REVIEW

N-Propargylic β-enaminocarbonyls: powerful and versatile building blocks in organic synthesis

Sattar Arshadi,[a] Esmail Vessally,*[a] Ladan Edjlali,*[b] Ebrahim Ghorbani-Kalhor[b] and Rahim Hosseinzadeh-Khanmiri[b]

Nitrogen-containing heterocyclic compounds are not only prevalent in an extensive number of natural products and synthetic pharmaceuticals but are also used as building blocks in organic synthesis. The efficient preparation of highly functionalized N-heterocycles from cheap and easily available starting materials has therefore become of central interest for synthetic organic chemists. This review gives an overview of new developments in synthesis of highly substituted N-heterocycles, including pyrroles, pyridines, pyrrolines, piperidines, azepines, and related compounds, from N-propargylic β-enaminocarbonyls (N-propargylic β-enaminones and β-enaminoesters) in recent years. Mechanistic aspects of the reactions are considered and discussed in detail.

1. Introduction

Needless to say, nitrogen-based heterocycles, including pyrroles, pyridines, pyrrolines, piperidines, azepines, and related compounds, are key structural units for a large array of drugs and natural products.[1] Therefore, the development of practical and convenient methodologies that benefit from cheap, readily available, and relatively simple substrates for the construction of these N-heterocyclic compounds is highly desirable. N-propargylamines represent one of the low-cost, readily accessible, and versatile building blocks in organic synthesis for generation of N-heterocyclic molecules.[2] N-propargylic β-enaminocarbonyls are one of the novel and specific class of these compounds having diverse reaction patterns and applied in the assembly of various heterocycles (Fig. 1). Since a large number of developments in the use of N-propargylic β-enaminocarbonyls in heterocyclic synthesis have occurred from 2006 to present, a comprehensive review on this interesting field seems to be timely. In this review, we have classified these reactions based on the desired products. Mechanistic aspects of the reactions are considered and discussed in detail.

aDepartment of Chemistry, Payame Noor University, Tehran, Iran. E-mail: vessally@yahoo.com
bDepartment of Chemistry, Tabriz Branch, Islamic Azad University, Tabriz, Iran. E-mail: l_edjlali@iaut.ac.ir

Sattar Arshadi was born in Miandoab, West Azarbayjan province, Iran, in 1973. He received his B.Sc. degree in chemistry in the University of Kermanshah (1997) and his M.Sc. (2000) under supervision of Professor Issa Yavari and Ph.D. (2004) in organic chemistry under supervision of Professor M.Z. Kassaee Both in Tarbiat Modarres University, Tehran, Iran. Then, he went to the University of Payame Noor as an assistant professor (2005). His main research interest is computational chemistry (especially on rearrangements and interactions in nano systems), organic synthesis and spectral studies of organic compounds.

Esmail Vessally was born in Sharabiyan, Sarab, Iran, in 1973. He received his B.S. degree in pure chemistry from University of Tabriz, Tabriz, Iran, and his M.S. degree in organic chemistry from Tehran University, Tehran, Iran, in 1999 under the supervision of Prof. H. Pirelahi. He completed his Ph.D. degree in 2005 under the supervision of Prof. M.Z. Kassaee. Now he is working at Payame Noor University as associate professor. His research interests include theoretical organic chemistry, new methodologies in organic synthesis and spectral studies of organic compounds.

2. Pyrroles

Pioneering works devoted to the synthesis of functionalized pyrroles **2** through intramolecular cyclization of *N*-propargylic *β*-enaminones **1** have been reported by Cacchi *et al.*, who used Cs_2CO_3 as catalyst. This reaction was run in anhydrous DMSO at room temperature and tolerated the presence of a variety of sensitive functional groups, such as hydroxyl, nitro, methoxy, acetyl, ester, bromo, and chloro groups (Scheme 1). This made possible the further derivatization of the products. According to the author proposed mechanism, this transformation proceeded *via* a 5-*exo-dig* cyclization/protonation/isomerization sequential process.[3]

Subsequently, the Komeyama laboratory reported the synthesis of 3-carboxylated pyrroles **5** through a bismuth catalyzed intramolecular cyclization of *N*-propargylic *β*-enaminoesters **A** (generated *in situ* from *N*-propargyl amine **3** and *β*-keto esters **4**) in refluxing toluene (Scheme 2a). They showed that the use of 1,3-diketones (instead of *β*-keto esters) as starting materials gave mixtures of pyrroles **5** and **6** (Scheme 2b). These observations would be explained by the instability of $^+C(O)OR$. Thus, in the case of *β*-keto esters, deprotonate is preferred to decarboxylation. But in the case of 1,3-diketones, competition between the deprotonation and deacylation gave a mixture of products (Scheme 3).[4]

Following these works, Saito, Konishi, and Hanzawa were able to demonstrate that a series of 3-carboxylated pyrroles **8** could be obtained from corresponding *N*-propargylic *β*-enaminoesters **7** through a silver catalyzed amino-Claisen rearrangement/ heterocyclization sequential process. This $[(IP)Au(MeCN)]BF_4$ catalyzed reaction is equally efficient for both the internal and external alkynes. The reaction was run in CH_2Cl_2–HFIP (3 : 1) at room temperature and generally provided the highly substituted pyrroles **8** in good to high yields (Scheme 4a).[5] Shortly afterward, Chiba *et al.* developed a new methodology for the construction of 4-carbonylpyrroles **10** by the copper-mediated aerobic carboxygenation of *N*-propargylic *β*-enaminoesters **9** under oxygen atmosphere (Scheme 4b). Among the various copper catalysts like $CuBr·SMe_2$, $CuCl_2$, $CuCl$, $CuBr_2$, $Cu(OAc)_2$; $CuCl_2$ was the most efficient for the transformation. DABCO (1,4-diazabicyclo[2.2.2] octane) is required as additive and the DMSO as the solvent for this method and this protocol is applicable for the both electron reach and electron poor substrates.[6]

In 2012, Zhao and co-workers published an efficient protocol for the synthesis 2-ethylthio-pyrroles **13** *via* base catalyzed 5-*exo-dig* cyclization of *N*-propargylic *β*-enaminoes **A** were prepared *in situ* by intermolecular Michael addition of N-propargylamines **11** to *α*-acylketene dithioacetals **12** (Scheme 5). The authors determined that the use of K_2CO_3/DMF system provided the optimal conditions for this reaction. The most striking feature of this protocol is excellent functional group tolerance to

Ladan Edjlali was born in Tabriz, Iran, in 1960. She received her B.S. degree in Applied Chemistry from University of Tabriz, Iran, and her M.S. degree in organic chemistry from University of Tabriz, Tabriz, Iran, in 1993 under the supervision of Prof. Y. Mirzaei. She completed his Ph.D. degree in 2000 under the supervision of Prof. Y. Mirzaei and Prof. S. M. Golabi. Now she is working at Islamic Azad University, Tabriz Branch as Associate Professor. Her research interests include organic synthesis and new methodologies in organic synthesis.

Ebrahim Ghorbani Kalhor is an associate professor of analytical chemistry in the department of chemistry at the university of Islamic Azad University, Tabriz Branch, where he has been a faculty member since 2009. He was born in Ahar, Iran in 1972. He received his B.S. degree in applied chemistry from Bu Ali Sina University, Hamedan, Iran in 1995 and h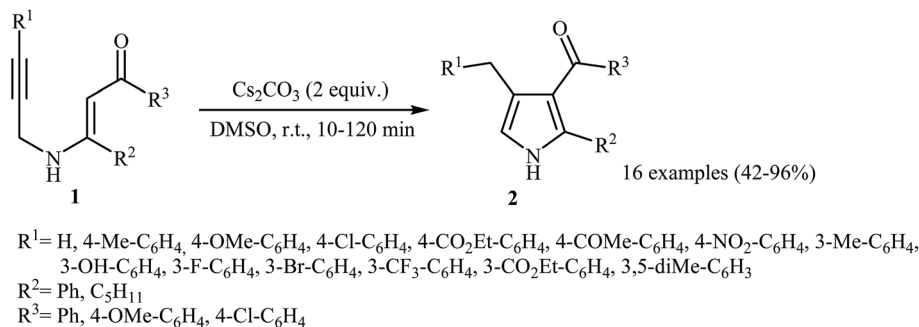is M.S. degree in analytical chemistry from Urmia University, Urmia, Iran, under the supervision of Prof. M. A. Farajzadeh in 1999. Kalhor completed his Ph.D. at Tabriz University, Tabriz, Iran, in 2005 under the supervision of Prof. M. H. Sorouraddin and Prof. M.R. Rashidi. His research interests include chemometrics, nano particles, nano composites, separation science, solid phase micro extraction, sample pretreatment, molecular spectroscopy, modelling and experimental design.

Rahim Hosseinzadeh-Khanmiri was born in Azarshahr, Iran, in 1979. He received his B.S. degree in Pure Chemistry from University of Tabriz, Tabriz, Iran, and his M.S. degree in organic chemistry from Kharazmi University, Tehran, Iran, in 2007 under the supervision of Prof. M. A. Bigdeli. He completed his Ph.D. degree in 2014 under the supervision of Prof. S. A. Moghimi and prof. Ahmad Shaabani in Shahid Beheshti University, Tehran, Iran. Now he is working at Tabriz Branch, Islamic Azad University, Tabriz, Iran as Assistant Professor. His research interests include organic synthesis, catalyst, nano, organic and green chemistry.

Scheme 1 Base-catalyzed synthesis of pyrroles **2** from *N*-propargylic β-enaminones **1**.
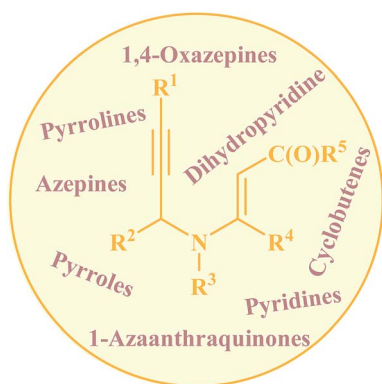

Fig. 1 Some important synthetic compounds derived from *N*-propargylic β-enaminocarbonyls.
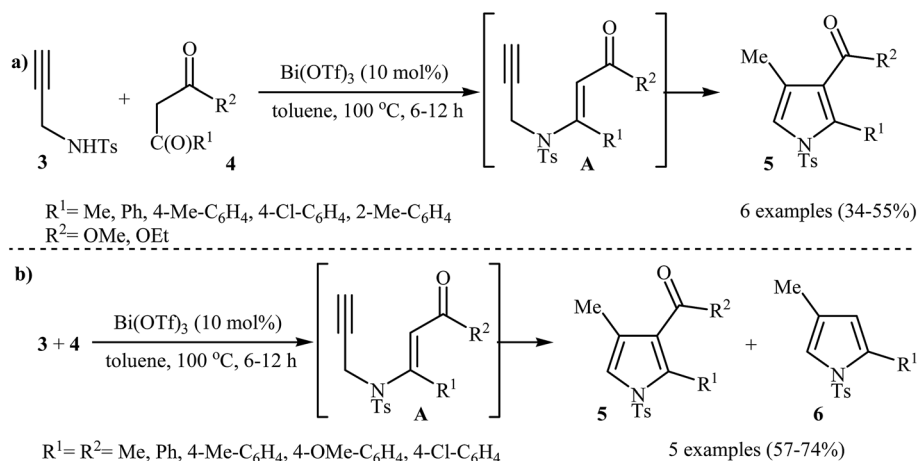
produce highly functionalized pyrroles **13** from simple starting materials. It is noted that when external *N*-propargylamines (R¹ = H) were used as substrates, the reaction was performed in the absence of an external base and the corresponding products were obtained in high to excellent yields.[7]

Recently, Jin and co-workers demonstrated that polysubstituted pyrroles **16** can be readily prepared in the reaction

of *N*-propargylamines **14** with activated alkynes **15** in the presence of 20 mol% of K₃PO₄ as catalyst in DMSO at 120 °C (Scheme 6) The authors suggested that the reaction proceeds *via* the formation of *N*-propargylic β-enaminoester intermediates **A** through Michael addition of *N*-propargylamines **14** to alkynes **15**, which after a 5-*exo-dig* cyclization process delivers the 3-carboxylated pyrroles **16** in good yields.[8]
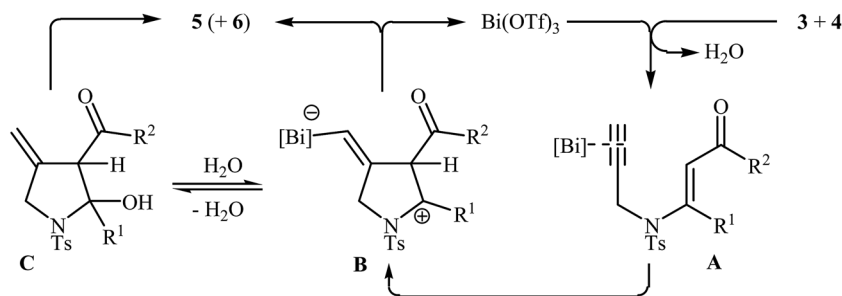
Later, Zhang's research team reported a direct synthesis of polysubstituted pyrrole derivatives **18** *via* base-catalyzed intramolecular cyclization of *N*-propargylic β-enaminones **17** (Scheme 7). Thus, the careful analysis of the optimized reactions revealed that the optimum condition for this transformation was the addition of 1 equiv. of *t*BuOK, at room temperature, to a solution of *N*-propargylic β-enaminones **17** in DMF. The reaction conditions allowed the use of substrates bearing a variety of sensitive functional groups including flouro, chloro, methoxy, and acetyl functionalities. According to the author proposed mechanism, the reaction proceeded *via* a propargyl−allenyl isomerization/5-*exo-dig* cyclization/proton transfer sequential process.[9]

A notable contribution to this field was reported by Wan and co-workers in 2012. They found that β-(arylsulfonyl)methyl pyrroles **20** could be prepared from *N*-propargylic β-enaminoesters **19** using 10 mol% of Cs₂CO₃ as base in DMF at 80 °C.
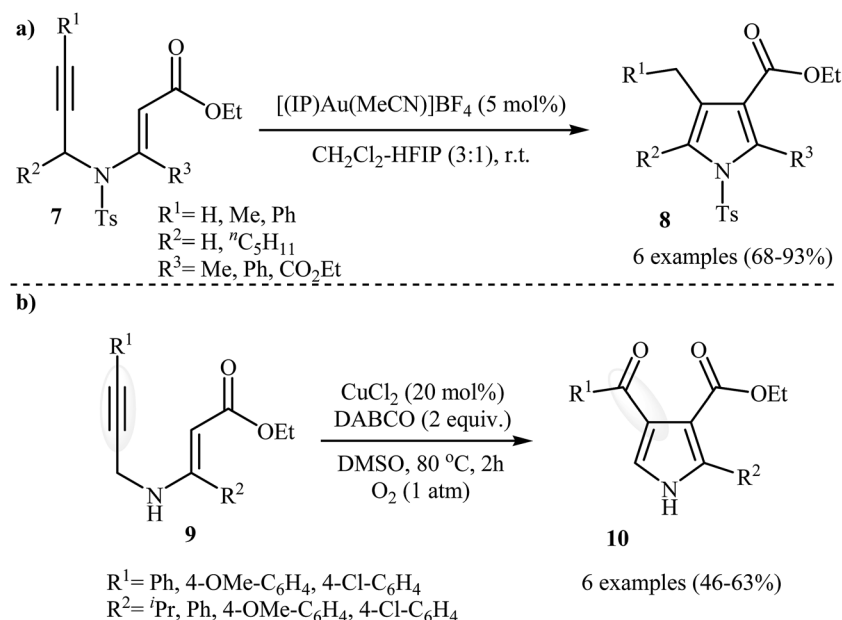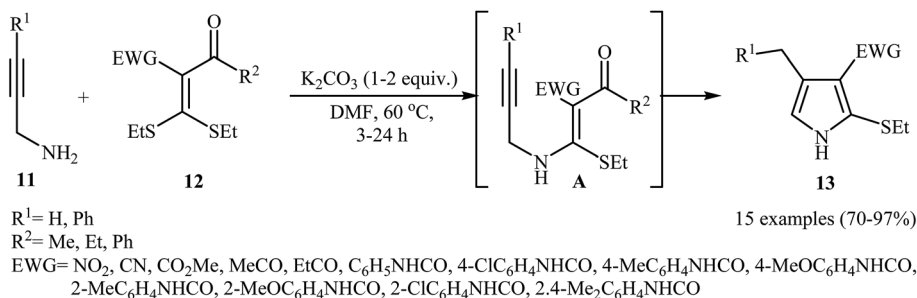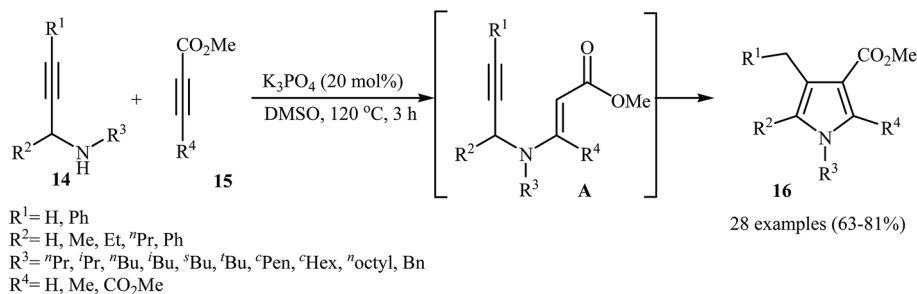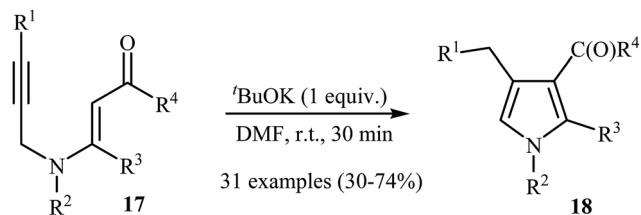

Scheme 2 (a) One-pot synthesis of pyrroles **5** from *N*-propargyl amine **3** and β-keto esters **4**; (b) Synthesis of pyrroles **5** and **6** from *N*-propargyl amine **3** and 1,3-diketones **4**.

Scheme 3 Possible route for the formation of **5** and **6**.

a)

R^1= H, Me, Ph
R^2= H, $^nC_5H_{11}$
R^3= Me, Ph, CO_2Et

[(IP)Au(MeCN)]BF$_4$ (5 mol%)

CH$_2$Cl$_2$-HFIP (3:1), r.t.

8

6 examples (68-93%)

b)

CuCl$_2$ (20 mol%)
DABCO (2 equiv.)

DMSO, 80 °C, 2h
O$_2$ (1 atm)

10

6 examples (46-63%)

R^1= Ph, 4-OMe-C$_6$H$_4$, 4-Cl-C$_6$H$_4$
R^2= ^iPr, Ph, 4-OMe-C$_6$H$_4$, 4-Cl-C$_6$H$_4$

Scheme 4 (a) Synthesis of highly substituted pyrroles **8** through Au-catalyzed cyclization of *N*-propargylic β-enaminoesters **7**; (b) Synthesis of 4-carbonylpyrroles **10** via copper-mediated aerobic carbooxygenation of *N*-propargylic β-enaminoesters **9**.

K$_2$CO$_3$ (1-2 equiv.)

DMF, 60 °C,
3-24 h

13

15 examples (70-97%)

R^1= H, Ph
R^2= Me, Et, Ph
EWG= NO$_2$, CN, CO$_2$Me, MeCO, EtCO, C$_6$H$_5$NHCO, 4-ClC$_6$H$_4$NHCO, 4-MeC$_6$H$_4$NHCO, 4-MeOC$_6$H$_4$NHCO, 2-MeC$_6$H$_4$NHCO, 2-MeOC$_6$H$_4$NHCO, 2-ClC$_6$H$_4$NHCO, 2.4-Me$_2$C$_6$H$_4$NHCO

Scheme 5 Synthesis 2-ethylthio-pyrroles **13** developed by Zhao.

K$_3$PO$_4$ (20 mol%)

DMSO, 120 °C, 3 h

16

28 examples (63-81%)

R^1= H, Ph
R^2= H, Me, Et, ^nPr, Ph
R^3= ^nPr, ^iPr, ^nBu, ^iBu, ^sBu, ^tBu, ^cPen, ^cHex, ^noctyl, Bn
R^4= H, Me, CO$_2$Me

Scheme 6 Synthesis of polysubstituted pyrroles **16** from *N*-propargylamines **14** and activated alkynes **15**.
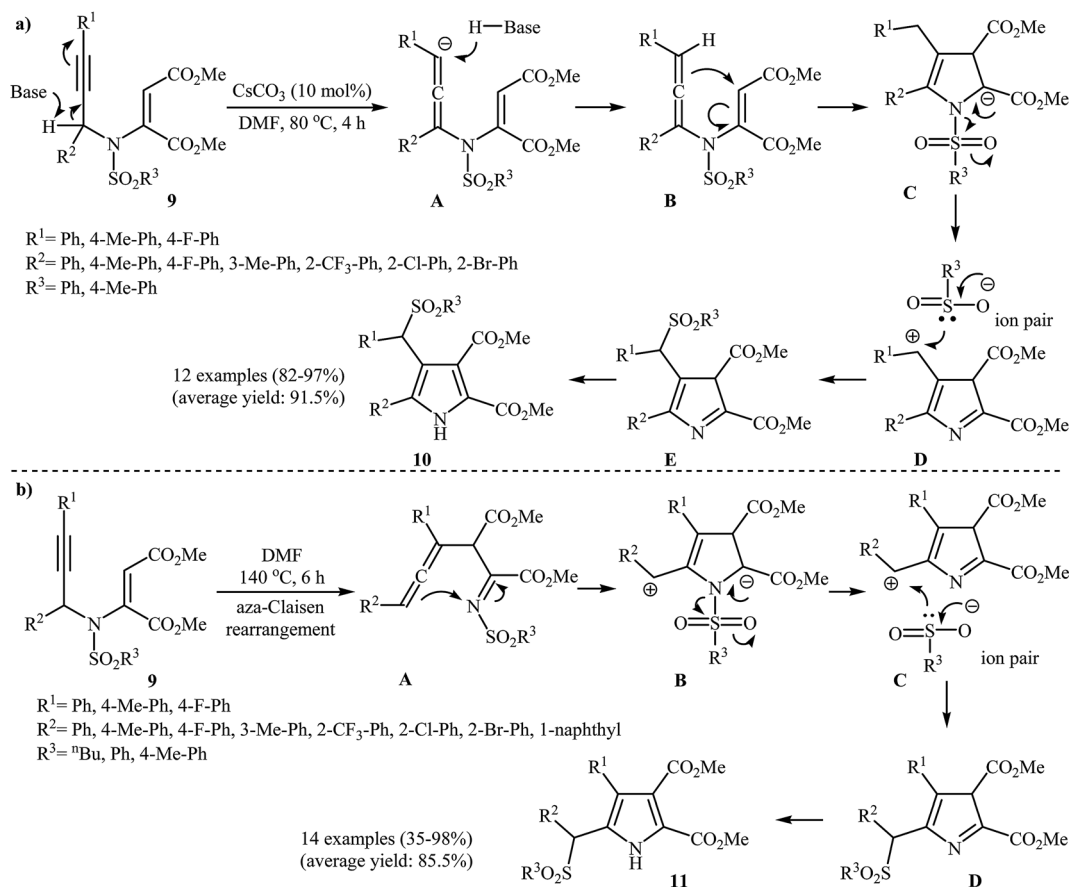
Scheme 7 Base-catalyzed synthesis of pyrrole derivatives **18** described by Zhang.

According to a plausible mechanistic pathway, this reaction proceeds through an aza-Claisen rearrangment/cyclization/sulfonyl group migration/aromatization sequential process (Scheme 8a). The authors claimed their reaction was the first example of sulfonyl group migration in pyrrole synthesis. The results demonstrated that the electronic characters of substrates had little effect on the rate of the reaction. Under optimized conditions, the reaction tolerates both electron-donating and electron-withdrawing substituents and gave the corresponding highly substituted N–H free pyrroles **20** in high to excellent yields. Interestingly, when the reaction was carried out in DMF at 140 °C under catalyst-free conditions, α-(arylsulfonyl)methyl pyrroles **21** were isolated instead of β-(arylsulfonyl)methyl pyrroles **20**. The mechanism proposed by the authors to explain this transformation is outlined in Scheme 8b.[10] Recently, the same authors applied this methodology to synthesis of a series of 2-trifluoromethyl-5-(arylsulfonyl)methyl pyrroles and 2-trifluoromethyl-4-(arylsulfonyl)methyl pyrroles from corresponding trifluoromethyl-substituted N-propargylic β-enaminoesters.[11]
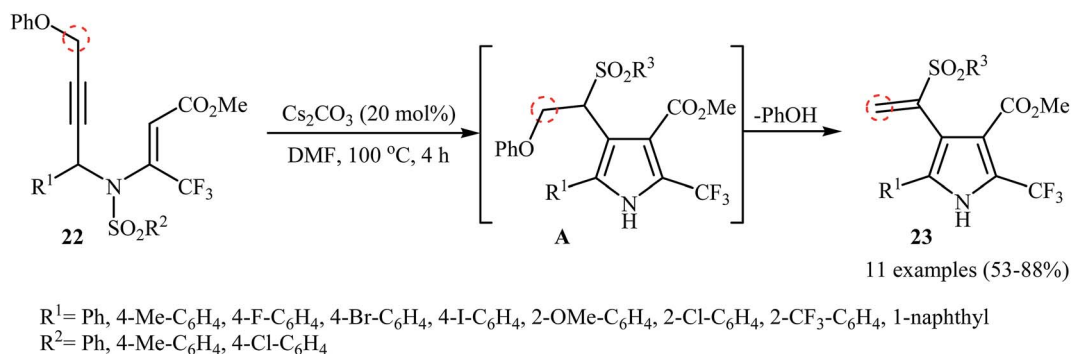
The groups of Wan also were able to demonstrate that a series of sulfonyl vinyl-substituted pyrroles **23** could be obtained from the corresponding phenoxysubstituted N-propargylic β-enaminoesters **22** employing 20 mol% of Cs$_2$CO$_3$ as catalyst in anhydrous DMF (Scheme 9). The reaction proceeds along the similar mechanistic pathway that described in Scheme 4a to afford intermediate **A**. This intermediate undergoes spontaneous phenol elimination to produce the observed products **23**.[12]

More recently, Cui and co-workers described a general and efficient synthesis of a diverse collection of biologically important highly substituted N-(2-pyridyl)pyrroles **25** via the KOH-promoted regiospecific cyclization of the corresponding N-
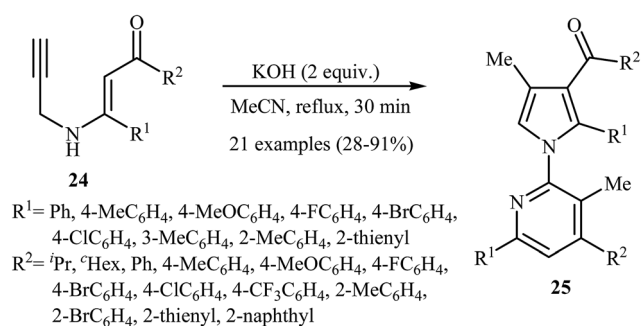

Scheme 8 (a) Base-catalyzed synthesis of β-(arylsulfonyl)methyl pyrroles **20** developed by Wan; (b) thermal cyclization of **19** for the synthesis of α-(arylsulfonyl)methyl pyrroles **21** reported by Wan.

R[1]= Ph, 4-Me-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Br-C$_6$H$_4$, 4-I-C$_6$H$_4$, 2-OMe-C$_6$H$_4$, 2-Cl-C$_6$H$_4$, 2-CF$_3$-C$_6$H$_4$, 1-naphthyl
R[2]= Ph, 4-Me-C$_6$H$_4$, 4-Cl-C$_6$H$_4$

Scheme 9 Wan's synthesis of sulfonyl vinyl-substituted pyrroles **23**.
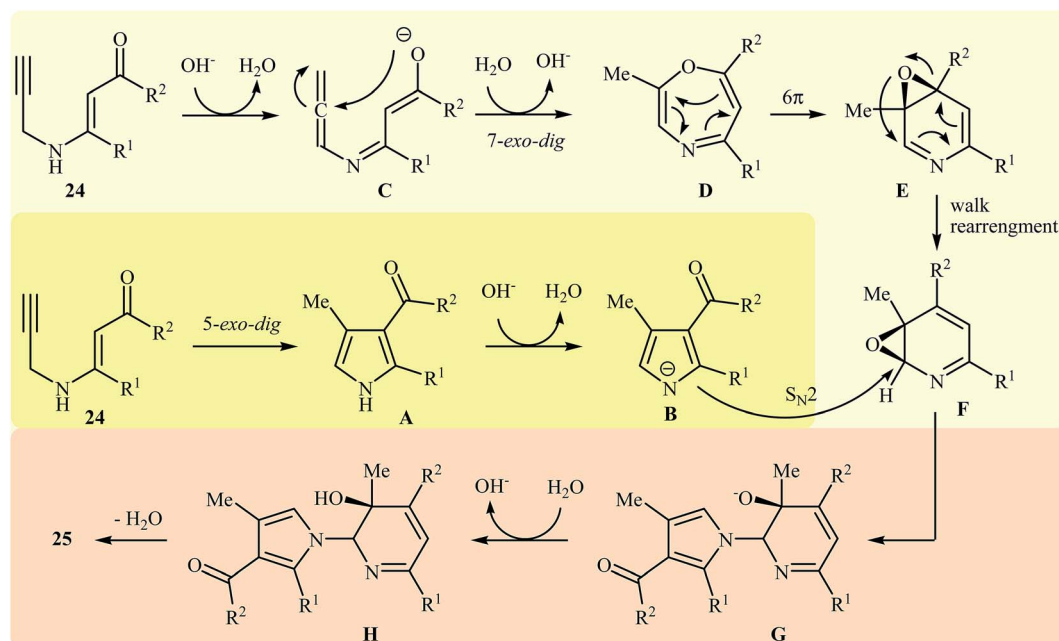

Scheme 10 Base-mediated cascade synthesis of *N*-(2-pyridyl) pyrroles **25** from *N*-propargylic *β*-enaminones **24** developed by Cui.

propargylic *β*-enaminones **24** under reflux conditions in aceto-nitrile (Scheme 10). This procedure simultaneously facilitated the construction of a pyridine scaffold and generation of a pyrrole ring from simple starting materials and the only by-

product is one equivalent of water. The proposed mechanism for this reaction involves the following steps (Scheme 11): (i) formation of a pyrrole anion intermediate **B** through intramolecular 5-*exo-dig* cyclization of *N*-propargylic *β*-enami-none **24**; (ii) formation of a 7-oxa-5-aza-bicyclo[4.1.0]hepta-2,4-diene intermediate **F** from another molecule of *N*-propargylic *β*-enaminone **24** *via* propargyl−allenyl isomerization/intramolecular 7-*exo-dig* cyclization/6π-electrocyclization/walk rearrangement sequential process; (iii) S$_N$2 attack of interme-diate **B** to dihydropyridine **F** to generate *trans*-2,3- dihydropyr-idine intermediate **G**; and (iv) protonation and aromatization of **G** to produce final product **25**.[13]
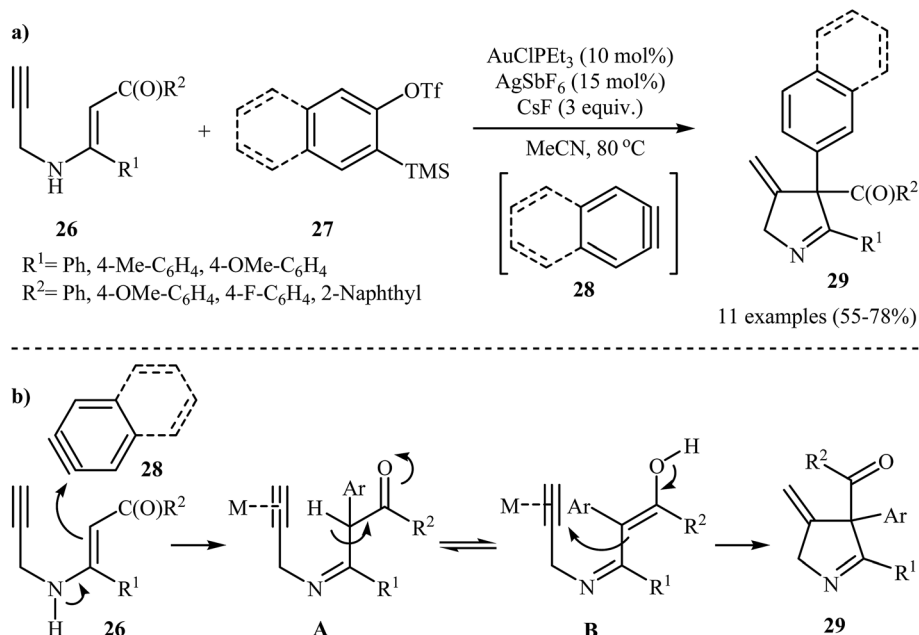
3. Pyrrolines

In 2014, the Karunakar group have developed a new and straightforward approach for the synthesis of substituted 1-pyrrolines **29** *via* a one-pot, Au(ɪ)-catalyzed reaction between *N*-
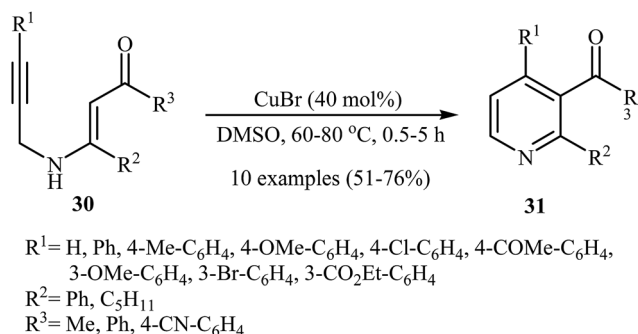

Scheme 11 Mechanism that accounts for the formation of **25**.

Scheme 12 (a) Synthesis of pyrrolines **29** developed by Karunakar; (b) plausible mechanism for the formation of **29**.

R^1= H, Ph, 4-Me-C$_6$H$_4$, 4-OMe-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-COMe-C$_6$H$_4$,
3-OMe-C$_6$H$_4$, 3-Br-C$_6$H$_4$, 3-CO$_2$Et-C$_6$H$_4$
R^2= Ph, C$_5$H$_{11}$
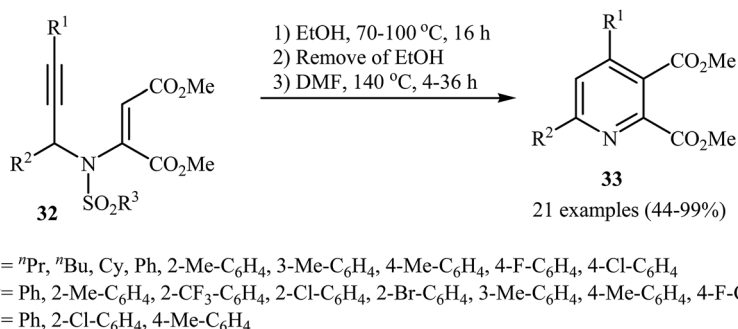R^3= Me, Ph, 4-CN-C$_6$H$_4$

Scheme 13 Cu(I)-catalyzed synthesis of pyridines **31** from *N*-propargylic β-enaminones **30**.

propargylic β-enaminones **26** and arynes **28** (generated *in situ* from 2-(trimethylsilyl)aryl trifluoromethanesulfonates **27** and CsF) (Scheme 12a). AuClPEt$_3$/AgSbF$_6$ was the best catalytic system and acetonitrile was the best solvent for this reaction.

The results demonstrated that the enaminones bearing electron donating groups, like Me and OMe, gave higher yields than those having an electron withdrawing group, like F group. The author proposed mechanism for this transformation is depicted in Scheme 12b.[14]
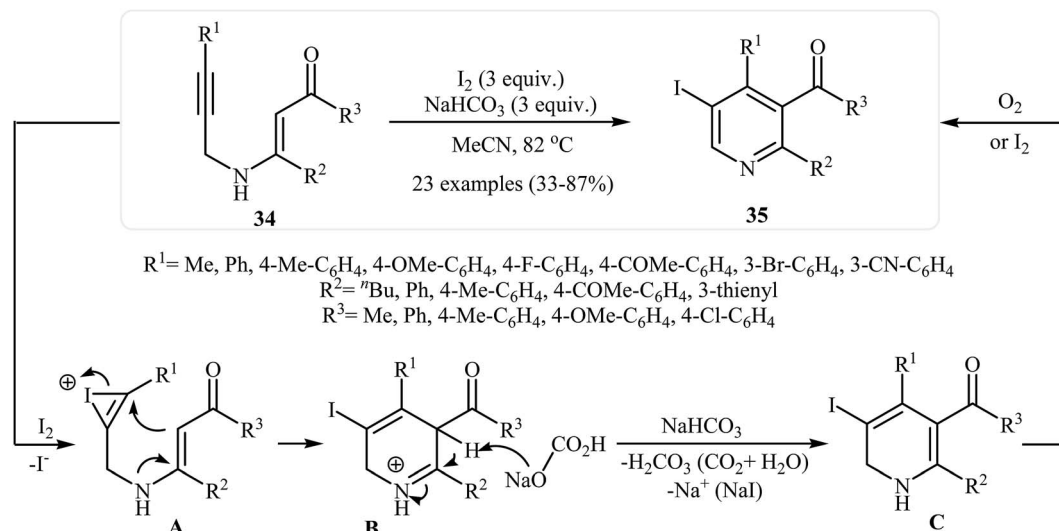
4. Pyridines

After the pioneering work of Cacchi and co-workers in 2008, who showed that highly substituted pyridines **31** could be readily synthesized in one step from easy available *N*-propargylic β-enaminones **30** through Cu-catalyzed 6-*endo-dig* cyclization strategy (Scheme 13),[3] this methodology has developed into a general powerful tool for the synthesis of a wide range of pyridine derivatives, including natural products.[15] In 2013, Wan's group developed a convenient one-pot three step methodology for the synthesis of 2,3,4,6-tetrasubstituted pyridines **33** from the *N*-sulfonylated *N*-propargylic β-enaminoesters **32** through an intramolecular cyclization/sulfinyl acids elimination cascade
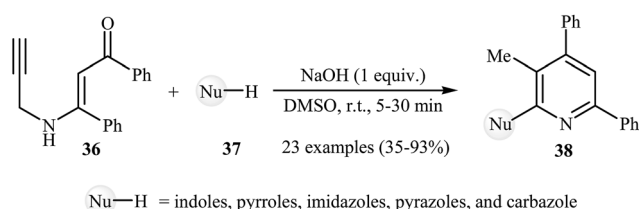

R^1= ^{n}Pr, ^{n}Bu, Cy, Ph, 2-Me-C$_6$H$_4$, 3-Me-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-Cl-C$_6$H$_4$
R^2= Ph, 2-Me-C$_6$H$_4$, 2-CF$_3$-C$_6$H$_4$, 2-Cl-C$_6$H$_4$, 2-Br-C$_6$H$_4$, 3-Me-C$_6$H$_4$, 4-Me-C$_6$H$_4$, 4-F-C$_6$H$_4$, 1-Naphthyl
R^3= Ph, 2-Cl-C$_6$H$_4$, 4-Me-C$_6$H$_4$

Scheme 14 Synthesis of 2,3,4,6-tetrasubstituted pyridines **33** described by Cacchi.

Scheme 15 Synthesis of 5-iodopyridines **35** from N-propargylic β-enaminones **34** via iodinemediated electrophilic cyclization.
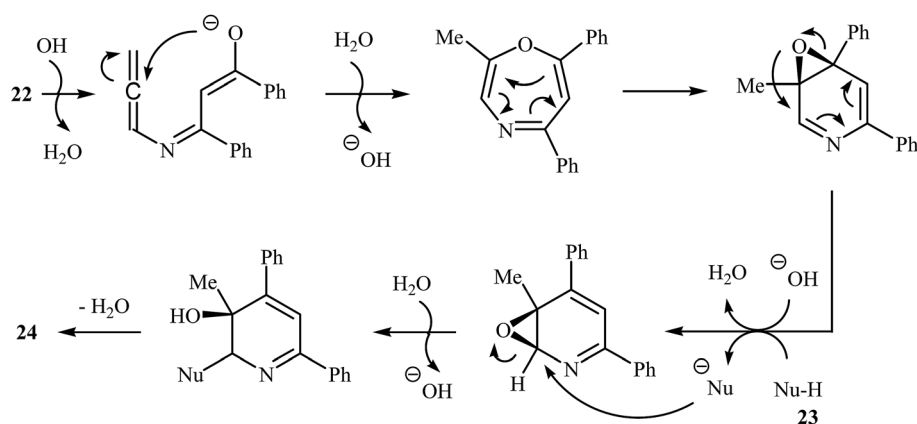

Scheme 16 Synthesis of 2-(1-heteroaryl) pyridines **38** developed by Cheng.

process (Scheme 14). Thus, in the first step a solution of **32** (0.2 mmol) in ethanol (2 mL) was heated at 70-100 °C for 16 h under argon atmosphere. In the next step the ethanol solvent was removed *in vacuo*. Finally, to the residue was added DMF (1 mL) and the mixture was heated at 140 °C for 4-36 h under argon atmosphere.[16]
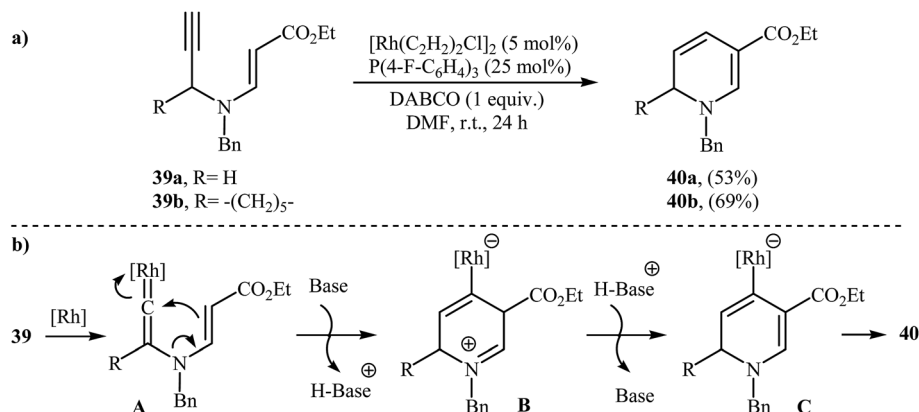
Recently an alternative intramolecular electrophilic cyclization of N-propargylic β-enaminones was reported by Zora and

coworkers. In this study, 5-iodopyridines **35** were obtained in good yields by reaction of N-propargylic β-enaminones **34** with 3.0 equiv of I_2 in MeCN at 82 °C in the presence of NaHCO$_3$ as base. The reaction proceeded *via* a 6-*endo-dig* process, giving only the six-membered rings. The authors proposed a mechanism initiated by the reaction of the alkyne moiety of starting β-enaminone **34** and iodine followed by an electrophilic cyclization with subsequent deprotonation/oxidation to explain the cyclized products obtained (Scheme 15).[17] Subsequently, the above cyclization products, applied by the same authors to the synthesis of more functionalized pyridines *via* transition metal-catalyzed processes, such as Sonogashira and Suzuki–Miyaura cross-coupling reactions.[18,19]
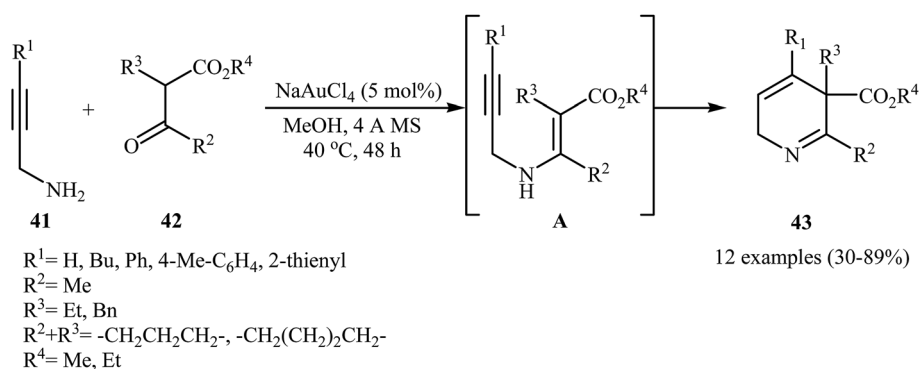
Recently, Cheng *et al.* developed a simple and efficient methodology for the synthesis of 2-(1-heteroaryl) pyridines **38** by the reaction between 1,3-diphenyl-3-(prop-2-ynylamino)prop-2-en-1-one **36** and N-heteroarenes **37** (Scheme 16).[20] NaOH was the most efficient catalyst among the bases such as LiO^{t}Bu, NaO^{t}Bu, K$_2$CO$_3$, KOH, Et$_3$N *etc* for this reaction. This NaOH-

Scheme 17 Mechanistic proposal for the reaction in Scheme 15.

Scheme 18 (a) Rh-catalyzed synthesis of 1,6-dihydropyridine-3-carboxylates **40** reported by Kim and Lee; (b) Mechanism that accounts for the formation of **40**.

Scheme 19 Au-catalyzed synthesis of highly substituted 2,5-dihydropyridines **43** from *N*-propargyl amines **41** and *β*-keto esters **42** through a *N*-propargylic *β*-enaminoester intermediate **A**.
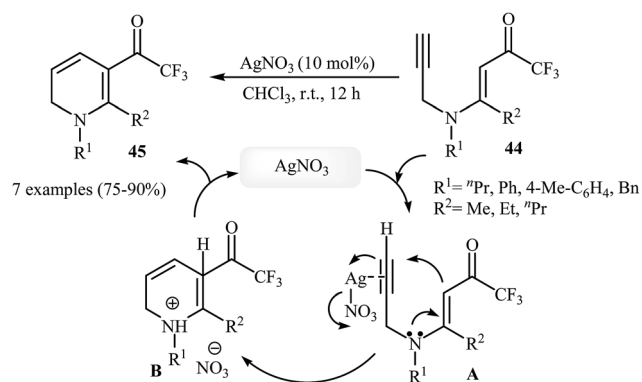
catalyzed reaction is applicable for a diverse set of nitrogen nucleophilic source, such as indole, pyrrole, imidazole, pyrazole, carbazole, and benzimidazole. However, the reaction of benzimidazole and **36** gave the desired product in unsatisfactory yield and aniline, benzylamine, succinimide, acetanilide, and benzyl thiol failed to participate in the reaction. According to the suggested reaction mechanism (Scheme 17), the reaction proceeds *via* a propargyl–allenyl isomerization/enolization/7-*exo-dig* cyclization/6π-electrocyclization/walk rearrangement/epoxide ring opening/dehydrative aromatization sequential process.

5. Dihydropyridine

N-propargylic *β*-enaminoesters **39** were found by Kim and Lee to undergo intramolecular cyclization in the presence of catalytic amount of [Rh(C₂H₂)₂Cl]₂, using P(4 F-C₆H₄)₃ as ligand and DABCO as base in DMF at room temperature, to afford 1,6-dihydropyridine-3-carboxylates **40** in moderate yields (Scheme 18a). The mechanistic course of this reaction sequence is shown in Scheme 18b, and involves the initial formation of the rhodium vinylidene complex **A** from the reaction of alkyne moiety of **39** with rhodium. Intramolecular cyclization of **A**
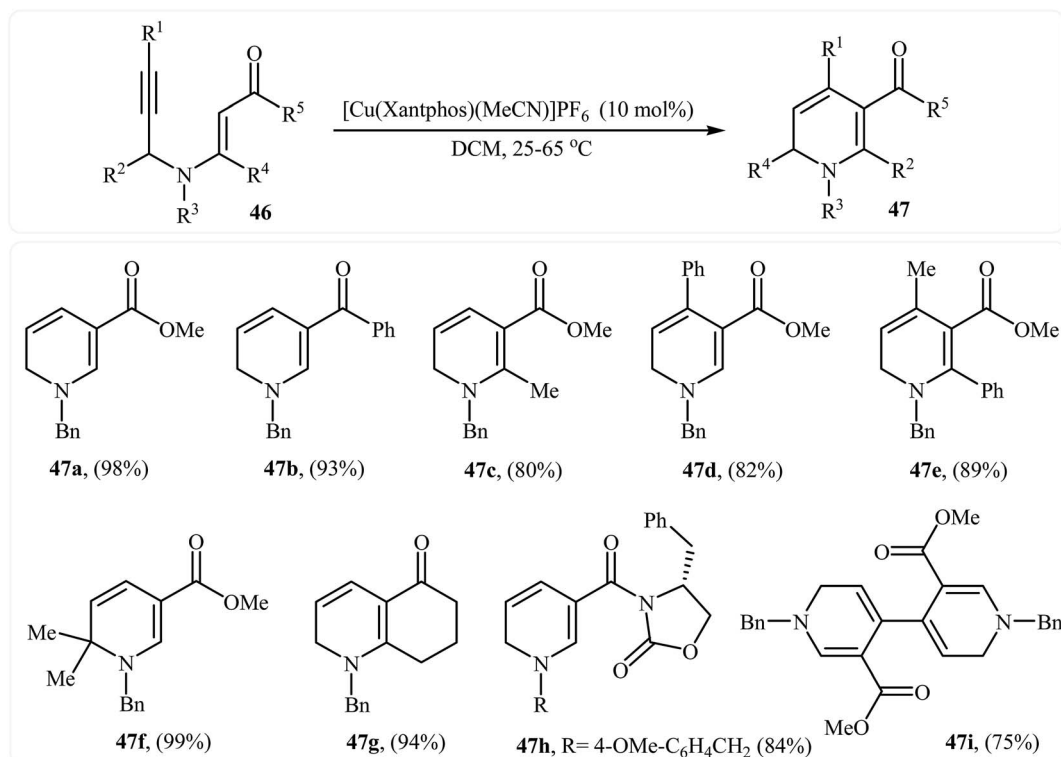
yields intermediate **B**, which undergoes deprotonation to furnish intermediate **C**. Finally, protodemetalation of intermediate **C** affords the observed dihydropyridines **40**.[21]

The preparation of 2,5-dihydropyridines **43** can be achieved through a 6-*endo-dig* cyclization of *N*-propargylic *β*-enaminesters **A** (generated *in situ* from condensation of *N*-propargyl
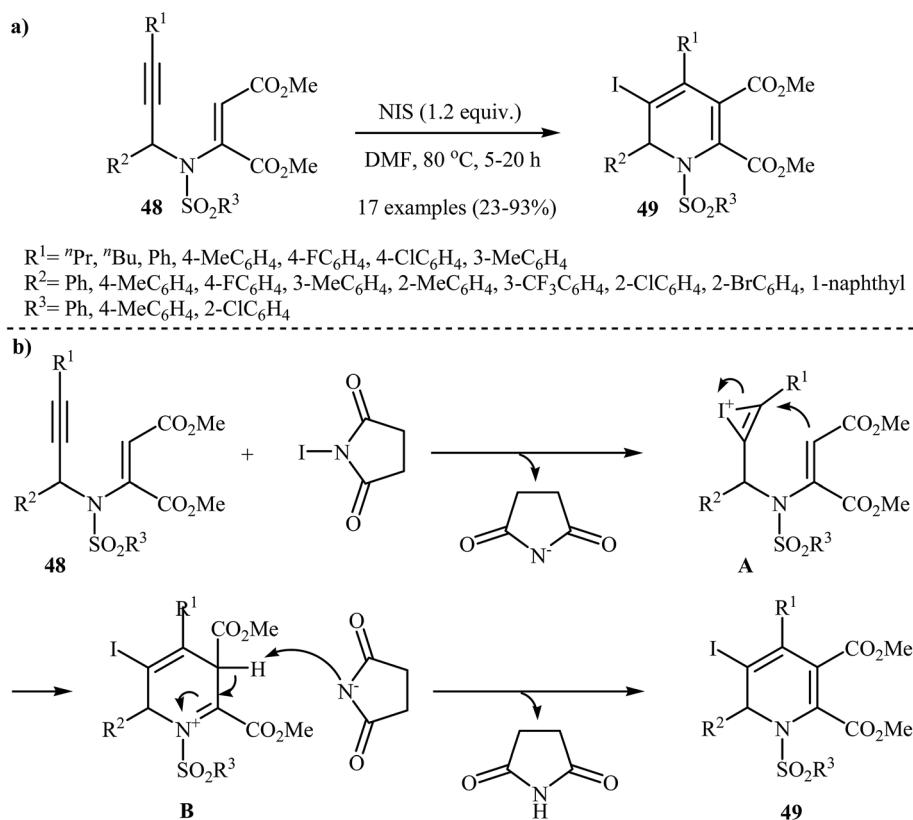

Scheme 20 Construction of trifluoromethylated 1,2-dihydropyridines **45** through Au(ı)-catalyzed 6-*endo-dig* cyclization of *N*-propargylic *β*-enaminones **44**.
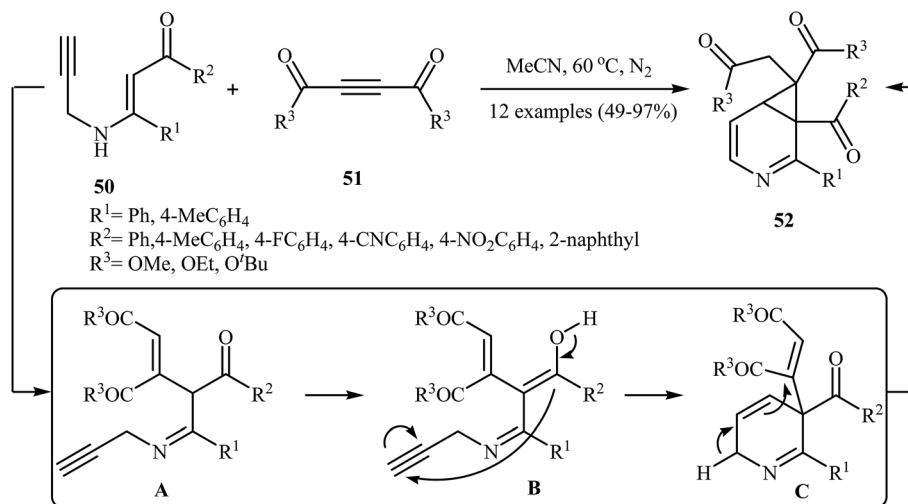
Scheme 21 Synthesis of highly substituted 1,2-dihydropyridines **47** through Cu(I)-catalyzed 6-*endo* cyclization of *N*-propargylic *β*-enamino-carbonyls **46**.

R^1 = ^{n}Pr, ^{n}Bu, Ph, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-MeC$_6$H$_4$
R^2 = Ph, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, 3-CF$_3$C$_6$H$_4$, 2-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, 1-naphthyl
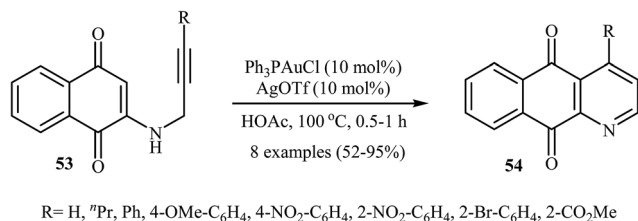R^3 = Ph, 4-MeC$_6$H$_4$, 2-ClC$_6$H$_4$

Scheme 22 (a) *N*-iodosuccinimide-induced electrophilic iodocyclization of *N*-propargylic *β*-enaminoesters **48** to 3-iodo-1,2-dihydropyridine product **49**; (b) Proposed mechanism for formation of **49**.

Scheme 23 Catalyst-free synthesis of 3-azabicyclo[4.1.0]hepta-2,4-dienes **52** reported by Karunakar.

R= H, ^nPr, Ph, 4-OMe-C_6H_4, 4-NO_2-C_6H_4, 2-NO_2-C_6H_4, 2-Br-C_6H_4, 2-CO_2Me
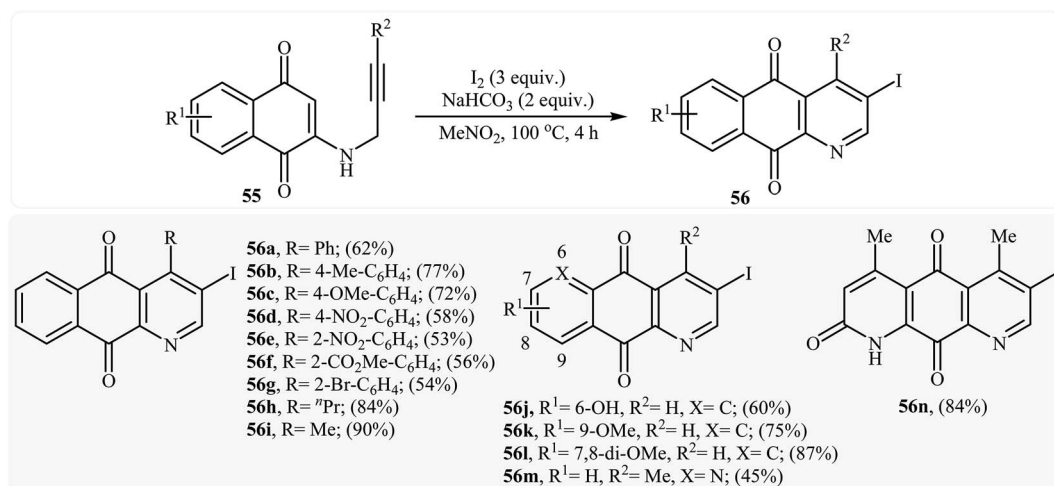
Scheme 24 Wang's synthesis of azaanthraquinones **54** from *N*-propargylamino quinones **53**.

amines **41** and β-keto esters **42**) (Scheme 19). The best condition used for this transformation was 5 mol% of NaAuCl$_4$ and MeOH at 40 °C.[22]

In 2013, Martins and co-workers disclosed a mild and practical access to trifluoromethylated 1,2-dihydropyridines **45** through Au(I)-catalyzed 6-*endo-dig* cyclization of corresponding *N*-propargylic β-enaminones **44** (Scheme 20). A number of 1,2-dihydropyridines containing aromatic or aliphatic motifs were

readily afforded in high yields. Mechanistically, the triple bond is activated by coordination with silver to form a π-alkyne complex **A**, which then undergoes a 6-*endo-dig* cyclization to produce cationic intermediate **B**. Subsequently, an intramolecular proto-demetalation leads to the product **44**.[23] In a closely related investigation, the Oguri group found that *N*-propargylic β-enaminocarbonyls **46** were converted to the corresponding substituted 1,2-dihydropyridines **47**, *via* 6-*endo-dig* cyclization using [Cu(Xantphos)(MeCN)]PF$_6$ as catalyst in DCM at room temperature (Scheme 21).[24]

Recently, Wan and co-workers performed the iodocyclization of *N*-propargylic β-enaminoesters **48** with *N*-iodosuccinimide as electrophilic source and developed a route to obtain 3-iodo-1,2 dihydropyridines **49** in good yields (Scheme 22a). A plausible mechanism for these electrophilic cyclizations is shown in Scheme 22b, where intermediate **A**, generated by the attack of iodonium ion to the alkyne moiety, undergoes 6-*endo-dig* cyclization, and then deprotonation, to afford 3-iodo-1,2-dihydropyridine product **49**.[25]

Scheme 25 Formation of 3-iodo-1-azaanthraquinones **56** by the iodocyclization of *N*-propargylamino quinones **55**.

In 2014, Karunakar *et al.* synthesized 3-azabicyclo[4.1.0]hepta-2,4-dienes **52**, a cyclopropane fused dihydropyridine system, by the catalyst- and base-free cascade reaction between internal *N*-propargylic β-enaminones **50** and acetylenedicarboxylates **51** (Scheme 23). Among the various solvents like DMF, THF, DCM, EtOH, EtOAc, CHCl₃, MeCN, toluene, 1,4-dioxane, H₂O; MeCN was the most efficient for this reaction. The results demonstrated that *N*-propargylic β-enaminones bearing electron-donating groups afforded higher yields in comparison to those bearing electron- withdrawing groups. Following is the decreasing order of reactivity of acetylenedicarboxylates in this reaction: diethyl but-2-ynedioate > di-*tert*-butyl but-2-ynedioate > dimethyl but-2-ynedioate.[26]

6. 1-Azaanthraquinones

In 2010, the groups of Wang published an elegant and novel protocol for the synthesis of substituted azaanthraquinones using Au(ɪ)-catalyzed 6-*endo-dig* cycloisomerization of *N*-propargylamino quinones **53**.[27] Thus, the optimized reactions revealed that the optimum condition for this cyclization reaction was the combination of Ph₃PAuCl (10 mol%) and AgOTf (10 mol%) as catalytic system using acetic acid as the solvent, at 100 °C. Under optimized conditions, the reaction tolerates both terminal and internal alkynes and gave the products **54** in good yields (Scheme 24). This reaction proceeds through 6-*endo-dig* cyclization followed by a sequential tautomerization/aromatization. It is noted that the protocol was successfully applied for the synthesis of alkaloid cleistopholine and its analogues.
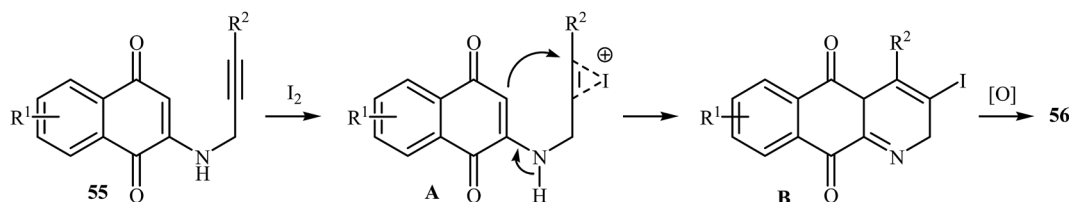
In a subsequent study, the same research team reported the preparation of a variety of 3-iodo-1-azaanthraquinones **56** in moderate to high yields *via* iodocyclization of *N*-propargylamino quinones **55** (Scheme 25). The reactions were carried out in nitromethane at 100 °C with 3 equiv of molecular iodine as the electrophilic source and NaHCO₃ (2 equiv) as the base. The mechanism shown in Scheme 26 was proposed for this process. It consists of the following key steps: (1) initial formation of iodonium ion **A** *via* coordination of iodine with the C–C triple bond of alkyne; (2) nucleophilic attack by the double bond of the aminoquinone through 6-*endo-dig* manner to afford the intermediate **B**; and (3) oxidative aromatization of intermediate **B** to give the observed product **36**.[28] Soon after, the authors extended this chemistry to synthesis of 3-chloro-1-azaanthraquinones employing CuCl₂ as electrophilic source.[29]
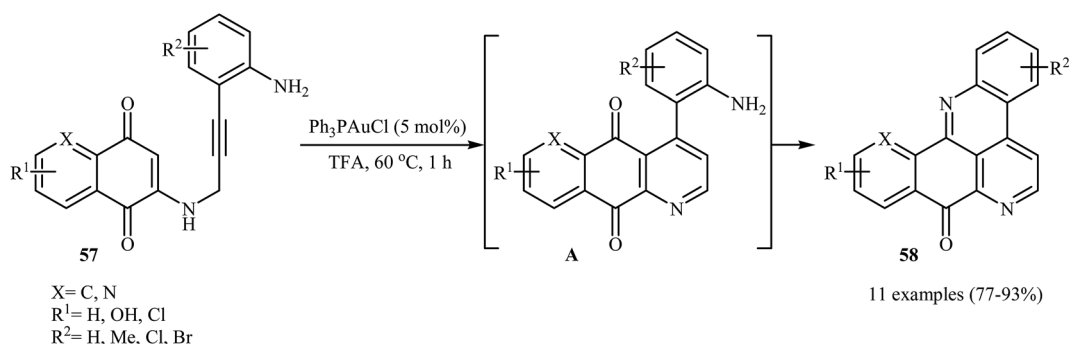
Follow these works, the authors reported the preparation of a variety of pentacyclic pyrido[4,3,2-mn]acridin-8-ones **58** in good to high yields *via* an Au(ɪ)-catalyzed domino reaction of *N*-propargylaminoquinones **57** (Scheme 27). Among the various gold catalysts like AuCl, AuCl₃, Ph₃PAuCl, NaAuCl₄·H₂O; Ph₃-PAuCl was the most efficient for the transformation. The results demonstrated that the substrates bearing electron-donating groups on the aniline ring afforded relatively higher yields in comparison to those bearing electron withdrawing groups.[30]

7. 1,4-Oxazepines

In 2015, the Karunakar group have developed a new and straightforward approach for the synthesis of 1,4-oxazepine derivatives **60** *via* a one-pot gold-catalyzed intramolecular cyclization of *N*-propargylic β-enaminones **59** (Scheme 28). Thus, the careful analysis of the optimized reactions revealed that the optimum condition for this cyclization was the addition of AuCl₃ (10 mol%), and AgSbF₆ (15 mol%), at 28 °C, to a solution of *N*-propargylic β-enaminones in MeOH. The reaction scope appears that the *N*-propargylic β-enaminones with electron-donating groups on the benzene rings are reactive than

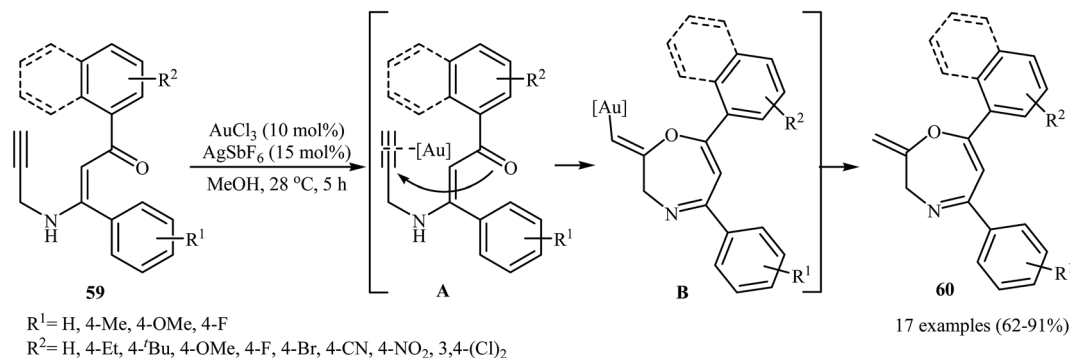**Scheme 26** Mechanism that accounts for the formation of **56**.

X= C, N
R¹= H, OH, Cl
R²= H, Me, Cl, Br

11 examples (77-93%)

Scheme 27 Au(ɪ)-catalyzed synthesis of pentacyclic pyrido[4,3,2-mn]acridin-8-ones **58** from *N*-propargylaminoquinones **57**.

Scheme 28   Au-catalyzed intramolecular cyclization of *N*-propargylic β-enaminones **59** for the synthesis of 1,4-Oxazepine derivatives **60**.

those with electron-poor aryl groups. According to mechanistic studies, it proceeds through the coordination of $AuCl_3$ to the triple bond of **59**, following the *7-exo-dig* cyclization *via* nucleophilic attack of carbonyl oxygen onto the activated triple bond to give intermediate **B**, which undergoes protodemetalation to yield 1,4-oxazepine derivatives **60**.[31]

8. Azepines

The reported methods for synthesis of azepine cores *via* intramolecular cyclization of *N*-propargylic β-enaminocarbonyls are very scarce and to the best of our awareness there is only one report for such reactions. More recently, Sahoo's research team reported a beautiful protocol for synthesis of hitherto unknown cyclobutene fused azepine heterocycles **62** by cycloisomerization of corresponding alkyne-tethered ketene *N*,*N*-acetals **61** in the
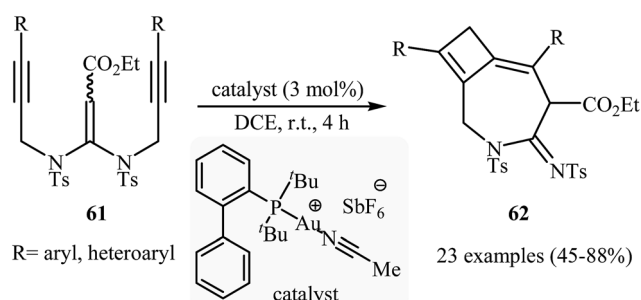
presence of [JohnphosAu(I) (MeCN)]$^{+}$SbF$_6^{-}$ as catalyst (Scheme 29). This reaction was run in 1,2-dichloroethane at room temperature and tolerated various sensitive functional groups (including nitro, cyano, chloro, ketone, and ester), and in all cases provided fused azepines **2** in moderate to good yields.[32] In this study, the authors also evaluated the mechanistic details of this electrophilic cyclization. To determine the advanced intermediates of the reaction, the authors monitored the reaction by ^{1}H NMR spectroscopy. Among the data that could be obtained by ^{1}H NMR spectroscopy, the most relevant for the proposal was those shown in Scheme 30.
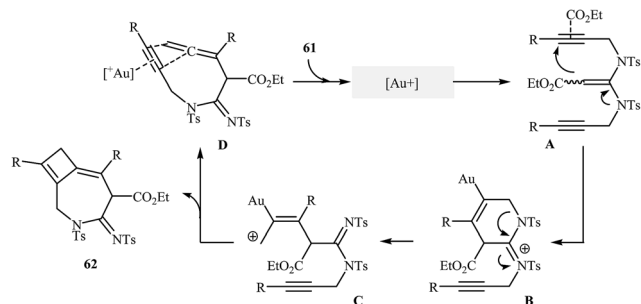
9. Summary and outlook

Synthesis of nitrogen-based heterocycles *via* cyclization of *N*-propargylic β-enaminocarbonyls, in both inter- and interamolecular manner, have witnessed rapid and comprehensive development in the past ten years. In comparison with many well-established traditional and modern methods, the preparation of *N*-heterocycles (such as pyrroles, pyrrolines, pyridines, piperidine as well as azaanthraquinones, and so forth) from titled compounds showed a wider tolerance to important functional groups. This made possible the further derivatization of the products. As illustrated, high atom economy and shorter synthetic routes are the key features of these reactions. Also interesting is the fact that most of the cyclization reactions covered in this review could be easily adapted to the gram-scale synthesis of *N*-heterocycles. The present methodologies are meaningful and particularly attractive for the fact that those *N*-heterocycles are the structural component of a vast number of biologically active natural and unnatural compounds. We believe that these salient features of *N*-propargylic β-enaminocarbonyls in the synthesis of *N*-heterocycles will further elicit widespread attention in the quest for more applications and utilities, serving as a powerful and versatile substrate in the synthesis of important *N*-heterocycles and complex natural products.

Scheme 29   Au-catalyzed intramolecular cyclization of alkyne-tethered ketene *N*,*N*-acetals **61** for the synthesis of cyclobutene fused azepine heterocycles **62**.

Acknowledgements

Scheme 30   Mechanistic proposal for the reactions in Scheme 18.

University for their valuable comments and suggestions to improve the quality of the paper.

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