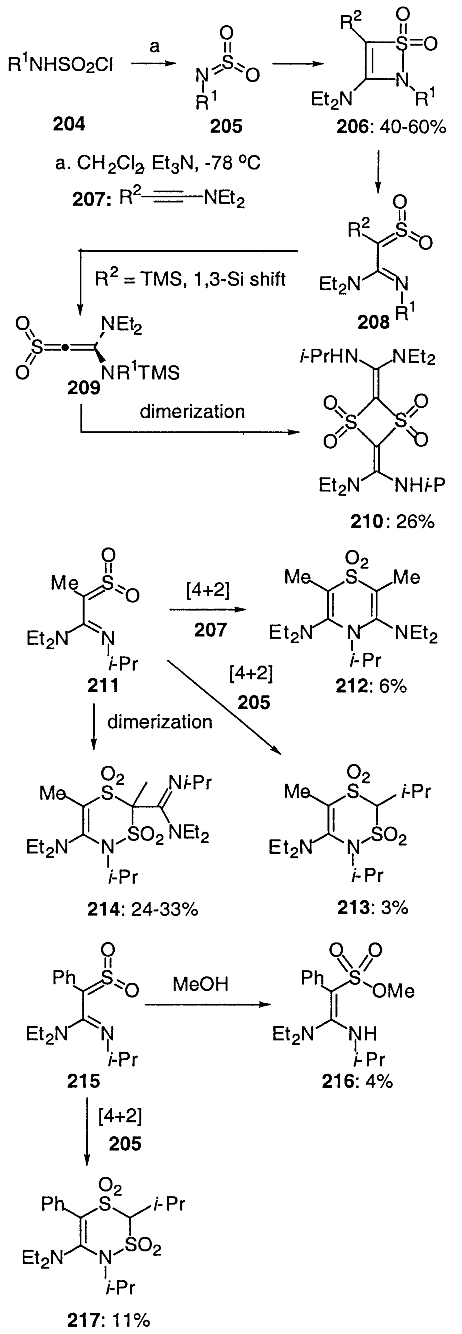
Scheme 50.



Scheme 51.



Scheme 52.



Scheme 53.

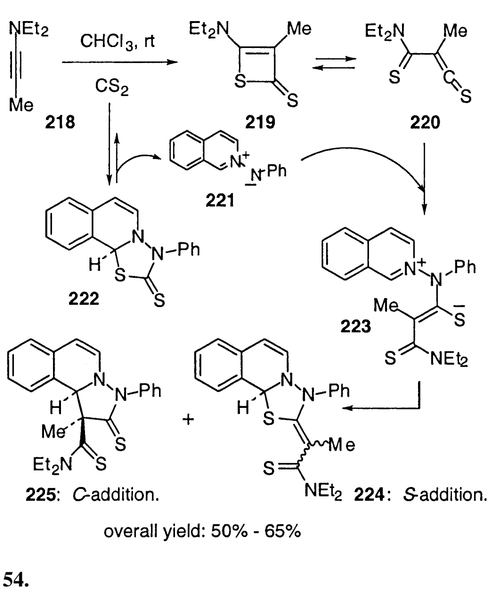
formation of diphenyl diselenide in 80% yield, with only 12% of dithioxo compound **199** formed.[65] Sulfur-containing heterocycle[66] **203** (Scheme 52) has been found to form when phenyl ynamine **200** is treated with carbon disulfide at elevated pressure. Following [2+2] cycloaddition, the 1:1 adduct **201** undergoes ring opening, and the resultant thione thioallene **202** undergoes dimerization, generating 1,3-dithietane **203**.[66]

Schaumann[67] has studied the reactivity of ynamines (Scheme 53) with *N*-sulfonylalkylamines **205**. Sulfonylalkylamines **205** undergo [2+2] cycloaddition with ynamines to afford the cyclic products **206** as the major products in moderate yields. Thiazetes **206** can then undergo ring-opening to form the reactive dienes **208**, which have been used in a variety of other reactions.[67] In the case of trimethylsiyl substituted ynamine, a 1,3-*Si* shift may occur, to generate heterocumulene **209**, which undergoes regio- and stereospecific [2+2] cyclodimerization.[67]

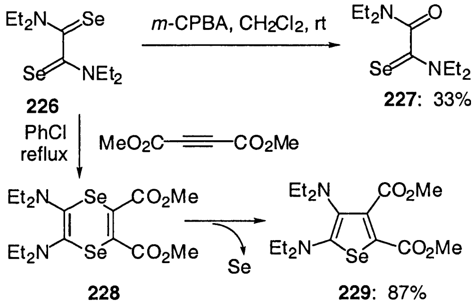
Other cyclizations that were observed for isopropyl derivative **211** include [4+2] cycloaddition with excess ynamine to afford the symmetric product **212**, and self-dimerization to afford **213** and **214**, resulting from cyclization with unreacted **205**. Diene derivative **215** could be observed to undergo cycloaddition with unreacted **205** or addition of methanol across the diene system.[67] Unfortunately, the majority of the reactions involving **205** were low-yielding.

Huisgen[68] has studied the cycloaddition of ynamine **218** with **222**. At room temperature, **222** exists in equilibrium (Scheme 54) with dipolar isoquinolinium **221** and carbon disulfide, and was expected to undergo dipolar cycloadditon of **221** with ynamine **218**. Instead, carbon disulfide underwent cycloaddition with **218**, and the ring- opened thioketene **220** served as a dipolarophile for **221**. Intermediate **223** may undergo either *S*- addition to afford **224**, or *C*-addition to furnish **225**, the outcome of which was observed to favor **225** for reactions where excess CS_2 was introduced.[69]

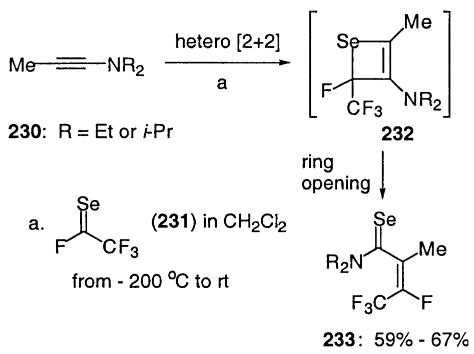
Nakayama[69] has synthesized diselenide **226** (Scheme 55) in



Scheme 54.



Scheme 55.



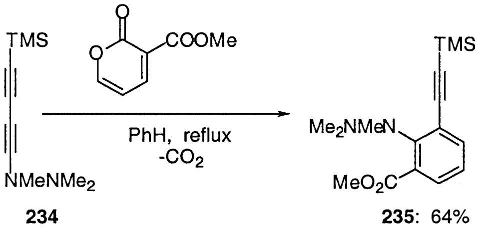
Scheme 56.

81% yield, analogously to his disulfides (Scheme 51)[65] from bis-ynamine and elemental selenium. Further reactions of **226** showed that transposition of a selenium atom for oxygen afforded the amide **227** upon treatment of **226** with peroxide. In addition, **226** could serve as a diene for a [4+2] cycloaddition with DMAD, where 1,4-diselenin **228** extrudes selenium to afford Se heterocycle **229** in good yield.[69]

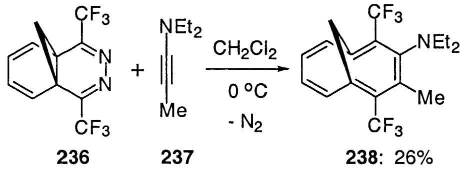
Grobe[70] (Scheme 56) has utilized selenocarbonylfluoride **231** in a regiospecific [2+2] cycloaddition with ynamines **230**. Adduct **232** is not observable by NMR measurements, and undergoes fast ring-opening in a stereoselective fashion to afford the selenoacrylamides **233**, where the *cis* relationship between the F and CH_3 was determined by X-ray analysis.[70]

2.2.2.3. [2+4] Cycloadditions

2.2.2.3.1. Formation of carbocycles. Himbert's[22a] ynehydrazine **234** has been used in a cycloaddition reaction with an α-pyrone (Scheme 57), to afford the decarboxylated adduct **235**. Himbert observed that this reaction was extremely sluggish at ambient temperature (10 days, still incomplete), and only after elevating the temperature to 80°C was the reaction efficient.[22a]



Scheme 57.



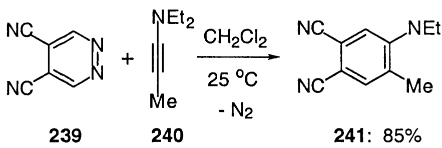
Scheme 58.

Two cyclization studies have been reported where cycloaddition is accompanied by loss of N_2. Seitz's cyclization[71] of ynamine **237** with the diazadiene-substituted propellane **236** proceeds in moderate yield to afford the 1,6-methano[10]annulene **238** upon loss of N_2 (Scheme 58). Turchi and Nesi[72] have reported the synthesis of aniline **241** by a comparable cycloaddition between **240** and dicyanopyridazine **239** (Scheme 59).

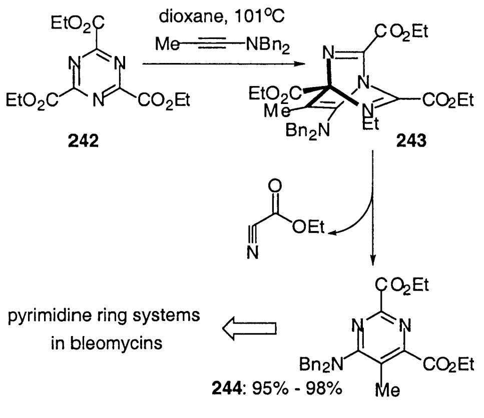
2.2.2.3.2. Formation of N- and P-heterocycles. In the total synthesis of bleomycin A_2 and analogues,[73] Boger utilized the cycloaddition of **242** with a dibenzyl ynamine to construct the pyrimidine core of the natural product (Scheme 60). To drive the reaction, optimal conditions used a polar solvent (dioxane) and high temperature, in order to aid the subsequent loss of ethyl cyanoformate.

Padwa has shown that the 1,4-dipolar cycloaddition[74] of ynamine with cross-conjugated heteroaromatic betaines **245** also proceed in high yield to afford the 2-pyridones **247** upon loss of COS from precursors **246** (Scheme 61).

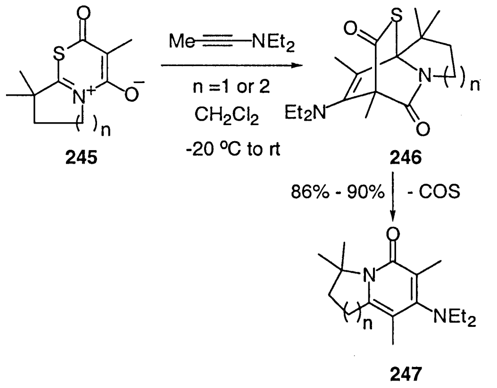
Iwamoto[75] has extensively studied the reaction of 1-substituted phthalazines **248** with ynamines. The reaction pathways varied according to the substituent at C1. For the case



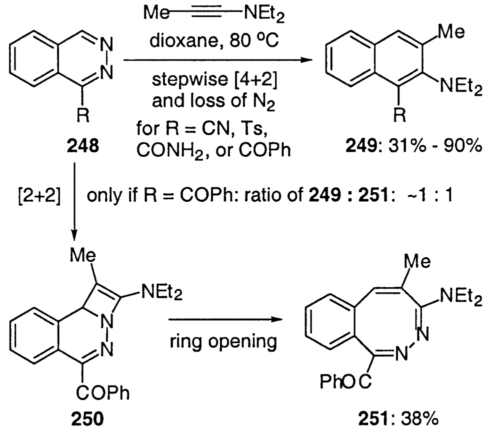
Scheme 59.



Scheme 60.

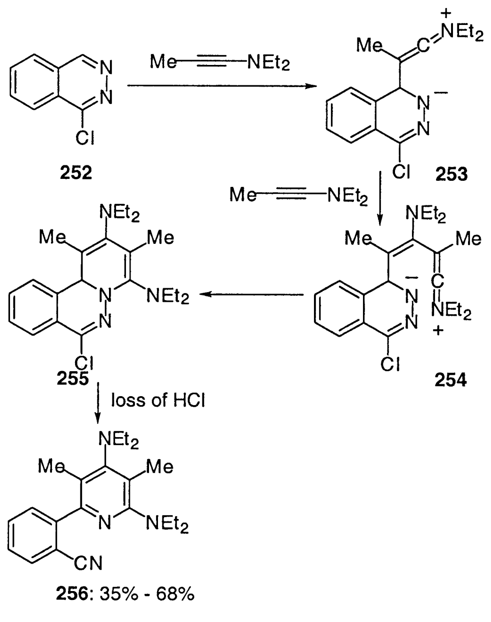


Scheme 61.

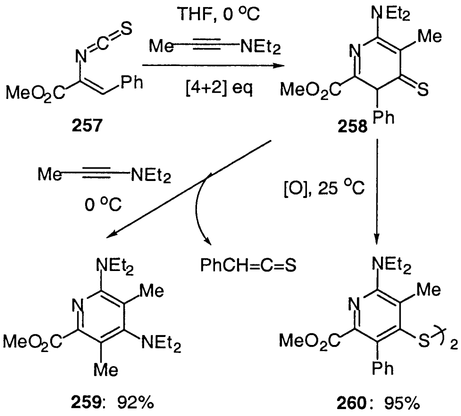


Scheme 62.

of nitrile, tosyl, and carboxamide substitution (Scheme 62), the 2-aminonaphthalene products **249** were exclusively observed in 57–90% yield,[75b] via a [4+2] cycloaddition/ N_2 loss (Type A).



Scheme 63.



Scheme 64.

In the case of the phenyl ketone [2+2] cycloaddition (Type B) competed with Type A cycloaddition. This reaction was chemoselective for the N3–C4 double bond. Following ring opening, the eight-membered ring product **251** was isolated along with the Type A cycloadduct in a nearly 1:1 ratio.

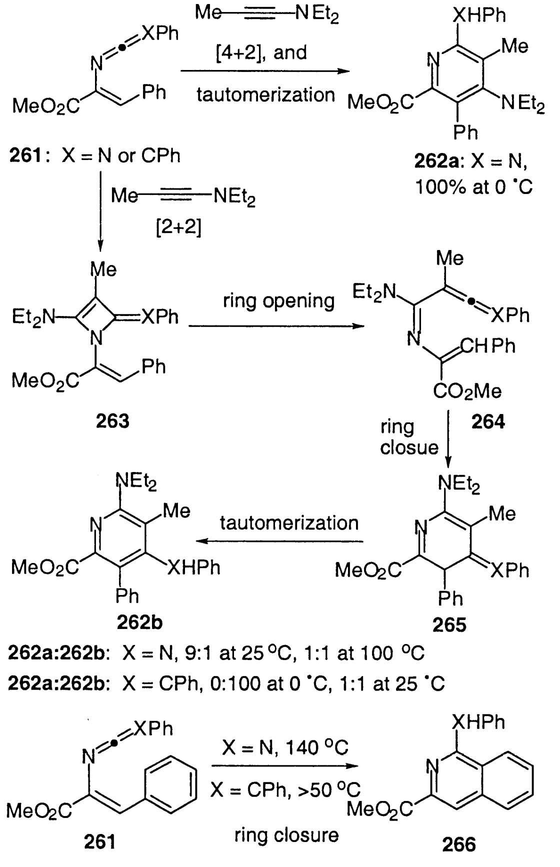
In the case of halogenated phthalazine **252**, another pathway (Type C) was observed (Scheme 63).[75a] The treatment of **252** with two equivalents of ynamine afforded the biaryl adduct **256**. The proposed pathway for formation of **256** involved addition of the ynamine to C4 of the phthalazine. This was followed by incorporation of the second equivalent of ynamine (**253**→**254**).

The ketene-immonium ion **254** undergoes intramolecular cyclization and subsequent N–N bond cleavage with concomitant loss of HCl to give **256**. Iwamoto has expanded this chemistry to other fused pyridazines, to form a variety of heterobiaryls (thiazoyl-, furanyl-, pyrrolyl-, and indolyl-pyridyl biaryls).[75a,b,f]

N-Vinylisocyanate **257** has been found to undergo one of two domino reactions[76] (Scheme 64) to construct substituted pyridines **259** or **260**. When a solution of **257** is treated with ynamine, cycloaddition to form the thione **258** is observed. Depending upon the reaction temperature, **258** will either undergo a second cyclization with ynamine to form the diaminopyridine **259**, or will be oxidized to the dimeric disulfide; in either case, high yield is observed.

Barluenga et al.[77] have also studied the reaction of ynamines with *N*-vinyl carbodiimides (**261**, X=N) and *N*-vinyl ketenimines (**261**, X=CPh) (Scheme 65). Three competitive processes were observed, and were found to be largely temperature and substrate dependent. For carbodiimide **261** (X=N) at 0°C, the [4+2] cyclization product **262a** is the sole product observed.

At elevated temperatures, [2+2] cyclization becomes competitive, giving ratios of **262a**:**262b** of 9:1 and 1:1 at 25 and 100°C, respectively. When the reaction is conducted in xylenes at reflux, a third process is observed, and isoquinoline **266** is obtained in 100% selectivity and yield.[77] Ketenimine **261** (X=CPh) shows a different temperature profile. The [2+2] cycloadduct **262b** is favored at low temperature while an equal amount of **262a** and **262b** are

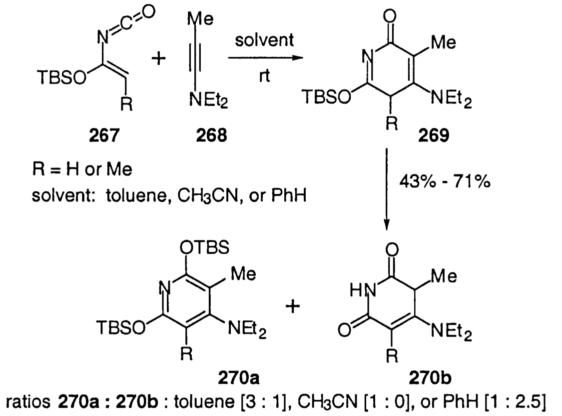


Scheme 65.

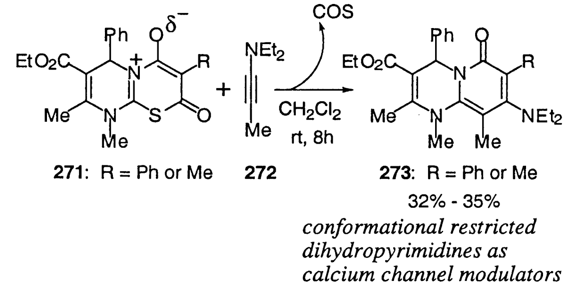
formed at 25°C. Isoquinoline adduct **266** is again formed at elevated temperatures, in this case requiring only >50°C.[77]

Ghosez[78] has found that isocyanates **267** undergo rapid cycloaddition (Scheme 66) with **268** to afford a mixture of [4+2] adducts **270a** and **270b**. Presumably, **270a** and **270b** result from the aromatization and tautomerization of **269**, respectively.

Kappe has investigated[79] the utility of ynamine **272** in the synthesis of conformationally restricted dihydropyrimidines **273**. The dipolar cycloaddition of **272** with betaine **271** proceeds under mild reaction conditions with loss of COS, affording **273** in moderate yield (Scheme 67).



Scheme 66.



Scheme 67.

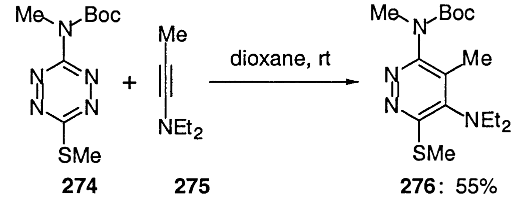
The regioselective cyclization between tetrazine **274** and ynamine **275** was reported by Boger. Interestingly, adduct **276** was obtained only after **274** was functionalized as the *N*-methyl derivative (Scheme 68).[80]

Babaev[81] found that the ynamine **278** underwent [4+2] cycloaddition with indolizidine **277**, to afford the *N*-oxide **279** (Scheme 69). This result was somewhat unexpected, as **277** is known to undergo [8+2] cycloadditions with other dienophiles.[81]

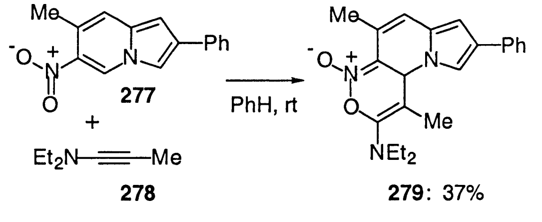
Nesi has observed that oxazoles **280** undergo a series of hetero cyclizations (Scheme 70) with **281** to afford the fused oxazolo[4,5-*c*]isoxazoles **284** in good yields.[82] Bicycles **284** were obtained as single diasteomers, suggesting a concerted retro-hetero[4+2] process versus a diradical ring opening.

Regitz et al. have studied cyclization[83] reactions of 1,3-diphosphacyclobutadienes and found that reaction of **286** (prepared in situ from **285**) with bis(diethylamino)acetylene (Scheme 71) affords the Dewar-1,3-diphosphabenzene **287**, whose structure was confirmed by X-ray analysis of the tungsten complex.

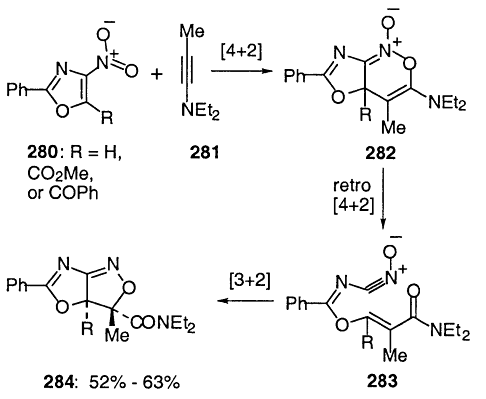
2.2.2.3.3. Formation of oxygen heterocycles. Dell[28] has found that push–pull ynamines undergo hetero [4+2]



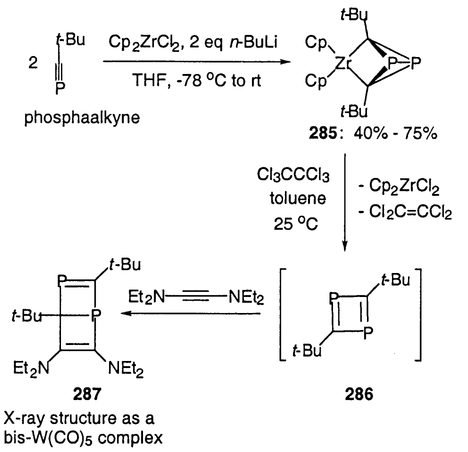
Scheme 68.



Scheme 69.



Scheme 70.

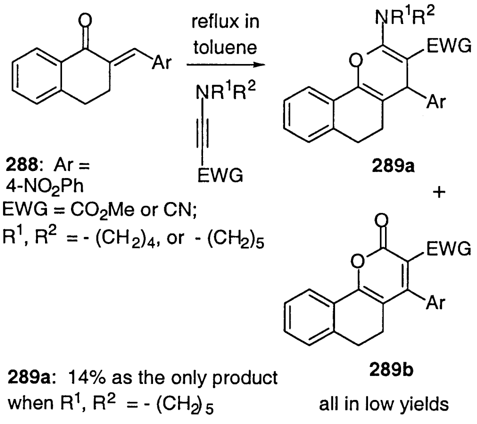


Scheme 71.

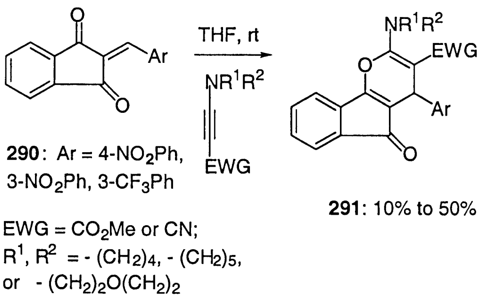
cycloadditions with tetralone **288**, to give a mixture of pyrans **289a** and **289b** in low yield (Scheme 72).

By switching to a more reactive heterodiene (**290**, Scheme 73), pyrans **291** were generated in sufficient yield to allow for structure–activity relationship studies to determine that the adducts had poor biological activity.

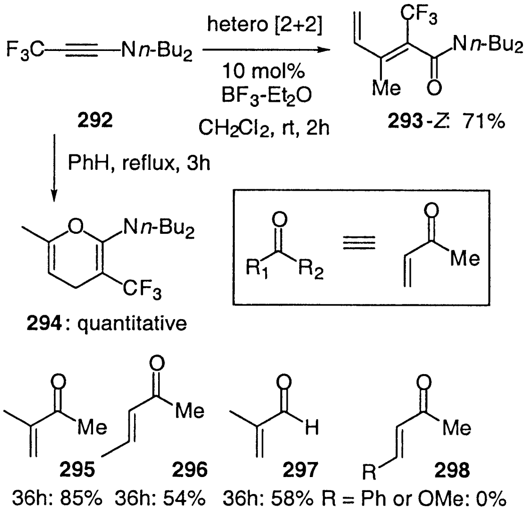
In contrast to their behavior in the presence of Lewis acids[64] where [2+2] cycloadducts were formed (Scheme 50), Ishihara found that hetero [4+2] cycloadducts were formed in the absence of Lewis acid catalysts (Scheme 74).[84] Substituted methyl vinyl ketones **295** and **296** gave reduced yields of dihydropyrans, as did methacrolein. Attempts to cyclize heterodienes **298** afforded no dihydropyran products.



Scheme 72.

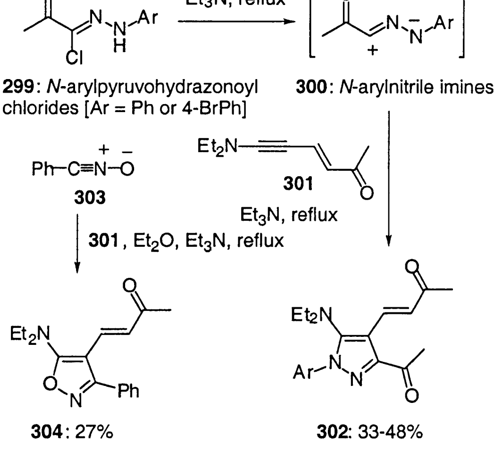


Scheme 73.

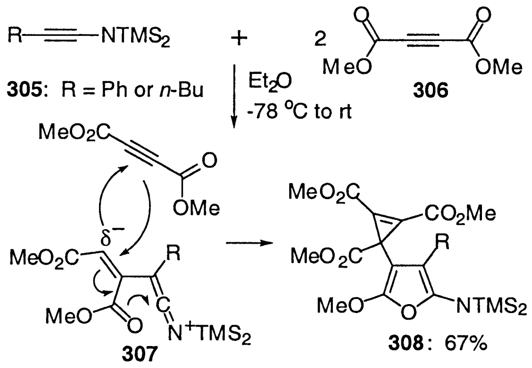


Scheme 74.

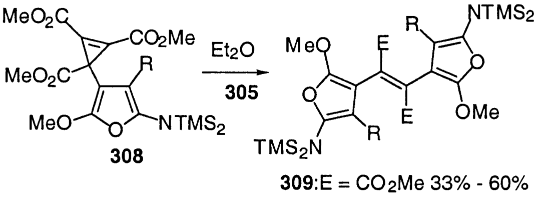
2.2.2.4. [3+n] Cycloadditions. Generation of dipolar *N*-arylnitrile imines **300** from **299** allowed Sukhova et al.[85] to generate pyrazoles **302** from push–pull ynamine



Scheme 75.



Scheme 76.



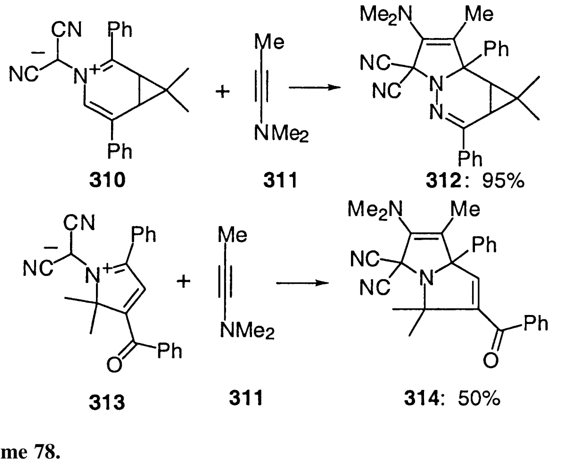
Scheme 77.

301 (Scheme 75). Complete regioselectivity was observed in the cyclization reaction. In a similar fashion, the use of nitrile oxide **303** provided isoxazole **304**.

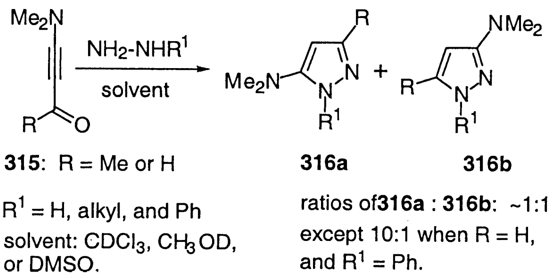
Würthwein[55] has demonstrated how silylated ynamines **305** can undergo a sequential addition to two equivalents of **306** (Scheme 76), generating the novel furan/cyclopropene adduct **308** in good yield.

This reaction may be envisioned as occurring via addition of **305** to the acetylene fragment of **306**. The resultant iminium **307** can then undergo cyclopropanation of another electron-poor alkyne, with concomitant furan formation. Probing these substrates further (Scheme 77), Würthwein[55] demonstrated that **308** could undergo reaction with a second equivalent of **305**, to generate the symetrical olefin **309**.

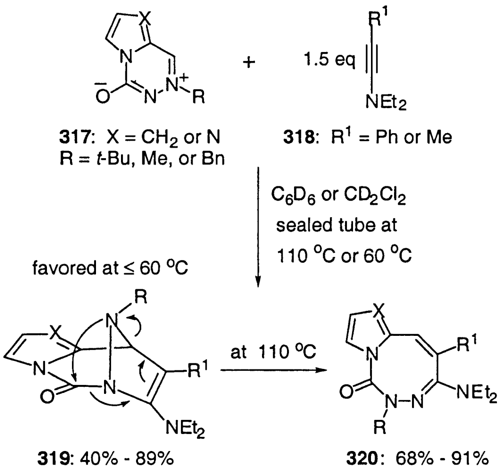
Sauer[86] has utilized ynamine **311** as a dipolarophile in reactions with bifunctional dipolar-azadienes **310** and **313**. In both instances the [3+2] cycloadducts were isolated (Scheme 78).



Scheme 78.



Scheme 79.



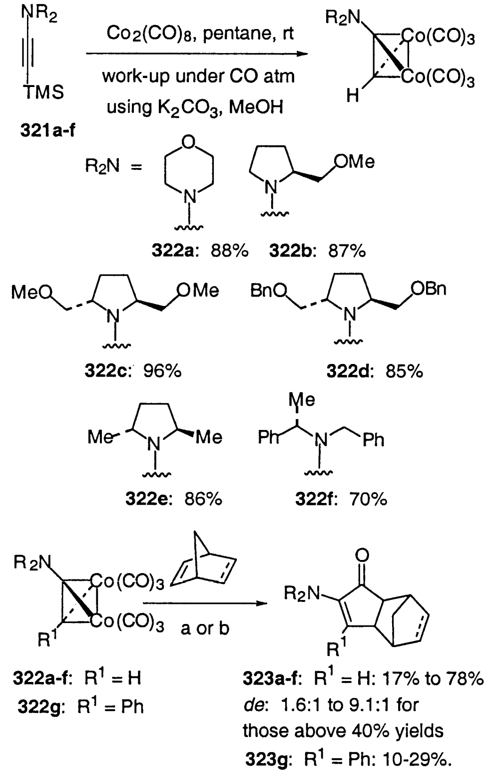
Scheme 80.

The reaction of push–pull ynamine **315** with hydrazines[87] (Scheme 79) was studied spectroscopically by Zakhartsova et al. Competitive cyclization to form isomeric pyrazoles **316a** and **316b** was found to be only moderately effected by the hydrazine substitution, except in the case of phenyl hydrazine, which gave a 10:1 ratio of **316a**:**316b**. It was determined that addition of the hydrazine occurred first at the ketone, rather than initial addition to the alkyne.[87]

Cyclization of betaines **317** with ynamines **318** by Komatsu[88] allowed for the construction of either bridged tricycles **319** or the thermally rearranged fused bicyclic adducts **320** (Scheme 80). Tricycles **319** were isolated as major products when the reaction was carried out at lower temperature, and **319** was isolated in 89% when the reaction was conducted at room temperature for one of the examples.[88]

2.2.2.5. Metal mediated cycloadditions

2.2.2.5.1. [2+2+1] Cycloadditions. Pericàs' elegant utilization of chiral ynamines **321** in Pauson–Khand reactions[21] involves complexation of the ynamine as the dicobalt hexacarbonyl complex directly during their synthesis (Scheme 81). Complexes **322** were notably stable, could be stored under CO atmosphere for months, and withstand chromatographic purification. Pauson–Khand reaction of **322** with norbornene or norbornadiene

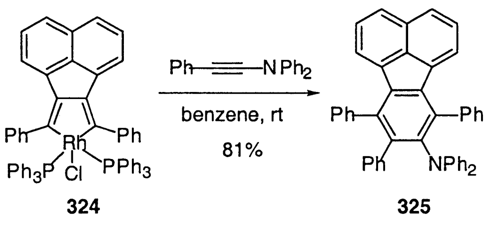


a. toluene, at -30 °C, 0 °C, or rt
b. NMO, CH_2Cl_2, at -20 °C or -30 °C

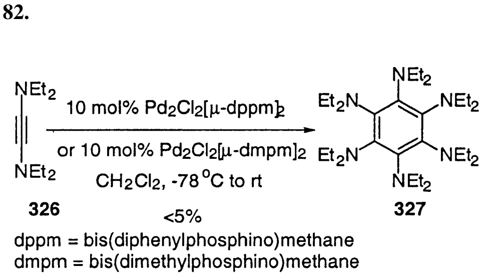
Scheme 81.

afforded the cycloadducts **323** as mixtures of diastereomers (dr=1.6:1 to 9.1:1 for yield >40%).

2.2.2.5.2. [2+2+2] Cycloadditions. Neidlein[89] has utilized triphenyl ynamine in a Rh-mediated [2+2+2] cycloaddition (Scheme 82) to afford the fluoranthene derivative **325** in excellent yield. Davies[90] has reported the isolation of hexakis(diethylamino)benzene (**327**) as a minor component from the reaction of bisynamine **326** and palladium (I) complexes (Scheme 83).

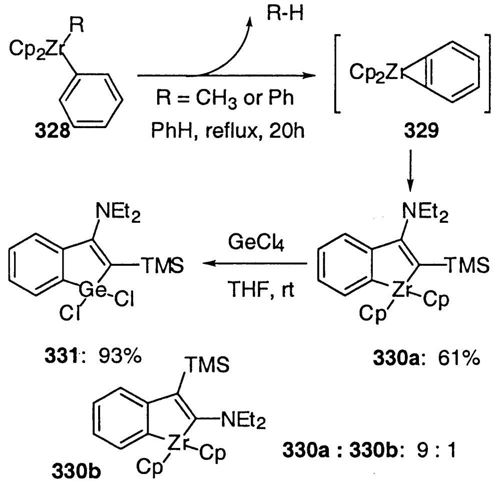


Scheme 82.

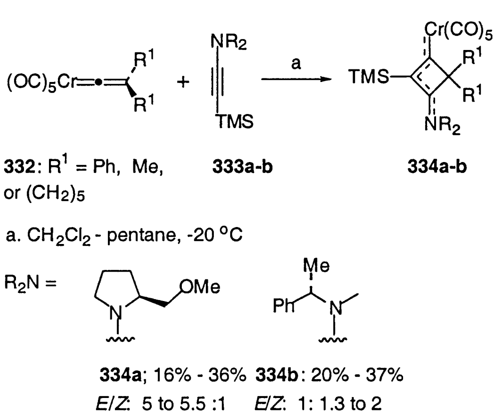


dppm = bis(diphenylphosphino)methane
dmpm = bis(dimethylphosphino)methane

Scheme 83.



Scheme 84.

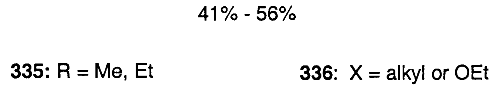


a. CH_2Cl_2 - pentane, -20 °C

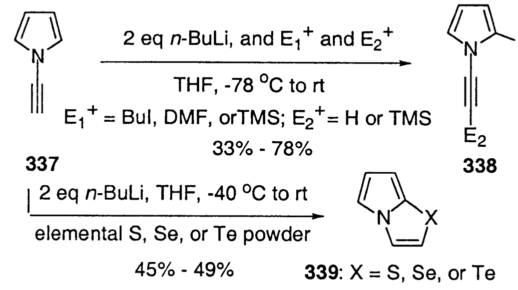
Scheme 85.

2.2.2.5.3. Other cycloadditions. Two other reactions of ynamines with transition metals have been reported which generated cycloadducts. Gautheron[91] has shown how zirconacycle **329** can incorporate an ynamine (Scheme 84) to generate the zirconaindenes **330a** and **330b**, and the subsequent germaindene **331**. A 9:1 regioselectivity is observed in the ynamine insertion. Fischer[19,92] has explored the reaction of allenylidene metal complexes **332** with chiral ynamines **333** and has isolated the cyclobutenylidene complexes **334** in modest yield along with ring-opened pentatrienylidene complexes (Scheme 85).

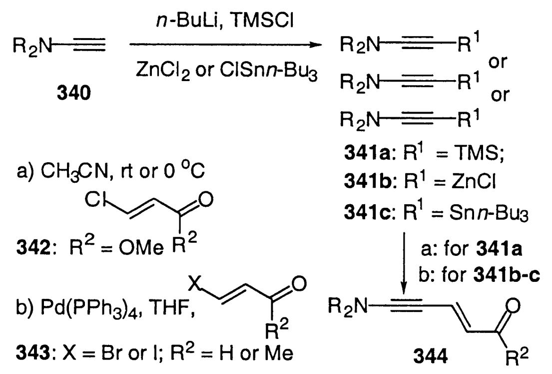
2.2.3. Functionalizations. Lukashev[45] has synthesized the phosphorous-containing ynamines **336** by in situ trapping with chlorophosphines (Scheme 86). Brandsma[93] has found that treatment of ethynylpyrrole (**337**) with two equivalents of *n*-butyl lithium generates a dianion which can be selectively trapped with an electrophile to afford the



Scheme 86.



Scheme 87.



Scheme 88.

2-substituted pyrrole (Scheme 87). When trapped with elemental S, Se, or Te, the bicyclic heterocycles were formed.

Neuenschwander[24,29] has utilized un-substituted ynamine **340** as a starting material for the synthesis of a variety of substituted ynamines (Scheme 88). Silylated or metallated ynamines **341** are then coupled to haloenones by either thermal or palladium(0) mediated conditions to afford a variety of push–pull ynamines.

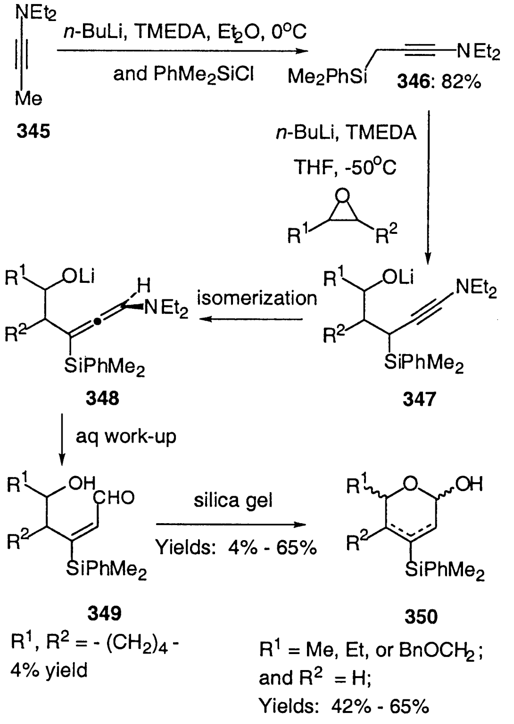
Finally, Schaumann[94] has utilized deprotonated γ-silylated ynamine **346** as a nucleophile to open epoxides (Scheme 89). Upon aqueous workup, the pyranols **350** are isolated in moderate yield. With cyclohexene oxide the intermediary hydroxy-aldehyde **349** was isolated in 4% yield.

3. Part II—Ynamides

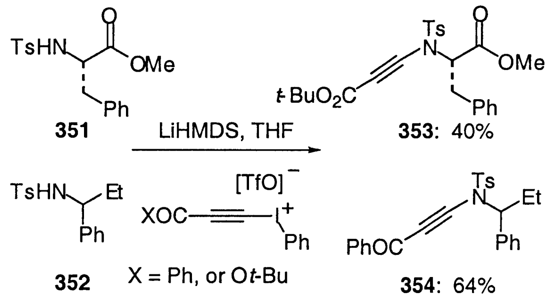
3.1. Synthesis of ynamides

3.1.1. Synthesis of chiral ynamides. In 1996, Feldman[95] and coworkers accomplished the first synthesis of a chiral ynamide since Novikov's[18] work. The authors utilized iodonium triflate salts, reacting them with α-substituted ethyl-tosylamides **351** and **352** (Scheme 90). They obtained the ynamides **353** and **354** as undesired products in moderate yields in their attempts to synthesize pyrrole and indole targets.

Witulski[96] utilized iodonium triflate salt **355** in reactions with various electron-deficient amines to provide ynamides **356** in good to excellent yields (Scheme 91). Ynamides **356** are Pauson–Khand precursors. The electon-withdrawing group on the nitrogen atom served as a protecting group as well as a means of tuning the electron density of the ynamine.

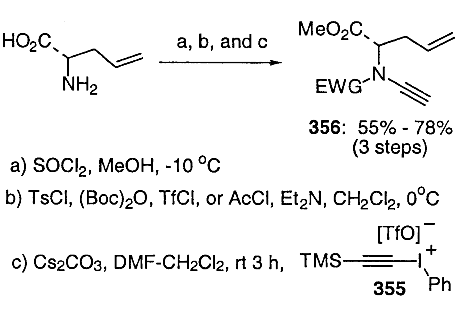


Scheme 89.

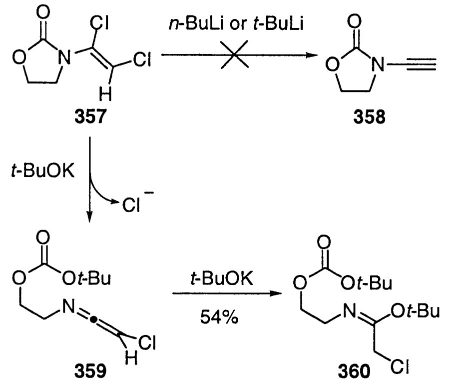


Scheme 90.

Hsung[97] et al. recently published an attempt to form a ynamine via the elimination of dicholoroenamine **357**, similar to other work previously reported[6–11] (Scheme 92). This method failed to yield the desired ynamine **358**, but instead



Scheme 91.

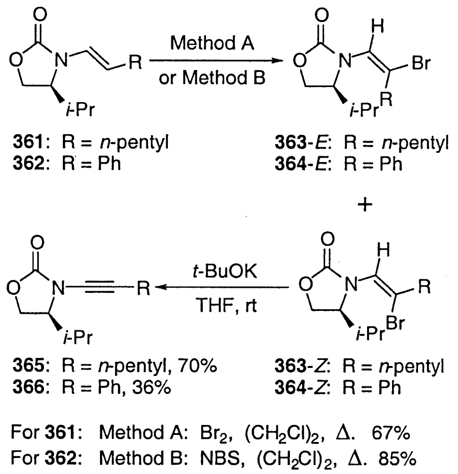


Scheme 92.

gave **360** in 54% yield. Presumably **360** comes from attack of *t*-BuOK on chloroketimine **359**.

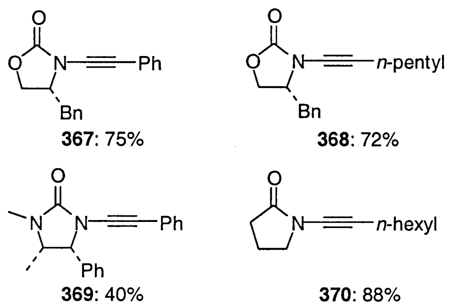
The authors embarked on a protocol of β-bromination of enamides followed by elimination of the (*Z*)-β-bromoenamides such as that used by Dell[28] (Scheme 13) previously in their ynamine synthesis.

It was found that by either refluxing enamide **361** with bromine in 1,2-dichloroethane (Method A in Scheme 93), or refluxing enamide **362** with *N*-bromosuccinimide (NBS) in 1,2-dichloroethane (Method B), the desired bromoenamides **363** and **364** could be prepared in good yields. Method A provided **363** with an *E*/*Z* ratio of 1:8; Method B favored the **364**-*E* isomer with an *E*/*Z* ratio of 1.5:1. These ratios were typical for bromination of other substrates.

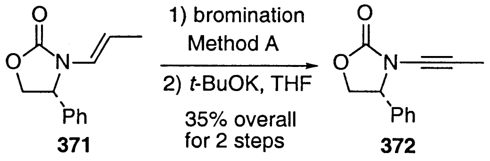


For **361**: Method A: Br_2, $(CH_2Cl)_2$, Δ. 67%
For **362**: Method B: NBS, $(CH_2Cl)_2$, Δ. 85%

Product Chart



Scheme 93.



Scheme 94.

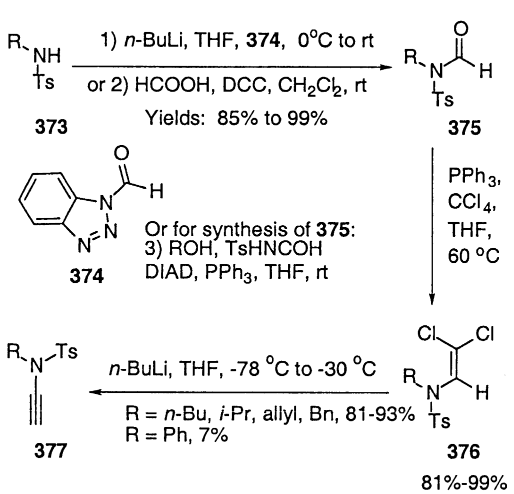
Method A appears to work well when the substituent R is alkyl, while Method B only works well when R is aromatic. Subsequent treatment of the *Z*-bromoenamides **363**-*Z* and **364**-*Z* with *t*-BuOK in THF yielded ynamides **365** and **366** in 70 and 36% yield, respectively. Ynamides **367–370** were synthesized in moderate to excellent yields using this protocol.

All efforts to eliminate the *E*-bromoenamides failed. These ynamides are quite stable to hydrolysis and can survive silica gel chromatography. Presumably they should retain sufficient reactivity to be utilized in various addition and cycloaddition reactions.

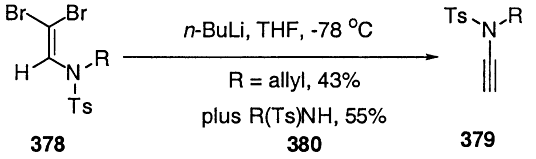
Recently, Hsung[97] reported the first synthesis of ynamine **372**, the first chiral, electron-deficient variant of Ficini's *N*,*N*-diethyl-1-amino-1-propyne. Ynamine **372** was prepared in 36% overall yield from chiral enamide **371** (Scheme 94). The modest yield is due in part to poor bromination selectivity, yielding the β-bromoenamides in a 1:2 *E*/*Z* ratio. Ynamide **372** also displays an apparent increased sensitivity to hydrolysis during elimination and chromatography compared to ynamides **365–370**.

3.1.2. Synthesis of achiral ynamides

3.1.2.1. Elimination protocols. Brückner[98] recently published a facile elimination method for the synthesis of achiral tosyl-ynamides (Scheme 95). Formamides **375** are derived from tosyl-amines **373** via deprotonation and treatment with formyl benzotriazole (**374**), or DCC coupling with formic acid. Alternatively formamides **375** can be



Scheme 95.



Scheme 96.

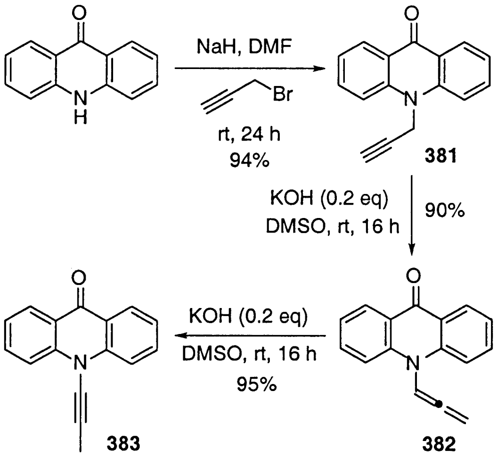
prepared directly from the reaction of an alcohol and tosylformamide under Mitsunobu conditions.

Treatment of tosyl-formamides **375** with triphenylphosphine and carbon tetrachloride leads to dichlorovinylamides **376** in excellent yield. Subsequent elimination with *n*-BuLi at low temperature yielded various alkyl, alkenyl, and aryl functionalized tosyl-ynamides **377** in 80–97% yield. The benefits of this method include its amenability to scale-up and the avoidance of potentially explosive iodonium triflate salts.

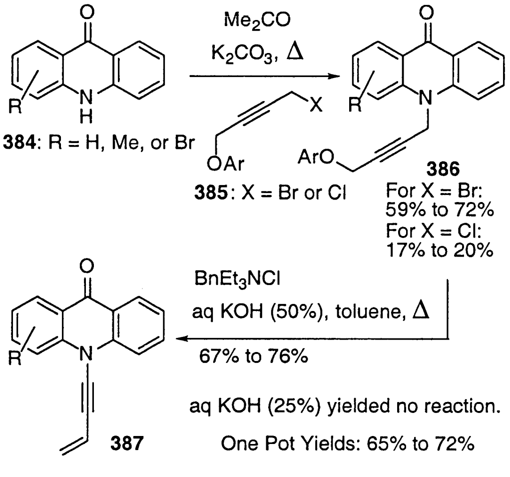
Brückner's[98] initial studies with the dibromovinyl amides such as **378** (Scheme 96) were unsatisfactory as reaction with *n*-BuLi resulted in mixtures of ynamides **379** and starting tosylamides **380**.

Zaugg[3] originally reported the synthesis of vinylogous ynamide **383** in 1958; since then several syntheses have been reported including one by Katritzky,[99] and most recently Hsung,[100] who improved on the efficiency of the reaction (see Scheme 97). Deprotonation and propargylation of acridone yielded compound **381**. Isomerization to ynamide **383** via the intermediate allenamide **382** was accomplished in 80% overall yield. This stable, crystalline vinylogous ynamide is easily accessible, and the ynamide moiety possesses good reactivity for cycloaddition reactions outlined in Section 3.2.2.1.

Majumdar[101] has done related work on biologically interesting acridone systems. The authors alkylate substituted acridones **384** with propargyl halides **385**, yielding propargylated acridones **386** (Scheme 98). Isomerization of the propargyl group is affected by KOH under phase-transfer conditions affording the vinylogous enynamides **387**.



Scheme 97.

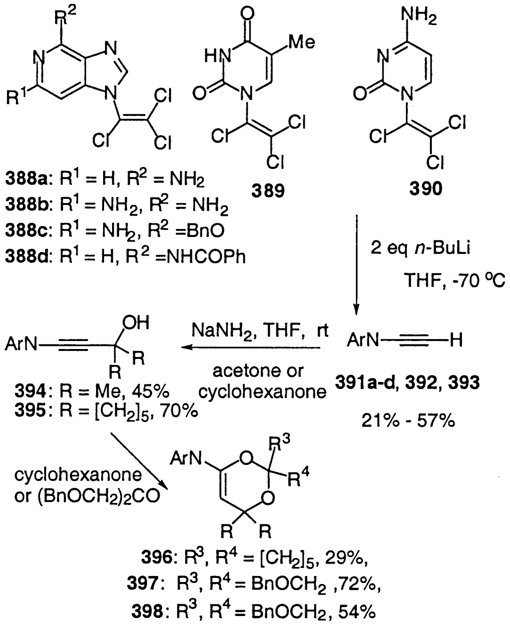


Scheme 98.

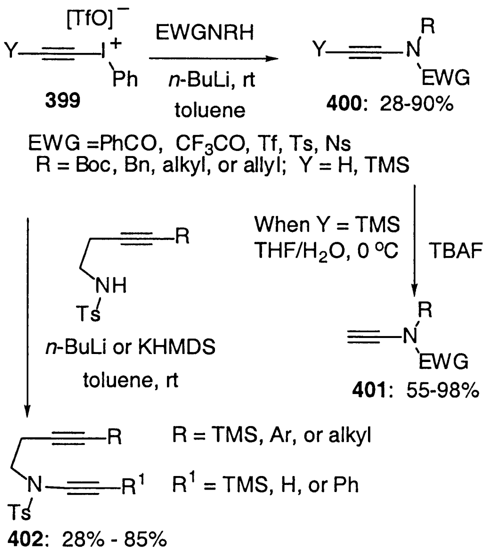
More impressively, the authors found that the 2-step sequence can be carried out in one pot utilizing chloro-substituted 1-aryloxy-but-2-ynes to give 10-enynyl acridones **387** in one-pot yields ranging from 65 to 72%. The reactivity of these interesting enyne systems was not further investigated.

Zemlicka and coworkers[102] prepared numerous ynamines derived from nucleic acid bases. Such compounds can serve as synthetic intermediates for the preparation of new therapeutic analogues. This includes their use in the synthesis of polyacetylene polymers for the inhibition of RNA polymerase and other biological functions.

Chloroenamines **388a–d**, **389**, and **390** were prepared in moderate yields from the reaction of deprotonated purine or pyrimidine bases with tetrachloroethylene (Scheme 99). Treatment of **388–390** with *n*-BuLi at low temperature afforded the respective ynamines **391a–d**, **392**, **393** in



Scheme 99.



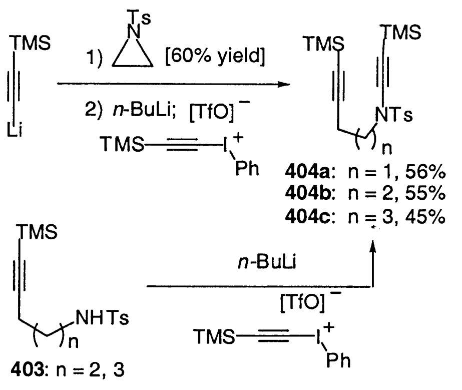
Scheme 100.

44–57% yields, with the exception of the 2-amino-6-benzyloxypurin-N^9-yl ynamine **391c** (21%).

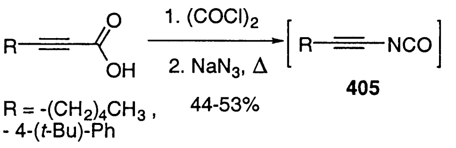
The sodium salt of ynamide **391a** reacted with acetone to give carbinol **394**, but the reaction of cyclohexanone with **391a** furnished some cyclized product **396** as well as carbinol **395**. Interestingly, neither pyrimidine nor purine ynamines **391a** or **392** reacted with dibenzyloxyacetone to afford carbinols regardless of reaction conditions, but gave only cyclic ketals **397** and **398** in 72 and 54% yield, respectively.

3.1.2.2. Alkynyliodonium salts. Witulski[103] has utilized iodonium triflate salts **399** in the synthesis of a variety of electron-deficient ynamines **400** (Scheme 100), when Y=TMS, deprotection with tetrabutylammonium fluoride (TBAF) yielded the terminal ynamines **401**. Diynes **402** can also be synthesized via this route in variable yields. These diyne precursors are poised for intramolecular cycloaddition reactions.

Rainier and Imbriglio[104] have combined the use of iodonium triflate salts and *N*-tosyl aziridines for the formation of diyne ynamide **404a** (Scheme 101). When *n*>1 (**404b,c**), *N*-tosyl alkynes **403**, derived from Mitsunobu coupling of protected *N*-tosyl amines with yn-1-ols, were utilized. These versatile diynes can be utilized in a variety of inter- and intramolecular cycloaddition reactions.



Scheme 101.

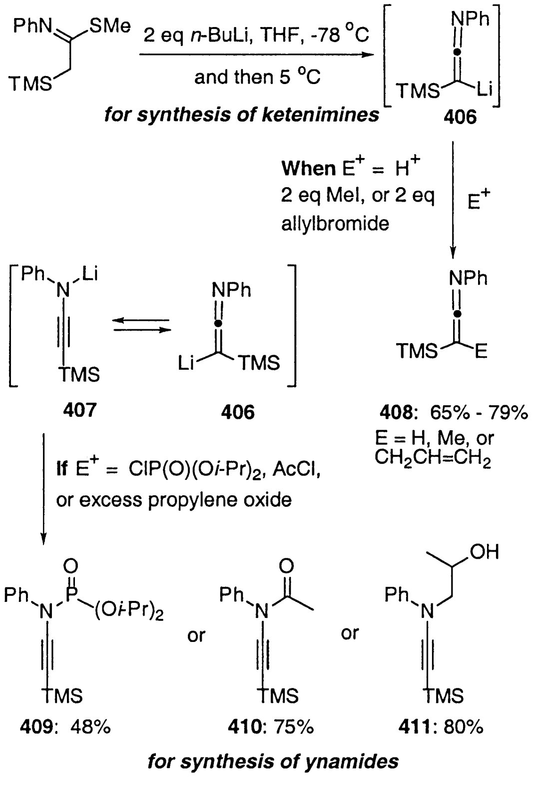


Scheme 102.

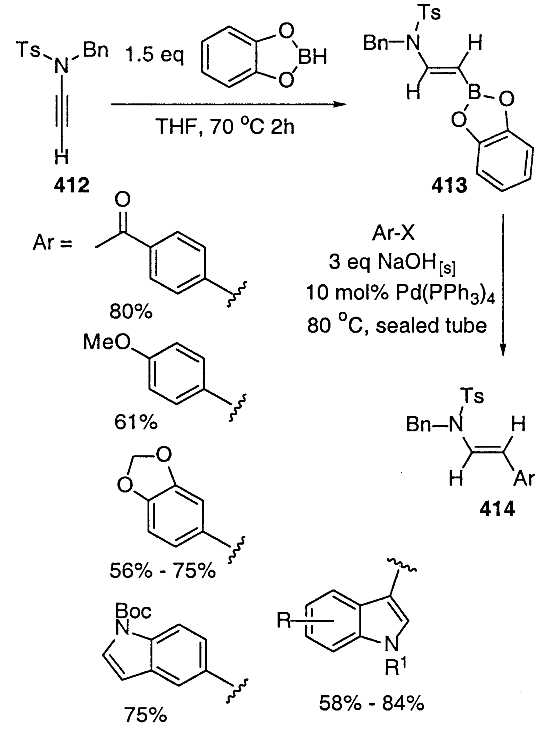
3.1.2.3. Other methods. Chen[105] has synthesized a variation of ynamides known as alkynyl isocyanates. The isocyanates **405** are prepared from 2-octynoic- and 3-[4-(*t*-butyl)phenyl]prop-2-ynoic acids via their acyl chlorides (Scheme 102).

Sodium azide attack of the acyl chloride yields isolable azides, which upon heating undergo Curtius rearrangement to yield the corresponding alkynyl isocyanates **405** in 44 and 53% respective overall yields. The isocyanates are not isolable and are protected quantitatively as their $Co_2(CO)_6$ complexes in solution before further manipulation. Attempts to isolate the neat complexes resulted in the exclusive recovery of polymeric material.

Fromont and Masson[106] found that treatment of *S*-methyl-α-(trimethylsilyl)-ethanimidothiolate with 2 equiv. of *n*-BuLi at −78°C, followed by warming to 5°C, led to the formation of β-lithiated-β-silylated ketenimine **406** (Scheme 103). Ketenimine **406** is in equilibrium with *N*-lithiated ynamine **407**.



Scheme 103.

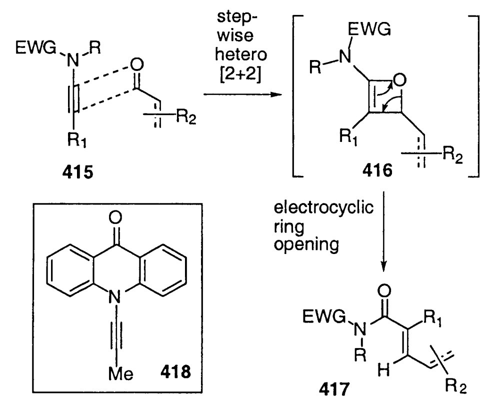


Scheme 104.

Intermediate **406** can be selectively protonated (after addition of one equivalent of propylene oxide to trap the by-product lithium methylthiolate), methylated, or allylated, yielding the new ketenimines **408**. However, treatment of the lithiated intermediate with more reactive electrophiles favored reaction at the nitrogen (**407**). Reaction at room temperature with excess diisopropyl chlorophosphate, acetyl chloride, or propylene oxide yielded ynamides **409** and **410** and ynamine **411** in good to excellent yields.

3.2. Reactions of ynamides

3.2.1. Addition reactions. Witulski[107] affected the reduction of ynamides **412** with catecholborane to give the *E*-vinylborane **413** selectively (Scheme 104). While **413** could be isolated and characterized by NMR, a one-pot procedure was utilized for a Suzuki–Miyaura[108] cross-coupling reaction of borane **413** with aryl iodides or bromides to yield the corresponding (*E*)-β-arylenamides **414** in 61–80% yield. β-Arylenamides are important structural components in a wide variety of natural products including tuberine, erbstatin, and aspergillamide.



Scheme 105.

3.2.2. Cycloaddition reactions

3.2.2.1. [2+2] and [4+2] Cycloadditions. Hsung[100] and coworkers reported the reactivity of ynamides **415** in [4+2] and [2+2] cycloaddition reactions. As shown in Scheme 105, hetero [2+2] cycloaddition reactions of ynamides **415** with aldehydes can lead to an oxetane intermediate (**416**) that would undergo an electrocyclic ring opening to give alkenes **417**.

Acridone-based ynamides **418** were very reactive toward an array of aldehydes (2 equiv.) under Lewis acidic conditions (0.1 or 0.25 equiv. of BF_3–Et_2O) to provide trisubstituted alkenes **419a–h** (see Table 1) in high yields and with high *E* selectivities.

The authors proposed that the observed stereoselectivity is a kinetic selectivity. When ynamide **418** was reacted with cyclohexane–carboxaldehyde at −80°C for 3 h only the *E* isomer of **419h** was observed. Molecular modeling (Spartan AM1) of the proposed oxetane intermediate also suggests that the ring-opening rotation leading to the *E*-alkene is favored due to steric arguments.

Under the same reaction conditions, ynamide **418** reacted with α,β-unsaturated aldehydes to give dienes **420** and **421** in excellent yields and *E*-selectivities via the hetero [2+2] pathway (Scheme 106). In contrast, hetero [4+2] cycloadduct **422** was obtained in 64% yield as the only product when methyl vinyl ketone was used. In this instance a full equivalent of Lewis acid was required to drive the reaction to completion. Compounds **420–422** represent unique synthons for further transformation.

The acridone moiety can be easily cleaved under mildly basic conditions. Treatment of alkene **419c** with 1 M LiOH at room temperature yielded hydrolysis product **423** in 90% yield with no observable isomerization. Acridone was recovered in ≥90% after acid–base workup, and thus can be recycled (Scheme 107).

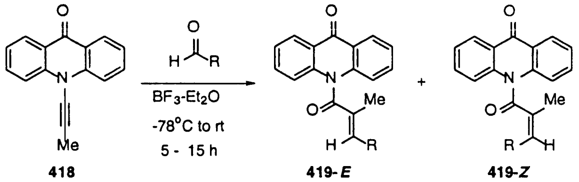
3.2.2.2. Metal mediated cycloadditions

3.2.2.2.1. [2+2+1] Cycloadditions. Schottelius[105] utilized complexed isocyanates **425** (Scheme 108), synthesized from acids **424**, in alcoholysis reactions to yield the protected alkynylcarbamates **426** in moderate yields (60–66%). If the reaction solution is not thoroughly degassed, the $Co_2(CO)_6$ complexes decomposed leading to lower yields.

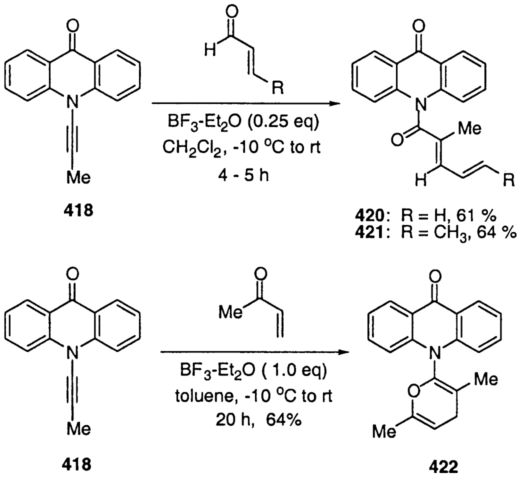
The attempted oxidative removal of the $Co_2(CO)_6$ protecting group from carbamates **426** with ceric ammonium nitrate (CAN) and conventional workup did not result in the regeneration of the alkyne, but rather in the clean production of maleic anhydride derivatives **427**.

Attempted hydrolysis of anhydrides **427** presumably

Table 1.



Entry	R	LA (equiv)	Solvent	Product	Yield (%)	Ratio (*E*/*Z*)
1	Me	0.25	Toluene	A	78	≥95:5
2	Et	0.25	Toluene	B	60	92:8
3	Et	0.25	CH_2Cl_2	B	55	95:5
4	Ph	0.10	Toluene	C	67	≥94:6
5	Ph	0.25	CH_2Cl_2	C	91	≥95:5
6	*n*-hex	0.25	Toluene	D	58	94:6
7	*n*-hex	0.25	CH_2Cl_2	D	70	≥95:5
8	$(CH_2)_4$ OTBS	0.25	CH_2Cl_2	E	53	≥95:5
9	*i*-Pr	0.25	CH_2Cl_2	F	61	95:5
10	*t*-Bu	0.25	CH_2Cl_2	G	64	95:5
11	C_6H_{11}	0.25	CH_2Cl_2	H	69	≥95:5

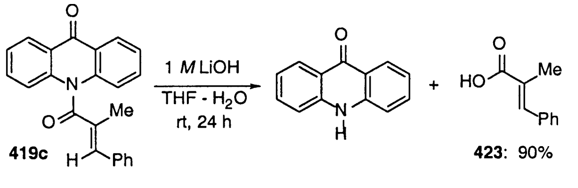


Scheme 106.

produces the diacid, which spontaneously dehydrates to the anhydride. Similar 2,3-didehydroaspartic-acid derivatives have been identified as amino acid components of various peptides, including hexapeptide mycotoxin phomopsin A.[109]

Witulski[103a] and coworkers explored the efficiency of tosyl-ynamides in Pauson–Khand reactions. The $[Co_2(CO)_6]$-alkylnylamides **429** (Scheme 109) form almost quantitatively by addition of tosyl-ynamide **428** to a solution of $Co_2(CO)_8$ in CH_2Cl_2.

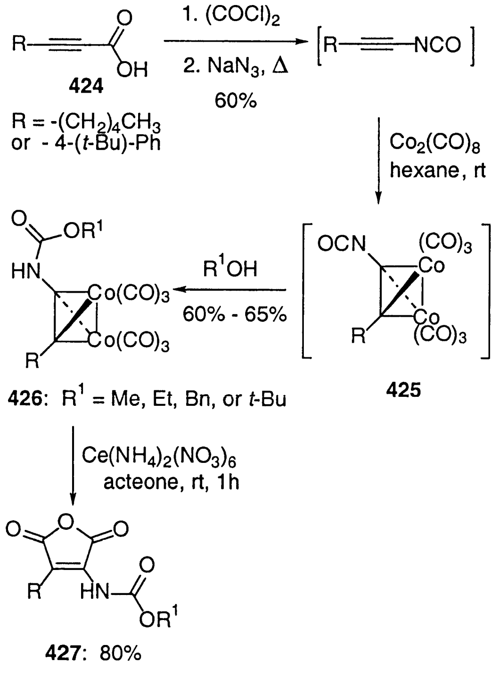
The authors report that complexes **429** can be isolated; however, they are transformed immediately to [2+2+1] cycloaddition products by adding an olefin and trimethylamine-*N*-oxide (TMANO) as a promoter. Reaction of complexes **429** with alkenes **430** under Pauson–Khand conditions afford products **431**–**436** (Table 2) in 48–98% yield. Alkenes **430e** and **430f** each give a 5:1 mixture of regioisomers.



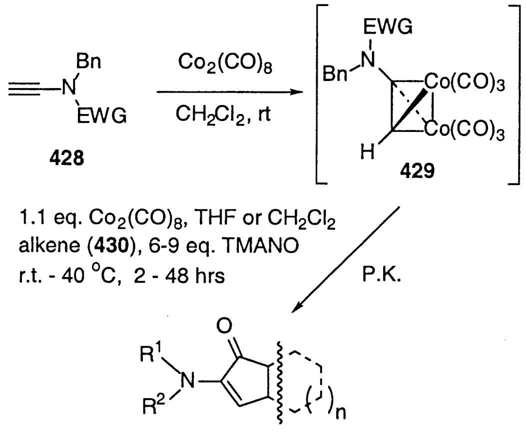
Scheme 107.

Witulski[103a] also extended the Pauson–Khand methodology to intramolecular reactions. In the presence of TMANO as a promoter, enynes **439** underwent intramolecular [2+2+1] cycloadditions to yield products **440** in 40–60% isolated yields (Scheme 110).

They found the intramolecular cycloadditions to be extremely diastereoselective for β-branched, as well as α-branched 1-alkylnylamides **439**. In all cases only one diastereoisomer was observed. These cycloadditions



Scheme 108.

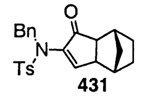
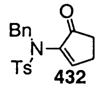
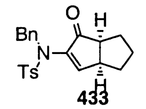
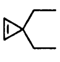
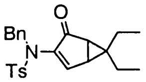
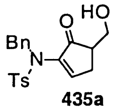
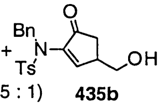
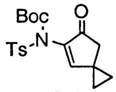
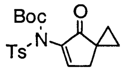
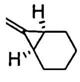
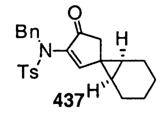
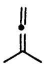
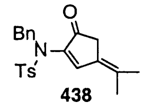


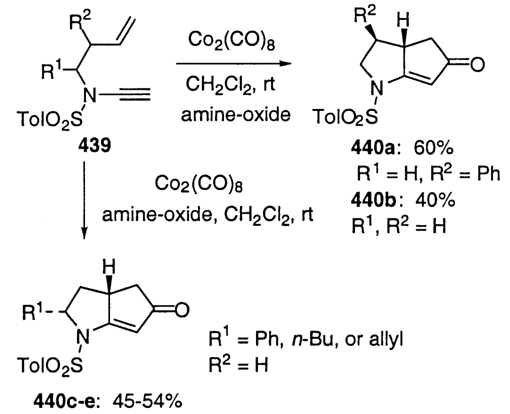
Scheme 109.

showcase a new strategy for the stereoselective synthesis of nitrogen-containing hetereocycles, albeit in modest yields for the intramolecular variant.

Witulski[96] and coworkers also investigated a series of ynamides possessing different electron-withdrawing groups (EWGs). When enynes **441** (Scheme 111) were subjected to Pauson–Khand reaction conditions, the [2+2+1] cycloaddition products **442a–d** were obtained in 60–69% yield only when EWG=Ts, Tf, and 2-pyridyl-SO_2, and in 35% yield when EWG=Ns ($4\text{-}NO_2C_6H_4SO_2$). In all cases the reaction proceeded in >95% diastereoselectivity.

Table 2.

 **430a**	 **431**	89%
 **430b**	 **432**	52%
 **430c**	 **433**	70%
 **430d**	 **434**	49%
 **430e**	 +  **435a** (5 : 1) **435b**	48%
 **430f**	 +  **436a** (5 : 1) **436b**	98%
 **430g**	 **437**	60%
 **430h**	 **438**	57%

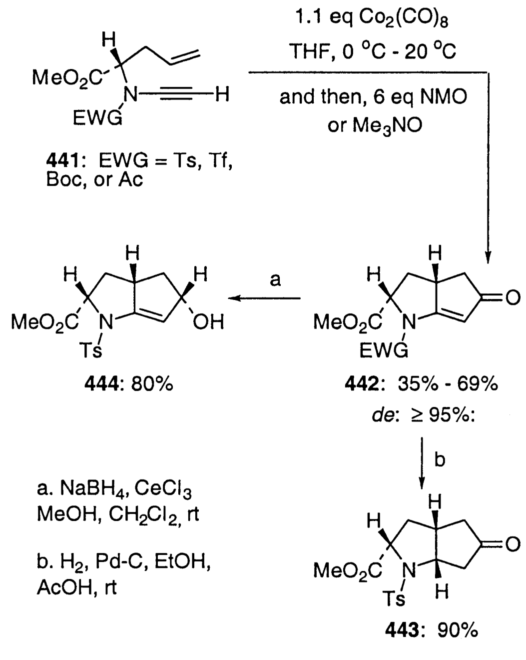


Scheme 110.

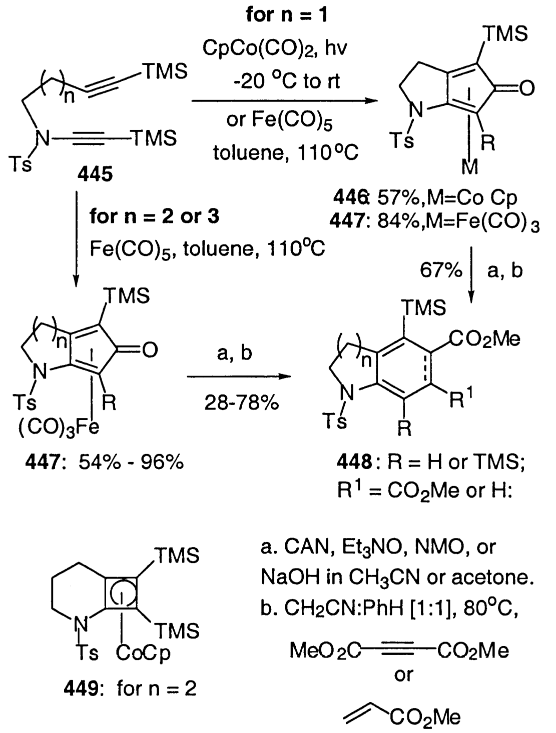
Witulski also showed that the Pauson–Khand products could be further elaborated. Compound **442a** (EWG=Ts) was stereoselectively hydrogenated to cyclopentanone **443** in 90% yield. Luche reduction of **442a** proceeded with excellent selectivity as well, giving exclusively the acid-sensitive allylic alcohol **444** in 80% yield. Through the use of the intramolecular Pauson–Khand reaction, the authors affected the stereoselective formation of various proline derivatives.

Ranier and Imbriglio[104] recently published some cycloaddition strategies utilizing *N*-tosyl-ynamines. Yne-ynamine cyclization precursors **445** (Scheme 112) were converted to the corresponding cobalt and iron cyclopentadienone complexes **446** and **447** via [2+2+1] cycloaddition reactions. The authors found it necessary to use iron when the linker *n*>1, because cobalt yielded only the cyclobutadiene complex **449** in these instances.

The cobalt complex **446** underwent decomplexation using



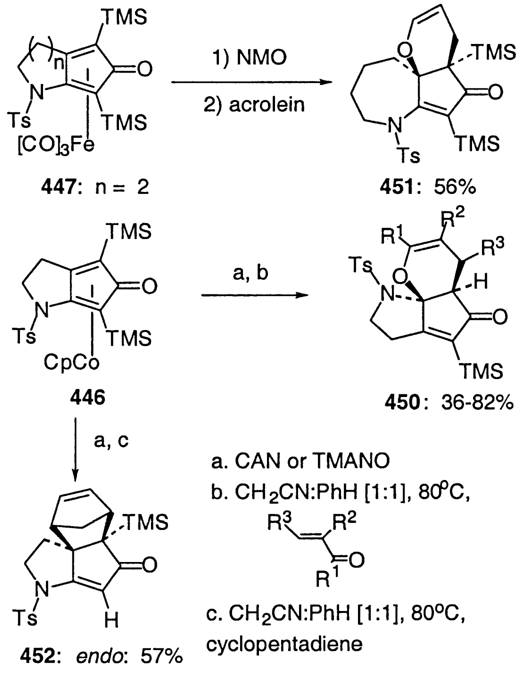
Scheme 111.



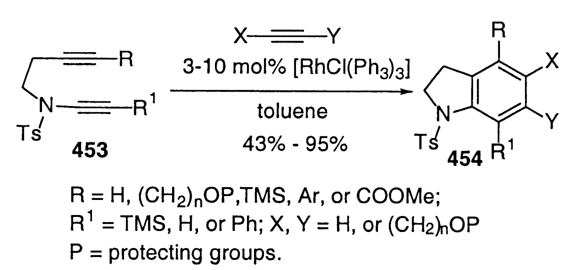
Scheme 112.

ceric ammonium nitrate (CAN) and subsequent cycloaddition with dienophiles dimethyl acetylenedicarboxylate (DMAD) or methyl acrylate to give products **448** after decarbonylation. Decomplexation of the iron complexes **447** were affected utilizing oxidants trimethylamine-*N*-oxide (TMANO), or *N*-morpholine-*N*-oxide (NMO), followed by cycloaddition with dienophiles DMAD and methyl acrylate to afford products **448**.

Rainier and Imbriglio[104] further investigated reactions of dienone complexes **446** and **447** as dienophiles in hetero-Diels–Alder cycloadditions (Scheme 113). Complexes **446** and **447** were exposed to acrolein under the previously discussed cycloaddition conditions. While the dihydropyrrole cyclopentadienone from **446** reacted exclusively at the vinylogous amide to give the hetero-Diels–Alder cycloadduct **450** in 82% yield, the azapine from the iron complex **447** reacted at the isolated enone to give **451** in 56% yield.



Scheme 113.

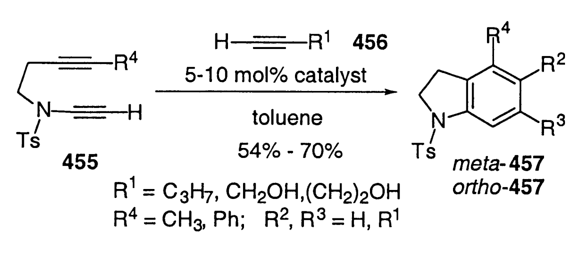


Scheme 114.

The authors also demonstrated that the reaction can be general, as **446** also reacted with methyl vinyl ketone, crotonaldehyde, and methacrolein, yielding the corresponding cycloadducts **450** in 36–74% yield. Complex **445** also reacted with cyclopentadiene to yield the endo-adduct **452** in 57% yield. The authors utilized combination of metal mediated yne-ynamine [2+2+1] cycloaddition and subsequent metal-free 3-aminocyclopentadien-ones as 4π and 2π components in chemoselective cycloaddition reactions.

3.2.2.2.2. [2+2+2] Cycloadditions. Witulski[103b] et al. report the use of yne-ynamines in [2+2+2] cycloadditions for the synthesis of 2,3-dihydroindoles. Tosyl-ynamides **453** (Scheme 114), when subjected to acetylenes and the Grubbs catalyst yield cyclotrimerization products **454** in moderate to excellent yields. The regioselectivity of X or Y depends heavily on the extent of steric interaction from R or R^1 groups.

More recently Witulski and coworkers have reported the



Scheme 115.

Table 3.

Entry	R^4	R^1	Catalyst	Yield (*m*:*o*) (**457**)
1	CH_3	CH_2OH	A (5%)	70 (9:1)
2	CH_3	$(CH_2)_2OH$	A (10%)	54 (9:1)
3	CH_3	$(CH_2)_3OH$	A (10%)	57 (9:1)
4	Ph	CH_2OH	A (10%)	60 (9.5:1)
5	CH_3	C_3H_7	B (5%)	54 (1:10)
6	CH_3	CH_2OH	B (5%)	67 (1:20)
7	CH_3	$(CH_2)_2OH$	B (5%)	66 (1:3)
8	Ph	CH_2OH	B (5%)	70 (1:1)

regioselective synthesis of 4,5- and 4,6-indolines[110] utilizing either Grubbs' or Wilkinson's catalysts. The reactions of diynes **455** and monoalkynes **456** (Scheme 115, Table 3), the authors obtained 4,6-indolines (*meta*-**457**) in 54–70% yield with high *meta–ortho* selectivity using Grubbs catalyst (Catalyst A). Upon using Wilkinson's catalyst (Catalyst B), the authors witnessed a reversal of cyclotrimerization regiochemistry producing predominately the 4,5-indolines (*ortho*-457), with the exception of reaction entry 8, which occurred with no selectivity.

Acknowledgements

R. P. H. thanks American Chemical Society Petroleum Research Fund [Type-G] for financial support. R. P. H. also thanks R. W. Johnson Pharmaceutical Research Institute for a generous grant from the Focused Giving Award. J. A. M. thanks the University of Minnesota for a Graduate Dissertation Fellowship.

References

1. Bode, J. *Ann.* **1892**, *267*, 268 (see also p 286).
2. For a correction of this claim see: Klages, F.; Drerup, E. *Ann.* **1941**, *547*, 65.
3. Zaugg, H. E.; Swett, L. R.; Stone, G. R. *J. Org. Chem.* **1958**, *23*, 1389.
4. Wolf, V.; Kowitz, F. *Ann.* **1960**, *638*, 33.
5. Viehe, H. G. *Angew Chem., Int. Ed. Engl.* **1963**, *2*, 477.
6. Viehe, H. G. *Angew Chem., Int. Ed. Engl.* **1967**, *6*, 767.
7. Viehe, H. G. *Chemistry of Acetylenes*; Marcel Dekker: New York, 1969; Chapter 12, pp 861–912.
8. Ficini, J. *Tetrahedron* **1976**, *32*, 448.
9. Pitacco, G.; Valentin, E. *Enamines, Ynamines*. In: *The Chemistry of Functional Groups*; Patai, S., Ed., John Wiley & Sons: New York, 1979; Chapter 15, pp 623–714.
10. Collard-Motte, J.; Janousek, Z. *Top. Curr. Chem.* **1985**, *130*, 89.
11. Himbert, G. In *Methoden Der Organischen Chemie (Houben-Weyl)*, Kropf, H., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1993; pp. 3267–3443.
12. Genet, J. P.; Kahn, P.; Ficini, J. *Tetrahedron Lett.* **1980**, 1521.
13. van Elburg, P. A.; Honig, G. W. N.; Reinhoudt, D. N. *Tetrahedron Lett.* **1987**, 6397.
14. (a) Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 917. (b) Goffin, E.; Legrand, Y.; Viehe, H. G. *J. Chem. Res., (Synopsis)* **1977**, 105.
15. (a) Galy, J. P.; Elguero, J.; Vincent, E. J.; Galy, A. M.; Barbe, J. *Synthesis* **1979**, 944. (b) Mahamoud, A.; Galy, J. P.; Vincent, E. J.; Barbe, J. *Synthesis* **1981**, 917. (c) Radl, S.; Kovarova, L.; Holubeck, J. *Coll. Czech. Chem. Commun.* **1991**, *56*, 439. (d) Radl, S.; Kovarova, L. *Collect. Czech. Chem. Commun.* **1991**, *56*, 2413.
16. Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852.
17. Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A. *Tetrahedron Lett.* **1985**, *26*, 4141.
18. (a) Novikov, M. S.; Khlebnikov, A. F.; Kostikov, R. R. *J. Org. Chem. USSR* **1991**, *27*, 1576. (b) Tikhomirov, D. A.; Eremeev, A. V. *Chem. Heterocycl. Comp.* **1987**, *23*, 1141.
19. For studies related to physical properties of ynamines which are not reviewed here: (a) Andraos, J.; Chiang, Y.; Grant, A. S.; Guo, H.-X.; Kresge, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 7411. (b) Chiang, Y.; Grant, A. S.; Kresge, A. J.; Paine, S. W. *J. Am. Chem. Soc.* **1996**, *118*, 4366. (c) Chiang, Y.; Kresge, A. J.; Paine, S. W.; Popik, V. V. *J. Phys. Org. Chem.* **1996**, *9*, 361. (d) Kresge, A. J.; Paine, S. W. *Can. J. Chem.* **1996**, *74*, 1373. (e) Chiang, Y.; Grant, A. S.; Guo, H.-X.; Kresge, A. J.; Paine, S. W. *J. Org. Chem.* **1997**, *62*, 5363. (f) Alvarez, R. M.; Hanack, M.; Schmid, T.; Subramanian, L. R. *J. Phys. Org. Chem.* **1995**, *8*, 191. (g) Brown, R. F. C.; Choi, N.; Coulston, K. J.; Eastwood, F. W.; Ercole, F.; Horvath, J. M.; Mattinson, M.; Mulder, R. J.; Ooi, H. C. *Liebigs Ann./Recueil* **1997**, 1931.
20. Fischer, H.; Podschadly, O.; Roth, G.; Herminghaus, S.; Klewitz, S.; Heck, J.; Houbrechts, S.; Meyer, T. *J. Organomet. Chem.* **1997**, *541*, 321.
21. Balsells, J.; Vázquez, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2000**, *65*, 7291.
22. (a) Löffler, A.; Himbert, G. *Synthesis* **1994**, 383. (b) Himbert, G.; Naßhan, H.; Gerulat, O. *Synthesis* **1997**, 293.
23. Wilhelm, P.; Boss, C.; Pfammatter, M.; Thommen, M.; Ploom, T.; Schauder, S.; Berger, U.; Vanhelmont, F.; Förtsch, M.; Hauser, J.; Bürgi, H.-B. *Acta Crystallogr. Sect. C Cryst. Struct. Commun.* **1996**, 2004.
24. Berger, D.; Wilhelm, P.; Neuenschwander, M. *Helv. Chim. Acta* **1999**, *82*, 326.
25. Pielichowski, J.; Chrzaszcz, R. *Bull. Soc. Chim. Belg.* **1995**, *104*, 117.
26. (a) Trofimov, B. A.; Tarasova, O. A.; Brandsma, L. *Russ. J. Org. Chem.* **1994**, *30*, 335. (b) Brandsma, L.; Mal'kina, A. G.; Trofimov, B. A. *Synth. Commun.* **1994**, *24*, 2721.
27. Sobenina, L. N.; Dyachkova, S. G.; Stepanova, Z. V.; Toryashinova, D. S. D.; Albanov, A. I.; Ushakov, I. A.; Demenev, A. P.; Mikhaleva, A. I.; Trofimov, B. A. *Russ. J. Org. Chem.* **1999**, *35*, 916.
28. Bloxham, J.; Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3055.
29. (a) Berger, D.; Bartlome, A.; Neuenschwander, M. *Helv. Chim. Acta* **1996**, *79*, 179. (b) Berger, D.; Neuenschwander, M. *Helv. Chim. Acta* **1996**, *79*, 192. (c) Fischer, F.; Berger, D.; Neuenschwander, M. *Helv. Chim. Acta* **1998**, *81*, 1792. (d) Fischer, F.; Neuenschwander, M. *Helv. Chim. Acta* **1998**, *81*, 2282. (e) Wilhelm, P.; Neuenschwander, M. *Helv. Chim. Acta* **1999**, *82*, 338. (f) Bacilieri, C.; Neuenschwander, M. *Helv. Chim. Acta* **2000**, *83*, 641.
30. Yamanaka, H.; Mantani, T.; Shiomi, K.; Ishihara, T. *Chem. Lett.* **1998**, 615.
31. Bartel, C.; Bostschwina, P.; Bürger, H.; Guarniers, A.; Heyl, A.; Huckauf, A.; Lentz, D.; Merzliak, T.; Mkadmi, E. B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2879.
32. Katritzky, A. R.; Wang, J.; Karodia, N.; Li, J. *J. Org. Chem.* **1997**, *62*, 4142.
33. Katritzky, A. R.; Zhang, S.; Fang, Y. *Org. Lett.* **2000**, *2*, 3789.
34. Mal'kina, A. G.; Tarasova, O. A.; Verkruijsse, H. D.; van der Kerk, A. C. H. T. M.; Brandsma, L.; Trofimov, B. A. *Recl. Trav. Chim. Pays-Bas.* **1995**, *114*, 18.
35. Zama, Y.; Okamoto, Y.; Takagi, K.; Kurasawa, Y.; Takada, A. *J. Heterocycl. Chem.* **1995**, *32*, 851.
36. Murch, P.; Williamson, B. L.; Stang, P. J. *Synthesis* **1994**, 1255.
37. Zhdankin, V. V.; Stang, P. J. *Tetrahedron* **1998**, *54*, 10927.
38. (a) Kitamura, T.; Tashi, N.; Tsuda, K.; Fujiwara, Y.

Tetrahedron Lett. **1998**, *39*, 3787. (b) Kitamura, T.; Tashi, N.; Tsuda, K.; Chen, H.; Fujiwara, Y. *Heterocycles* **2000**, *52*, 303.

39. Tretyakov, E. V.; Vasilevsky, S. F. *Russ. Chem. Bull.* **1998**, *47*, 1233.
40. Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
41. Hitchcock, P. B.; Lappert, M. F.; Layh, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 501.
42. Brown, R. F. C.; Eastwood, F. W.; Fallon, G. D.; Lee, S. C.; McGeary, R. P. *Aust. J. Chem.* **1994**, *47*, 991.
43. Capella, L.; Capperucci, A.; Curotto, G.; Lazzari, D.; Dembech, P.; Reginato, G.; Ricci, A. *Tetrahedron Lett.* **1993**, *34*, 3311.
44. Schmid, T.; Hanack, M.; Maichle, C.; Strahle, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 258.
45. Lukashev, N. V.; Zhichkin, P. E.; Tarasenko, E. A.; Luzikov, Y. N.; Kazankova, M. A. *Russ. J. Gen. Chem.* **1993**, *63*, 1234.
46. Sukhova, L. N.; Ostroumov, I. G.; Maretina, I. A. *Russ. J. Org. Chem.* **1994**, *30*, 54.
47. Fuchs, E.; Krebs, F.; Heydt, H.; Regitz, M. *Tetrahedron* **1994**, *50*, 759.
48. Trostyanskaya, I. G.; Lutsenko, S. V.; Efimova, I. V.; Kazankova, M. A.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1996**, *32*, 1015.
49. Schank, K.; Beck, H.; Himbert, G. *Synthesis* **1998**, 1718.
50. (a) Fischer, F.; Berger, D.; Neuenschwander, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2138. (b) Berger, D.; Neuenschwander, M. *Chimia* **1995**, *49*, 72 see also p 75. (c) Bacilieri, C.; Reic, S.; Neuenschwander, M. *Helv. Chim. Acta* **2000**, *83*, 1182.
51. Pirrung, M. C.; Zhang, J.; Morehead Jr, A. T. *Tetrahedron Lett.* **1994**, *35*, 6229.
52. (a) Lukashev, N. V.; Zhichkin, P. E.; Kazankova, M. A.; Beletskaya, I. P. *Tetrahedron Lett.* **1993**, *34*, 1331. (b) Lukashev, N. V.; Averin, A. D.; Zhichkin, P. E.; Kazankova, M. A.; Beletskaya, I. P. *Phosphorus Sulfur Silicon Relat. Elem.* **1996**, *109–110*, 609. (c) Averin, A. D.; Lukashev, N. V.; Borisenko, A. A.; Kazankova, M. A.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1996**, *32*, 407.
53. (a) Averin, A. D.; Lukashev, N. V.; Borisenko, A. A.; Kazankova, M. A.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1995**, *31*, 367. (b) Averin, A. D.; Lukashev, N. V.; Borisenko, A. A.; Kazankova, M. A.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1995**, *31*, 445.
54. (a) Foote, C. S. *NATO ASI Ser. C Math. Phys. Sci.* **1994**, 79. (b) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4271. (c) Zhang, X.; Fan, A.; Foote, C. S. *J. Org. Chem.* **1996**, *61*, 5456. (d) Bernstein, R.; Foote, C. S. *Tetrahedron Lett.* **1998**, *39*, 7051.
55. Schulte, N.; Möller, M. H.; Rodewald, U.; Würthwein, E.-U. *Chem. Ber.* **1994**, *127*, 1287.
56. Plancquaert, M.-A.; Janousek, Z.; Viehe, H. G. *J. Prakt. Chem.* **1994**, *336*, 19.
57. Müller, M.; Förster, W.-R.; Holst, A.; Kingma, A. J.; Schaumann, E.; Adiwidjaja, G. *Chem. Eur. J.* **1996**, *2*, 949.
58. Abramovitch, R. A.; Shinkai, I.; Mavunkel, B. J.; More, K. M.; O'Connor, S.; Ooi, G. H.; Pennington, W. T.; Srinivasan, P. C.; Stowers, J. R. *Tetrahedron* **1996**, *52*, 3339.
59. Wentrup, C.; Rao, V. V. R.; Frank, W.; Fulloon, B. E.; Moloney, D. W. J.; Mosandl, T. *J. Org. Chem.* **1999**, *64*, 3608.
60. Himbert, G.; Gerulat, O.; Matheis, S.; Bergsträßer, U. *Tetrahedron Lett.* **1998**, *39*, 6671.
61. Averin, A. D.; Mukhaiimana, P.; Lukashev, N. V.; Borisenko, A. A.; Kazankova, M. A.; Beletskaya, I. P. *Russ. J. Gen. Chem.* **1998**, *68*, 1383.
62. Guillaume, M.; Janousek, Z.; Viehe, H. G.; Wynants, C.; Declercq, J.-P.; Tinant, B. *J. Fluor. Chem.* **1994**, *69*, 253.
63. Tsuda, T.; Hokazono, H.; Toyota, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2417.
64. Mantani, T.; Shiomi, K.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **1999**, 855.
65. (a) Nakayama, J.; Choi, K. S.; Akiyama, I.; Hoshino, M. *Tetrahedron Lett.* **1993**, *34*, 115. (b) Choi, K. S.; Akiyama, I.; Hoshino, M.; Nakayama, J. *Bull. Chem. Soc. Jpn* **1993**, *66*, 623.
66. Shibuya, I.; Goto, M.; Oishi, A.; Tsuchiya, T.; Taguchi, Y.; Nakayama, J. *Heterocycles* **1995**, *41*, 1935.
67. Tornus, I.; Schaumann, E.; Mayer, R.; Adiwidjaja, G. *Liebigs Ann.* **1995**, 1795.
68. Temme, R.; Polborn, K.; Huisgen, R. *Tetrahedron* **1998**, *54*, 9849.
69. Nakayama, J.; Mizumura, A.; Akiyama, I.; Nishio, T.; Iida, I. *Chem. Lett.* **1994**, 77.
70. Blau, H.; Grobe, J.; Le Van, D.; Krebs, B.; Läge, M. *Chem. Ber./Recueil* **1997**, *130*, 913.
71. Laue, J.; Seitz, G. *Liebigs Ann.* **1996**, 773.
72. Turchi, S.; Nesi, R.; Giomi, D. *Tetrahedron* **1998**, *54*, 1809.
73. (a) Boger, D. L.; Honda, T.; Dang, Q. *J. Am. Chem. Soc.* **1994**, *116*, 5619. (b) Boger, D. L.; Ramsey, T. M.; Cai, H.; Hoehn, S. T.; Kozarich, J. W.; Stubbe, J. *J. Am. Chem. Soc.* **1998**, *120*, 53.
74. Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron* **1995**, *51*, 6651.
75. (a) Iwamoto, K.-I.; Suzuki, S.; Oishi, E.; Tanji, K.-I.; Miyashita, A.; Higashino, T. *Chem. Pharm. Bull.* **1994**, *42*, 413. (b) Oishi, E.; Iwamoto, K.-I.; Okada, T.; Suzuki, S.; Tanji, K.-I.; Miyashita, A.; Higashino, T. *Chem. Pharm. Bull.* **1994**, *42*, 2219. (c) Iwamoto, K.-I.; Suzuki, S.; Oishi, E.; Tanji, K.-I.; Miyashita, A.; Higashino, T. *Chem. Pharm. Bull.* **1995**, *43*, 679. (d) Iwamoto, K.-I.; Suzuki, S.; Oishi, E.; Miyashita, A.; Higashino, T. *Heterocycles* **1996**, *43*, 199. (e) Iwamoto, K.-I.; Fukuta, H.; Suzuki, S.; Maruyama, J.; Oishi, E.; Miyashita, A.; Higashino, T. *Heterocycles* **1996**, *43*, 2409. (f) Iwamoto, K.-I.; Oishi, E.; Sano, T.; Tsuchiya, A.; Suzuki, Y.; Higashino, T.; Miyashita, A. *Heterocycles* **1997**, *45*, 1551.
76. (a) Barluenga, J.; Ferrero, M.; Peláez-Arango, E.; López-Ortiz, F.; Palacios, F. *J. Chem. Soc., Chem. Commun.* **1994**, 865. (b) Peláez-Arango, E.; López-Ortiz, F.; Barluenga, J.; Ferrero, M.; Palacios, F. *Magn. Reson. Chem.* **1994**, *32*, 646.
77. (a) Peláez-Arango, E.; Ferrero, M.; López-Ortiz, F. *Magn. Reson. Chem.* **1996**, *34*, 368. (b) Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron* **1997**, *53*, 4521.
78. Tollenaere, C. D.; Ghosez, L. *Bull. Soc. Chim. Fr.* **1997**, *134*, 989.
79. Kappe, C. O.; Peters, K.; Peters, E.-M. *J. Org. Chem.* **1997**, *62*, 3109.
80. Boger, D. L.; Schaum, R. P.; Garbaccio, R. M. *J. Org. Chem.* **1998**, *63*, 6329.
81. Babaev, E. V.; Simonyan, V. V.; Pasichnichenko, Y. K.; Nosova, V. M.; Kisin, A. V.; Jug, K. *J. Org. Chem.* **1999**, *64*, 9057.

82. Nesi, R.; Turchi, S.; Giomi, D.; Danesi, A. *Tetrahedron* **1999**, *55*, 13809.
83. Mack, A.; Tabellion, F.; Peters, C.; Nachbauer, A.; Bergsträsser, U.; Preuss, F.; Regitz, M. *Phosphorus Sulfur Silicon Relat. Elem.* **1999**, *144–146*, 261.
84. Mantani, T.; Konno, T.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, 666.
85. (a) Sukhova, L. N.; Ostroumov, I. G.; Bel'skii, V. K.; Maretina, I. A.; Galishev, V. A. *Russ. J. Org. Chem.* **1993**, *29*, 1028. (b) Sukhova, L. N.; Ostroumov, I. G.; Bel'skii, V. K.; Galishev, V. A.; Maretina, I. A. *Russ. J. Org. Chem.* **1994**, *30*, 49.
86. (a) Riebel, P.; Weber, A.; Troll, T.; Sauer, J. *Tetrahedron Lett.* **1996**, *37*, 1583. (b) Riebel, P.; Weber, A.; Troll, T.; Sauer, J.; Breu, J.; Nöth, H. *Tetrahedron Lett.* **1996**, *37*, 1587.
87. Zakhartsova, E. N.; Pankratov, A. N.; Ostroumov, I. G.; Maretina, I. A. *Izv. Vyssh. Vchebn. Zaved., Khim. Khim. Tekhnol.* **1998**, *41*, 28.
88. Sakai, N.; Funabashi, M.; Hamada, T.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, *55*, 13703.
89. Neidlein, R.; Kux, U. *Helv. Chim. Acta* **1994**, *77*, 1051.
90. Klopfenstein, S. R.; Kluwe, C.; Kirschbaum, K.; Davies, J. A. *Can. J. Chem.* **1996**, *74*, 2331.
91. Kanj, A.; Meunier, P.; Gautheron, B.; Dubrac, J.; Daran, J.-C. *J. Organomet. Chem.* **1993**, *454*, 51.
92. Roth, G.; Reindl, D.; Gockel, M.; Troll, C.; Fischer, H. *Organometallics* **1998**, *17*, 1393.
93. (a) Mal'kina, A. G.; den Besten, R.; van der Kerk, A. C. H. T. M.; Brandsma, L.; Trofimov, B. A. *J. Organomet. Chem.* **1995**, *493*, 271. (b) Tarasova, O. A.; Brandsma, L.; Verkruijsse, H. D.; Mal'kina, A. G.; Trofimov, B. A. *Russ. J. Org. Chem.* **1996**, *32*, 1164.
94. Schabbert, S.; Schaumann, E. *Tetrahedron* **1999**, *55*, 1271.
95. Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440.
96. Witulski, B.; Gößmann, M. *Chem. Commun.* **1999**, 1879.
97. Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.
98. Brückner, D. *Synlett* **2000**, 1402.
99. Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852.
100. Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J.; Xiong, H.; Mulder, J. A. *Org. Lett.* **1999**, *1*, 1237.
101. Majumdar, K. C.; Ghosh, S. K. *Synth. Commun.* **1994**, *24*, 217.
102. Joshi, R. V.; Xu, Z.-Q.; Ksebati, M. B.; Kessel, D.; Corbett, T. H.; Drach, J. C.; Zemlicka, J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1089.
103. (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 489. (b) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *38*, 2426. (c) Witulski, B.; Gößmann, M. *Synlett* **2000**, 1793.
104. (a) Rainier, J. D.; Imbriglio, J. E. *J. Org. Chem.* **2000**, *65*, 7272. (b) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037.
105. Schottelius, M. J.; Chen, P. *Helv. Chim. Acta* **1998**, *81*, 2341.
106. Fromont, C.; Masson, S. *Tetrahedron* **1999**, *55*, 5405.
107. Witulski, B.; Buschmann, N.; Bergsträßer, U. *Tetrahedron* **2000**, *56*, 8473.
108. (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*, Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.
109. Culvenor, C. C. J.; Edgar, J. A.; McKay, M. F.; Gorst-Allman, C. P.; Marasas, W. F. O.; Steyn, P. S.; Vleggaar, R.; Wessels, P. L. *Tetrahedron* **1989**, *45*, 2351.
110. Witulski, B.; Stengel, T.; Fernàndez-Hernàndez, J. M. *Chem. Commun.* **2000**, 1965.

Biographical sketch

Craig A. Zificsak was born in Stevens Point, Wisconsin in 1976. He received a BS in Chemistry from the University of Wisconsin—Stevens Point in 1998. He is currently enrolled in the PhD program at the University of Minnesota under the supervision of Professor Richard P. Hsung. His thesis research involves the development of new methodology and the synthesis of natural products.

Richard P. Hsung graduated with an Honors B.S. degree in Mathematics and Chemistry from Calvin College [Grand Rapids, Michigan] in 1988. He attended The University of Chicago [Chicago] for graduate study in organic chemistry and obtained his M.S. degree [synthetic approaches to taxusin] in 1990 under the supervision of Professor Jeffrey D. Winkler. He received his Ph.D. degree [asymmetric benzannulation reactions of Fischer's chromium carbenes] in 1994 under the supervision of Professor William D. Wulff. After pursuing research in the area of surface chemistry as a post-doctoral fellow in the laboratory of Professor Lawrence R. Sita at The University of Chicago between 1995 and 1996, he joined the laboratory of Professor Gilbert Stork as a National Institutes of Health post-doctoral fellow at Columbia University [New York City]. In 1997, he moved to University of Minnesota [Minneapolis, Minnesota] as an assistant professor of organic chemistry. His research interests involve cycloaddition approaches to synthesis of natural products and developing stereoselective methods using allenamides and ynamides. He is a recipient of R. W. Johnson Pharmaceutical Research Institute Focused Giving Award in 1998. In 2001, he received a McKnight Junior Faculty Award from University of Minnesota and a Camille Dreyfus Teacher-Scholar Award from Camille and Henry Dreyfus Foundation. Recently, he was also given a National Science Foundation Career Award.

Jason A. Mulder was born in Cadillac, Michigan in 1975. He received a B.S. in Chemistry from Calvin College, Grand Rapids, MI in 1997. He is currently enrolled in the Ph.D. program at the University of Minnesota under the supervision of Professor Richard P. Hsung. His research involves synthetic studies of ynamides and their reactivity in rearrangement and cycloaddition reactions.

C. Rameshkumar was born in Nadoorkarai, Tamil Nadu, India. He obtained his BSc degree in Chemistry from Pioneer Kumaraswamy College, Nagercoil (India) and MSc degree in Organic Chemistry from Annamalai University. He received his PhD degree from the University of Hyderabad in 2000 under the supervision of Professor M. Periasamy. He is currently working as a postdoctoral associate under the supervision of Professor Richard P. Hsung.

Biographical sketch

Lin-Li Wei was born in Guangxi, P.R. China. She obtained her BS and MS degree in Chemistry from Peking University in 1992 and 1995, respectively. In 1999, she received her PhD degree in Organic Chemistry from the National University of Singapore. From September 1998 to April 2001, she was a postdoctoral associate in Professor Hsung's group at the University of Minnesota, Minneapolis. Her research mainly focused on natural product synthesis and developments of novel methodologies, i.e. the chemistry of allenamides and ynamides, and formal [3+3] cycloadditions for constructing heterocylces. Currently, she is working for Selectide, a subsidiary of Aventis Pharmaceuticals Inc.