The Synthesis of Aromatic Heterocycles from Propargylic Compounds

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Abstract: It is well known that the aromatic heterocyclic compounds are the most ubiquitous motifs and are found in many natural products and pharmaceuticals that exhibit remarkable biological activities. Significant effort continues to be given to the development of new methods for their construction. Although a number of methods have been established to construct these compounds, the development of novel methods that allow the facile assembly of substituted heterocycles from readily available starting materials remains an important objective. In recent years, propargylic compounds that contain many reactive centers have attracted a lot of attention for their various transformations. Chemists have conducted a detailed investigation of their cyclization with nucleophiles. The cyclization of propargylic compounds with a variety of nucleophiles is a very efficient method for producing furans, pyrroles, thiazoles, indoles, imidazoles, indolizines, oxazoles, pyridines, quinolines, thiophenes, and so on. In this review, we highlight the substantial progress that has been made in this area between 2000 and mid-2012, and give examples of the reactions of propargylic compounds with a variety of substrates to produce heterocycles.

Keywords: alkynes · cyclization · heterocycles · propargylic compounds · synthetic methods

1. Introduction

Propargylic compounds comprise one of the most important and most useful classes of substrates in organic synthesis. The π-nucleophilic character of the triple bond is a common functional group, which makes it a versatile entity for further chemical transformations. Furthermore, propargylic compounds are easily prepared by the reaction of terminal alkynes with an electrophilic carbon center. The transformation of various propargylic compounds has been defined through careful studies in recent years.[1] The transition-metal-catalyzed reaction of propargylic compounds with various nucleophiles has emerged as an attractive method for constructing aromatic heterocycles.[2] Herein, we summarize the recent developments in the synthesis of heterocycles from functionalized propargylic compounds.

In this review, we define some cyclization models (Figure 1). Before the main section, which is arranged by class of aromatic heterocycle, first some concepts will be defined. The bonds between C3 and X could be a single or double bond, as can those between X and Y, or Y and Z. When the aromatic heterocycles are directly formed by the attack of Z at the C2 position after the triple bond is activated by a catalyst, we define this as the C2-Z cyclization model. The C1-Y and C1-Z cyclization models are also defined according to a similar rule. However, when the cyclization occurs after a Claisen rearrangement or a migration process, we call it the rearrangement model. Thereby, we introduce each of the five-membered heterocycles discussed in the following order: 1) C1-Y cyclization model; 2) C2-Z cyclization model, and 3) rearrangement model. The C1-Z cyclization model is only relevant for the six-membered rings.

2 The Synthesis of Five-Membered Heterocycles

2.1. Furan

Furans are an important class of five-membered heterocycles that can be broadly found as a structural unit in numerous natural products and pharmaceuticals.[3] Furthermore, they have become important and useful synthetic building blocks.[4a] For these reasons, a tremendous number of efficient synthetic methods to construct the furan core and substituted furans are known and continue attracting the interest of synthetic chemists.[4b,c] The vast majority of the routes to produce substituted furans have involved cyclization approaches starting from acyclic precursors.

C1-Y Cyclization Model

In 2004, Larock and co-workers[5a] reported a highly efficient, Au-catalyzed (1 mol% AuCl3), atom-economical approach to produce substituted furans (Scheme 1). Overall, ready access to a wide variety of polysubstituted furans was achieved upon reaction of various 2-(1-alkynyl)-2-alken-1-ones with an unprecedented set of nucleophiles under very mild reaction conditions. Alcohols and 1,3-diketones, as well as various electron-rich aromatics, serve as efficient nucleophiles in this process. Similar results can also be achieved through an electrophile-induced cyclization process.[5b] 3-Butyne-1,2-diols also can afford the corresponding substituted furans in high yields by a Ru-catalyzed intramolecular cyclization, but only terminal alkynes were tested.[5c]

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Propargylic oxirane derivatives have played an important role in the construction of 2,3,5-trisubstituted furans. In 2001, Aurrecoechea et al. reported a practical and convenient route to synthesize 2,3,5-trisubstituted furans by using 4,5-epoxyalk-2-ynyl esters as precursors under mild reaction conditions. The reaction was performed in a one-pot sequence comprising Sm$_2$-promoted reduction and Pd$^2+$-mediated cycloisomerization of intermediate 2,3,4-trien-1-ols (Scheme 2). In 2008, a fascinating strategy for the synthesis of trisubstituted 3-iodofuran was developed by Liang and co-workers based on iodocyclization of propargylic oxirane compounds (Scheme 3). However, the reactant scope is limited, as the substituents on the oxirane must be aliphatic or cycloalkyls.

In 2011, Connell and co-workers succeeded in solving this problem. They developed an exciting method to synthesize various aromatic and aliphatic 2,3,5-trisubstituted furans from acetylenic epoxides by InCl$_3$ catalysis under mild and simple reaction conditions (Scheme 4). The starting materials are readily accessible and are prepared by treatment of α-haloketones with lithium acetylides.

Abstract in Chinese:
芳香杂环化合物普遍存在许多天然产物中，并且具有显著的生物活性。对于这些化合物的合成，人们不断进行探索。虽然过去已经建立许多方法，但发展一种从简单易得的化合物出发来巧妙地构建相关杂环，依然是一个重要的研究方向。炔基化合物由于存在着多个反应中心，而得到广泛的应用。对其与亲核试剂的环化反应，人们进行了系列的研究。通过这类环化，可以很简便构建呋喃、吡喃、噻喃、哌喃、中氮环、噻唑、噻唑、异噻唑、唑啉、噁唑、吡啶和嘧啶等。这篇综述总结了从2000年到2012年6月炔基化合物构建杂环的相关研究进展。

关键词：炔基化合物、杂环、环化
C2-Z Cyclization Model

In 2007, our group [7] reported a straightforward synthetic route to trisubstituted furans. This process first entails the nucleophilic substitution of propargylic acetates 10 with enoxysilanes 11 to form the γ-alkynyl ketones 12 in the presence of a catalytic amount of FeCl₃ (Scheme 5). The transformation into trisubstituted furans 13 occurs through a cyclization procedure catalyzed by 4-toluenesulfonic acid (TsOH) without purification of the γ-alkynyl ketones intermediates.

Scheme 5.

Starting from the reactants in the C1-Y cyclization model, such as propargylic oxirane derivatives, or from enoxysilanes in the C2-Z cyclization procedure, the introduction of substituents at the C4 position of the corresponding furans by a transition-metal-catalyzed cycloisomerization approach is difficult. Conditions developed recently in investigations of a one-pot synthesis by Cadierno et al. [8a] involve the initial propargylation of the 1,3-dicarbonyl compound 15 promoted by trifluoroacetic acid, and subsequent cycloisomerization of the resulting γ-ketoalkyne 16 catalyzed by the 16-electron allyl–Ru(II) complex [Ru(η⁴-2-C₃H₄Me)(CO)(dppe)]·SbF₆ ([Ru]; dppe = 1,1'-bis(diphenylphosphino)ferrocene), to prepare the tetrasubstituted furans 17 (Scheme 6). However, the catalyst used was very complex and a large amount of trifluoroacetic acid was required. The same reaction catalyzed by other catalysts, such as the simple Brønsted acid p-toluenesulfonic acid (PTSA) monohydrate [8b] has also been reported.

Scheme 6.

Rearrangement Model

As mentioned above, introducing a substituent at the C4 position of furans by using a transition-metal-catalyzed cycloisomerization approach is difficult. Synthetic methods that proceed through the rearrangement model provide an alternative choice.

In 2004, Gevorgyan and co-workers [10a] wanted to use [3,3] acyloxy migration to produce 27 from allene 28 en route to acyloxy-substituted furan 29 (Scheme 9). As expected, furan 29 was formed, but was accompanied by traces of the unexpected regioisomer 30. Addition of triethylamine to the reaction mixture shifted the product distribution toward predominant formation of furan 30. The mechanism was believed to be as shown in Scheme 10, as opposed to a 1,2 acyloxy migration. As part of this work,
ketones 35 smoothly underwent the postulated [3,3] shift/1,2-migration/cycloisomerization sequence to directly afford tetrasubstituted furans 37 in excellent yields (Scheme 11). The mechanism was proven by Fang et al.\textsuperscript{11} by using DFT calculations in 2011. Similar work, which uses a metal-catalyzed 1,2-shift of diverse migrating groups in allenyl systems to construct densely functionalized furans or other heterocycles, was also reported by Gevorgyan and co-workers in 2007.\textsuperscript{10b}

Propargyl vinyl ethers are commonly used in a Claisen rearrangement process to furnish polysubstituted furans that contain carbonyl or ester groups. In 2005, Kirsch and co-workers\textsuperscript{12a} used [(PPh\textsubscript{3})AuCl]/AgBF\textsubscript{4} (2 mol%) as the catalyst in the reaction of propargyl vinyl ethers to furnish tri- and tetrasubstituted furans in 72-99\% yield. The reaction is a cascade of a Claisen rearrangement and heterocyclization at room temperature. The typical structure of these products must have a methyl group at the C5 position and an ester or a carbonyl group at the C3 position. The reaction proceeds well for secondary propargyl vinyl ethers that contain not only aryl groups, but also alkyl groups. However, lower yields are obtained when tertiary substrates are used. A similar synthesis of tetrasubstituted furans 41, which contain carbonyl or ester groups at the C2 or C3 positions and a methyl group at the C5 position, was reported by Jiang and co-workers\textsuperscript{12b} in 2010. In this case, the reaction was catalyzed by AgOAc (5 mol\%) in the presence of PPh\textsubscript{3} (10 mol\%) at 50 °C and proceeds according to the same reaction mechanism for propargyl vinyl ethers 40 (which were formed in situ from alkynols 39 and diethyl but-2-ynedioate 38, Scheme 12). However, this achievement cannot change the fact that this protocol is also ineffective with tertiary propargyl vinyl ethers. Could this problem be solved? The answer was given by García-Tellado\textsuperscript{12c} and co-workers in 2011, who reported a metal-free transformation of tertiary propargyl vinyl ethers 42 to form the trisubstituted C2-chain functionalized furans 45 by a microwave-assisted tandem Claisen rearrangement/S-exo-dig O-cyclization reaction (Scheme 13). Products 50, which contain a formyl group or a carbonyl group at the C5 position, were prepared from the same substrates by Jiang and co-workers\textsuperscript{12d}.
in 2009 by using CuI (2.5 mol%) as catalyst and O₂ as the oxidant at 80°C through a domino rearrangement/dehydrogenation oxidation/carbene oxidation procedure. The mechanism is detailed in Scheme 14. A method that uses Fe(ClO₄)₃·xH₂O as the bifunctional catalyst was also disclosed by Jiang et al.\(^\text{[12e]}\) in 2010.

### 2.2. Pyrrole

Pyrrole is one of the most important simple heterocycles. It is an indispensable structural motif in many natural products and drug molecules\(^\text{[13a]}\) and also plays an important role in materials science\(^\text{[13b]}\) as well as in heterocyclic chemistry.\(^\text{[13c]}\) A huge effort has been made to develop efficient syntheses of pyrroles\(^\text{[14]}\).

#### CI-Y Cyclization Model

In 2004, Agarwal and Knöllker\(^\text{[15a]}\) developed a method to access pyrroles 55 by a Ag⁺-promoted oxidative cyclization of homopropargylamines 51 at room temperature. The mechanism for this process was proposed as shown in Scheme 15. More recently, Trost et al.\(^\text{[15b]}\) reported an atom-economic route to 2,4-disubstituted pyrroles 60, which involves a cascade Pd-catalyzed addition reaction, 5-endo-dig cyclization, and tautomerization process from electron-deficient propargyl amine 56 and alkynes 57 (Scheme 16). By using this strategy, 2,3,4-trisubstituted pyrroles also can be formed.

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**Scheme 13.**

**Scheme 14.**

**Scheme 15.**

**Scheme 16.** Boc = tert-butyloxycarbonyl; TDMPP = tris(2,6-dimethoxyphenyl)phosphine

Propargylic aziridines can also be used in the synthesis of the substituted pyrroles. In 2009, Davies and Martin\(^\text{[16a]}\) developed an atom-economic pathway to construct aryl-substituted N-tosyl pyrroles 62 and 63. This reaction is catalyzed by an Au catalyst and uses alkynyl aziridines 61 as starting materials. The interesting result is that when
[PPh₃AuOTs] is used as the catalyst, 2,5-substituted pyrroles 62 are formed, however, catalyzed by [PPh₃AuOTf] (Tf = trifluoromethanesulfonate) the reaction will lead to 2,4-substituted pyrroles 63 (Scheme 17). However, the scope is very limited and the reaction cannot tolerate functional groups. Furthermore, only disubstituted products can be prepared. In 2010, Liu and co-workers reported an efficient route to synthesize 2,3,5-trisubstituted N-phthalimidopyrroles 66, including pyrrole-2-carboxylates or 2-pyrrolyl ketones, by a Au/Ag-catalyzed cycloisomerization process (Scheme 18). This reaction is a good choice for the synthesis of 2,3,5-trisubstituted pyrroles, but when using alcoholic substrate 67 as the starting material, C=C bond cleavage will occur and product 68, in which the R₁ group is lost, will be afforded (Scheme 19).

An unusual tandem cyclization/ring-opening/Wagner–Meerwein approach to trisubstituted and cycloalkene-fused pyrroles 74 from propargylic aziridines 69 was disclosed by Tu and co-workers in 2009. The unique structures of the products demonstrated the potential applications of this reaction for synthesizing structurally diverse alkaloids. A plausible mechanism for the reaction is outlined in Scheme 20. More recently, in 2011, a similar method was also used to synthesize cyclopenta[b]pyrroles by a Pd-catalyzed cascade cyclization/ring expansion of 2-alkynyl-1-azaspiro[2.3]hexanes.

C2-Z Cyclization Model

In 2003, Gabriele et al. reported a general and regioselective synthesis of substituted pyrroles 76 by cycloisomerization of (Z)-2-en-4-ynylamines 75 (Scheme 21). The result is very surprising; spontaneous cycloisomerization leading to substituted pyrroles 76b occurred in the course of preparing enynamines 75b, which contain a terminal triple bond or a triple bond substituted with a phenyl or a CH₂OTHP (THP = tetrahydropyranyl) group (Scheme 21b). However, when the triple bond was substituted with an alkyl or alkenyl group, enynamines 75a were stable and could be converted into the corresponding pyrroles 76a by metal catalysis (Scheme 21a). The interesting thing is that CuCl₂ was found to be an excellent catalyst for cycloisomerization of substrates substituted at the C3 position, whereas PdX₂ in conjunction with KX (X = Cl, I) was the better catalyst for the reaction of enynamines that are not substituted at the C3 position. However, the reactions...
were usually carried out in a dipolar aprotic solvent such as DMA, and, especially for enynamines with a substituent at the C3 position, a high temperature of 100°C was required. On the other hand, the corresponding enynamines are generally prepared from (Z)-enynols through tedious synthetic route. Therefore, a simple methodology that uses mild conditions urgently needed. In 2009, Liu and co-workers[17b] developed an efficient one-pot synthesis of multisubstituted pyrroles 80 from suitably substituted (Z)-enynols 77 with amines or sulfonamides 78 under mild reaction conditions. The reaction is a cascade amination and cycloisomerization in the same vessel (Scheme 22). Similar structures can also be obtained by the reaction of a propargylic alcohol, a ketone, and the amine.[17c]

![Scheme 22](image)

In 2007, Cadierno et al.[18a] developed a synthetic route to fully substituted pyrroles 83 through a one-pot, three-component coupling reaction between easily accessible terminal secondary propargylic alcohols 81, readily available 1,3-dicarbonyl compounds 82, and primary amines catalyzed by the 16-electron allyl-Ru II complex [Ru(η)1-2-C5H4Me)(CO)(dpdf)]SbF6 ([Ru])/CF3CO2H (Scheme 23). However, two or more catalysts are needed in these reactions and the Ru catalyst used is very complex. A similar reaction catalyzed by a single and very simple catalyst, InCl3, was reported by our group[18b] in 2008 (Scheme 24). Fully substituted pyrroles 88 also can be produced from propargylic acetates 86, enoxysilanes 87, and primary amines 84, by a regioselective propargylation/amination/cycloisomerization process catalyzed by ZnCl (Scheme 25). This protocol was also reported by our group[19] in 2010.

**Rearrangement Model**

Using the rearrangement model gives us an alternative protocol by which to approach fully substituted pyrroles. In 2006, Binder and Kirsch[20a] described a cascade reaction that proceeds through a AgI-catalyzed propargyl-Claisen rearrangement, an amine condensation, and a Au I-catalyzed 5-exo-dig heterocyclization to afford fully substituted 5-methylpyrroles 91 from readily accessed propargyl vinyl ethers 89 and aromatic amines (Scheme 26). The resulting 5-methylpyrroles can further be transformed into 5-formyl-
pyrroles by 2-iodoxybenzoic acid (IBX)-mediated oxidation. More recently, a similar result was also achieved by the direct amino-Claisen rearrangement of N-propargyl β-enaminone derivatives \(^92\) and the cyclization of α-allenyl β-enaminone intermediates \(^93\) (Scheme 27), as reported by A. Saito et al. \(^{20b}\) in 2010. However, all of the products must have a carbonyl group at the C3 position and the diversity of the products is limited. Therefore, exploiting new substrates to synthesize fully substituted pyrroles that contain different functional groups remains a tough task.

### 2.3. Indole

The indole core can be found in numerous drugs and natural products, and marine indole alkaloids are potential new drug leads for the control of depression and anxiety.\(^{[21]}\) Plenty of synthetic methodologies to approach substituted indoles have been developed.\(^{[22]}\)

#### CI-Y Cyclization Model

In 2003, Barluenga et al.\(^{[23a]}\) described a robust route to furnish 3-iodoindoles \(^96\) from N-protected ortho-(alkynyl) anilines \(^95\), promoted by the iodinating agent IPy \(_2\)BF\(_4\) and its activation reagent HBF\(_4\) (1 equiv, Scheme 28). It was the first report of the addition of protected and unprotected anilines to internal alkynes through a simple iodination reaction. However, the yield is very poor when \(R^2\) is a group other than aryl or heteroaryl. On the other hand, the reactivity of substituted anilines hasn’t been exploited. Furthermore, the iodinating agent used is expensive, plus HBF\(_4\) is very toxic. A similar approach under mild reaction conditions was developed by Larock and co-workers.\(^{[23b]}\) This strategy is based on simple iodocyclization of N-substituted ortho-(alkynyl) anilines \(^97\), which are prepared by the Pd/Cu-catalyzed cross-coupling of N,N-dialkyl-ortho-iodoanilines and terminal alkynes. Alkyl-, aryl-, and vinyl-substituted alkynes all react well, as do unsubstituted and substituted anilines, including those that contain strong electron-withdrawing functional groups. The mechanism is also clear (Scheme 29).

#### C2-Z Cyclization Model

In 2007, Fensterbank and co-workers\(^{[24a]}\) devised a new synthetic route to construct substituted indoles from 2-propargyl anilines catalyzed by PtCl\(_2\) or a proton catalyst. The result is intriguing. Whereas N-allyl precursor \(^101\) furnishes a normal 5-exo-dig isomerization product \(^102\) (Scheme 30a), N,N-diallyl precursor \(^103\) provides rearrangement product \(^104\) by a cascade 5-exo-dig cyclization and 3-aza-Cope rearrangement procedure, as do the N-methyl and N-allyl precursors (Scheme 30b). To our surprise, these transformations also occur smoothly in excellent yields when SiO\(_2\) is used as the catalyst. When \(^105\) is used as the substrate, another rearrangement product \(^113\) was obtained (Scheme 31), and the ratio of products depends on the catalysts used and reaction temperature.
In 2010, Chan and co-workers\textsuperscript{[24b]} described a versatile approach for indole synthesis through the Au/Ag-catalyzed cycloisomerization reaction of 2-tosylaminophenylprop-1-yn-3-ols\textsuperscript{114}. This type of substrate is fascinating because differently substituted groups furnish different indoles under the same reaction condition (Scheme 32). When $R_1 = \text{Ar}$, indenyl-fused indole\textsuperscript{119} will form through a protodeau-ration and intramolecular Friedel–Crafts alkylation procedure (route 1 in Scheme 32), but when $R_1 = \text{CHR}_2\text{R}_3$, 2-vinyl-1H-indoles of the type\textsuperscript{124} will be delivered by proto-deauration and dehydration steps (route 3 in Scheme 32). If $R_1 = \text{H}$, the reaction will provide the (1H-indol-2-yl) methanol product\textsuperscript{121} from a more rapid protodeauration/1,3-al-lylic alcohol isomerization (route 2a in Scheme 32). On the contrary, if a strong nucleophile is present, 2-alkyl-1H-indole adduct\textsuperscript{122} will be obtained for the preferential S$_2$2' substitution (route 2b in Scheme 32). However, one drawback is that when aniline moieties that contain an electron-donating group, such as methyl, a mixture of unknown side products is obtained as well as the desired product.

Rearrangement Model

In 2007, A. Saito et al.\textsuperscript{[25a]} reported a Rh-catalyzed aromatic amino-Claisen rearrangement of N-propargyl anilines\textsuperscript{125} to generate 2,3-disubstituted indoles\textsuperscript{127} under mild conditions. A phosphine ligand is indispensable in this method. It is believed that the reaction proceeds by a Rh-catalyzed aromatic amino-Claisen rearrangement of\textsuperscript{125} and subsequent cyclization of ortho-allylaniline\textsuperscript{126} to furnish the target product\textsuperscript{127} (Scheme 33). This method gives excellent yields in the case of internal alkynes, but is not fit for terminal alkynes or those with alkyl substituents at the propargylic position. The chemoselectivity of this method is also poor. When a meta-OMe-substituted aniline derivative is used as the substrate, the para product (attack at the position para to the OMe group) is generated as the major product as well as almost half the amount of the ortho product (attack at the ortho position to the OMe group). The same procedure was also be achieved catalyzed by [RhH(CO)(Ph$_3$P)$_3$]/(CF$_3$)$_2$CHOH in 2009.\textsuperscript{[25b]} However, the problems mentioned above have not been solved yet.

2.4. Indolizine

Indolizines are a class of compounds that all contain an N-bridgehead bicyclic ring, and these compounds have extremely important applications in pharmaceutical use.\textsuperscript{[26]} Many synthetic routes have been reported.\textsuperscript{[27]} Synthetic methods that start from propargylic compounds almost always use pyridine propargylic alcohols and derivatives as substrates.

CI-Y Cyclization Model

Easy access to 1,3-disubstituted indolizines\textsuperscript{129} by a simple cycloisomerization process from pyridine propargylic pivaloates\textsuperscript{128} catalyzed by PtCl$_2$ at 70°C was described by Sarpong and co-workers\textsuperscript{[28a]} in 2007 (Scheme 34a). The addition of the bulky electron-rich phosphine ligands 2-(di-tert-butylphosphinio)biphenyl or 2-(dicyclohexylphosphinio)bi-

Scheme 32.

Scheme 33. HFIP = hexafluoro-2-propanol
phenyl results in increased yields and shorter reaction times. An alternative protocol was introduced by Liu and co-workers,[28b] whose method involves Cu-catalyzed cycloisomerizations of 2-pyridylsubstituted propargylic acetates and its derivatives \(130\) at room temperature in the presence of \(\text{Et}_3\text{N}\) (1 equiv, Scheme 34b). The base- and ligand-free conditions of this process were developed by Gevorgyan and co-workers[28c] in the same year (Scheme 35).

1,2,3-Trisubstituted indolizines cannot be prepared by using the methods mentioned above or the rearrangement strategies (see “rearrangement model” in this section, below). One of the possible ways to synthesize such compounds was developed by Gevorgyan and co-workers[29] in 2010. They found that treatment of 2-pyridylsubstituted propargylic acetates and its derivatives \(134\) with \(\text{ArI}\) \(135\) (1.5 equiv) and \(\text{PdCl}_2(\text{PPh}_3)_2\) (5 mol%) in \(N,N\)-dimethylformamide (DMF) at 120°C for 4 h provides 1,2,3-trisubstituted indolizines \(136\) in high yield (Scheme 36). Two equivalents of base (\(\text{K}_2\text{CO}_3\)), one equivalent of additive tetrabutylammonium iodide (TBAI) and \(\text{PPh}_3\) (40 mol%) were also required in this protocol, as these reagents can remarkably improve the yield. It is believed that this reaction proceeds by the Pd-catalyzed coupling of aryl halides with propargylic esters or ethers and subsequent 5-endo-dig cyclization (Scheme 37).

**Rearrangement Model**

A Pt-catalyzed cascade 1,2-migration/cycloisomerization procedure to synthesize 2,3-disubstituted indolizines \(143\) accompanied with small amount of 1,3-disubstituted products \(144\) was reported by Hardin and Sarpong (Scheme 38).[30] In this protocol, \(\text{PPh}_3\) was required to improve the yield, and the iodide counterion played a crucial role in remarkably
increasing the ratio of 2,3-/1,3-disubstituted products. Even though the electronic effect of the acyl, alkyne, and propargylic carbon substituents has a significant effect on controlling the product ratio, it cannot change the fact that the 2,3-disubstituted indolizine is the major product. The reaction mechanism was also investigated (Scheme 39).

2.5. Imidazole, Oxazole & Thiazole

Newly discovered and structurally diverse natural products that contain imidazole, oxazole, or thiazole units have a wide variety of biological activities.[31] Various methods have been developed for the synthesis of these compounds.[32]

**Imidazole**

Rapid access to highly substituted 2-aminoimidazoles 156 from propargyl cyanamides 153 and amines 154 was developed by Looper and co-workers[33a] in 2009 by using a La(O Tf) 3 catalyst (Scheme 40). This reaction proceeds by the addition of amine 154 to cyanamide 153 to form the propargyl guanidine 155, then a subsequent hydroamination/isomerization process, which provides a unique disconnection for rapid access to more complex natural product skeletons. However, this process also has its intrinsic disadvantages, that is, a high catalyst loading (30 mol%) and excess amine (3–5 equiv) were required. Primary amines were not favored in this procedure. In 2011, the same group[33b] developed another strategy to construct the same substituted 2-aminoimidazoles 160 by a Ag-catalyzed 5-exo-dig cyclization of di-Boc-protected propargylguanidine 157 (Scheme 41). This procedure was conducted in the presence of AgOAc (10 mol%) in CH 2 Cl 2 at room temperature and resulted in 5-exo-dig product 158. Compound 158 has the Z-alkene configuration and Boc protecting groups on the two N atoms, which can lead to substituted 2-aminoimidazoles 160 after deprotection. However, the 5-exo-dig product is not exclusive (it is accompanied by the 6-endo product 159), and the chemoselectivity is not so ideal. On the other hand, other synthetic routes to the products substrates are tedious and complex.

More recently, Wu and co-workers[33c] presented an Au/Ag-mediated synthetic route to 2,4-disubstituted imidazoles 164 and 165, which contain fluoroalkyl groups at the C2 position, from propargyl amidines 163. Amidines 163 can be easily prepared from imidoylchlorides 161 and secondary propargylamine 162 (Scheme 42). 2-Fluoroalkyl-5-methylimidazoles 164 were formed by a simple 5-exo-dig cyclization process at 60 °C by using [PPh 3 AuCl] (5 mol%) and

Scheme 39.

Scheme 40. PMB = para-methoxybenzyl.

Scheme 41.
AgBF₄ (10 mol%) as the catalysts. However, when the reaction was catalyzed by the same catalysts in the presence of N-iodosuccinimide (NIS)/K₂CO₃ in air 2-fluoroalkyl imidazole-5-carbaldehydes 165 were obtained. Further investigation revealed that the carbonyl oxygen atom was derived from atmospheric O₂. The mechanism is detailed in Scheme 43. However, the scope is limited to strongly electron-withdrawing groups Rᵣ as well as the secondary terminal alkynylamine. Therefore, developing a facile protocol from readily available substrates to prepare diverse substituted 2-aminoimidazoles still remains an attractive challenge.

Oxazole

The synthesis of 2,5-disubstituted oxazoles 173 from the corresponding propargylcarboxamides 171 catalyzed by AuCl under mild reaction conditions was described by Hashmi et al. [34a] in 2004 (Scheme 44a). It is noteworthy that an intermediate 5-methylene-4,5-dihydrooxazole 172 can be detected and accumulated in up to 95% prevalence when monitoring the conversion by 1H NMR spectroscopy. This result indicates a cyclization/isomerization reaction mechanism. It is also the first direct and catalytic preparative approach to such intermediates, which could react with electrophiles other than a proton to give different functionalized products (Scheme 44b). [34b] However, the internal alkyne does not react under the same conditions, which means that the terminal alkyne[14b] is crucial for this process. The direct synthesis of 2-substituted 5-oxazolecarbaldehydes 175 by using a similar substrate was conducted by treatment with [PdCl₂(MeCN)₂] (5 mol%) in the presence of a stoichiometric amount of benzoquinone (BQ) oxidant or CuCl₂/O₂, as reported by Brogini and co-workers (Scheme 45). [34d] The mechanism is detailed in Scheme 46.

In 2004, Wipf et al. [35a] reported a method to synthesize 2,4,5-trisubstituted oxazoles 185 catalyzed by SiO₂ at room temperature (Scheme 47). This reaction, which is also suitable for the synthesis of 2,5-disubstituted oxazoles, proceeds...
by simple cycloisomerization of propargyl amides. The scope is limited and the synthetic route to substrates is tedious and intricate. All the products contain a carbonyl group on the C5 position. In 2009, an efficient one-pot propargylation/cycloisomerization tandem process for the synthesis of 2,4,5-trisubstituted oxazoles from propargylic alcohols and amides in the presence of PTSA (1 equiv) in toluene at reflux was conducted by our group ([35b]). This reaction is tolerant of air and gives water as the only byproduct. Propargylic alcohols that contain terminal or internal alkyne groups underwent this reaction successfully. More recently, a strategy mediated by CeCl₃·7H₂O/NaI/I₂ under microwave irradiation to synthesize 2,4,5-trisubstituted oxazoles which can have a carbonyl group at the C4 position has also been reported by Giovannini and co-workers ([35c]) in 2012.

**Thiazole**

In 2009, Yoshimatsu et al. ([36a]) developed a new strategy for the preparation of 2,4,5-trisubstituted thiazoles by reaction of 3-sulphanyl and 3-selanylpropargyl alcohols with thioamides (Scheme 49). The use of Sc(OTf)₃ (5 mol%), MeNO₂/H₂O (10:1), and Bu₄NHSO₄ (10 mol%) at reflux provided the best yield of the product. This reaction is believed to proceed by unprecedented intermediate α-sulphanyl or α-selanyl propadienyl cations. All the products contain a 5-sulphanyl or a 5-selanyl group. Added to this is that the substrate scope is limited to secondary aromatic propargylic alcohols. Phase-transfer reagent Bu₄NHSO₄ was also required. A more flexible and rapid route to three different 2,4,5-trisubstituted thiazoles were described by our group ([36b]) in 2010. The different structure of thiazoles 196, 197, and 198 was quite dependent on the substrate structure (Scheme 50). A wide range of secondary propargylic alcohols or tertiary propargylic alcohols that contain not only terminal alkyne groups, but also internal alkyne groups can effectively be used, and a number of functional groups, such as cyclopropyl, cyclohexenyl, bromo, chloro, ester, and methoxy are tolerated under the reaction conditions. The mechanism is detailed in Scheme 51. A similar synthetic route to approach thiazoles catalyzed by p-TsOH·H₂O (5 mol%) was developed by Chan and co-workers ([36c]).
2.6. Isoxazole & Pyrazole

Isoxazoles and pyrazoles are two kinds of important heterocyclic compounds for their interesting biological activities. For this reason, many synthetic routes have been extensively exploited in the past. Because of their similar structure as well as their same C1-Y cyclization model (defined by us), isoxazoles and pyrazoles will be introduced together.

Isoxazole

The traditional synthesis of 4-haloisoxazoles was by halogenating the corresponding isoxazoles, which requires harsh reaction conditions. A new procedure that uses mild conditions for the synthesis of 3,5-disubstituted 4-haloisoxazoles was developed by Waldo and Larock in 2005 (Scheme 52). This strategy required three steps from the initial starting materials (acid chloride/terminal acetylene or lithium acetylide/aldehyde). The electrophilic cyclization is the key step to construct the in the presence of different electrophiles at room temperature, which are very mild conditions. The best result was obtained when using ICl as the electrophile. The resulting 4-iodoisoxazoles undergo various Pd-catalyzed reactions to yield 3,4,5-trisubstituted isoxazoles. A more convenient and time-saving approach to 3,4,5-trisubstituted isoxazoles was described by Vrancken and co-workers in 2011. This procedure uses readily available propargylic alcohols and Fe- and Pd-catalytic systems sequentially in an uninterrupted one-pot substitution/annulation/cross-coupling/hydrogenolysis/oxidation sequence (Scheme 53). More recently, in 2012, Chen and co-workers synthesized 4-alkenyl-3,4,5-trisubstituted isoxazoles from the reaction of O-methyl oximes with alkenes by a Pd-catalyzed cascade 5-endo-dig cyclization-alkenylation process. The addition of one equivalent of nBu4NBr can significantly increase the yields. One example of the synthesis of a naphthoisoxazole was reported by a cascade cyclization-alkenylation-Heck reaction from the special structure of the substrates (Scheme 54).

Pyrazole

The first example of the synthesis of pyrazoles from propargyl N-sulfonylhydrazones catalyzed by an AgI catalyst was described by Lee and Chung in 2008. This procedure was conducted in the presence of AgSbF6.
(5 mol%) at room temperature for 3–5 h, during which a migration of sulfonyl groups (Ts, Ms) was detected (Scheme 55). This method allows the efficient and regioselective synthesis of 1,3-disubstituted pyrazoles as well as 1,5- and 1,3,5-trisubstituted pyrazoles. However, this method cannot be used to synthesize pyrazoles substituted at the C4 position. In 2010, Wada and co-workers\cite{40b} disclosed switchable access to substituted dihydropyrazoles 245 and pyrazoles 246 from common hydrazides 244 by a reagent-controlled iodocyclization process (Scheme 56a). When NIS (3 equiv) is used as the catalyst and BF$_3$ · OEt$_2$ (3 equiv) as the additive, substituted 4-iodopyrazoles 246 with a 1-isopropyloxycarbonyl group will be obtained, which is one of the disadvantages of this method. A similar procedure driven by I$_2$ as the catalyst in the presence of NaHCO$_3$ was reported by Zora et al.\cite{40c} in 2011, whose products 249 can contain not only alkyl groups but also aryl groups at the N1 position (Scheme 56b). Though iodine-containing products can be further elaborated to a wide range of 2,3-disubstituted products through a simple coupling reaction.\cite{43b} However, it is difficult to attach an

2.7. Thiophene

Thiophenes are an important class of five-membered heterocycles that are the parent compounds of a very large number of alkaloids and medicinally important compounds.\cite{41} Numerous synthetic methodologies exist for the synthesis of thiophenes.\cite{42}
alkyl group. A facile synthesis of benzo[b]thiophenes 254 that contain an alkyl group at the C3 position was described by Nakamura et al.\[43c\] in 2006. This reaction proceeds by cyclization of (α-alkoxyalkyl)(ortho-alkynylphenyl) sulfides 253 and a subsequent migration of the α-alkoxyalkyl group in the presence of AuCl (2 mol%) at 25 °C (Scheme 58).

\[
\text{Cyclization of (para-Methoxyphenyl)methyl sulfides and allyl sulfides also reacted well} \quad \text{254}
\]

CHCl₃ as the solvent. When R² is an alkyl group, 2-(1-iodoalkenyl) products will be obtained under the same conditions, but changing the solvent to ethanol will result in the 2-acyl products (Scheme 61).

**Scheme 59.**

**C2-Z Cyclization Model**

In 2003, Hessian and Flynn\[44\] disclosed a remarkably effective synthetic route to give selective access to 2-acyl or 2-(1-iodoalkenyl)benzo[b]thiophene from 2-thiophenyl propynols by a 5exo-iodocyclization then subsequent tandem rearrangement and elimination or substitution processes (Scheme 60). Different types of product were obtained depending on the structure of the substrates and the conditions used. In the cases where R² is an aryl group, 2-acyl products are obtained in the presence of I₂ at 18 °C in CHCl₃ as the solvent. When R² is an alkyl group, 2-(1-iodoalkenyl) products will be obtained under the same conditions, but changing the solvent to ethanol will result in the 2-acyl products (Scheme 61).

**Scheme 60.**

**Rearrangement Model**

A thio-Claisen rearrangement (TCR) used to synthesize the substituted thiophenes 268 was described by Zhou et al.\[45\] in 2010. This protocol uses propargylic compounds 267 as the starting materials and is conducted in the present of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.2 equiv) at room temperature by a sulfur-assisted five-reaction cascade sequence. In this sequence, the allenyl allyl sulfides generated in situ undergo TCR, intramolecular Michael addition, and 1,5-proton migration/aromatization to obtain allyl thio-
phen-2-yl acetates, propionates, and ketones 268 as the final products (Scheme 62). An isotope-labeling experiment was also conducted to examine the mechanism (Scheme 63). This method provides a very convenient way to prepare substituted thiophenes with an electron-withdrawing group and an olefin, but the R3 group at the propargylic position must have an α proton to undergo successful enolization of the intermediate enethione to enethiol. Meanwhile, steric hindrance of the allyl group with a substituent at the C3 position (see intermediate 269, Scheme 63) will prevent the reaction occurring.

**3. The Synthesis of Six-Membered Heterocycles**

**3.1. Quinoline & Isoquinoline**

Quinoline and isoquinoline are extremely common structural motifs in various natural products and biologically active pharmaceuticals.[46] Much attention has been focused on developing diverse synthetic methods.[47] The C1-Z cyclization model will be discussed in this section.

In 2004, Akiyama and co-workers[48a] described a protocol to produce 2-arylated quinolines 274 from alkynyl imines 273. The imines underwent [4+2] electrocyclization in the presence of [W(CO)5(THF)] (20 mol%, Scheme 64). It is believed that the reaction proceeds via a tungsten-vinyldene complex, according to the deuterium-labeling study. However, the scope is limited to terminal alkynyl imines and only 2-substituted products can be formed.

In 2007, Sandelier and DeShong[48b] reported a synthetic route to access 2-substituted and 2,4-disubstituted quinolines 276 from ortho-nitropheryl propargyl alcohols 275 by a cascade reduction/Meyer–Schuster rearrangement/heteroannulation procedure in the presence of reductants under acidic condition (Scheme 65 and 66). The use of secondary propargyl alcohols gave much lower yields of the desired products relative to tertiary propargyl alcohols. The synthesis of 3-substituted quinolines has remained a big challenge in the case of using propargylic compounds as the starting materials. Substituted quinolines 285 that contain an iodo or phenylseleno group at the C3 position, prepared from propargylic aniline 284 through electrophilic cyclization in the presence of an electrophile (2–3 equiv) and NaHCO3 (2 equiv), were described by Larock and co-workers[48c] in 2005 (Scheme 67). The resulting 3-iodoquinolines 285 offer considerable potential for further elaboration to furnish the 3-substituted quinolines. However, this method cannot offer the unique chemoselectivity when meta-substituted propargylic anilines are used as the substrate, and the yields are lower for substrates that contain an alkyl group at the alkynyl position.
Isoquinoline

In 2002, Roesch and Larock [49] used iminoalkynes 286 to form 3-substituted isoquinolines 287 by a simple cyclization procedure in the presence of CuI (10 mol%) at 100 °C. This protocol is suitable for most cases other than R = alkyl (Scheme 68). By using the same substrates, 3,4-disubstituted products can be formed by using different protocols. Products that contain an iodo, PhS, p-O2NC6H4S, or PhSe group at the C4 position, which can be transformed to other substituted groups, were synthesized through an electrophile-induced cyclization process [50a].

More directly, 3,4-disubstituted products can be formed by the Pd-catalyzed cross-coupling of N-tert-butyl-ortho-(1-alkynyl) benzaldimines with aryl, allylic, and alkynyl halides [50b, c]. Similarly, the 3-substituted 4-arylisouquinolines can be prepared by treating N-tert-butyl-2-(1-alkynyl) benzaldimines with aryl halides in the presence of CO and a Pd catalyst [50d]. However, this method is not useful to obtain products that contain substituents at the C1 position because of the inherent structural defect of iminoalkynes. In 2008, Yamamoto and co-workers [51a] used 2-alkynyl-1-methylene azide aromatics 288 to react with iodine and/or other iodide donors to achieve the synthesis of 1,3-disubstituted 4-iodoisoquinolines 291, which can be further transformed to 1,3,4-trisubstituted isouquinolines (Scheme 69). Similar results also can be achieved by an Ag-catalyzed process [51b].

Scheme 68.

3.2. Pyridine & Pyrimidine

Substituted pyridines and pyrimidines constitute two kinds of compounds which have extremely important biological and pharmaceutical properties [52]. Many synthetic methods have been exploited [53] and the C1-Z cyclization model will be discussed in this section.

Pyridine

In 2006, Movassaghi and Hill [54a] used a Ru complex to mediate the cyclization of 3-azadienynes 293, which can be prepared from the reaction of N-vinyl or N-aryl amides 292 with copper acetylide, to construct pyridine rings. This reaction was conducted in the presence of [CpRu(PPh3)3Cl] (10 mol%), SPhos (10 mol%), and NH4PF6 (1 equiv) at 105 °C (Scheme 70). This route provides a direct conversion of 3-azadienynes into pyridine derivatives 294.
of C-silyl alkynyl imines to the corresponding azaheterocycles, which can avoid the isolation of the more sensitive terminal alkynyl imines. To our delight, even reactions with highly sensitive N-vinyl/heterocyclic imines can provide excellent results by using this protocol. However, the scope is limited to C-silyl alkynyl imines or the terminal alkynyl imines and only 2,5-disubstituted and 2,3-fused-5-substituted products can be prepared. The synthesis of 2,3,4-trisubstituted pyridines \[298\] was reported by Cacchi et al.\,[54b] whose method involves the cyclozation of N-propargylic enamiones \[297\] and a subsequent oxidation step catalyzed by CuBr at 60°C or 80°C (Scheme 71). The mechanism is detailed in Scheme 72. This route provides a good method to construct pyridine rings that contain a carbonyl group at the C3 position. However, a method to obtain 5-substituted and fully substituted pyridines still remains undeveloped.

**Pyrimidine**

In 2009, Grée and co-workers\,[55] presented a synthetic route to prepare chiral pyrimidines (\(\pm\)-304) with a fluorine atom in the benzylic position in high enantiomeric excesses from optically active propargylic compounds (\(\pm\)-302). The interesting thing is that both the use of optically active propargylic fluorides (\(\pm\)-305) and the fluorination of the chiral pyrimidine (\(\pm\)-303) in the final stage give excellent results in terms of enantiocontrol (Scheme 73). By using this method, pyrimidines with difluoromethyl side chains also can be synthesized. In 2011, our group\,[52b] also disclosed a new approach to the tandem synthesis of 2,4-disubstituted or 2,4,6-trisubstituted pyrimidines 308 from propargylic alcohols 306 with amidine 307. This reaction proceeds through a cascade propargylation-cyclization-oxidation sequence catalyzed by Cu(OTf)\(_2\) (20 mol %) under very mild reaction conditions. The mechanism is detailed in Scheme 74. However, a synthetic method obtain the 5-substituted product from propargylic compounds continues to be a big challenge.

### 3. Conclusion

In this Focus Review, we have summarized the recent research progress on the construction of aromatic heterocycles from propargylic compounds. Taking a panoramic look...
at this review, we can see that aromatic heterocycles, including five-membered rings and six-membered rings, can be easily prepared under mild reaction conditions in satisfactory yields by using easily available propargylic compounds as the starting materials. Furthermore, as a result of their unique structure, propargylic compounds can be further elaborated to relevant nature products or drugs within few steps, such as in the synthesis of Naamine A by Looper and co-workers.  

Despite lots of achievement having been made in the past, much endeavor is still required. Firstly, reliable syntheses of many aromatic heterocycles that contain substituents at specific positions have not yet been developed, such as the direct synthesis of fully aryl- or alkyl-substituted pyrazoles, as well as 5-substituted pyridines and pyrimidines. The synthesis of heterocycles that contain diverse functional groups also needs further development. Secondly, the synthesis of chiral aromatic heterocyclic compounds by the asymmetric nucleophilic substitution reaction of propargyl alcohols and subsequent cyclization procedure, or direct synthesis from optically active propargylic compounds still remains a big challenge. This area is attracting interest, but only a little research has been reported so far.  

Finally, exploiting new synthetic routes to natural products and drugs is still an important objective, although some targets have already been achieved. This is also an ongoing interest in our group. 

Acknowledgements

We thank the NSFC (No. 21072159), the 973 Projects (No.2011CB935901) for financial support of this project.