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A new avenue to the synthesis of highly substituted pyrroles: synthesis from *N*-propargylamines (A Review)

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Abstract

Pyrroles have attracted much attention due to their potential biological activities. Developing more efficient methods for generation of pyrrole cores with unusual substitution patterns e.g. 2,4-disubstituted pyrroles is particularly interesting. This review gives an overview of new developments in synthesis of highly substituted pyrroles from *N*-propargylamines in recent years.

Key words: Pyrrole, *N*-propargylamine, 5-*exo*-*dig* cyclization, 5-*endo*-*dig* cyclization, Diels-Alder Reaction

1. Introduction

The pyrrole compound is not only prevalent in a wide variety of important classes of natural products[1] and synthetic pharmaceuticals[2] but also used as a building block in organic synthesis[3]. Consequently, many efforts have been devoted to the design of expedient and efficient synthetic routes to this heterocycle. Some of the most popular methods for their preparation include the Knorr[4], Pall-Knorr[5], Hantzsch[6], aza-Wittig[7], metal-catalyzed cross-coupling[8], and especially multicomponent reactions[9]. Widespread use of these methods is limited by require expensive metal catalysts, by the production of harmful waste streams, or both.

The *N*-propargylamine motifs are privileged scaffolds in chemistry due to their presence in a large number of natural and unnatural compounds with important properties, both in pharmacology and materials science[10]. Overall, they are highly useful building blocks in organic synthesis and have been abundantly used as precursors in the synthesis of heterocyclic compounds[11] and complex natural products[12]. In this regard, the synthesis of pyrrole cores from *N*-propargylamines have undergone an explosive growth in recent years. Synthesis of pyrroles from *N*-propargylamines provides a novel avenue to titled compounds

that in the most cases, have many advantages over more conventional methodologies, which can be summarized as follows:

1. Nontoxic by-products
2. High atom economy
3. Ease of handling
4. Environmentally friendly processes
5. High yielding, wide in scope
6. Mild synthetic route for compounds with unusual substitution patterns (e.g. 2,4-disubstituted pyrroles)

To the best of our awareness, a comprehensive review has not appeared on synthesis of pyrroles from *N*-propargylamines in literature so far. In this review, we have classified these reactions based on the type (e.g. intra- and intermolecular reactions) and the starting materials (e.g. cyclization of *N*-vinylpropargylamines, *N*-allylpropargylamines, and *N*-propargylpropargylamine). The main methods for synthesis of titled compounds from *N*-propargylamines are summarized in Fig. 1.

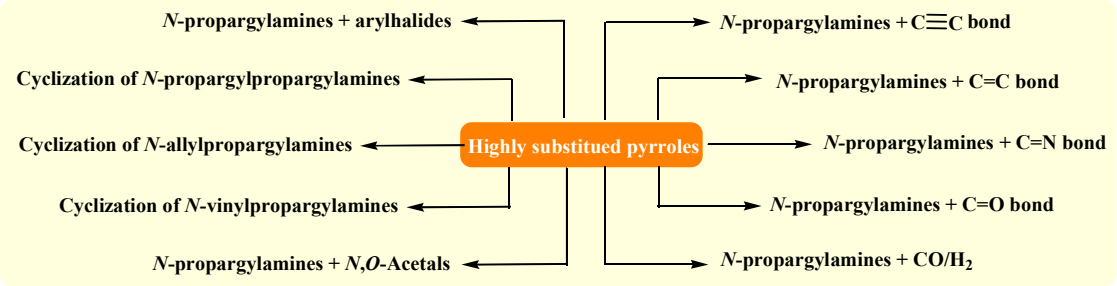


Figure 1. The main approaches for synthesis of highly substituted pyrroles from *N*-propargylamines.

2. Synthesis of Highly Substituted Pyrroles from *N*-propargylamines *via* Intermolecular Reactions

2. 1. From N-propargylamines and Carbonyl Compounds

In 1988, Tsuda, and co-workers reported an example of cycloaddition of *N*-propargylamines with aldehydes. They showed that *N*-(pent-2-ynyl)-*N*-propylpent-2-yn-1-amine **1** underwent a cyclization reaction with benzaldehyde in the presence of $Ni(COD)_2$ as catalyst, PPh_3 as ligand in THF at 120 ^oC. The desired product **3** was obtained in excellent yield of 97%. They probed the mechanism of the reaction and found that the reaction proceeded by generation of

a 1,2 bis(alkylidene)cycloalkane intermediate **B**, followed by cycloisomerization of the resulting dihydropyrrole **C** from rearrangement of **B** to corresponding pyrrole **3** (Figure 2)[13].

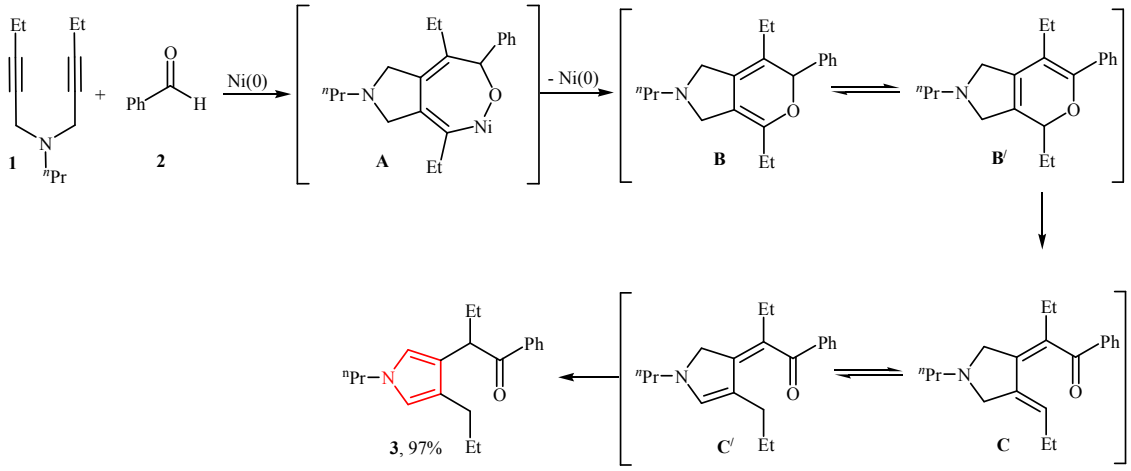
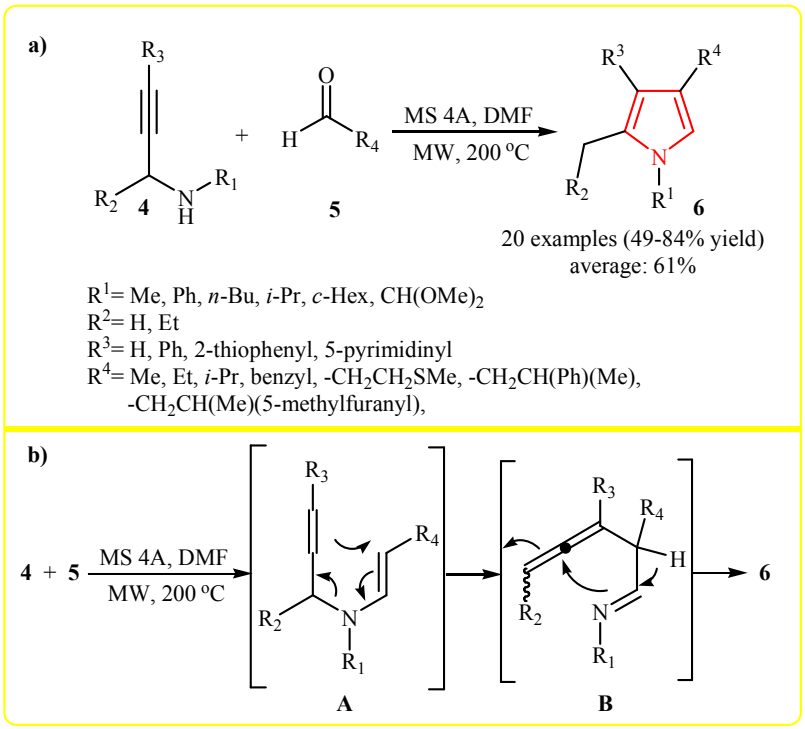


Figure 2. Proposed mechanism for synthesis of pyrrole **3** *via* cycloaddition of *N*-propargylamine 1 with aldehyde **2**

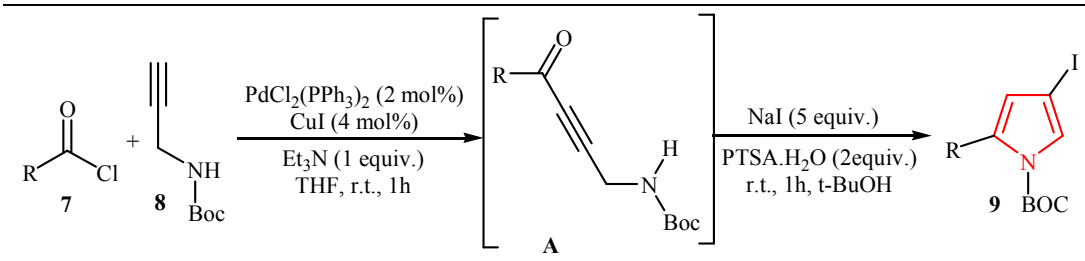
Comprehensive synthesis of a diverse collection of highly substituted pyrroles **6** from treatment of *N*-propargylamines **4** with aldehydes **5** was reported by Bremner and Organ. The reaction was undertaken at 200 ^{o}C under microwave irradiation in presence of 4 Å molecular sieves in DMF. The reaction scope appears to be quite broad as alkyl, aryl, and hetaryl groups were tolerated at various substitution sites of both reaction components and gave corresponding pyrroles **6** in good yields (Scheme 1a). According to the proposed mechanism, the reaction involves: 1) the condensation of **4** with **5** which results the intermediate enynamine **A**; 2) [3,3]-pericyclic rearrangement of **A** to form the imino-allene intermediate **B**; and 3) cyclization of **B** to afford pyrrole **6** (Scheme 1b)[14].



Scheme 1. a) Microwave-assisted synthesis of pyrroles **6** from treatment of *N*-propargylamines **4** with aldehydes **5**. b) Proposed mechanism for formation of **6**

Müller's group described the synthesis of 2-substituted *N*-Boc-4-iodopyrroles **9** *via* an efficient Pd/Cu-catalyzed one-pot three component reaction of acid chlorides **7**, *N*-Boc-protected propargylamine **8**, and NaI. The reaction starts with the formation of an alkynone intermediate **A** *via* Sonogashira cross-coupling reaction of **7** with **8**, and then the addition-cyclocondensation of A with NaI furnishes corresponding pyrroles in good yields (Table 1). The authors extended the applicability of this protocol for the synthesis of 4-Alkynyl-*N*-Boc-pyrroles **11** by addition of another terminal alkyne **10** to the reaction mixture (Scheme 2)[15].

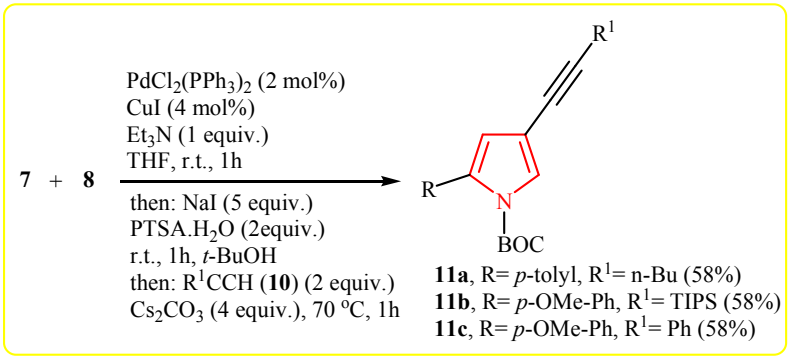
Table 1. Pd/Cu-catalyzed one-pot three-Component synthesis of 4-iodopyrroles



Entry	R	Yield (%)	Entry	R	Yield (%)
1	4-Me-Ph	73	7	4-F-Ph	75

2	3-Me-Ph	74	8	2-thienyl	63
3	2-Me-Ph	72	9	*β*-styryl	70[a]
4	4-OMe-Ph	73	10	Cyclopropyl	69[b]
5	Ph	72	11	1-adamantyl	61[a]
6	4-Cl-Ph	62			

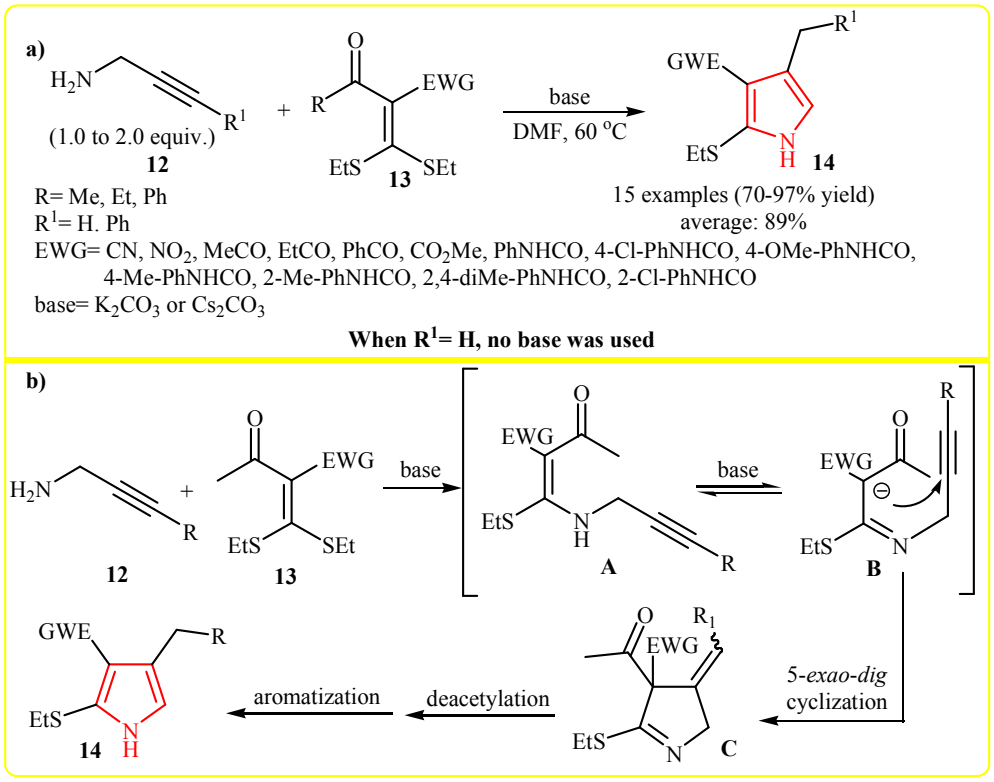
[a] The reaction time for the coupling step was 21 h. [b] The reaction time for the coupling step was 3 h.



Scheme 2. Coupling-addition-cyclocondensation-coupling sequence to 4-alkynyl-*N*-Boc-pyrroles **11**.

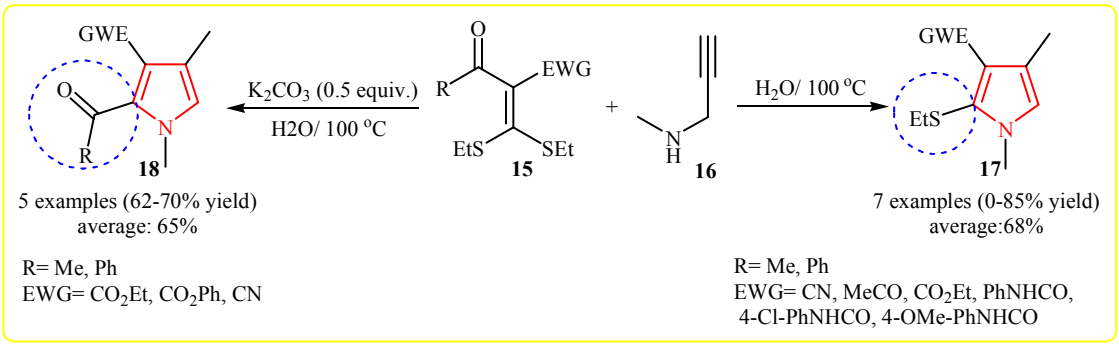
2.2. From N-propargylamines and C-C double or triple bond

An interesting approach toward the synthesis of highly substituted pyrroles *via* cycloadition of *N*-propargylamines and C-C double bonds was developed by Zhao *et al* (Scheme 3a,b). Thus, a variety of trisubstitued pyrroles **14** were synthesized *via* the base catalyzed [2+3]-cycloadition of propargylamines **12** and *α*-acylketene dithioacetals **13** in DMF (Scheme 3a). According to the proposed mechanism, the reaction starts with intramolecular Michael addition of **12** to **13** to form the intermediates **A** and **B**. Subsequently the 5-*exo-dig* cyclization of **B**-isomer give intermediate **C** that undergoes a sequential deacetylation and aromatization to afford expected pyrroles **14** (Scheme 3b)[16].

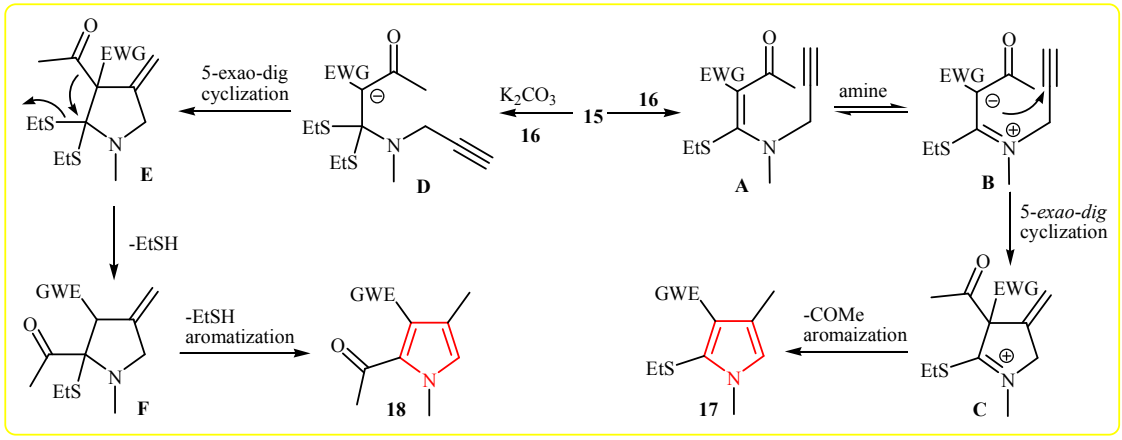


Scheme 3. a) [3+2] cycloaddition of propargylamines **12** and α-acylketene dithioacetals **13** to pyrroles **14**. b) Proposed mechanism for formation of **14**.

Shortly after, the same group expanded this methodology to the synthesis of 1,2,3,4-tetrasubstituted pyrroles **17**, **18** by cycloadition of acetyl ketene dithioacetals **15** and secondary propargylamine (*N*-methylprop-2-yn-1-amine) **16** in water. Interestingly, this protocol showed different reaction behaviors depending on the addition or absence of an external base. In the presence and absence of an external base, the reaction gave the 1,2,3,4-tetrasubstituted pyrroles bearing a acetyl group and ethylthio group at the C2 of the pyrrole core, respectively (Scheme 4)[17]. A plausible mechanisms for formation of **17** and **18** is depicted in Scheme 5.

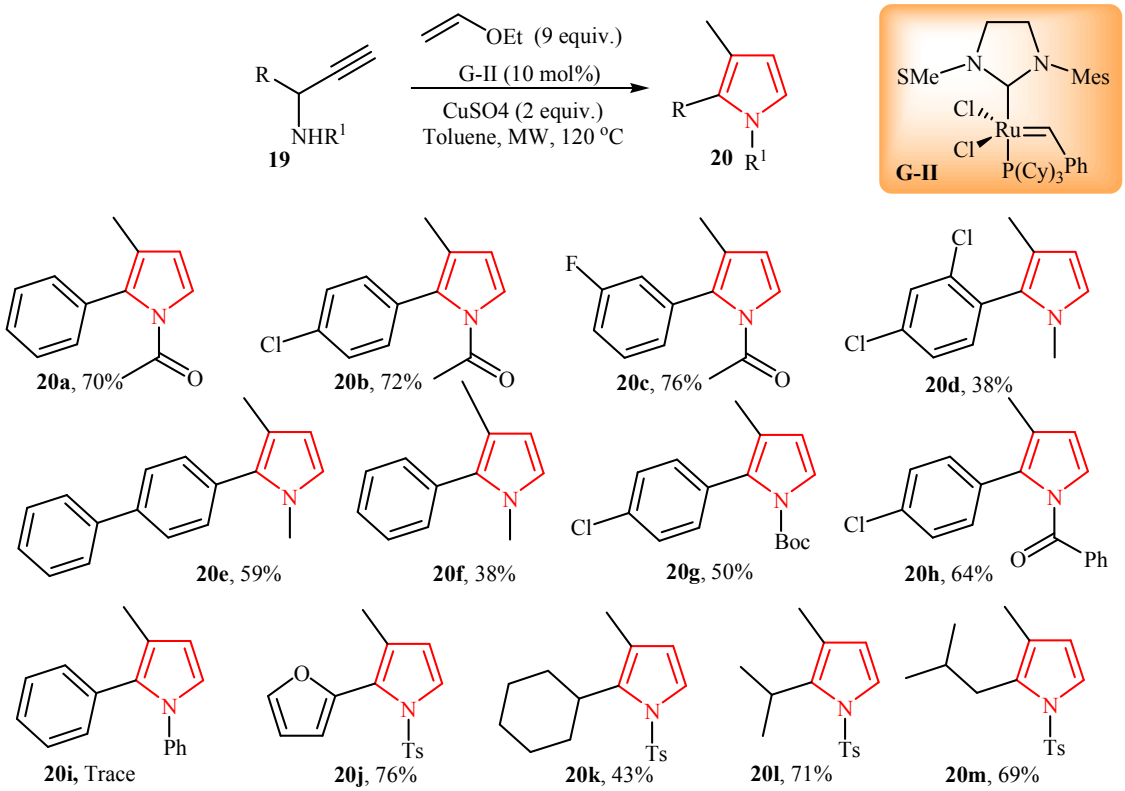


Scheme 4. Synthesis of 1,2,3,4-tetrasubstituted pyrroles by cycloadition of *N*-methylprop-2-yn-1-amine and acetyl ketene dithioacetals



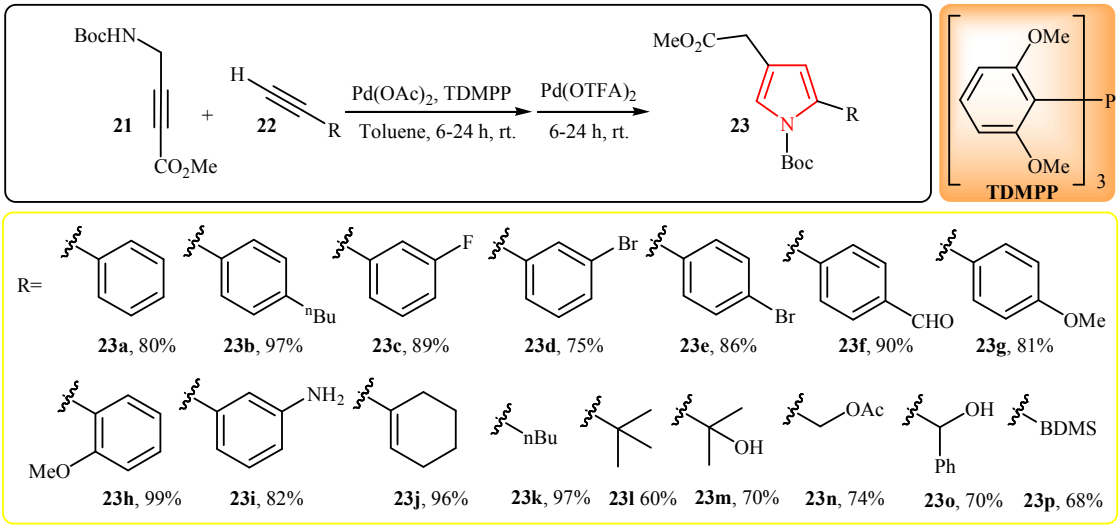
Scheme 5. Proposed mechanisms for formation of **3** and **4**.

Very recently, Castagnolo and co-workers reported an interesting method for synthesis of 1,2,3-substituted pyrroles **20** *via* enyne cross metathesis of propargylamines **19** with ethyl-vinyl ether in the presence of Grubbs'catalyst under microwave irradiation. It is noted that the presence of $CuSO_4$ as promoter is vital for this reaction. Under optimized condition, the reaction worked well with both alkyl and aryl substituted amines. However, the scope of the reaction is limited to electron-poor amines and sterically hindered *N*-propargylamine failed to react under aforementioned conditions (Scheme 6)[18].



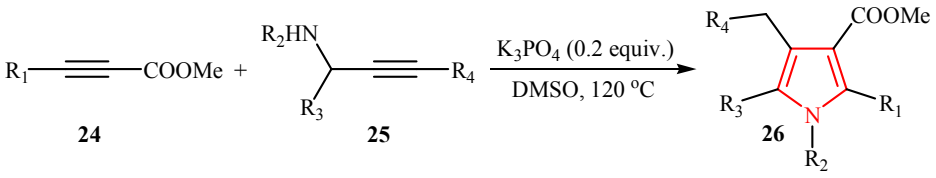
Scheme 6. Synthesis of 1,2,3-substituted pyrroles **20** from propargylamines **19**.

In 2011, Trost *et al*. developed the synthesis of pyrroles **23** by Pd(II)-catalyzed cascade reaction of *N*-propargylamines and alkynes. Thus, the reaction of *tert*-butyl 3-(methoxycarbonyl)prop-2-ynylcarbamate **21** and alkynes **22** furnishes 2,4-disubstituted pyrroles **23** in good to excellent yields (Scheme 7)[19]. The reaction proceeds *via* addition of alkyne to **21** followed by a 5-*endo*-*dig*-cyclization and tautomerization of the ynenoate intermediate into pyrrole **23**. It is interesting to note that the electronic character of the substituents in the alkynes had little effect on the facility of reaction. Generally, all of electron-rich, electron-poor and branched alkynes can efficiently react under optimized condition. Furthermore, the reaction is tolerant toward a wide variety of functional groups such as amino, hydroxyl, carbonyl, alkoxide and halogens that can undergo in further reaction to produce unique pyrrole scaffolds.



Scheme 7. One-pot synthesis of pyrroles **23** *via* Pd(II)-catalyzed cascade reaction of *N*-propargylamine **21** and alkynes **22**.

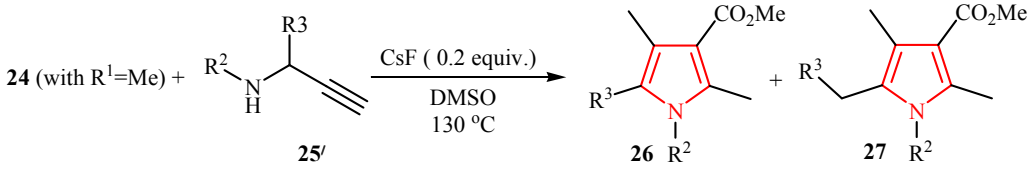
Very recently, an efficient transition-metal-free reaction between activated alkynes **24** with primary and secondary *N*-propargylamines **25** that leads to polysubstituted (tri-, tetra-, and penta-substituted) pyrroles **26** using K_3PO_4 as catalyst in DMSO was reported by Jin *et al* (Scheme 8). Interestingly, when the base was changed to CsF the reaction of **24** (with R^1=Me) with *N*-propargylamines **25′** *via* a Michael addition/aza-Claisen rearrangement/cyclization sequential process afforded pyrroles **27** as desired product with a different substituent pattern (Table 2)[20].



R^1= H, Me, COOMe
R^2= Bn, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, s-Bu, *t*-Bu, cyclopentyl, cyclohexyl, *n*-octyl,
R^3= H, Me, Et, Ph, *n*-Pr
R^4= H, Ph, Bn

Scheme 8. Cascade synthesis of polysubstituted pyrroles **26.**

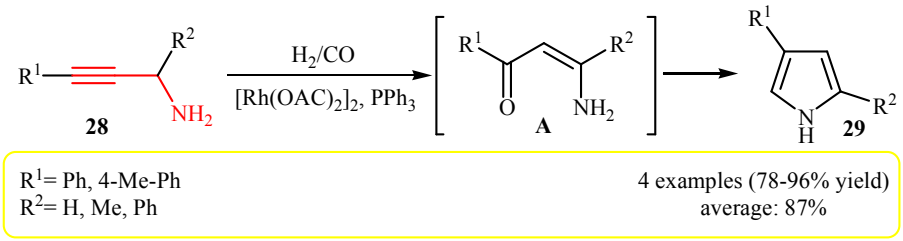
Table 2. CsF-catalyzed formation of polysubstituted pyrroles **26** and **27.**



Entry	R^2	R^3	Yield (%)	
			26	**27**
1	Bn	H	13	52
2	*n*-Bu	H	20	40
3	*i*-Bu	H	21	42
4	*n*-octyl	H	20	40
5	Bn	Me	12	48

2. 3. From hydroformylation of N-propargylamines

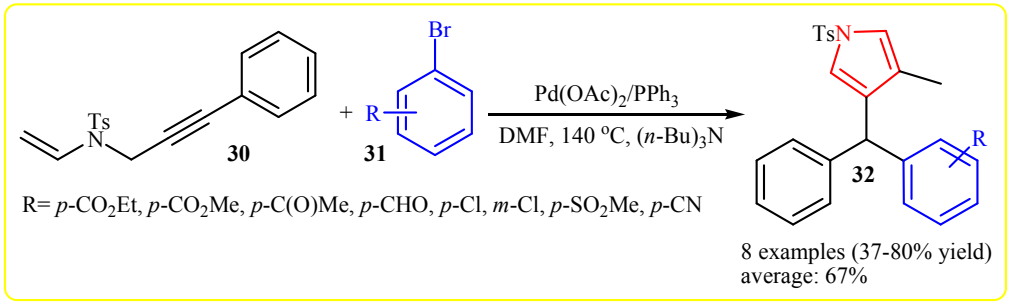
The hydroformylation reaction is the simultaneous addition of one mole each of hydrogen and carbon monoxide to a carbon-carbon double or triple bond by transition-metal catalyst, to produce two new C-C and C-H bonds[21]. Tons of chemicals are produced every year *via* this transformation and the production capacities is growing day by day[22]. In 1991, Campi and co-workers reported a different application for this reaction, when the propargylamines **28** underwent a hydroformylation and then cyclization reaction with CO/H_2 in the presence of $[Rh(OAC)_2]_2/PPh_3$ as catalytic system to form *β*-arylpyrroles **29** in good to high yields (Scheme 9). However, the reaction does not work well with alkylpropargylamines, due to the formation of significant amounts of furan-2-ones as side products (18-23%). Mechanistically, this transformation involves carbonyl reduction and removal of the amine function by hydrogenolysis[23]. To the best of our awareness this is the only example of *N*-propargylamine hydroformylation reported so far.



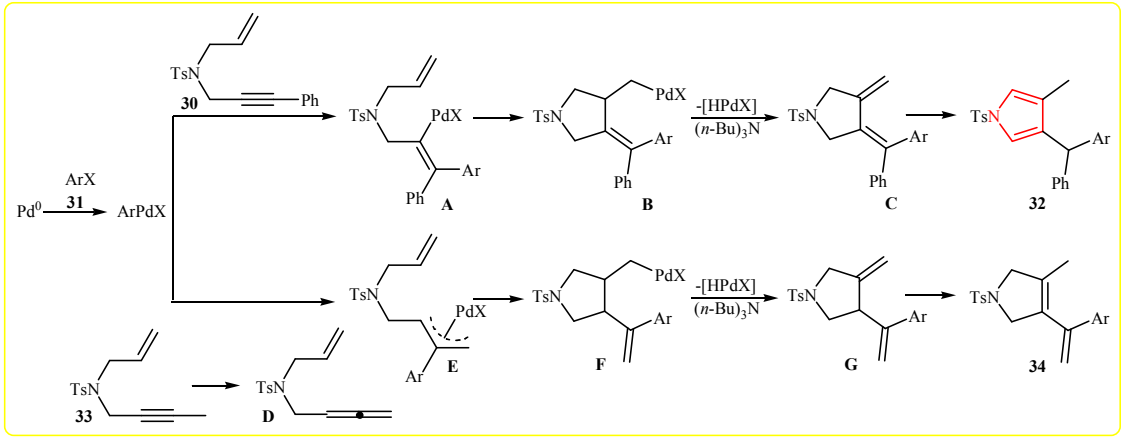
Scheme 9. Synthesis of 2,4-disubstituent pyrroles **29** *via* hydroformylation of *N*-propargylamines **28**.

2. 4. Miscellaneous

In 2010, Meng, Hu and Wang developed the synthesis of 1,4,5-trisubstituted pyrroles **32** *via* Pd(II)-catalyzed coupling/cycloisomerization of *N*-allyl-4-methyl-N-(3-phenylprop-2-ynyl)benzenesulfonamide **30** and bromobenzenes **31**, using PPh_3 as ligand, $(n\text{-}Bu)_3N$ as base and DMF as solvent at 140 °C. The electronic character of the aryl halides had remarkably strong effect on the reaction. the reaction tolerates electron-donating substituents at *meta* and *para* positions of aryl moiety and gave corresponding coupling products in good to high yields, but extension of the reaction to electron-withdrawing aryl rings was failed (Scheme 10). Interestingly, when substituent (Ph) at the terminus of the alkynes was changed to methyl, instead of pyrroles, the reaction afforded nonaromatic heterocycle derivatives **34** in moderate to good yields (8 examples with average yield of 65%). The authors proposed the below mechanism for this reactions (Scheme 11)[24].



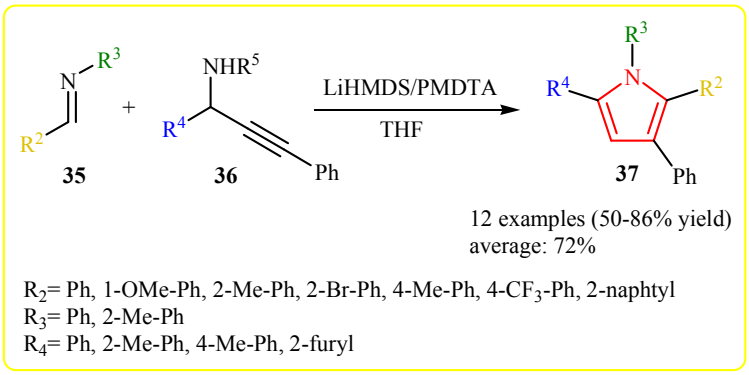
Scheme 10. Synthesis of trisubstituted pyrroles **32** from **30** and aryl halides **31**.



Scheme 11. Proposed mechanistic pathways for the formation of different heterocyclic compounds **32** and **34**.

An efficient synthesis of derivatives of the 1,2,3,5-tetraaryl pyrrole scaffold has been developed by Wan *et al*. The treatment of imines **35** with *N*-propargylamines **36** in presence

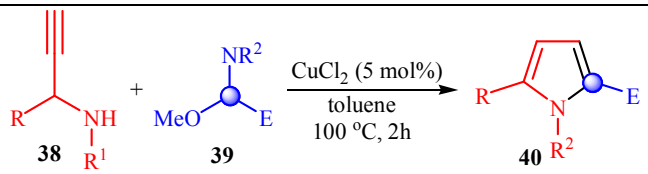
of bis(trimethylsilyl)amide (LiHMDS) as base and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) as the additive in THF, was found to afford pyrroles **37**. A broad scope of substituted imines, regardless of the electronic effects and the position of the substituents, and a variety of *N*-propargylamines, such as aryl and heteroarylated propargylamines could efficiently be employed in this reaction (Scheme 12)[25].



Scheme 12. Synthesis of pyrrole **37** *via* treatment of imines **35** with *N*-propargylamines **36**

More recently, Sakai and co-workers reported a very beautiful example of a copper-catalyzed synthesis of substituted pyrroles **40** from *N*-propargylamines **38** and *N*,*O*-acetals **39**. Conceptually, the reaction is based on the [4+1] annulation that *N*,*O*-acetals function as a C1 unit. The reaction tolerates both primary and secondary propargylamines and a variety of *N*,*O*-acetals that have an enolizable substituent adjacent to the central sp^3-carbon (Table 3)[26].

Table 3. Copper(II)-catalyzed [4+1] annulation of *N*-propargylamines with *N*,*O*-acetals.



Entry	R	R^1	R^2	E	Yield (%)	Entry	R	R^1	R^2	E	Yield (%)
1	H	2-Me-Ph	-$(CH_2)_5$-	CO_2Me	86	13	H	H	-$(CH_2)_5$-	CO_2Me	ND[b]
2	H	3-Me-Ph	-$(CH_2)_5$-	CO_2Me	80	14	H	Ph	Et	CO_2Me	85
3	H	4-Me-Ph	-$(CH_2)_5$-	CO_2Me	80	15	H	Ph	-$(CH_2)_5$-	COPh	43
4	H	4-NMe_2-Ph	-$(CH_2)_5$-	CO_2Me	81	16	H	Ph	-$(CH_2)_5$-	$CONR_2$	58
5	H	4-OMe-Ph	-$(CH_2)_5$-	CO_2Me	90	17	H	Ph	-$(CH_2)_5$-	Ph	ND[b]
6	H	2-OH-Ph	-$(CH_2)_5$-	CO_2Me	CM[a]	18	H	Ph	-$(CH_2)_5$-	H	ND[b]
7	H	4-F-Ph	-$(CH_2)_5$-	CO_2Me	81	19	$(CH_2)_2Ph$	Ph	-$(CH_2)_5$-	CO_2Me	70
8	H	4-Cl-Ph	-$(CH_2)_5$-	CO_2Me	87	20	c-hexyl	Ph	-$(CH_2)_5$-	CO_2Me	60
9	H	4-Br-Ph	-$(CH_2)_5$-	CO_2Me	83	21	Ph	Ph	-$(CH_2)_5$-	CO_2Me	90
10	H	4-CF_3-Ph	-$(CH_2)_5$-	CO_2Me	84	22	4-Me-Ph	Ph	-$(CH_2)_5$-	CO_2Me	91

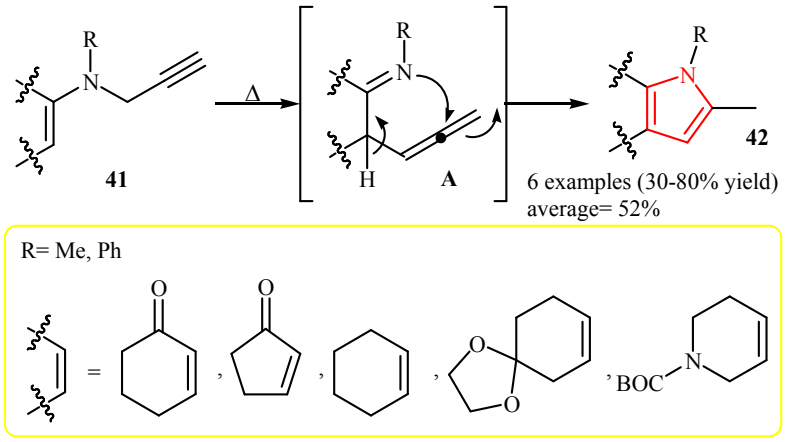
11	H	4-Ac-Ph	$-(CH_2)_5-$	CO_2Me	77	23	4-Cl-Ph	Ph	$-(CH_2)_5-$	CO_2Me	77
12	H	4-CN-Ph	$-(CH_2)_5-$	CO_2Me	70	24	H	*t*-Bu	$-(CH_2)_5-$	CO_2Me	31

[a]CM: complex mixture. [b]ND: not determined.

3. Synthesis of Highly Substituted Pyrroles from *N*-propargylamines *via* Intramolecular Reactions

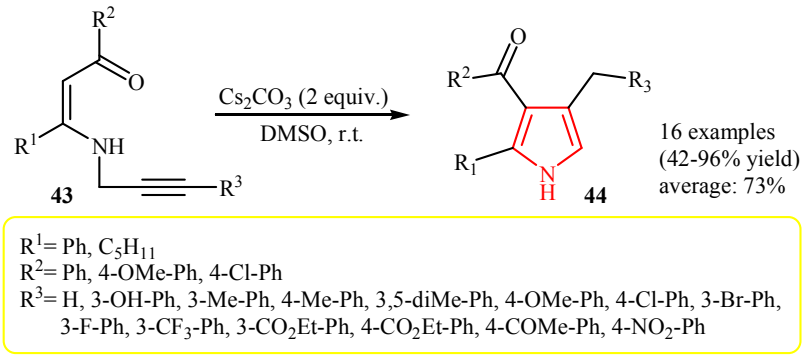
3. 1. From N-vinylpropargylamines

The thermal rearrangement of *N*-vinylpropargylamines into pyrroles was first introduced by Cossy and co-workers in 1996. It was demonstrated that various annulated[b]pyrroles **42** could be prepared in moderate to good yields *via* a tandem aza-Claisen rearrangement-cyclization reaction of *N*-vinylpropargylamines **41** (Scheme 13)[27].



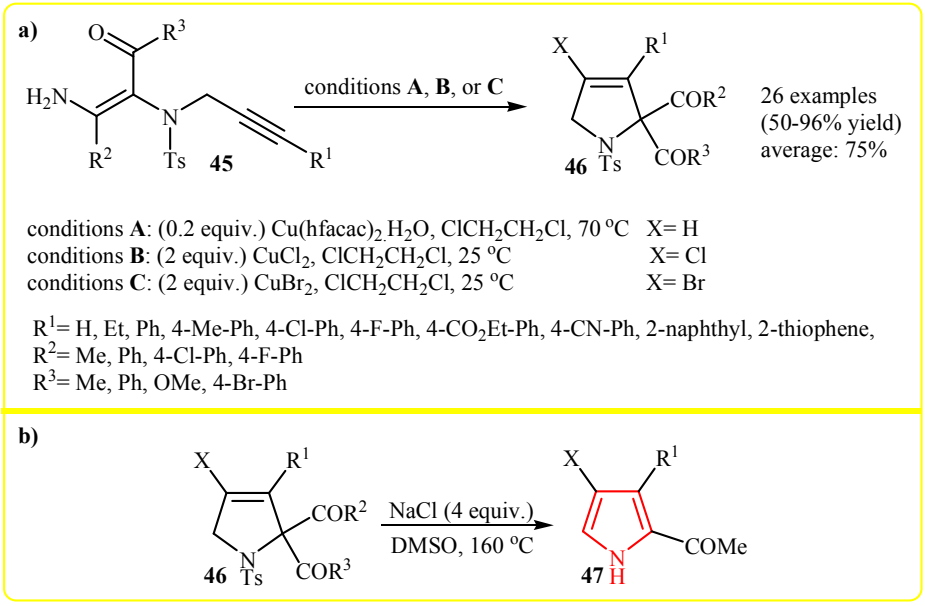
Scheme 13. The thermal rearrangement of *N*-vinylpropargylamines **41** into pyrroles **42**.

Later, in 2008, Cacchi and co-workers extended this chemistry to an intramolecular cyclization-protonation-isomerization cascade of *N*-vinylpropargylamines **43** to N-H free 2,3,4-trisubstituted pyrroles **44** using Cs_2CO_3 as catalyst in anhydrous DMSO at room temperature (Scheme 14)[28]. The scope of the Au-catalyzed version of this reaction was investigated by Saito *et al*. thus, it was shown that fully substituted pyrroles possessing an ester functional group at C-3 position could efficiently be synthesized from *N*-vinylpropargylamines using the (IP)Au(MeCN)]BF_4/ HFIP system at room temrature[29].



Scheme 14. Synthesis of NH Free Polysubstituted Pyrroles **44** from **43**.

Along this line, very recently Wang and co-workers reported the copper(II)-mediated electrophilic cyclization transformation of *N*-protected *N*-vinylpropargylamines **45** into highly substituted 3-pyrrolines **46** (Scheme 15a)[30] which can be easily converted to trisubstituted pyrroles **47** by treatment with sodium chloride (Scheme 15b)[31].

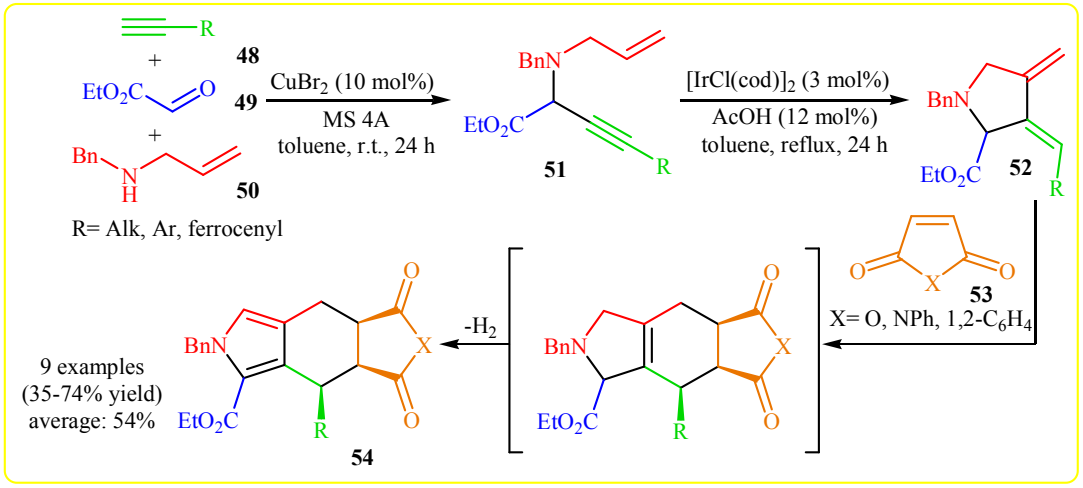


Scheme 15. a) Construction of highly substituted 3-pyrrolines **46** from *N*-protected *N*-vinylpropargylamines **45**, b) convert of **46** into trisubstituted pyrroles **47**.

3. 2. From N-allylpropargylamines

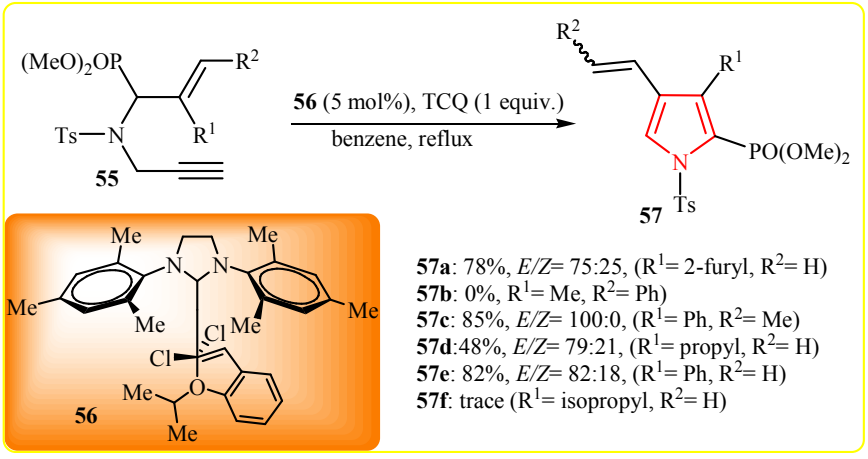
In 2005, Yamamoto and co-workers developed the synthesis of polycyclic pyrrole-2-carboxylates **54** from acetylenes **48**, ethyl glyoxylate **49**, benzylallylamine **50**, and activated alkenes **53** *via* a semi one-pot Mannich reaction/isomerization/Diels−Alder reaction/ dehydrogenative aromatization sequence. Thus, at the first step, the Cu-catalyzed three-component (acetylenes **48**, ethyl glyoxylate **49**, benzylallylamine **50)** Mannich reaction gives

N-allylpropargylamine **51**, which undergoes an Ir-catalyzed cycloisomerization into diene **52**. The formed diene **52** is converted to pyrrole **54** upon a subsequent Diels−Alder reaction with dienophile **53**, followed by a dehydrogenative aromatization (Scheme 16)[32].



Scheme 16. Synthesis of polycyclic pyrrole-2-carboxylates **54** *via* a transition metal-catalyzed four-component coupling approach

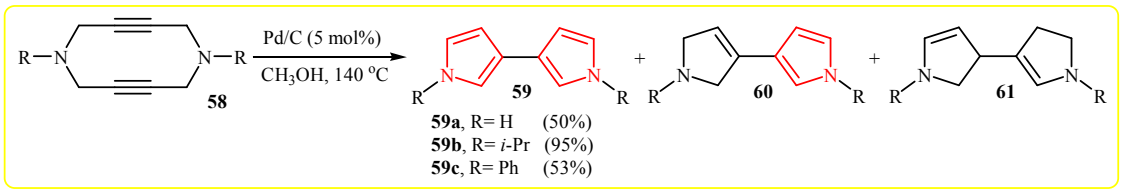
Follow this work, the Stevens group suggested the RCM/oxidation protocol for synthesis of 2-phosphono pyrroles **57** from the corresponding *N*-allylpropargylamine **55** using second-generation Grubbs catalyst **56** and tetrachloro-1,4- benzoquinone (TCQ) as an oxidant in benzene under reflux. However, it is limited to substrates bearing small substituents on C=C bond (Scheme 17)[33].



Scheme 17. Metathesis–oxidation sequence for the synthesis of 2-phosphono pyrroles **57** from *N*-allylpropargylamine **55**

3. 3. From N-propargylpropargylamines

Gleiter and Ritter developed an efficient Pd-catalyzed synthesis of *N*,*N*′-dialkyl-3,3'-bispyrroles **59** from *N*-propargylamines **58** in methanol at 140 °C (Scheme 18). According to the proposed mechanism, the reaction based on two allylic rearrangements and two dehydrogenation steps. It should be noted that the aforementioned temperature is vital for this reaction, because at lower temperatures than 140 °C the yield of pyrroles **59** is decreased in favor of the dihydro- **60** and the tetrahydro- **61** derivatives[34].



Scheme 18. The Pd-catalyzed rearrangement of *N*-propargylamines **58**.

After this work, in 2007, Tanaka *et al*. reported that vinylpyrroles **64** could be prepared *via* the Rh-catalyzed cycloisomerization of the corresponding 1,6-diynes **62**. The authors proposed the Rh-catalyzed mechanism shown in Figure 3. First, Rh(I) complex **A** is formed by reaction between the cationic Rh(I)/Segphos complex and 1,2-cyclohexanedione **63**. This intermediate reacts with the diyne **62** leading to hodacyclopentadiene intermediate **B**. Finally, the β-hydride elimination and double-bond isomerization of **B** affords the observed product[35].

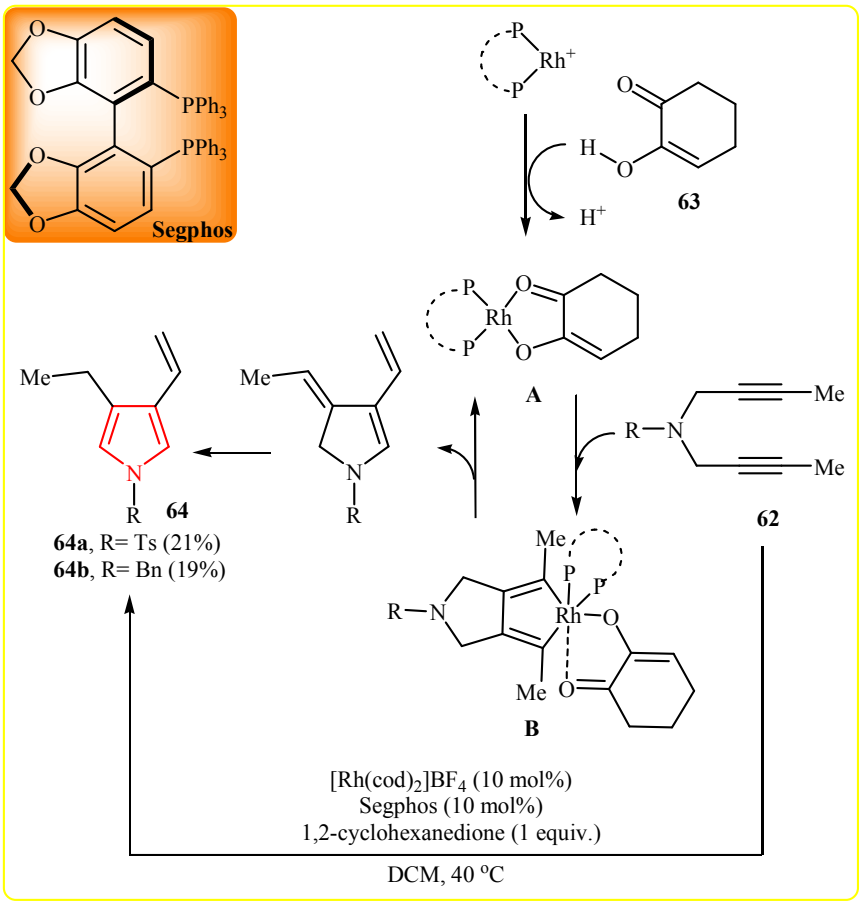
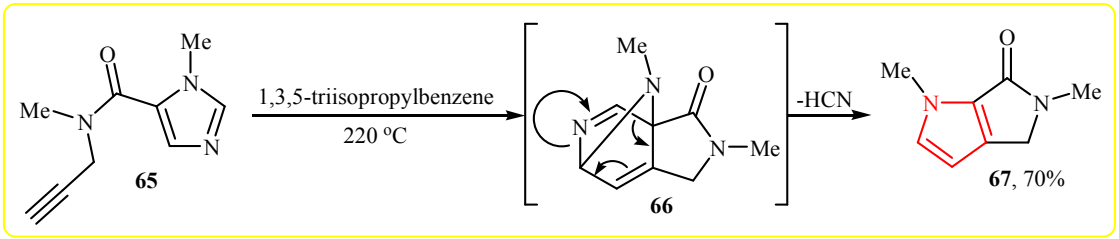


Figure 3. Rh-catalyzed synthesis of vinylpyrroles **64** from1,6-diynes **62**.

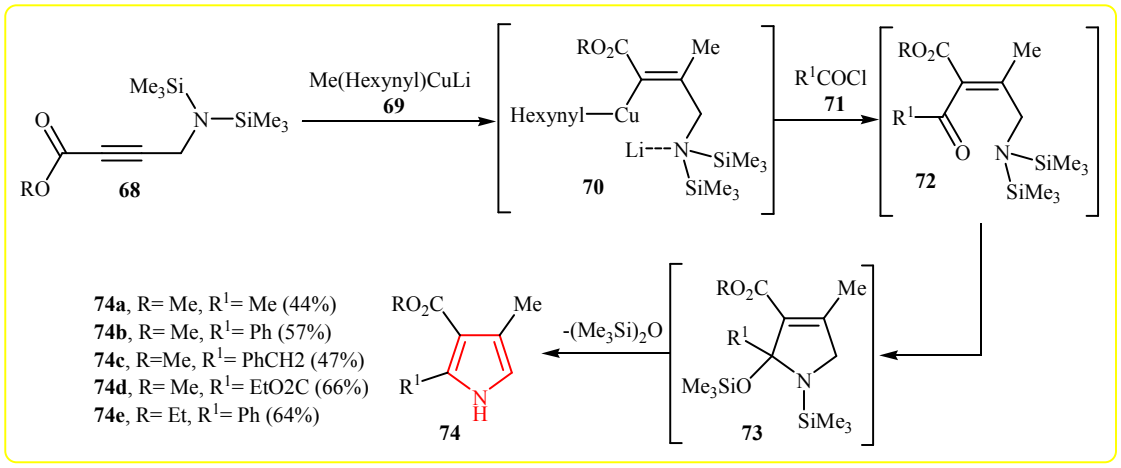
3. 4. Miscellaneous

An interesting and rare example for synthesis of bicyclic pyrroles was reported by Wuonola and Smallheer in 1993. Thus, in refluxing 1,3,5-triisopropylbenzene, an intramolecular Diels-Alder reaction of imidazolecarboxamide **65**, between *N*-propargylamine motif and imidazole, afforded pyrrole **67** in yield of 70%. The mechanism proposed by the authors to explain this reaction is based on the formation of the isoquinoline system **66**, followed by expulsion of a molecule of HCN (Scheme 19)[36].



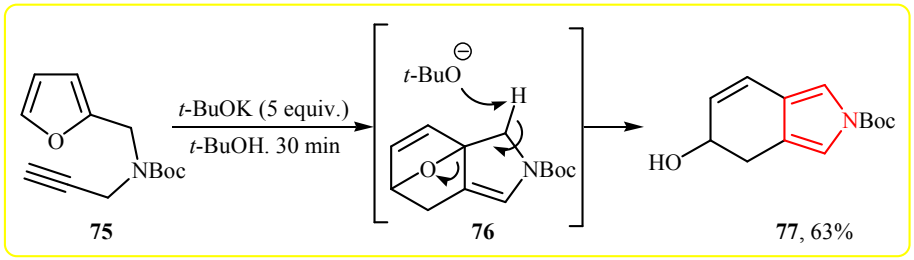
Scheme 19. Synthesis of bicyclic pyrrole **67** by intramolecular Diels-Alder reaction to the imidazole nucleus **65**.

A process for the synthesis of N-H free trisubstituted pyrroles **74** involves the addition of arganocuprates **69** to a silylated propargylamine **68** to led vinyl cuprate **70** followd by addition of acid chlorides **71** to give intermediate **72**. Finally, a cyclization-elimination sequence of **72** which resulted in the formation of the expected pyrroles **74** (Scheme 20). The $(Me_3)_2SiN$ group play three successive roles in this one pot reaction: 1) it is a protected primary amino group allowing the cuprate reaction. 2) It directs the stereochemisty of the cuprate addtion by stabilizing the *trans*-adduct *via* chelation. 3) It is reactive enough to cause cyclization upon nucleophilic attack at the *cis*-orientated carbonyl group[37].



Scheme 20. Synthesis of pyrroles **74** from silylated propargylamines **68**.

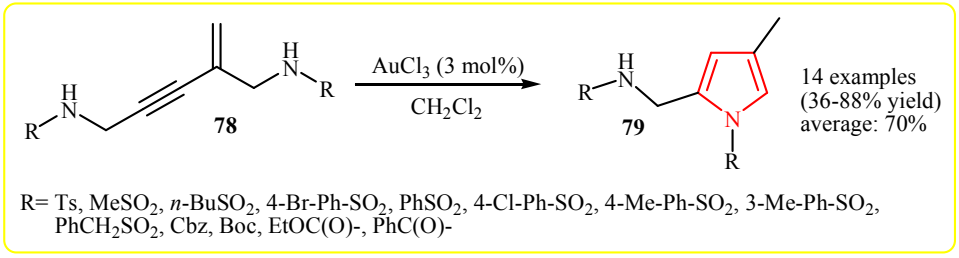
Lee and co-workers showed that Boc-protected furfuryl propargylamine **75** underwent a spontaneous intramolecular Diels-Alder reaction and then ring opening that afforded the bicyclic pyrrole **77** in yield of 63% in the presence of a base in *t*-BuOH (Scheme 21)[38].



Scheme 21. One-pot synthesis of bicyclic pyrrole **77** from furfuryl propargylamine **75**.

In 2009, Zhao and co-workers reported the synthesis of trisubstituted pyrroles **79** *via* the Au(III)-catalyzed hydroamination (5-*endo-dig* cyclization) of the corresponding amino-functionalized enynes **78**. The reaction provides *N*-alkyl-, *N*-arylsulfonyl-, and carbamoyl and

benzoyl-protected pyrroles **79** bearing a C2-aminomethyl group, in good yields (Scheme 22)[39].



Scheme 22. Synthesis of *N*-protected pyrroles **79** *via* the Au(III)-catalyzed hydroamination of amino-functionalized enynes **78**.

Recently, Yeh *et al*. introduced a sequential reaction for the synthesis of 2,3-disubstituted pyrroles **83** from 3,5,5-trimethyl-2,3-epoxycyclohexan-1-ones incorporating a (3-arylpropargyltosylamino)methyl tether at the C-2 position **80,** beginning with activation of the oxirane by TMSOTf occurred to give the semipinacol rearrangement product **81**, which upon intramolecular [2+2] cycloaddition and [2+2] cycloreversion (alkyne-ketone metathesis) steps furnished *N*-tosyldihydropyrrole derivative **82**. A subsequent oxidation followed by basic treatment occurred to generate pyrrole **83** (Figure 4)[40]. It is noted that the reaction tolerates electron-neutral and -rich substituents at aryl moiety and gave corresponding pyrroles in good yields, but it could not be extended to electron-poor rings.

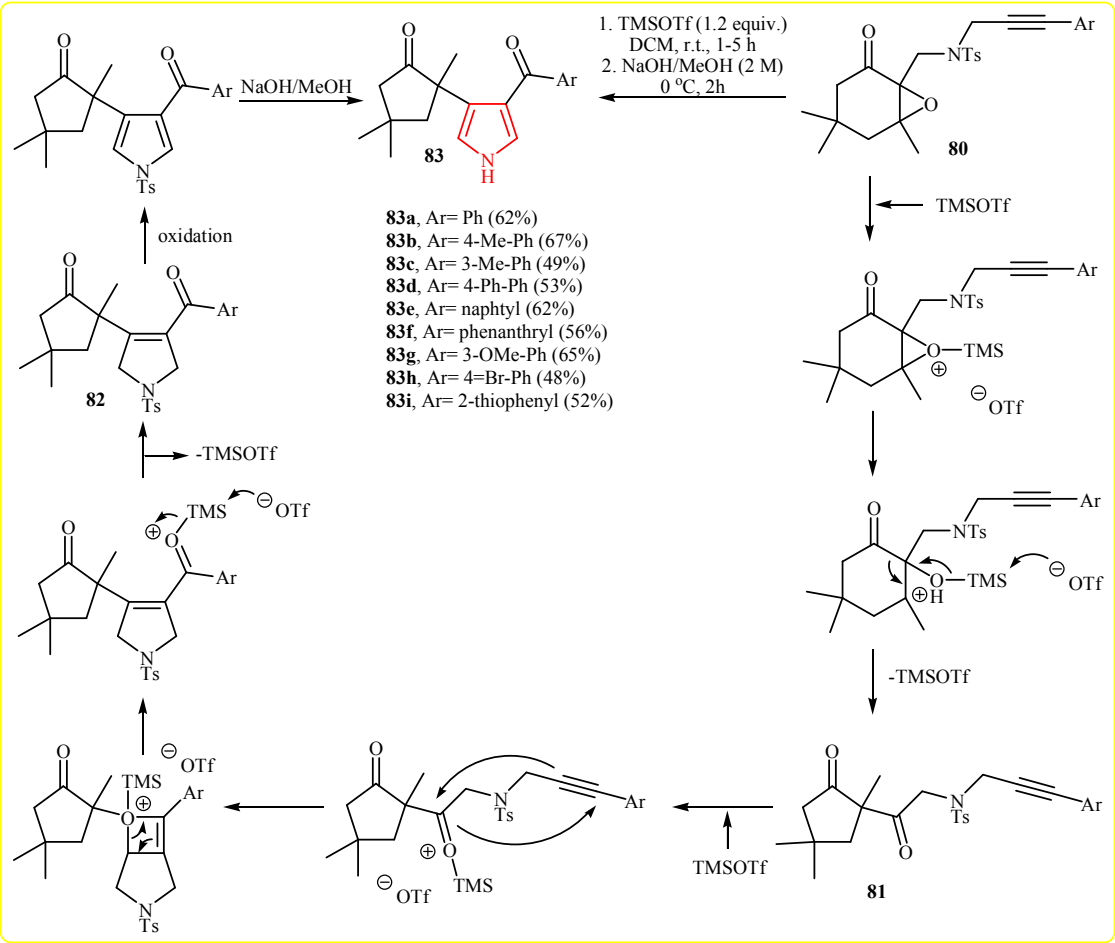
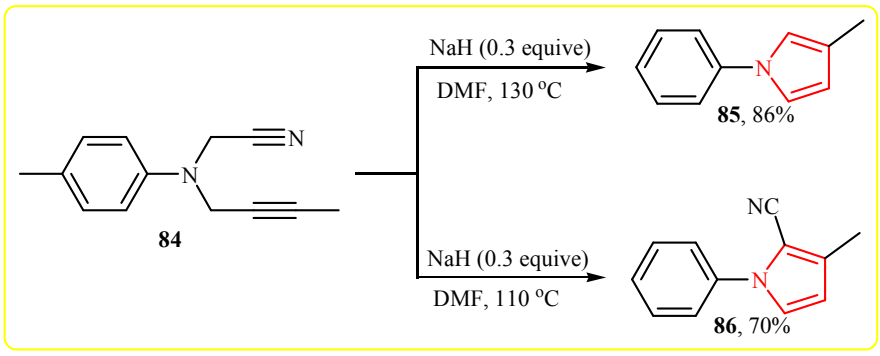
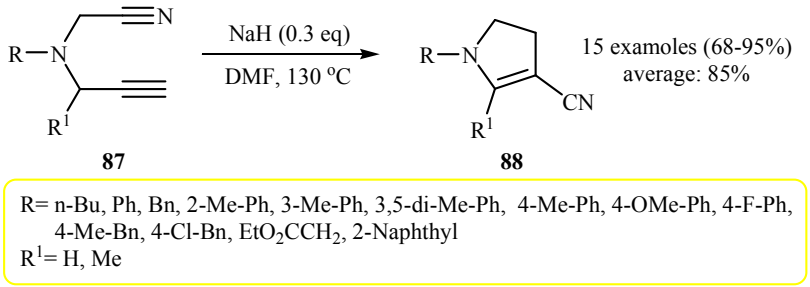


Figure 4. The synthesis of 2,3-disubstituted pyrroles **83** *via* TMSOTf-assisted cyclization reaction of **80**.

More recently, Zhao and co-workers reported an example of base-catalyzed intramolecular cyclization reaction of *N*-cyanopropargylamines. They showed that *N*-cyanopropargylamine **84** underwent cyclization–decyanation-aromatization in the presence of NaH as catalyst in DMF at 130 °C. The corresponding pyrrole **85** was obtained in yield of 86%. Interestingly, when the reaction was performed at 110 °C, pyrrole **86** was produced in 70% yield along with 10% of **85** (Scheme 23). It should be mentioned that the scope of the reaction is limited to internal alkynes only, because the substrates with terminal alkynes **87** gave dihydro pyrroles **88** instead of pyrroles (Scheme 24)[41].



Scheme 23. NaH-catalyzed intramolecular cyclization reaction of **85**.



Scheme 24. Cycloisomerization of 5-cyano-pentyne derivatives **87** to 3-cyano-4,5-dihydro-1H-pyrroles **88**

4. Summary and outlook

In conclusion, this review provides concise overview on the synthesis of highly substituted pyrroles from *N*-propargylamines *via* intra- or intermolecular cyclization reaction. In many cases, the use of this avenue for synthesis of pyrrole core provides milder conditions and simpler procedures than previously reported examples. This research area has still further possibilities for growth (For instance, by expanding of the substrates scope to *N*-propargylsulfamates or *N*-propargylsulfonamides for synthesis of special pyrroles) and we believed that the highly versatile and extremely effective procedures for the synthesis of highly substituted pyrroles from *N*-propargylamines will be attainable in the near future.

References

1. (a) A. Grube, E. Lichte and M. Köck, *J. Nat. Prod.*, 2006, **69**, 125-127; (b) B. M. Trost and G. Dong, *Org. lett.*, 2007, **9**, 2357-2359; (c) S. T. Handy and Y. Zhang, *Org. Prep. Proced. Int.*, 2005, **37**, 411-445; (d) A. Fürstner, *Synlett.*, 1999, **10**, 1523-1533; (e) L. Naumovski, J. Ramos, M. Sirisawad, J. Chen, P. Thiemann, P. Lecane, D. Magda, Z. Wang, C. Cortez and G. Boswell, *Mol. Cancer. Ther.*, 2005, **4**, 968-976; (f) T. Bando and H. Sugiyama, *Acc. Chem. Res.*, 2006, **39**, 935-944; (g) Y. Arikawa, H. Nishida, O. Kurasawa, A. Hasuoka,

K. Hirase, N. Inatomi, Y. Hori, J. Matsukawa, A. Imanishi and M. Kondo, *J. Med. Chem.*, 2012, **55**, 4446-4456.

2. V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, *RSC Adv.*, 2015, **5**, 15233-15266.
3. (a) F. Bellina and R. Rossi, *Tetrahedron*., 2006, **62**, 7213-7256; (b) V. Blangy, C. Heiss, V. Khlebnikov, C. Letondor, H. Stoeckli-Evans and R. Neier, *Angew. Chem. Int. Ed.*,, 2009, **48**, 1688-1691; (c) M. Takase, N. Yoshida, T. Narita, T. Fujio, T. Nishinaga and M. Iyoda, *RSC Adv.*, 2012, **2**, 3221-3224; (d) P. Liu, X. Wang and Y. Wang, *ACS. Sustain. Chem. Eng.*, 2014, **2**, 1795-1801.
4. L. Knorr, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1635-1642.
5. C. Paal, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 367-371
6. A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 1474-1476.
7. (a) A. R. Katritzky, J. Jiang and P. J. Steel, *J. Org. Chem.*, 1994, **59**, 4551-4555; (b) I. Freifeld, H. Shojaei and P. Langer, *J. Org. Chem.*, 2006, **71**, 4965-4968; (c) P. Langer, *Synthesis.*, 2009, **2009**, 227-242; (d) A. A. Fesenko and A. D. Shutalev, *J. Org. Chem.*, 2013, **78**, 1190-1207.
8. (a)M. N. Zhao, Z. H. Ren, Y. Y. Wang and Z. H. Guan, *Chem. Eur. J.*, 2014, **20**, 1839-1842; (b) M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.*, 2014, **16**, 608-611.
9. (a) V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Soc. Rev.*, 2010, **39**, 4402-4421; (b) V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Soc. Rev.*, 2014, **43**, 4633-4657.
10. (a) M. Namicinski, L. Pulaski, A. Kochman, J. Skolimowski, G. Bartosz and D. Metodiewa, *In Vivo*., 2004, **18**, 171-180; (b) S. Dragoni, V. Porcari, M. Valoti, M. Travagli and D. Castagnolo, *J. Pharm. Pharmacol.*, 2006, **58**, 561-565; (c) Y. Kleiner, O. Bar-Am, T. Amit, A. Berdichevski, E. Liani, G. Maor, I. Reiter, M. B. Youdim and O. Binah, *J. Cardiovasc. Pharmacol.*, 2008, **52**, 268-277; (d) F. T. Zindo, J. Joubert and S. F. Malan, *Future Med. Chem.*, 2015, **7**, 609-629; (e) R. A. Hauser, *Int. J. Neurosci.*, 2011, **121**, 53-62; (f) I. Bolea, A. Gella and M. Unzeta, *J. Neural. Transm*., 2013, **120**, 893-902; (g) M. Yogev-Falach, O. Bar-Am, T. Amit, O. Weinreb and M. B. Youdim, *FASEB J.*, 2006, **20**, 2177-2179; (h) P. L. McCormack, *CNS drugs.*, 2014, **28**, 1083-1097; (i) M. Xue, H. Huang, Y. Ke, C. Chu and X. Liang, *J. Chromatogr. A*., 2009, **1216**, 8623-8629; (j) H. Huang, Y. Jin, M. Xue, L. Yu, Q. Fu, Y. Ke, C. Chu and X. Liang, *Chem. Commun*., 2009, 6973-6975; (k) Y. S. Gal, B. Jung, W. C. Lee and S. k. Choi, *J. Polym. Sci. A Polym. Chem.*, 1992, **30**, 2657-2662.
11. (a) F. J. Fananás, T. Arto, A. Mendoza and F. Rodriguez, *Org. Lett.*, 2011, **13**, 4184-4187; (b) T. P. Lebold, A. B. Leduc and M. A. Kerr, *Org. Lett.*, 2009, **11**, 3770-3772; (c) D. F. Harvey and D. M. Sigano, *J. Org. Chem.*, 1996, **61**, 2268-2272; (d) B. Nilsson and U. Hacksell, *J. Heterocyclic. Chem.*, 1989, **26**, 269-275; (e) A. Arcadi, S. Cacchi, L. Cascia, G. Fabrizi and F. Marinelli, *Org. Lett.*, 2001, **3**, 2501-2504; (f) M. Zhu, W. Fu, G. Zou, C. Xun, D. Deng and B. Ji, *J. Fluorine. Chem.*, 2012, **135**, 195-199; (g) Z. Jiang, P. Lu and Y. Wang, *Org. Lett.*, 2012, **14**, 6266-6269.
12. (a) B. Jiang and M. Xu, *Angew. Chem. Int. Ed.*, 2004, **43**, 2543-2546; (b) J. J. Fleming and J. Du Bois, *J. Am. Chem. Soc.*, 2006, **128**, 3926-3927.
13. T. Tsuda, T. Kiyoi, T. Miyane and T. Saegusa, *J. Am. Chem. Soc*, 1988, **110**, 8570-8572.
14. W. S. Bremner and M. G. Organ, *J. Comb. Chem.*, 2007, **10**, 142-147.
15. E. Merkul, C. Boersch, W. Frank and T. J. Müller, *Org. Lett.*, 2009, **11**, 2269-2272.
16. Y. L. Zhao, C. H. Di, S. D. Liu, J. Meng and Q. Liu, *Adv. Synth. Catal.*, 2012, **354**, 3545-3550.

17. C.-Q. Ren, C.-H. Di, Y.-L. Zhao and J.-P. Zhang, *Tetrahedron Lett.*, 2013, **54**, 1478-1481.
18. H. Chachignon, N. Scalacci, E. Petricci and D. Castagnolo, *J. Org. Chem.*, 2015, **80**, 5287-5295.
19. B. M. Trost, J.-P. Lumb and J. M. Azzarelli, *J. Am. Chem. Soc.*, 2011, **133**, 740-743.
20. J. Weng, Y. Chen, B. Yue, M. Xu and H. Jin, *Eur. J. Org. Chem.*, 2015, **2015**, 3164-3170.
21. (a) R. Franke, D. Selent and A. Börner, *Chem. Rev.*, 2012, **112**, 5675-5732; (b) M. Beller, B. Cornils, C. D. Frohning and C. W. Kohlpaintner, *J Mol. Catal. A-Chem.*, 1995, **104**, 17-85; (c) D. E. Fogg and E. N. dos Santos, *Coord. Chem. Rev.*, 2004, **248**, 2365-2379; (d) R. S. Dickson, T. De Simone, E. M. Campi and W. R. Jackson, *Inorg. Chim. Acta*., 1994, **220**, 187-192.
22. (a) H.-W. Bohnen and B. Cornils, *Adv. Catal.*, 2002, **47**, 1-64; (b) S. N. Bizzarri, S. Fenelon, S and M. Ishikawa-Yamaki. Chemical Economics Handbook; SRI International: Menlo Park, **1999**; pp 682.7000A; (c) S. Naqvi. Oxo Alcohols. Process Economics Program Report 21E; SRI Consulting: Menlo Park, CA, **2010**.
23. (a) E. M. Campi, W. R. Jackson and Y. Nilsson, *Tetrahedron lett.*, 1991, **32**, 1093-1094; (b) E. Campi, G. Fallon, W. Jackson and Y. Nilsson, *Aust. J. Chem.*, 1992, **45**, 1167-1178.
24. T.-j. Meng, Y. Hu and S. Wang, *J. Org. Chem.*, 2009, **75**, 582-588.
25. Y. Hu, C. Wang, D. Wang, F. Wu and B. Wan, *Org. lett.*, 2013, **15**, 3146-3149.
26. N. Sakai, H. Hori and Y. Ogiwara, *Eur. J. Org. Chem.*, 2015, 1905-1909.
27. J. Cossy, C. Poitevin, L. Sallé and D. G. Pardo, *Tetrahedron lett.*, 1996, **37**, 6709-6710.
28. S. Cacchi, G. Fabrizi and E. Filisti, *Org. Lett*, 2008, **10**, 2629-2632.
29. A. Saito, T. Konishi and Y. Hanzawa, *Org. Lett*, 2009, **12**, 372-374.
30. C. Zheng, Y. Wang and R. Fan, *Org. Lett*, 2015, **17**, 916-919.
31. A. P. Krapcho and J. F. Weimaster, *J. Org. Chem*, 1980, **45**, 4105-4111.
32. Y. Yamamoto, H. Hayashi, T. Saigoku and H. Nishiyama, *J. Am. Chem. Soc.*, 2005, **127**, 10804-10805.
33. N. Dieltiens, K. Moonen and C. V. Stevens, *Chem. Eur. J*, 2007, **13**, 203-214.
34. R. Gleiter and J. Ritter, *Tetrahedron.*, 1996, **52**, 10383-10388.
35. K. Tanaka, Y. Otake and M. Hirano, *Org. Lett.*, 2007, **9**, 3953-3956.
36. M. A. Wuonola and J. M. Smallheer, *Tetrahedron lett.*, 1992, **33**, 5697-5698.
37. R. J. Corriu, G. Bolin, J. Iqbal, J. J. Moreau and C. Vernhet, *Tetrahedron.*, 1993, **49**, 4603-4618.
38. M. Lee, H. Moritomo and K. Kanematsu, *J. Chem. Soc., Chem. Commun.*, 1994, 1535-1535.
39. H. M. Peng, J. Zhao and X. Li, *Adv. Synth. Catal.*, 2009, **351**, 1371-1377.
40. M.-C. P. Yeh, M.-N. Lin, C.-H. Hsu and C.-J. Liang, *J. Org. Chem*, 2013, **78**, 12381-12396.
41. J. Meng, Y.-J. Li, Y.-L. Zhao, X.-B. Bu and Q. Liu, *Chem. Commun.*, 2014, **50**, 12490-12492.